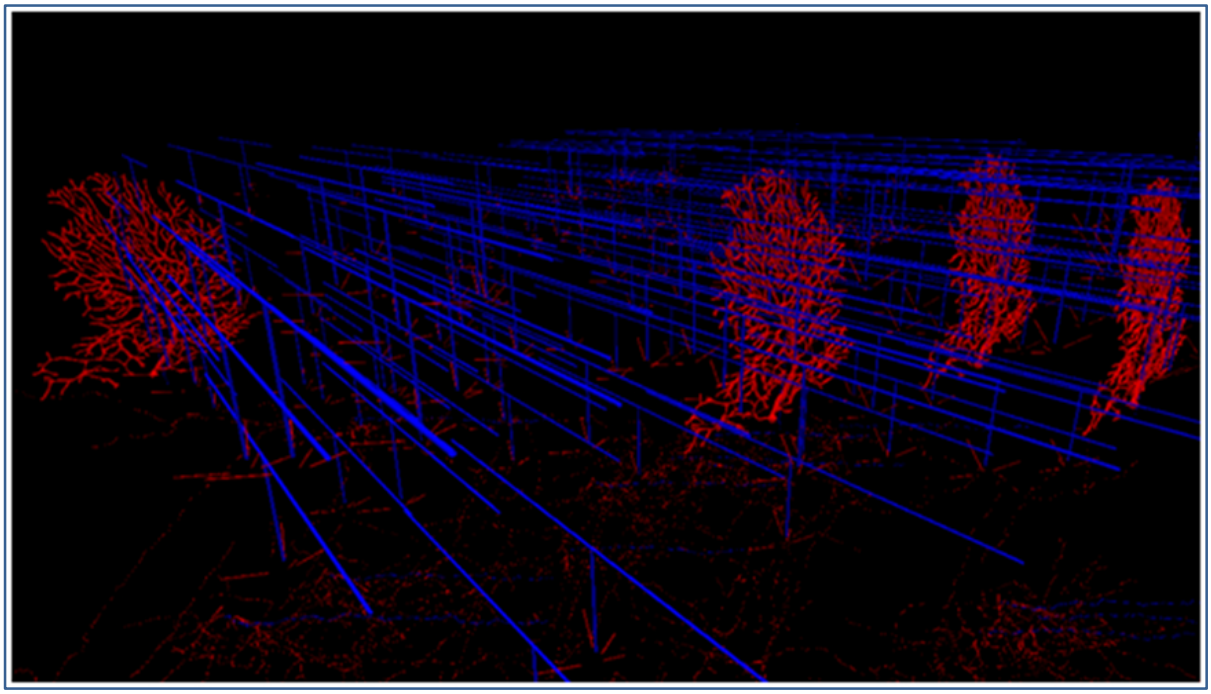

**Figure 1: Detailed single cell models of neurons of the cerebellar cortex are developed within the OptimizerFramework and assembled into large-scale networks using the Brain Simulation Platform (see Tasks 6.2.3 Models of Cerebellum and 6.3.3 Tools for Cellular Reconstruction).**

| Project Number: | 720270 | Project Title: | Human Brain Project SGA1 |
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|---|---|
| Authors: | See list of Contributors |
| Compiling Editors: | Felix SCHÜRMANN, EPFL (P1)<br>Jeanette HELLGREN KOTALESKI, KTH (P39)<br>Katrien VAN LOOK, EPFL (P1)<br>Daniel VARE, KTH (P39) |
| Contributors: | The following PIs and their teams contributed (listed by institution):<br>EPFL (P1): Henry MARKRAM, Felix SCHÜRMANN, Jean-Denis COURCOL, Fabien DELALONDRE, Csaba EROE, Michael GEVAERT, Marc-Oliver GEWALTIG, Daniel KELLER, James KING, Eilif MULLER, Aleksandr OVCHARENKO, Armando ROMANI, Christian RÖSSERT, Till SCHUMANN, Werner VAN GEIT, Katrien VAN LOOK, Willem WYBO<br>EPFL (P1): Ursula RÖTHLISBERGER, Daniele NARZI<br>CNRS (P10): Andrew DAVISON, Shailesh APPUKUTTAN, Pedro GARCIA-RODRIGUEZ, Lungsi SHARMA<br>CNRS (P10): Richard LAVERY, Juliette MARTIN<br>CNR (P12): Michele MIGLIORE, Luca Leonardo BOLOGNA, Rosanna MIGLIORE<br>ENS (P17): Antoine TRILLER, Pablo SERNA<br>JUELICH (P20): Paolo CARLONI, Rodrigo CASASNOVAS PERERA<br>JUELICH (P20): Markus DIESMANN, Jochen EPPLER, Tammo IPPEN (also NMBU)<br>HITS (P24): Rebecca WADE, Neil BRUCE<br>IEM HAS (P30): Szabolcs KÁLI<br>KI (P37): Sten GRILLNER, Alexander KOZLOV, Shreyas SURYANARAYANA, Peter WALLEN<br>KTH (P39): Jeanette HELLGREN KOTALESKI, Olivia ERIKSSON, Anu NAIR, Robert LINDROOS, Parul TEWATIA, Daniel VARE<br>NMBU (P44): Hans Ekkehard PLESSER, Tammo IPPEN (also JUELICH)<br>HUJI (P60): Idan SEGEV |

| | |
|---|---|
| | UPM (P68): Javier DEFELIPE<br>UNIPV (P70): Egidio D'ANGELO, Simona TRITTO<br>UCL (P82): Audrey MERCER<br>IRB/JUELICH: Modesto OROZCO, Francesco COLIZZI<br>OIST: Erik DE SCHUTTER<br>YALE: Michael HINES |
| SciTechCoord Review: | EPFL (P1): Jeff MULLER, Martin TELEFONT, Marie-Elisabeth COLIN<br>UHEI (P47): Martina SCHMALHOLZ, Sabine SCHNEIDER |
| Editorial Review: | EPFL (P1): Guy WILLIS, Colin McKINNON |


| | |
|---|---|
| Abstract: | The overall goal of SP6 is to develop data-driven reconstructions of brain tissue at different biological scales, and to develop model building workflows and simulation capabilities to explore these reconstructions in the HBP Brain Simulation Platform (BSP). In the first year of SGA1, scientific work has progressed for showing that molecular level simulations can guide models of receptor-induced cascades as well as for the modelling of four selected brain regions, namely the somatosensory cortex, hippocampus, cerebellum and basal ganglia. These scientific co-design drivers have guided the design of the software tools, the implementation of the model building workflows and the operation of the BSP. As per the feedback from the reviewers at the end of the Ramp-Up Phase (RUP), additional efforts have been spent to make the platform appeal to the more average user. This work has resulted in a major rework of the packaging of the Platform's functionality more tailored to a wider group of users and is scheduled to be released soon. In terms of remarkable scientific results, a first ever model of a human pyramidal neuron built using the SP6 single cell modelling workflow was published in *eLife*. |



| | |
|---|---|
| Keywords: | Brain Simulation Platform, BSP, results for SGA1 period 1, Milestones |

# Table of Contents

# List of Figures

## List of Tables

# 1. SP Leader's Overview

## 1.1 Key Personnel

Subproject Leader: Henry MARKRAM (EPFL)

Subproject Deputy Leader: Felix SCHÜRMANN (EPFL)

Subproject Deputy Leader: Jeanette Hellgren KOTALESKI (KTH)

Subproject Manager: Daniel VARE (KTH)

Subproject Manager: Katrien VAN LOOK (EPFL)

## 1.2 Progress

The overall goal of SP6 is to develop data-driven reconstructions of brain tissue at different biological scales, and to develop model building workflows and simulation capabilities to explore these reconstructions in the HBP Brain Simulation Platform (BSP). In SGA1 SP6 consists of five WPs, where the first two WPs (6.1 & 6.2) develop and refine data-driven models at different levels of biological detail, and in doing so drive, in a co-design manner, the software tools, workflows and services of the BSP developed in WP6.3 and WP6.4 and which are mainly based of work from the HBP Ramp-Up Phase (RUP). WP6.5 coordinates the scientific, platform and community efforts for SP6.

A successful proof of concept that molecular level simulations can guide models of receptor-induced cascades has been made on the example of the regulation of cAMP production and a manuscript is in preparation. At the level of the microcircuit model building, work has progressed so that draft microcircuits now exist for all of the four brain regions modelled in SP6, the somatosensory cortex, hippocampus, cerebellum and basal ganglia. This model building process has guided the design of the software tools, the implementation of the model building workflows and the operation of the BSP. The different microcircuits have highlighted different needs regarding what the modelling workflow should ideally be able to support, and as a result the process to generalise the modelling workflows is developing further. This enhancement of the BSP driven by the model reconstruction work will be crucial for community users of the Platform.

As per the feedback from the reviewers at the end of the RUP, additional efforts have been spent to make the Platform appeal to the more average user. This work has resulted in a major rework of the packaging of thePplatform's functionality more tailored to a wider group of users. This allows more direct access to tasks of interests (e.g. electrical trace analysis, single cell model generation) but also provides an easier access to revalidate previously built models or spawn new work from an existing model. It is planned to soon release these improvements in a coordinated fashion with other Platforms in the HBP.

In terms of remarkable scientific results, a first ever model of a human pyramidal neuron built using the SP6 single cell modelling workflow was published in *eLife*.[1] One prediction from the modelling work is that the membrane capacitance in human neurons is lower than in mice and rodents, and this prediction was also verified experimentally.

Finally, the coordinating work in SP6 has progressed smoothly with monthly SP6-wide meetings. Also an explicit request to SPs 1-3 regarding data needed for the data–driven modelling in SP6 was provided in advance of the SGA2 planning process.

- Risks

[1] Eyal et al., Unique membrane properties and enhanced signal processing in human neocortical neurons. *Elife*. 2016 Oct 6;5.

One risk of the BSP is that access to most of its services requires any user to have an account and allocation to the HBP's High Performance Analytics and Computing (HPAC) Platform. To obtain such an allocation, a separate application to the HPC centres is required, which includes peer-review according to the centres' processes, independent of the HBP. While the peer-reviewed access to substantial compute resources is understandable, for the BSP this results in overhead even for basic platform integration and high entry barrier for interested external users. These problems have been mitigated so far in different ways due to efforts by all involved partners, but a base HPC allocation to the BSP would be an important mechanism to ensure a base operation of the platform and an easy entry for external users. If successful, the application to the EC call for "Interactive Computing e-infrastructure for the Human Brain Project FET Flagship (FPA)" can also help mitigate this risk.

## 1.3 Deviations

The reorganisation of the Neuroinformatics Platform (NIP) following the DPIT process has delayed joint interface work and integration between the two Platforms. At this point, this is mitigated by hosting certain datasets in proxy locations so that the development of the BSP can continue as planned. SP6 is engaging SP5 to see how this can be overcome before the end of the SGA1 phase.

A more important deviation to SP6 stems from the cancelling of the planned Open Call for T1.1.7, as this will delay the generation of molecular maps across the whole mouse brain. Such data sets are needed for the subcellular level modelling and the microcircuit level modelling (e.g. prediction of morphologies for brain regions where there are not enough morphologies recorded) and the absence thereof presents an important risk to data-driven scaffold whole brain modelling at the cellular level as e.g. foreseen for SGA2.

We will continue to monitor experimental activities outside of the HBP, but at this point there is no replacement for this strategic dataset. The delay in the data generation for the whole brain transcriptomics data therefore will make it difficult to build a cellular level full brain model of the mouse and likely also jeopardises future goals for a cellular whole brain human model. Accordingly, we will modify the goals for SGA2 to aim for a more modest goal leveraging the network-level whole brain efforts with the detailed cellular level models for the four brain regions (neocortex, cerebellum, hippocampus, basal ganglia).

With the data-driven modelling of the four brain regions at the cellular level and the data-driven network-level whole brain model together with the continued development of the accompanying software tools and model building workflows, SP6 will still be able to provide the necessary services and proof of concepts for data-driven models to the external community. But ultimately, less of the original modelling work will be done in HBP and more will have to rely on community contribution.

## 1.4 Impact of work done to date

The work done in SP6 so far is a fundamental step towards developing data-driven modelling workflows and a proof of concept that such data-driven modelling of the brain indeed is timely. SP6 strategies with regard to modelling work on all the different biological scales are novel and innovative. A primary focus is now on driving scientific success stories (within HBP and with external users), and on that front there is steady progress in several promising directions, including establishing vibrant model development user communities around collaborative data-driven modelling enabled by the BSP. Already the SP6-led community effort to build a mouse hippocampus microcircuit, using the BSP modelling workflows, has paved the way for successful collaborative community effort. Furthermore, data-driven models of human neocortical neurons predicted their unique properties (Eyal et al, 2016, *Elife* Oct 6;5) and it is foreseen that modelling of human neurons and microcircuits of those will attract much interest from the external community in the near future.

## 1.5 Priorities for the remainder of the phase

- Continue to mature the scaffold models of the four main regions of the brain (somatosensory cortex, hippocampus, basal ganglia, cerebellum), as they form the seeds for model development and user communities alike, and are central to our co-design and user engagement strategy.
- Develop community collaborative modelling of the hippocampus enabled by the BSP
- Further develop the scientific success story of collaborative modelling of human neurons beyond the observations made so far, and preparing for human microcircuit modelling.
- Continue to develop and generalise the existing software and tools for the Brain Simulation Platform, and with focus on usability and user friendliness.
- Advance both the subcellular level work as well as the whole brain modelling work.
- To reach out to the external community and offer *in silico* services and user-friendly modelling pipelines, starting with the single cell modelling pipeline.

## 1.6 The new, user-oriented, release of the Brain Simulation Platform

Following reviewers' suggestions, during SGA1 the Platform is extending its functionality as infrastructure provider, with a user-centric development. The new release is organised around many "Online Use Cases", of different complexity. An important aspect of this is that it is open to the entire neuroscience community. This means that no matter if you belong to an HBP partner Institution, an external Laboratory/Company, or you are just a curious student, you can be invited to have a HBP account and will have access to the Use Cases. Restrictions stemming from the original data (access rights set by Neuroinformatics Platform) or reliance on HPAC Platform account/allocation may still apply. A Guidebook provides step-by-step detailed instructions on how to configure and run each use case.

Each Use Case is clearly marked with icons indicating the expected user experience level, use-case maturity, and required level of HPC resources. Their complexity goes from the most user-friendly, for collaborative projects using GUIs and public HPC resources, to more technical ones, where a substantial expertise in implementing cellular level simulations is needed. However, users will be able to exploit the platform capabilities, to pursue scientific goals, independently from their background and skill level.

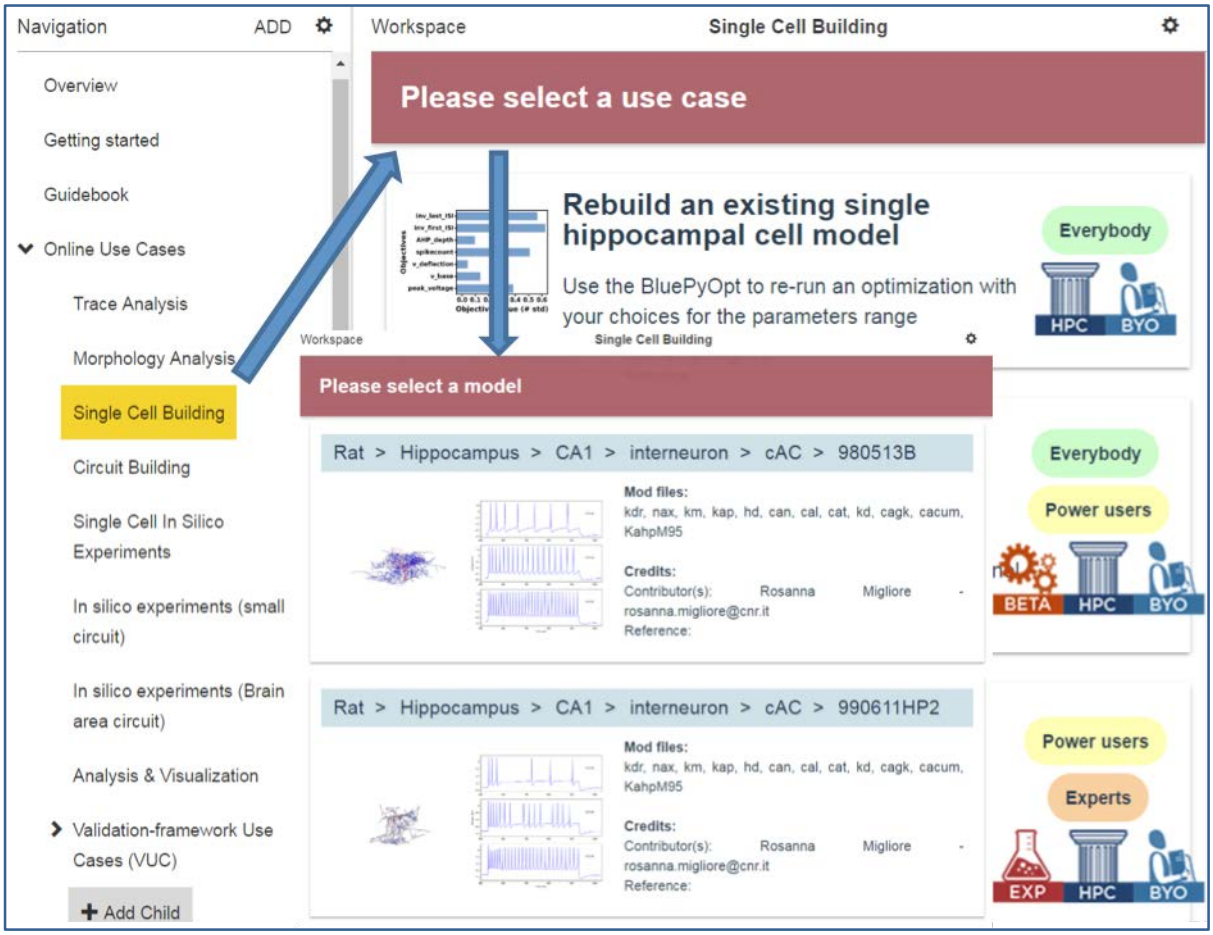


**Figure 2: Screenshot from the new version of the Brain Simulation Platform.**

# 2. WP6.1 Subcellular and Molecular Modelling

## 2.1 Key Personnel

Work Package Leader: Jeanette Hellgren KOTALESKI (KTH)

## 2.2 WP Leader's Overview

All milestones so far have successfully been fulfilled, and a joint manuscript is in preparation of how molecular dynamics simulation can provide useful information for models of signalling cascades. Also the individual Tasks have published additional results.

Task 6.1.1 has used a hierarchical multi-scale molecular simulation approach to calculate kinetic and thermodynamic rate constants and to identify and understand molecular events involved in neuronal cascades. The G protein regulation of adenylyl cyclase has functioned as a test case as that is important for Tasks 6.1.2 and 6.1.3.

Task 6.1.2 has built models of G protein coupled receptor induced cascades. Both Gs/Golf, Gi as well as Gq cascades have been covered.

Task 6.1.3 has built models on calcium dependent cascades with the goal to model their effects on the inhibition on dendritic spines and the consequences on the excitation-inhibition balance and subsequently on dendritic integration.

Task 6.1.4 is currently developing a proof of concept on the Collaboratory, using the Jupyter notebook, how to integrate models of receptor induced cascades built in Tasks 6.1.2 and 6.1.3.

The cancelling of the Open Call for T1.1.7 'Synapse Proteomes and Synaptomes' was unexpected, and this will delay the generation of molecular maps across the whole mouse brain. Such data sets are needed not only for the subcellular level modelling done in this WP, but also for the microcircuit modelling and, perhaps, especially for the data-driven whole brain modelling that was planned in SP6 for future SGAs.

As there are delays in the generation of synaptic and transcriptomics data, we have during SGA1 prioritised the recommendations from the RUP review, and started to develop further modelling approaches which test the robustness of the models, and which help interpret whether multiple solutions in the parameter space exist. We believe that in the long run our refinement of the workflow for model parameter estimation will speed up data-driven modelling at this subcellular level once whole mouse brain transcriptomics data is available. Also transcriptomics data generation is going on in many labs outside HBP so data is likely to appearing sooner or later. For example, data on striatum, one of the regions modelled in SP6 is already available and published by external researchers. However, the cancelling of the Open Call for T1.1.7 will slow down the data-driven modelling for many brain regions and of course at the whole brain level.

## 2.3 Priorities for the remainder of the phase

In WP 6.1 scaffold models of key signalling cascades in neurons are built. Model parameters are currently constrained mainly based on the literature and already available databases, but also we now have proofs of concept that molecular level simulations can provide reasonable suggestions regarding parameters. Work has, in addition, progressed towards the future goal of integrating subcellular cascades into principal neurons to study how, for instance, kinases affect membrane excitability. This suggest that it will become possible to significantly refine microcircuit models by going beyond the use of mainly ionotropic receptor interactions and also include muscarinic receptor effects. The latter is crucial for both neuromodulation and activity dependent synaptic plasticity. Priorities for the second year would be to continue in a focused manner both these lines of efforts, and support the development of the SP6 software and platform functionalities in a co-design manner.

## 2.4 Milestones

**Table 1: Milestones for WP6.1 - Subcellular and Molecular Modelling**

| MS No. | Milestone Name | Leader | Task(s) involved | Expected Month | Achieved Month | Comments |
|---|---|---|---|---|---|---|
| MS6.1.1 | Prediction of kinetic and thermodynamic parameters of selected cascade signalling events | JUELICH | T6.1.1 | MAR 2017 | MAR 2017 | The myristoylation of the inhibitory G protein is known to be essential in order to fulfil its function consisting of the complexation and inhibition of the adenylyl cyclase. The first article (entitled "Effect of N-Terminal Myristoylation on the Active Conformation of Gα"), by means of MD simulations, describes the conformational changes occurring in the solvated inhibitory G protein upon myristoylation. In the second article (entitled "Exploring the inhibition mechanism of adenylyl cyclase type 5 by N-terminal myristoylated Gαi1:GTP") the conformations sampled by the system consisting of the adenylyl cyclase in complex with the myristoiled inhibitory G protein are explored at physiological temperature through MD simulations. The two studies put the basis for the comprehension of the inhibition mechanism of the adenylyl cyclase, thus giving us the structural background in order to theoretically estimate the thermodynamic parameters governing the respective cascade signalling event by means of e.g. MM/PBSA calculations and QM/MM-based thermodynamic integration. Identification of the binding sites of regulatory proteins on the enzyme adenylyl cyclase (AC) is a key parameter for the construction of mathematical models of cAMP-dependent signalling cascades. Through comparisons of the isoform-specific regulation and isoform electrostatic conservation of AC, we have been able to gain insights into these binding sites, including a confirmation of the previously suggested binding site of inhibitory G proteins (Tong, Wade, Bruce, (2016), Proteins, 84, 1844). Binding and unbinding kinetics (i.e. kon and koff constants) determine the residence times of a ligand bound to a protein. Prediction of these kinetic constants is of high importance to create mathematical models of the signalling cascades, to design new ligands for therapeutic applications (i.e. drugs) or to investigate the distribution of neuroreceptors in the human brain (i.e. radioligands), among other applications. We have used a recent metadynamics-based type of molecular simulations for the calculation of koff of a relevant pharmaceutical system: a p38 MAP Kinase inhibitor from its protein target. In addition, we have identified and characterised the rate-determining step for the unbinding process, which is key to design new inhibitor structures with controlled residence times. |

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|---|---|---|---|---|---|---|
| | | | | | | (Unbinding kinetics of a p38 MAP kinase type II inhibitor from metadynamics simulations. Casasnovas R, Tiwary P, Limongelli V, Carloni P, Parrinello M. Journal of the American Chemical Society 2017, accepted DOI: 10.1021/jacs.6b12950.) |
| MS6.1.2 | Scaffold models of first draft Golf/s-, Gi- and Gq dependent cascades done | KTH | T6.1.2 | APR 2017 | MAR 2017 | MS 6.1.2 Scaffold models of first draft Golf/s-, Gi- and Gq dependent cascades done, Means of verification: a) A model on Golf signalling integrated with a calcium dependent cascade activating CaMKII was used to better understand the timing dependencies in reward learning in striatum (Nair AG, Bhalla US, Hellgren Kotaleski J. Role of DARPP-32 and ARPP-21 in the Emergence of Temporal Constraints on Striatal Calcium and Dopamine Integration, PLoS Computational Biology 2016 Sep 1;12(9):e1005080. doi: 10.1371/journal.pcbi.1005080.); (this is Component A for Task 6.1.2) b) A model of Gi signalling in the striatal direct- and indirect striatal medium spiny neurons has been submitted recently to PLoS Computational Biology; and some of these results will be presented during the IBAGS meeting this spring (speech title '"Reward learning - insights from subcellular level modelling ".'); c) A model of the Gq pathway leading to endocannabinoid production together with our CamKII model is used to test workflows for parameter estimation, and the result will be discussed at the yearly meeting of the Society for Computational Neuroscience (CNS abstract submitted 'Workflow for model building, parameter estimation and uncertainty analysis applied to calcium- and G-protein dependent subcellular signalling underlying synaptic plasticity'). |
| MS6.1.3 | Modelling and simulation of post-synaptic receptor tuning | ENS | T6.1.3 | JUNE 2017 | | |
| MS6.1.4 | Draft simulation experiments using cascade models integrated in single cell models | KTH | T6.1.4 | OCT 2017 | | |
| MS6.1.5 | Readiness evaluation of all components for release in Brain | KTH | T6.1.1, T6.1.2, T6.1.3, T6.1.4 | NOV 2017 | | |

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|---|---|---|---|---|---|---|
| | Simulation Platform under D6.5.2 | | | | | |

## 2.5 T6.1.1 Molecular Dynamics-Based Estimation of Parameters for Subcellular Modelling

### *2.5.1 Key Personnel*

Task Leader: Paolo CARLONI (JUELICH)

Other Researcher: Richard LAVERY (CNRS)

Other Researcher: Rebecca WADE (HITS)

Other Researcher: Ursula RÖTHLISBERGER (EPFL)

Other Researcher: Modesto OROZCO (IRB/JUELICH)

### *2.5.2 SGA1 DoA Goals*

Task 6.1.1 will use a hierarchical multi-scale molecular simulation approach to calculate kinetic and thermodynamic rate constants and to identify and understand molecular events involved in neuronal cascades. These include: protein-protein binding, protein diffusion in crowded environments, conformational transitions in proteins, kinetic and thermodynamic constants of protein-protein and protein-ligand association and dissociation.

Estimated interaction parameters will contribute to define the network topology and provide input parameters to initialise network simulations. Interactions with experimentalists in SP1 and SP2 will provide data input, crucial for both setting up the simulations and providing validation of their results. In particular, genetics studies in SP1 and SP2 will identify genetic variants and mutations that influence functional and behavioural phenotypes in humans and mice. Atomistic models developed in Task 6.1.1 will contribute to understanding the effect of these mutations at the molecular-level.

### *2.5.3 Task Achievement Summary*

Multiscale molecular simulations are well placed to provide both mechanistic insights and the estimation of key parameters in kinetic models of cellular signalling. As an example of this approach, we have been investigating the enzyme adenylyl cyclase (AC) 5. This protein is involved in cAMP-dependent signalling in striatal medium spiny neurons. cAMP is a second messenger involved in a large variety of neuronal cascades. Neuronal concentrations of cAMP are regulated by the activity AC5, which is in turn regulated by its interactions with stimulatory and inhibitory G-proteins ($G_s$ or $G_{olf,}$ and $G_i$, respectively). These are released from their cognate membrane-bound neuronal receptors in response to chemical signals coming from outside the cell.

AC5 is one of the nine adenylyl cyclase isoforms. All of them synthetise cAMP from ATP.

Several aspects of G-protein – AC5 interactions have been addressed here by molecular simulation. This allows us to predict structural, kinetic and thermodynamic properties of proteins and their complexes with ligands.

1) While the structure of the complex formed by AC5 and the stimulatory $G_s$ has been characterised experimentally, this is not true of the complex involving $G_i$. Comparisons of the computationally-derived electrostatic fields surrounding all isoforms of AC, in addition to knowledge of their differing regulation by $G_i$, provided confirmation of the location of $G_i$ binding to a groove on AC5, opposite the known $G_s$ binding site [Tong et al. (2016), *Proteins*, **84**, 1844].

2) High-power computer simulations have also helped to understand how G-proteins activate AC5. Simulating its behaviour in atomic detail and on the microsecond timescale has explained how G-protein binding can modify its activity by acting through the protein structure to change the conformation and dynamics of its binding site. This mechanism helps to understand why other members of the AC family respond differently to the same G-proteins [submitted].

3) The regulation of AC by G-proteins has been also studied with a coevolution-driven molecular approach. First, the major functional conformational transitions shared by all nine isoforms of ACs was defined by integrating co-evolutionary analysis with coarse molecular simulations [Sfriso P, et al. *Structure* 2016; **24**, 116]. Then, we focused on AC1 to map the energetics of such functional transitions with an accurate sampling procedure, using both a fine and coarse molecular representation (i.e. fully atomistic and Martini coarse graining, respectively). Currently, using the coarse representation, we can simulate larger systems and we are probing the capability of stimulatory and inhibitory G-proteins to modulate AC1 conformations. Preliminary results show agreement between microsecond-long atomistic simulations from the EPFL unit and coarse ones. This work aims at devising a strategy for a multi-scale view of AC regulations. It has been presented at the PLUMED Meeting, Trieste, May 22-27, 2017. (F. Colizzi, P. Sfriso, M. Orozco. Chasing the regulation of adenylyl cyclase by G-protein with coevolution-driven molecular simulations.)

4) The activity of $G_i$ is known to be dependent on the presence of an attached lipid moiety at its N-terminus. The structural changes induced in $G_i$ by this lipid modification were investigated by molecular dynamics simulations and by means of docking techniques complexes consisting of AC5 and the modified Gi and AC5 in complex with both $G_s$ and $G_i$. All atoms MD simulations of such systems in all possible combinations (i.e. AC5 alone, $G_i$ alone, $G_s$ alone, AC5: $G_i$, AC5:$G_s$, AC5:$G_i$:$G_s$) have been carried out at physiological temperature, pressure and ionic strength. Our simulations shed light on the possible structural reasons behind the activation and inhibition mechanisms of AC5 by G-proteins. Additionally, combining our simulations with energy calculations based on a semi-empirical force field, we suggest that the ternary complex formed by AC5 and both the stimulatory and inhibitory G proteins is energetically unfavourable. Finally, even for the case that the ternary complex is formed, our structural analysis shows that the active site of AC5 in the ternary complex has a behaviour very similar to that of AC5 in complex with the inhibitory G protein. This suggests that the simultaneous binding of both stimulatory and inhibitory G proteins to the adenylyl cyclase results in an inactive state of the AC enzyme.

5) Brownian dynamics simulations were performed to predict the rate constants of association of both stimulatory and inhibitory G-proteins to AC5.

6) QM/MM simulations of AC enzymatic reaction are performed with two different descriptions of the QM part, either using computationally cheap semi-empirical methods or more reliable DFT calculations. For the latter, we are now testing the convergence of the calculations by varying the computational setup. This allows identify an optimal starting point of the subsequent QM/MM simulations. The calculations are based on an MD-equilibrated structure of the AC5/$G_s$ complex, in the presence of the ATP substrate. These calculations are currently being carried out.

7) The calculated parameters and the information collected in this Task are being used for the kinetic modelling AC-based neuronal pathways by J. Kotaleski [in preparation].

8) We are exploring new approaches to calculate the dissociation constants (the so called $k_{off}$) of ligands from proteins, notoriously difficult to determine and very important pharmacologically: we need to know not only the affinity of a drug for a receptor, but also how long it stays bound. Here, we have investigated, through a recently developed metadynamics-based protocol, the unbinding mechanism in a test and well-characterised test-system, a ligand binding to a p38 MAP kinase protein. We have provided a thorough description of the ligand unbinding pathway identifying the most stable binding mode and other thermodynamically relevant poses (Chart I). From our simulations, we estimated the unbinding rate as $k_{off}$ = 0.020 ± 0.011 $s^{-1}$. This is in near agreement with the experimental value ($k_{off}$ = 0.14 $s^{-1}$). Next, we have developed a Markov state model that allowed identifying the rate-limiting step of the ligand unbinding process. Our calculations further show that the solvation of the ligand and that of the active site play

crucial roles in the unbinding process (Casasnovas et al, *Journal of the American Chemical Society,* 2017, 139, 4780). This study paves the way to investigations on the unbinding dynamics of ligands targeting neuroreceptors, and enzymes studied theoretically and experimentally in HBP. Indeed, as a next step, we are investigating the kinetics of unbinding from the muscarinic receptor, investigated in SP1.

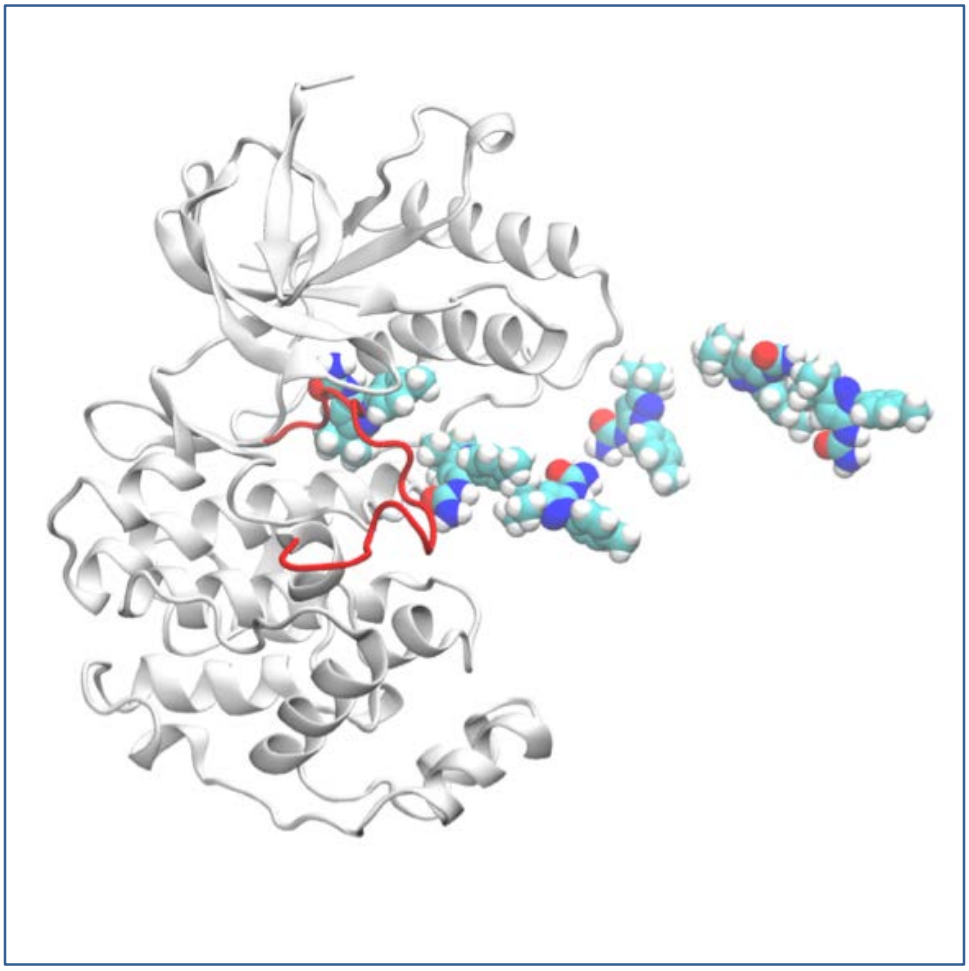

**Figure 3: Ligand unbinding process studied by molecular simulation.**

### *2.5.4 Component Progress*

#### 2.5.4.1 SP6-T6.1.1-SGA1-Brownian dynamics simulations

Description of Component: Brownian dynamics simulations will be used to estimate the association rate constants of proteins involved in cellular signalling.

Progress on Component: (**HITS**) Updates to the Brownian dynamics simulation software SDA, developed in T6.3.1, are being validated using a number of test cases. Initial testing shows that the more coarse-grained solute representation is able to reproduce the general concentration-dependent diffusive behaviour of proteins, with a reduction in computational cost to below 10% of the requirements of the all-atom solute model. At present, an adaptive-resolution model is being tested, in which the diffusion of proteins with all-atom representations, in a background of coarse-grained proteins, is simulated. This adaptive-resolution model will form the basis of the method for calculating protein association rate constants under crowding conditions, currently being developed in T6.3.1, which will be used for refining the predictions made in component SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-Brownian dynamics simulations | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Tools for Brownian dynamics simulations (software) | Coarse-grained and adaptive resolution simulation tools received from SP6-T6.3.1-SGA1-Tools for Brownian dynamics simulations were validated in this component. |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters (model). | Provided validated methods for predictions of association rate constants (partial release) |

### 2.5.4.2 SP6-T6.1.1-SGA1-Ligand design for brain imaging

Description of Component: Estimates of kinetic and thermodynamic parameters of neuronal receptor/ligand complex formation and dissociation to establish structure-kinetic relationships will allow design of chemical structures selective for specific receptors. These new molecules, after radiolabelling, will help imaging the distribution of such receptors in the human brain.

CDP to which Component contributes: CDP6, Modelling for Drug Discovery.

Progress on Component: (**JUELICH**) Predicting $k_{off}$ of ligands to proteins is notoriously difficult, yet this parameter is crucial for both systems biology modelling and pharmacology. A recently proposed method, based on metadynamics, paves the way to accurate predictions of this constant. Here we have used such new method to evaluate the $k_{off}$ of a small molecule binding to a protein. As a test case, we have focused on a well-characterised system, an inhibitor of the BIRB-796 family targeting the p38 MAP kinase protein. Our predictions are in good agreement with the experimental value (i.e. 0.020 ± 0.011 s-1 vs 0.14 s-1) and they provide a vivid picture of the unbinding process. In particular, they uncover a previously unrecognised role of ligand-solvent interactions for ligand unbinding.

We now plan to apply the method to a neuronal receptor studied experimentally by Prof. AMUNTS in the HBP. This is the M2 muscarinic receptor. We have inserted the receptor in complex with agonists and allosteric modulators in a model membrane of a human brain neuron. We are currently performing MD simulations to prepare the system for the $k_{off}$.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-Ligand design for brain imaging | |
|---|---|
| **Upstream Component** | **Status** |
| SP2 - Quantification of multiple receptor distributions for selected areas | We have discussed our progress in neuronal receptor modelling with Prof. Katrin AMUNTS. |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | We have received monthly progress updates of the SP6 group (complete). |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | Knowledge on the optimisation of collective variables for metadynamics & prediction of protein-ligand koff (complete). |
| | |
| **Downstream Component** | **Status** |
| SP2 - Quantification of multiple receptor distributions for selected areas (data) | We have discussed our progress in neuronal receptor modelling with Prof. Katrin AMUNTS. |
| SP2 - Multilevel maps of quantitative cell distributions and morphologies (data) | We have provided updates to Prof. PAVONE. |

### 2.5.4.3 SP6-T6.1.1-SGA1-QM/MM simulations for prediction of reaction kinetics

Description of Component: Quantum mechanical/molecular mechanical molecular dynamics simulations to estimate reaction kinetic parameters in a signalling cascade involving the enzyme adenylyl cyclase.

Progress on Component: (**EPFL**, **JUELICH**) QM/MM simulations of AC enzymatic reaction are here performed with two different descriptions of the QM part, either using computationally cheap semi-empirical methods or more reliable DFT calculations. The first have been completed. For the latter, it is very important to test the convergence of the calculations depending on different computational setups. This allows identify an optimal starting point of the subsequent QM/MM simulations. We are currently performing such tests, based on an MD-equilibrated structure of the AC5/$G_s$ complex, in the presence of the ATP substrate.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-QM/MM simulations for prediction of reaction kinetics | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | We have discussed our progress with Jeanette-KOTALESKI (complete). |
| PDB files of enzyme and regulatory proteins | We have received the initial structure for the MD simulation (complete). |
| HPC systems at BSC | We have received supercomputing time (complete). |
| HPC systems at JSC | We have received supercomputing time (complete). |
| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics (model). | We have received insights on the activation of the AC:ATP Michaelis complex from MD structural data (complete). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades (model) | P. CARLONI and Jeanette H KOTALESKI are drafting a paper reporting the modeling of G Protein-Coupled Receptor-Dependent Cascades based on molecular simulations. |

### 2.5.4.4 SP6-T6.1.1-SGA1-Coarse-grain protein model

Description of Component: Coarse-grain protein model is developed in order to estimate the thermodynamic stability of protein complexes involved in intracellular signalling.

Progress on Component: (**CNRS**) We are now working on replacing the all-atom representation with a coarse-grain model (PaLaCe II) and the molecular dynamics trajectory with either stochastic dynamics or Monte Carlo sampling, using experimental or homology derived protein structures and profiting from the interface prediction “arbitrary docking server”. The majority of the terms, including the polar contributions, are already successfully replaced with their coarse-grain equivalents.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-Coarse-grain protein model | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics (model). | We have received the trajectories of protein AC, Gai, Golf and the complex AC:Gai, and the parameters obtained by MD simulations. (complete). |
| | |
| **Downstream Component** | **Status** |

| | |
|---|---|
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters (model) | We are setting the calculation of the energetic terms for the binding affinity of complex AC:Gai. (Intermediate release). |

### 2.5.4.5 SP6-T6.1.1-SGA1-All Atom Molecular Dynamics

Description of Component: All atom molecular dynamics simulations are performed on experimental and homology model structures, in order to obtain structural and dynamic information on subcomponents of protein complexes involved in intracellular signalling.

Progress on Component: (**EPFL**) A systematic investigation of the conformations sampled by the *apo* form of the Adenylyl Cyclase (type 5 from *Rattus Norvegicus*, AC5) alone and in complex with stimulatory and/or myristoylated inhibitory G proteins (respectively, $G\alpha_{olf}$ and $G\alpha_{I}$ from *Rattus Norvegicus*) was carried out by classical all atom MD simulations on μs time scale. Starting from different x-ray structures found in the protein data bank (PDB ID: 4PAQ, 2K5U, 1AS3, 1AZS) and using the Modeller 9.14 package, six systems have been set up and simulated at constant temperature (310 K) and pressure (1 bar) in a water solution at physiological ionic concentration (150 mM). Here we report the list of the six simulations: 1) AC5 alone. 2) $G\alpha_i^{myr}$ alone. 3) $G\alpha_{olf}$ alone. 4) AC5 in complex with $G\alpha_i^{myr}$. 5) AC5 in complex with $G\alpha_{olf}$. 6) AC5 in complex with $G\alpha_i^{myr}$ and $G\alpha_{olf}$

Apart from the mere structural description of the six systems at finite temperature close to the physiological conditions, three main points should be addressed by the present study: 1. Impact of the myrystolation of the inhibitory $G\alpha_i$ protein on conformations sampled by the domain itself and on the intermolecular interactions between $G\alpha_i^{myr}$ and the adenylyl cyclase AC5. 2. Conformational description of the binding groove of the *apo* form of AC5 alone and upon the binding of $G\alpha_i^{myr}$ and $G\alpha_{olf}$ (singularly and simultaneously). 3. Existence of the ternary complex consisting of AC5, $G\alpha_i^{myr}$ and $G\alpha_{olf}$ at physiological conditions.

Additionally, in order to clarify the third point, the binding enthalpies for the complexation of the AC5/$G\alpha_i^{myr}$ complex by $G\alpha_{olf}$ and of the AC5/$G\alpha_{olf}$ complex by $G\alpha_i^{myr}$ have been estimated by MM/PBSA calculations. Such calculations have been carried out on at least 100 snapshots extracted from each equilibrated trajectory along at least 1 μs of equilibrated simulation.

Results for the three investigated points:

1. Myrystolation (already known experimentally to be necessary in order to fulfil the inhibitory function of $G\alpha_i$) was found to be crucial in order to stabilise the conformation of $G\alpha_i$ required for the optimal binding with AC5.

2. The binding of AC5 with $G\alpha_i^{myr}$ alone or with both $G\alpha_i^{myr}$ and $G\alpha^{olf}$ (i.e. ternary complex) results in a reduction of the binding groove accessibility to the cofactor eventually coming on. The binding of the AC5 with $G\alpha^{olf}$ alone, on the other side, stabilises the open conformation of the binding groove of AC5, thus facilitating the binding of the cofactor.

3. Despite along 5 μs of simulation the ternary complex seems to keep an overall stability, the MM/PBSA calculations show a binding enthalpy of about -325 KJ/mol for the binding of $G\alpha_i^{myr}$ to the AC5/$G\alpha_{olf}$ complex, while a binding enthalpy of about +1290 KJ/mol was found for the binding of $G\alpha_{olf}$ to the AC5/$G\alpha_i^{myr}$ complex.

Summarising, our results suggest that either the ternary complex is not present at physiological conditions or, due to the closure of the binding groove of AC5, it could be inactive.

(**IRB**) We are investigating the regulation of AC by G-proteins with a coevolution-driven molecular approach. First, we sampled the major functional conformational transitions shared by all the (nine) isoforms of hACs by integrating Direct Coupling Analysis with discrete Molecular Dynamics (methods ref: Sfriso P, et al. *Structure* 2016; 24, 116-126). Then, we focused on hAC1 to map the energetics of the functional transition with a path-based

metadynamics approach at different levels of molecular representation (Martini coarse graining and fully atomistic). Currently, using the Martini graining, we are probing the capability of stimulatory and inhibitory G-proteins to modulate hAC1 conformations. This work aims to devise a strategy for a multi-scale view of AC regulations.

(CNRS) We have performed on experimental and homology model structures, in order to obtain structural and dynamic information on subcomponents of protein complexes involved in intracellular signalling.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.1-SGA1- Homology structural models (model). | We have received the structure of protein AC. (complete). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Python scripts for MD analysis (software) | We have provided the trajectories of protein AC for the analysis. (complete). |
| SP6-T6.1.1-SGA1-QM/MM simulations for prediction of reaction kinetics (model) | We are providing the snapshots of the trajectory of the protein AC (partial release). |
| SP6-T6.1.1-SGA1-Coarse-grain protein model (model). | We are providing the non-bonded parameters to develop the protein coarse-grain model (partial release). |

### 2.5.4.6 SP6-T6.1.1-SGA1-Homology structural models

Description of Component: Structural information on proteins involved in intracellular signalling is obtained from experimental structures of proteins with closely related amino acid sequences.

Progress on Component: (**EPFL**) Classical MD simulations have been performed on the Gαi:AC5, Gαolf:AC5 and Gαi:AC5:Gαolf complexes as well as on a system including AC5 without Gα subunits. The AC5 structure in these complexes was based on PDB structure 1AZS, a substrate-free conformation of AC5. These simulations have led to a better understanding of the stimulatory and inhibitory mechanisms induced by Gαi and Gαolf on apo AC5 and their possible implications for substrate interaction. Four new models have been built to compare the apo AC5 simulations with a substrate-bound version of AC5. PDB structure 1CJK was employed as a template for AC5 during homology modelling of the holo complexes with the Modeller 9.14 package because this X-ray structure includes an analog of the substrate, Adenosine triphosphate (ATP), together with two Mg2+ ions, which are important for catalytic activity. Currently, classical molecular dynamics simulations are being performed on Gαi:AC5(ATP), Gαolf:AC5(ATP), Gαi:AC5(ATP):Gαolf and the AC5(ATP) system in order to compare apo and holo AC5, which could provide new insight into the difference or similarity of the effect of Gαi (and Gαolf) on the two forms of AC5 and their catalytic activity.

(**CNRS**) Homology models for all the AC5, Gsα and Gαi have been developed and steric docking based on these models has been performed. The structures resulting from the docking calculations where used for MD simulations.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-Homology structural models | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |

| Downstream Component | Status |
|---|---|
| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics (model). | We have provided the structure of protein AC. (complete). |

### 2.5.4.7 SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters

Description of Component: Estimates of kinetic and thermodynamic parameters of protein/protein and protein/ligand complex formation, protein conformational changes and enzymatic catalysis.

Progress on Component: (**CNRS**) We have developed some new homology models of AC5, with and without ATP. These new models have symmetrical conformations, with the two domains in open conformations. We have performed docking experiments using these models and the average structures of AC5 obtained from MD simulations.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.1-SGA1-Brownian dynamics simulations (model) | Provided validation of the BD tools developed in T6.3.1 and used in this component. |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades (model). | We have received information about key aspects of the topology of the cascade of G Protein-Coupled Receptor-Dependent Cascades from U. Roethlisberger's group. This is crucial for our project of modelling the cascade with kinetic modelling in collaboration with Jeanette KOTALESKI. |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations (software) | We are progressing with our highly scalable QM/MM, in a collaboration lead by Prof. Ursula ROETHLISBERGER |
| SP6-T6.1.1-SGA1-Coarse-grain protein model (model). | We are receiving the calculation of the energetic terms for the binding affinity of complex AC:Gai. (Intermediate release). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.1-SGA1-Ligand design for brain imaging (model) | We have provided knowledge on the optimisation of collective variables for metadynamics & prediction of protein-ligand koff (complete). |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations (software). | We are progressing in writing a document regarding the QM/MM code, in a collaboration lead by Prof. U. ROETHLISBERGER. |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades (model). | We are providing a draft describing the modelling of such cascade. |

## 2.6 T6.1.2 Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades Involved in Neuromodulation and Synaptic Signalling

### *2.6.1 Key Personnel*

Task Leader: Jeanette HELLGREN KOTALESKI (KTH)

Other Researcher: Parul TEWATIA (KTH), Anu NAIR (KTH), Olivia ERIKSSON (KTH)

### 2.6.2 SGA1 DoA Goals

This work will create scaffold models of GPCR cascades and their impact on effectors in the membrane (e.g. ion channels, receptors). We will use a framework for model parameter optimisation and for investigating model sensitivity to parameter variability. Parameterisation exploits results from molecular simulations in Task 6.1.1.

Subcellular models developed in this Task will subsequently be integrated in whole neuron models (see Task 6.1.4). Ultimately, this will make it possible to model neuromodulation, which plays an essential role in modulation of brain states and thus in cognition.

### 2.6.3 Task Achievement Summary

In Task 6.1.2, KTH has continued to build scaffold models of GPCR cascades. We have focussed on cascades important for synaptic plasticity and neuromodulation. A model of dopamine dependent plasticity was built and published (Nair AG, Bhalla US, Hellgren Kotaleski J. 'Role of DARPP-32 and ARPP-21 in the Emergence of Temporal Constraints on Striatal Calcium and Dopamine Integration', *PLoS Computational Biology*. 2016 Sep 1;12(9):e1005080. doi: 10.1371/journal.pcbi.1005080). This model integrates a calcium-activated cascade leading to CamKII activation and a G-protein (Golf) dependent cascade activated via dopamine type 1 receptors. The model predicted that specific points of interactions between these cascades, controlled via phosphorylation of the phosphoproteins DARPP-32 and ARPP-21, were important for allowing only inputs arriving with the correct order (dopamine after calcium) and within a certain time window to give rise to significant phosphorylation of target molecules predictive of synaptic strengthening.

We have also in parallel formulated or updated related scaffold models of other G-protein dependent cascades based on new data (submitted, in review). Such model Components can later on be adopted for the different types of principal neurons we are currently modelling in SP6 in the somatosensory cortex, hippocampus, basal ganglia and cerebellum. Data for model parameters either come from published papers, or else parameters are predicted using molecular dynamics approaches (manuscript in preparation together with Task 6.1.1). To make the model building process more transparent and reproducible we are furthermore developing and improving workflows for parameter optimisation. An early version of such a workflow was presented during the latest INCF Congress in August 2016, as well as during the workshop 'Collaborative Development of Data-Driven Models of Neural Systems', 18-21 September 2016 at Janelia Farm, US. A full manuscript of this workflow is currently in preparation and is estimated to be submitted before the summer 2017.

### 2.6.4 Component Progress

#### 2.6.4.1 SP6-T6.1.2-SGA1-Subcellular Model of Timing Dependent Reward/Dopamine Plasticity

Description of Component: In reward learning, the integration of NMDA-dependent calcium and dopamine by striatal projection neurons leads to potentiation of corticostriatal synapses through CaMKII/PP1 signalling. In order to elicit the CaMKII/PP1-dependent response, the calcium and dopamine inputs should arrive in temporal proximity and must follow a specific (dopamine after calcium) order. In this computational study, we propose that these temporal requirements emerge as a result of the coordinated signalling via two striatal phosphoproteins, DARPP-32 and ARPP-21. Model published 2016; doi: 10.1371/journal.pcbi.1005080.

Progress on Component: KTH published a model of Timing dependent reward plasticity (Nair AG, Bhalla US, Hellgren Kotaleski J. Role of DARPP-32 and ARPP-21 in the Emergence of Temporal Constraints on Striatal Calcium and Dopamine Integration, *PLoS Computational Biology*. 2016 Sep 1;12(9):e1005080. doi: 10.1371/journal.pcbi.1005080). Model deposited in SBML format on the bioModels database (accession number MODEL1603270000). Model will also be available in the Collab in time for the next joint platform release.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.2-SGA1-subcellular Model of Timing Dependent Reward/Dopamine Plasticity | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | A manuscript planned before end of SGA1 between the Tasks involved |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | Ongoing planning with SP1 (David STERRAT) |
| | |
| **Downstream component** | **Status** |
| Plasticity: STDP for a multi-compartment model with NMDA spikes (Algo STDPbackprop) | Informed when we met at a workshop in Fuerberg in the autumn (2016) that the CaMKII model components built in T6.1.2 can be used to estimate NMDA calcium dependent activation of CaMKII which is predictive of LTP in several synapse types |
| SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis | Gave advice to Antoine TRILLER about the use of the CaMKII model built in Task 6.1.2 |
| Motor control model | Models built in T6.1.2 constrain learning rules in the corticostrital system; 6.1.2 models provided to SP4; info provided to SP4 |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Scaffold models of receptor induced signalling is in the process of being integrated in whole cell models (a full manuscript in progress) |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | Planning is ongoing together with SP1 (David STERRAT) |
| Plasticity: Dendritic predictive plasticity that reproduces STDP data (Algo STDPpredictive) | Models of receptor induced cascades can be used to extract principles for phenomenological plasticity rules (built in SP4); ongoing interactions currently with modellers in SP4 |

### 2.6.4.2 SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades

Description of Component: Scaffold models of GPCR cascades and their impact on effectors in the membrane (e.g. ion channels, receptors) will be created.

Progress on Component: During the first year of SGA1, KTH has built models of G-protein coupled receptor (GPCR) induced cascades. Data to constrain model parameters was coming from the literature, from interactions with the molecular simulation researchers in SP6 and from collaboration with experimentalists. Three common forms of G-proteins in neurons are Gs/Golf activating adenylyl cyclases (AC) to produce more cAMP, Gi inhibiting some of the ACs (AC1, AC5 and AC6) and Gq activating phospholipase C (PLC). We have built and/or refined models of Golf, Gi and Gq cascades based on data from the principal neurons in the striatum. The resulting models have been submitted for publication, or presented at conferences. These model components can later on be adapted to, for instance, other principal neurons in the brain.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein Coupled Receptor Dependent Cascades | |
|---|---|
| **Upstream Component** | **Status** |
| STEPS | STEPS is used when simulating models built in 6.1.2, etc. |
| Association (co-clustering) of receptors and their effector ion channels in different neuronal compartments | No data received yet |
| Antibodies against targets identified in all genomic and proteomics tasks | No data received yet |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | Planning of a manuscript in progress with David STERRAT in SP1 |
| SP6-T6.1.1-SGA1-QM/MM simulations for prediction of reaction kinetics | Info from this T6.1.1. Component used when building the already published models in 6.1.2 (also additional info in manuscript) |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | Info from this T6.1.1. Component used when building the already published models in 6.1.2 (also additional info in manuscript) |
| Molecular Dynamics based parameters prediction | Info from this T6.1.1. Component used when building the already published models in 6.1.2 (also additional info in manuscript) |
| List of Synaptic Target Proteins | Has received a list of proteins from SP1 |
| Curated list of synaptic protein-protein interactions | Manuscript almost submitted (by SP1). Info received from SP1 and SP6 provided feedback on the manuscript |
| Curated data from neuroproteomics publications | Manuscript almost submitted (by SP1). Info received from SP1 and SP6 provided feedback on the manuscript |
| A mapping of computational models of synapses to proteins | Manuscript almost submitted (by SP1). Info received from SP1 and SP6 provided feedback on the manuscript |
| | |
| **Downstream Component** | **Status** |
| SGA2 - T6.1.3-C2 - Modelling modulation of inhibition downstream calcium signalling | Discussed with Antoine TRILLER |
| SP9 model: Principles for Brain-Like Computation | Discussed with SP9 during the Fuerberg workshop (autumn 2016) |
| SGA1/SGA2_T2.4.3 Genetic factors contributing to inter-individual variation on morphology and architecture | No data received yet |
| Plasticity: Dendritic predictive plasticity that reproduces STDP data (Algo STDPpredictive) | Discussed with SP4 during the Fuerberg workshop (autumn 2016) |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Models can be integrated in whole cell models (e.g. to study neuromodulation). Manuscript in preparation to prove this point. |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | Planning ongoing together with SP1 (David STERRAT) |

| | |
|---|---|
| Plasticity: Proof of concept detailed rule-based synaptic plasticity model | |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | Have discussed with Paolo Carloni what reaction parameters are needed |
| Computational, dynamic model of wild-type and PSD-95 KO LTP and LTD in a Schaffer Collateral synapse | Ongoing discussions |
| Analytical review of proteins contained in computational models of synaptic plasticity | Ongoing discussions |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Manuscript in progress. Also in parallel the Collab will be updated to demonstrate the process. |

## 2.7 T6.1.3 Data-Driven Modelling of $Ca^{2+}$ Dependent Cascades Controlling Synaptic Signalling and Homeostasis

### *2.7.1 Key Personnel*

Task Leader: Antoine TRILLER (ENS)

Other Researcher: Pablo SERNA (ENS)

### *2.7.2 SGA1 DoA Goals*

This Task will create scaffold models of calcium dependent cascades, in detailed neuron models with spines, and account for experimentally observed Ca2+ dynamics, buffers, pumps, enhancement of Ca2+ channels, etc. Modelling, which will be based on the STEPS simulator, will use High Performance capabilities provided by SP7, and enhancements to STEPS provided by T6.3.2. Parameterisation will exploit results from molecular simulations in Task 6.1.1. Subcellular models developed in this Task will be integrated in whole neuron models (see Task 6.1.4). Ultimately, this will make it possible to model the way in which Ca2+ modulates synaptic signalling, plasticity, and homeostasis – processes whose importance has been highlighted by *in silico* experiments performed during the RUP.

### *2.7.3 Task Achievement Summary*

We have developed tools derived from statistical thermodynamic to quantify morphological changes and energetic states of multi-molecular assemblies over time, responsible for the stability (tenacity) of the PSD. With these tools, we have analysed the scaffold protein gephyrin, which forms postsynaptic clusters that play a key role in the stabilisation of receptors at inhibitory synapses. While postsynaptic gephyrin clusters exhibit an internal microstructure composed of nano-domains, we found, that within the PSD, gephyrin molecules continuously undergo spatial reorganisation. This dynamic behaviour depends on neuronal activity and cytoskeleton integrity.

We were then able to propose an aggregation-removal model for the formation and size determination of post-synaptic scaffold domains. Post-synaptic domains have been classically conceived as resulting from local insertion and turnover of proteins at the synapse. Insertion is likely to occur outside the post-synaptic domains and proteins diffuse in the plane of the membrane prior to their accumulation at synapses. We have quantitatively investigated this scenario in the case of inhibitory synapse components: the glycine receptors (GlyR) and the associated gephyrin scaffolding protein. The observed domain sizes of scaffold clusters can be explained by a dynamic balance between the aggregation of gephyrin proteins diffusing while bound to GlyR and their turnover at the neuron membrane. We also predicted the existence of extrasynaptic clusters with a

characteristic size distribution that significantly contribute to the size fluctuations of synaptic domains. This allowed us to propose a metastable model for the regulation of inhibition.

Using Hodgkin-Huxley like models we have implemented the tuning of inhibition and its consequences on excitation in spines. We have studied its consequences in intracellular Ca2+ transients and modelled its dependence on the timing between inhibition and excitation.

- Ranft J, Almeida LG, Rodriguez PC, Triller A, Hakim V (2017) An aggregation-removal model for the formation and size determination of postsynaptic scaffold domains. *PLoS Computational Biology* 13(4): e1005516. https://doi.org/10.1371/journal. Pcbi.1005516
- Rodriguez PC, Almeida LG, Triller A. Continuous rearrangement of the postsynaptic gephyrin scaffolding domain: a super-resolution quantified and energetic approach. (Submitted.)

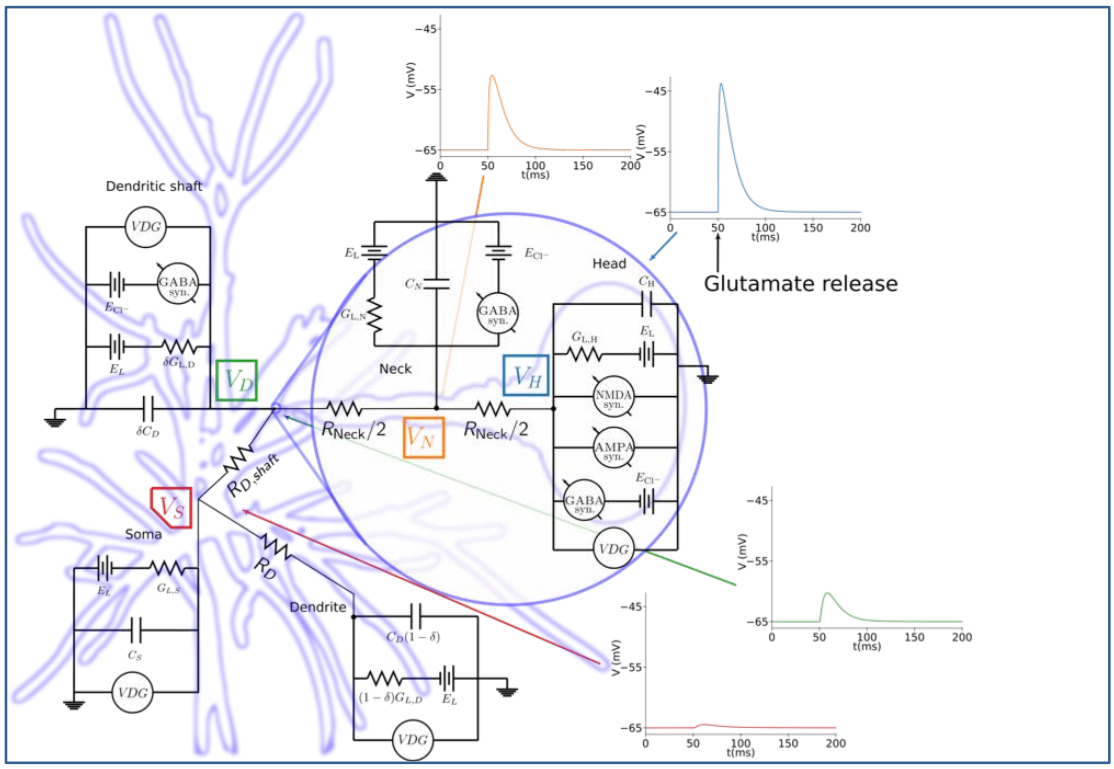


**Figure 4: Simplified circuit model of a dendritic spine in a L2/3 neuron, including voltage-dependent gates from Hodgkin-Huxley model, voltage-dependent calcium channels and synapses, both excitatory and inhibitory.**

**An EPSP has been elicited by a simulated glutamate release and subsequent opening of AMPA and NMDA receptors on the spine head. Drawn over sketched L2/3 neuron inspired by Smith et al, Nature 2013.**

### *2.7.4 Component Progress*

#### 2.7.4.1 Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis

Description of Component: This Task creates scaffold models of calcium-dependent cascades, in detailed neuron models with spines, and account for experimentally observed Ca2+ dynamics, buffers, pumps, enhancement of Ca2+ channels, etc.

The approach makes use of Hodgkin-Huxley like models adapted for implementing voltage-activated channels (Ca2+, K+, …). The sources of the signalling include both excitatory postsynaptic currents and back-propagating action potential. It includes molecular mechanisms such as: calcium influx from synaptic receptors and voltage activated channels,

calcium release from endoplasmic reticulum, or metabotropic glutamate receptors-dependant phosphorylation. The main focus is to model their effects on tuning inhibition and the consequences on the excitation-inhibition balance and subsequently on dendritic integration. The final aim is to produce a model based on actual neuronal physiology, accounting for the computational capacities of dendritic arborisation.

For extension to the whole neuron, the modelling, which will also be based on the STEPS simulator, will use High Performance capabilities provided by SP7, and enhancements to STEPS provided by T6.3.2. Parameterisation will exploit results from molecular simulations in Task 6.1.1.

Subcellular models developed in this Task will be integrated in whole neuron models (see above and Task 6.1.4). Ultimately, this will make it possible to model the way in which Ca2+ modulates synaptic signalling, plasticity, and homeostasis – processes whose importance has been highlighted by *in silico* experiments performed during the RUP.

Progress on Component: Component completed (50%). Using a super-resolution quantified and energetic approach of the continuous rearrangement of the postsynaptic gephyrin scaffolding domain allowed to access the effective energy responsible for the tenacity of the PSD despite molecular instability (submitted). We were then able to propose an aggregation-Removal Model for the Formation and size determination of post-synaptic scaffold domains (in revision). This allowed proposing a metastable model for the regulation of inhibition using Hodgkin-Huxley model and now permits to implement the tuning of inhibition and consequences on the excitation balance (see above). We hope to be able to posit a workable model in the next 6 months.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis** | |
|---|---|
| **Upstream Component** | **Status** |
| STEPS | This Component was ready to use and with high quality. No issue has been found. |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | Expected later release – it has not yet been used |
| SP6-T6.1.2-SGA1-Subcellular Model of Timing Dependent Reward/Dopamine Plasticity | Excellent quality, published in *Plos Computational Biology* |
| A mapping of computational models of synapses to proteins | Expected later release – it has not been used yet |
| STP model | |
| Association (co-clustering) of receptors and their effector ion channels in different neuronal compartments | Expected later release – it has not been used yet |
| Antibodies against targets identified in all genomic and proteomics tasks | Will be used when available |
| | |
| **Downstream component** | **Status** |
| SGA2 - T6.1.3-C2 - Modelling modulation of inhibition downstream calcium signalling | The outcome will be provided at the end of SGA1 |
| SGA2 - T6.3.6 - Collaboratory Configuration Tool | The outcome will be implemented in the collaborative tool at the end of SGA1 |

| | |
|---|---|
| A mapping of computational models of synapses to proteins (data) | We have published some of our results in a first manuscript in *Plos Computational. Biology* and submitted a second one. We have also provided the corresponding reports when required. |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Models are currently derived and will be available at the end of SGA1 |

## 2.8 T6.1.4 Integration of Subcellular Models in Single Neuron Models

### *2.8.1 Key Personnel*

Task Leader: Jeanette Hellgren KOTALESKI (KTH)

Other Researcher: Robert LINDROOS (KTH), Parul TEWATIA (KTH)

### *2.8.2 SGA1 DoA Goals*

This work will integrate subcellular scaffold models into models of main neuron types in e.g. cortex, hippocampus, cerebellum, basal ganglia. Neuron models incorporating subcellular models will make it possible to investigate the role of neuromodulation and its consequences for synaptic integration in active dendrites, etc.

### *2.8.3 Task Achievement Summary*

During the first year of SGA1, we have implemented a workflow in the Collaboratory using the iPython notebook, to automatise the integration of subcellular level models into single cell models. For this workflow we assume that the cellular level model is built in Neuron and that the subcellular level model is exist in SBML format. As a first proof of concept of the usefulness of this approach of integrating data over both the subcellular-cellular scale, we have together with Tasks 6.2.5 and 6.1.2 collected information on the effects of dopamine for the phosphorylation on various ion channels (or other effects signalling molecules such as cAMP and G proteins have on membrane conductances) in striatal principal neurons. A manuscript is in preparation suggesting how this approach of linking scales in a concrete manner can lead to novel predictions of the effects subcellular signalling has on the membrane of single neurons.

### *2.8.4 Component Progress*

#### 2.8.4.1 Position paper on the workflows and strategies for intracellular and synaptic modelling

Description of Component: Position paper on the workflows and strategies for intracellular and synaptic modelling.

Progress on Component: Component is in the planning stage together with SP1 collaborators (University of Edinburgh).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Position paper on the workflows and strategies for intracellular and synaptic modelling** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.2-SGA1-Subcellular Model of Timing Dependent Reward/Dopamine Plasticity | Releases: None within this reporting period. We (UEDIN) have been in discussion with other Partners (Dan KELLER, EPFL; Michel MIGLIORE, CNR; Jeanette Hällgren KOTALESKI, KTH; Paulo CARLONI, JUELI; Antoine TRILLER, ENS) about the paper, which is a joint effort. |

| | |
|---|---|
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades | Not used yet. |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Not used yet. |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | Not used yet. |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | Not used yet. |
| SP6-T6.4.3-SGA1-Model representations for synaptic plasticity | Not used yet. |
| Simulator-simulator interfaces | Not used yet. |
| | |
| **Downstream Component** | Status |
| SGA2 - T6.1.3-C2 - Modeling modulation of inhibition downstream calcium signaling | Releases: None within this reporting period. We (UEDIN) have been in discussion with other partners (Dan KELLER, EPFL; Michel MIGLIORE, CNR; Jeanette Hällgren KOTALESKI, KTH; Paulo CARLONI, JUELI; Antoine TRILLER, ENS) about the paper, which is a joint effort. |
| Co-organised workshops and/or other workmeetings | No release |
| SP12-SGA1 Philosophy briefing report 2 | No release |
| SP12-SGA1 Philosophy briefing report 1 | No release |
| SP9 model: Principles for Brain-Like Computation | No release |
| SP6-T6.4.3-SGA1-Model representations for synaptic plasticity | No release |
| SGA1/SGA2_T2.4.3 Genetic factors contributing to inter-individual variation on morphology and architecture | No release |
| SP6-T6.1.2-SGA1-Subcellular Model of Timing Dependent Reward/Dopamine Plasticity | No release |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades | No release |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | No release |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models | No release |
| NEST code with abstracted neuron model representations | No release |

### 2.8.4.2 SP6-T6.1.4-SGA1-Integration of Subcellular Models in Single Neuron Models

Description of Component: The SGA1 Task 6.1.4 will integrate subcellular scaffold models into models of the main neuron types in cortex, hippocampus, cerebellum, striatum, etc. Neuron models incorporating subcellular models will make it possible to investigate the role of neuromodulation and its consequences for synaptic integration in active dendrites, etc.

Progress on Component: During the first year of SGA1 KTH has started to prepare a Jupyter notebook in the Collaboratory to automatise the integration of subcellular level models into single cell models.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.1.4-SGA1-Integration of Subcellular Models in Single Neuron Models** | |
|---|---|
| **Upstream Component** | **Status** |
| STEPS | discussed with the STEPS developers |
| SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis | Integration of calcium dependent signalling integrated in whole cell models ongoing |
| SP6-T6.1.2-SGA1-Subcellular Model of Timing Dependent Reward/Dopamine Plasticity | This model component published, manuscript in preparation where parts of this model are integrated in whole neuron models |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades | Manuscript in preparation where parts of this model are integrated in whole neuron models |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | Paper in the planning stage with SP1 |
| Dopamine receptor induced signaling in striatum | Integration of dopamine dependent signalling integrated in model of a striatal principal neuron ongoing (manuscript in preparation related to neuromodulation) |
| | |
| **Downstream Component** | **Status** |
| SP12-SGA1 Philosophy briefing report 2 | No updates |
| SP12-SGA1 Philosophy briefing report 1 | No updates |
| SP9 model: Principles for Brain-Like Computation | discussed with SP9 during the Fuerberg meeting (autumn 2016) |
| SP6-T6.4.3-SGA1-Model representations for synaptic plasticity | discussions planned later on during SGA1 |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | manuscript in the planning process with SP1 (David sterrat) |
| Co-authored articles and/or special issues | No updates |
| Co-organised workshops and/or other workmeetings | No updates |

# 3. WP6.2 Cellular-Level and Whole-Brain Modelling

## 3.1 Key Personnel

Work Package Leader: Egidio D'ANGELO (UNIPV)

## 3.2 WP Leader's Overview

The goal of Work Package 6.2 is to build cellular level models of target areas of the rodent brain, providing the point neuron Whole Mouse Brain Model used for the experiments planned in CDP1, and Components for CDP2 products 3,4,5. The activity of WP6.2 developed along the programmed tasks.

T6.2.1 Models of human cells. The electrophysiological and morphological reconstruction of human pyramidal cells has been used to develop detailed models in NEURON. The results, leading to the discovery of substantial differences between human and rodent cells, have been published in a high profile journal (*eLife*).

T6.2.2 Models of somatosensory cortex. Models of individual spines in human L2/3 neurons have been developed based on more than 100 3D reconstructed spines, detailed passive models of human neurons were also characterised physiologically. Validation and refinement is being performed in collaboration with BBP and with other HBP collaborators.

T6.2.3 (SGA1) Models of cerebellum. The reconstruction of models of cerebellar neurons is proceeding in Python-NEURON. The model of Purkinje Cells (PCs) has been published and a second manuscript on the topic of synaptic activation is in preparation. Models of stellate cells, inferior olivary cells and deep cerebellar neurons are in progress. The models of granule cells, Golgi cells and Purkinje cells have been optimised using BluPyOpt. A new version of the cerebellar network models has been developed. In all these cases, the SP6 modelling work has been interfaced with the SP1 experimental work, the data have been transferred to SP5 and the experience gained has been used to refine tools and pipelines of the Brain Simulation Platform and for the implementation of the Collaboratory.

T6.2.4 (SGA1) Models of hippocampus. Models of rat hippocampal neurons were constructed through the use of reconstructed morphologies, recorded electrophysiological traces, and automated parameter optimisation. A database of optimised models has been internally organised and released; models have been presented in scientific context. A set of tests comparing the electrophysiological behaviour of models of CA1 pyramidal neurons to experimental data was designed and implemented. This validation suite was applied to the automatically tuned models of CA1 pyramidal cells. Both the optimisation and the validation procedure can be run from the Brain Simulation Platform. After the last stable release in June 2016, the hippocampal network model underwent a major revision that expanded the input data (morphological reconstructions and electrophysiological recordings), revised the model assumptions, and improved the toolchain to generate and simulate the model. In parallel, an increasing number of validations have been performed on the model to assess its validity and accordance with experimental evidence. All of these improvements will be part of a new release of the HBP hippocampal models planned for June 2017. Active outreach to the hippocampal community is on-going to establish community contributions to the model, and users of the model

T6.2.5 (SGA1) Models of basal ganglia. Models of different types of interneurons and projection neurons in striatum are being built based on detailed morphology and membrane properties, and distributed in geometrically defined populations. The two types of projection neurons expressing dopamine receptors of the D1 and D2 type respectively have been simulated based on detailed morphology and electrophysiological data regarding membrane properties, and similarly the other main type of interneuron the FS (fast-spiking) interneurons. These cells interact through GABAergic synapses. The synaptic properties of the interacting cells have also been simulated, as well as the cortical input synapses with

AMPA and voltage-dependent NMDA synapses. The population of cells in striatum is randomly distributed within a specified volume, in which each cell is isolated but with a dendritic arbor, and synapses are formed with axon collaterals according to known connectivity patterns. Information regarding cellular properties in other basal nuclei is being analysed.

T6.2.6 (SGA1) Models of whole mouse brain. Models of the whole mouse brain are proceeding according to the SGA1 planning and the related Milestone has been achieved. Simplified versions of these models will be used as brain models in the Neurorobotics Platform, and will also be implemented in the Neuromorphic Computing Systems. Preliminary results of this work were presented at the First JARA and reduced-size version of the mouse brain model have been delivered to SP10-WP10.1 for use in the mouse rehabilitation experiment; moreover, a reduced version of the mouse brain model has also been delivered to SP9 for tests with SpiNNaker.

T6.2.7 (SGA1) Simplification. An automated strategy for the simplification of morphologically detailed neuron and network models to point neurons has been developed, tested on the BBP cortical microcircuit model, and published in pre-print form on arXiv. Recent work focused on the further refinement of the synaptic simplification process, bringing a dramatic improvement to runtimes, and enabling a NEST implementation of the simplified circuit.

The work done is a fundamental step to develop the whole WP6.2 activity: The generation of detailed microcircuit models of the main brain regions which broadly integrate experimental knowledge, and to quantitatively simplify them (with systematic validation to the detailed reference) for use in whole-brain simulated environments. Moreover, we have tested and contributed to the development of pipelines needed to orient the Brain Simulation Platform toward a more general public.

## 3.3 Priorities for the remainder of the phase

The priorities for the remainder phase are the following:

- To complete the generation of fundamental neurons in order to fully implement the scaffold models of the four main regions of the brain that are still in progress (somatosensory cortex, hippocampus, basal ganglia, cerebellum).
- To complete the reconstruction of connectivities inside the four main regions of the brain that is still in progress (somatosensory cortex, hippocampus, basal ganglia, cerebellum).
- To advance the investigation of human neurons beyond the initial observations on pyramidal cells of the visual cortex
- To proceed towards automatic simplification of data-driven microcircuits for execution on NEST, and test the automated simplification workflow on other brain regions such as hippocampus, basal ganglia, cerebellum.
- To continue to contribute to the generalisation of existing software and tools for the BSP, as a consequence of ongoing modelling and simulation activity, in the generalisation of existing software and tools for the BSP.
- To proceed in the implementation of functionalities and pipelines in the Collabs
- To extend the engagement of the external community.

## 3.4 Milestones

**Table 2: Milestones for WP6.2 - Cellular-Level and Whole-Brain Modelling**

| MS No. | Milestone Name | Leader | Task(s) involved | Expected Month | Achieved Month | Comments |
|---|---|---|---|---|---|---|
| MS6.2.1 | Complete conductance-based model of human pyramidal cell | HUJI | T6.2.1 | MAR 2017 | MAR 2017 | This model has been finalised; just published in *eLife*: http://dx.doi.org/10.7554/eLife.16553.001. |
| MS6.2.2 | Initial model validation tests implemented to compare rat model with mouse data | UPM | T6.2.2 | MAR 2017 | MAR 2017 | A first set of validation tests has been created and integrated into the HBP Collaboratory. The model data tested in the validation test are coming from the neocortical microcircuit from the model developed during the RUP by the Blue Brain Project (Markram et al, *Cell*, 2015). The model data used are at this stage the layer thicknesses as available from the website (https://bbp.epfl.ch/nmc-portal/). These data have been integrated into the validation Collaboratory (https://collab.humanbrainproject.eu/#/collab/1771/nav/21438). The biological data used as reference are layer thicknesses from mouse (8 weeks, HLS1) with a shrinkage correction factor and have been integrated into Collaboratory. The validation test itself has been integrated into the framework developed by Task 6.4.4 as a SciUnit test (https://github.com/scidash/sciunit) in GitHub (https://github.com/appukuttan-shailesh/VF_test_cases). The test gives a Stouffer score that allows comparing how the model data match the biological data The validation tests results show unsurprisingly that the mouse data do not match the rat model data. The test results are available through the validation framework app (https://validation.brainsimulation.eu/view/results/) Further tests are being developed to emphasise the layers that mismatch. |
| MS6.2.3 | Initial scaffold model of the cerebellar cortex and deep nuclei | UNIPV | T6.2.3 | SEP 2017 | | |
| MS6.2.4 | Initial models of hippocampal neurons | IEM HAS | T6.2.4 | MAR 2017 | MAR 2017 | Both the optimised models and the validation suite have been presented at scientific meetings (e.g., at the Janelia Conference 'Collaborative Development |

| | | | | | | |
|---|---|---|---|---|---|---|
| | using a consensus validation suite are released | | | | | of Data-Driven Models of Neural Systems', 18-21 September 2016). The optimised models, the validation tests and the validation results are available on the HBP Collaboratory (see Collab "CA1 pyramidal cell validation"). |
| MS6.2.5 | Initial version of scaffold model of basal ganglia nuclei | KI | T6.2.5 | SEP 2017 | | |
| MS6.2.6 | Scaffold whole mouse brain simulation at the level of point neurons | EPFL | T6.2.6 | MAR 2017 | MAR 2017 | First full-scale mouse brain simulation achieved on Jülich Supercomputer. Preliminary results presented at First JARA-HPC Symposium, JHPCS 2016 Aachen, Germany, 4-5 October 2016 |
| MS6.2.7 | Simplification procedure (semi-automatic) from morphologically detailed models to point neuron models | EPFL | T6.2.7 | MAR 2017 | MAR 2017 | Simplification procedure has been improved compared to RUP milestone. Updated manuscript has been uploaded to arXiv: https://arxiv.org/abs/1604.00087v2. The pre-print publication on arXiv.org has been updated with the following: The soma-synaptic filter fitting approach using PRAXIS fitting has been replaced by a new method to automatically and directly extract the filters for each dendritic compartment using a Green's functions approach. Methods Section 2.1, Results Section 3.1 and Figures 1, 2, 4, 5 have been updated to reflect these changes. Furthermore the Discussion has been updated to incorporate the new findings on the reduction of post-synaptic filter variability. |
| MS6.2.8 | Readiness evaluation of all components for release in Brain Simulation Platform under D6.5.2 | UNIPV | T6.2.1, T6.2.2, T6.2.3, T6.2.4, T6.2.5, T6.2.6, T6.2.7 | NOV 2017 | | |

## 3.5 T6.2.1 Models of Human Cells

### *3.5.1 Key Personnel*

Task Leader: Idan SEGEV (HUJI)

### *3.5.2 SGA1 DoA Goals*

Task 6.2.1 will utilise physiological characterisation and 3D morphological reconstructions of pyramidal cells from human temporal cortex, and use modern statistical tools and cable theory to: objectively classify these cells into morphological and electrical subtypes; develop detailed compartmental models of their dendritic and axonal excitability (including Ca-, Na- and NMDA- spikes); develop detailed models for their synaptic inputs (AMPA- and NMDAreceptors) and passive cable models of their dendritic spines; and develop reduced/simplified models of these neurons for use in network models of human cortex. The models created by this work will contribute to the Human Brain Atlas developed in CDP3, though probably not in SGA1.

### *3.5.3 Task Achievement Summary*

We just completed the analysis of 3D morphologies of a large set of human L2/3 pyramidal neurons. This multi-feature analysis provided new insights regarding the unique structure of these cells, as summarised below. The paper is under review in *Cerebral Cortex*.

We employed feature-based statistical methods on a rare dataset of 60 3D reconstructed pyramidal neurons from layer 2/3 in the human temporal cortex (HL2/3 PCs) removed after brain surgery. Of these cells, 25 neurons were also characterised physiologically. Thirty-two morphological features were analysed (e.g., dendritic surface area, 36,333±18,157 $\mu m^2$; number of basal trees, 5.55±1.47; dendritic diameter, 0.76±0.28 µm). Eighteen features showed a significant gradual increase with depth from the pia (e.g., dendritic length, soma radius). The other features showed weak or no correlation with depth (e.g., dendritic diameter). The basal dendritic terminals in HL2/3 PCs are particularly elongated, enabling multiple nonlinear processing units in these dendrites. Unlike the morphological features, the active biophysical features (e.g., spike shapes and rates) and passive/cable features (e.g., somatic input resistance, 47.7±15.2 MΩ, membrane time constant, 12.03±1.79 msec, average dendritic cable length, 0.99±0.24) were depth- independent. A novel descriptor for apical dendritic topology yielded two distinct classes, termed hereby as “slim-tufted” and “profuse-tufted” HL2/3 PCs; the latter class tends to fire at higher rates. In mouse temporal cortex all L2/3 PCs belong to the slim-tufted class.

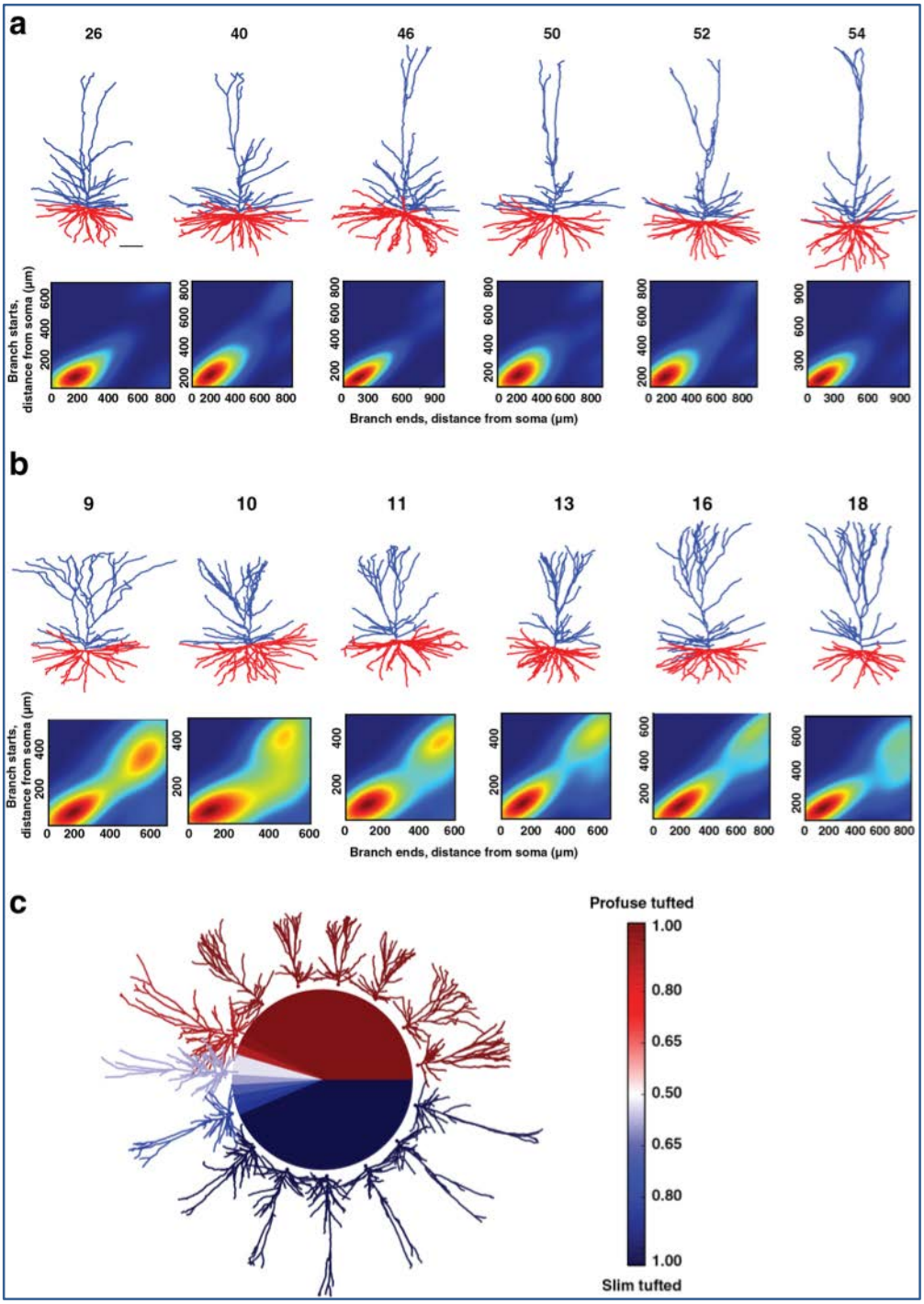


**Figure 5: Examples of the two pyramidal cell classes ("slim-tufted" and "profuse-tufted") in Human L2/3 temporal cortex.**

**a. Top, six 3D reconstructed exemplars of a slim-tufted Human L2/3 cell. Scale bar is 100 µm. Bottom, density plot of the cells on top (see Methods). b. Top, six 3D reconstructed exemplars of the profuse-tufted Human L2/3 cells. Bottom, density plot of the cells on top. c. Illustration of the separation of the two classes. The colours represent the probability of each neuron to be classified as a certain type: dark blue indicates slim-tufted; dark red indicates profuse-tufted. Note that the "profused tufted" cell type was not found in the temporal cortex of the mouse.**

**Deitcher Y, Eyal G, Kanari L, Verhoog MB, Atenekeng G, Mansvelder HD, De Kock CPJ, Segev I. Comprehensive morpho-electrotonic analysis shows two district classes of L2/3 pyramidal neurons in human temporal cortex (*Cerebral Cortex*, under review)**

### *3.5.4 Component Progress*

#### 3.5.4.1 SP6-T6.2.1-SGA1-models of nonlinear human neurons

Description of Component: We will add to the passive model somatic spiking activity, based on *in vivo* recordings from these cells (using our multiple objectives optimisations method)

CDP to which Component contributes: CDP3

Progress of Component: We added to the passive model somatic spiking activity, based on *in vivo* recordings from these cells (using our multiple objectives optimisations method).

We succeeded in using BluePyOpt to closely model somatic spikes in Human L2/3 pyramidal cells; both single spike and spike-train following depolarise step currents of various amplitudes (e-code). Data from Huib Mansvelder (SP2).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **T6.2.1-SGA1-Models of nonlinear human neurons** | |
|---|---|
| **Upstream Component** | **Status** |
| eFEL | We now included NMDA-nonlinearity, including dendritic NMDA spikes in human neuron models. NMDA model is based on new experimental data |
| BluePyOpt | We have used this tool for simulating neurons |
| NEURON | We have used this tool for simulations |
| Morphological and physiological data from the same neurons in adult human | This data was received on human data and was used in the modelling efforts; and is part of the combined publications with these two experimental teams |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.7-SGA1-Simplified brain models | The publication of the human neuron models could be used now for simplification efforts – for whole brain models |
| Simplified neuron models | The detailed models of human neurons presented hereby were the foundation for the simplified neurons models of human neurons developed by us in SP4 (T4.1.1) for this component.<br>The NMDA-based synaptic current model that we have developed will be used in both SP6 and SP4 for the study of synaptic plasticity rules.<br>Models for dendritic spines based on our study will be employed (by ourselves and by other SP6 tasks involved in large scale circuit models) for incorporating spines into the detailed neuron models and for modeling individual (excitatory) synaptic connections (as in Fig. 1D). |
| SGA2 - T6.1.3-C1 - Hodgkin-Huxley modelling of excitation-inhibition | We developed an analytic algorithm to faithfully map complex-to-simple neuron models |

#### 3.5.4.2 SP6-T6.2.1-SGA1-Modelling synaptic inputs to human dendritic spines

Description of Component: Based on physiological recordings from synaptically connected pair of human cells, we will build NMDA-based synaptic models that match the experimental EPSPs.

CDP to which Component contributes: CDP3

Progress of Component: Based on physiological recordings from synaptically connected pair of human cells, we already started building NMDA-based synaptic models that match the experimental EPSPs.

We now have a new updated model of the voltage-depend NMDA-current; which is presently the best, experimentally-based, model of the NMDA-based receptors available for cortical pyramidal neurons.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.2.1-SGA1-Modelling synaptic inputs to human dendritic spines | |
|---|---|
| **Upstream Component** | **Status** |
| NEURON | We have used this tool for simulations |
| Morphological and physiological data from the same neurons in adult human | This data was received on human data and was used in the modelling efforts; and is part of the combined publications with these two experimental teams |
| | |
| **Downstream Component** | **Status** |
| SGA2 - T6.1.3-C1 - Hodgkin-Huxley modelling of excitation-inhibition | We now generated axonal spiking activity in human neuron models that closely match experimental recordings in these cells |
| SP6-T6.2.7-SGA1-Simplified brain models | The publication of the human neuron models could be used now for simplification efforts – for whole brain models |
| Simplified neuron models | The detailed models of human neurons presented hereby were the foundation for the simplified neurons models of human neurons developed by us in SP4 (T4.1.1) for this component.<br>The NMDA-based synaptic current model that we have developed will be used in both SP6 and SP4 for the study of synaptic plasticity rules.<br>Models for dendritic spines based on our study will be employed (by ourselves and by other SP6 tasks involved in large scale circuit models) for incorporating spines into the detailed neuron models and for modelling individual (excitatory) synaptic connections. |

### 3.5.4.3 SP6-T6.2.1-SGA1-Models of human dendritic spines

Description of Component: Based on high-resolution reconstruction of dendritic spines from L2/3 human pyramidal cells we will construct detailed conductance-based models of these spines (for later use as locus for excitatory synaptic inputs).

CDP to which Component contributes: CDP3

Progress of Component: Based on high-resolution reconstruction of dendritic spines from L2/3 human pyramidal cells we will construct detailed conductance-based models of these spines (for later use as locus for excitatory synaptic inputs).

We have developed both models of individual spines in human L2/3 neurons, based on more than 100, 3D reconstructed, dendritic spines (by the team of Javier DEFELIPE, SP1).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.2.1-SGA1-Models of human dendritic spines | |
|---|---|
| **Upstream Component** | **Status** |

| | |
|---|---|
| NEURON | We now have detailed models of of L2/3-L2/3 excitatory synapses in human temporal cortex |
| Complex to simplified models | We found that human L2/3 neurons could not be morphed into mouse L2/3 neurons; as these morphologies are significantly (and importantly) different topologically |
| 3D reconstructions of 200 cells in human neocortex (temporal, cingulate and frontal) | 100 3D reconstructed neurons from L2/3 of the human temporal cortex received |
| | |
| **Downstream Component** | **Status** |
| SGA2 - T6.1.3-C1 - Hodgkin-Huxley modelling of excitation-inhibition | The models are available at the HBP Platform. |
| SP6-T6.2.7-SGA1-Simplified brain models | The publication of the human neuron models could be used now for simplification efforts – for whole brain models |
| complex to simplified models | We found that human L2/3 neurons could not be morphed into mouse L2/3 neurons; as these morphologies are significantly (and importantly) different topologically |

### 3.5.4.4 SP6-T6.2.1-SGA1-Detailed passive models of human neurons

Description of Component: We use 3D reconstructed human neurons from L2/3 of the temporal cortex. These same cells were also characterised physiologically via a brief somatic current step. Combining 3D anatomy + physiology enable us to build the passive skeleton models for these cells.

CDP to which Component contributes: CDP3

Progress of Component: We use 3D reconstructed human neurons from L2/3 of the temporal cortex. These same cells were also characterised physiologically via a brief somatic current step. Combining 3D anatomy + physiology enable us to build the passive skeleton models for these cells; this model provided a surprise as it predicted (and experimentally confirmed) that the specific capacitance of L2/3 human pyramidal cell is half that of rodents; this has important functional consequences

An updated version of passive cable properties of human neuron was released (and published) - DOI: http://dx.doi.org/10.7554/eLife.16553

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.1-SGA1-Detailed passive models of human neurons** | |
|---|---|
| **Upstream Component** | **Status** |
| NEURON | We now have detailed models of of L2/3-L2/3 excitatory synapses in human temporal cortex |
| Morphological and physiological data from the same neurons in adult human | We have now used the detailed morphology and physiology of human L2/3 neurons, and the conductance-based models we built based on it, to develop models of excitatory (AMPA-NMDA) synapses for these neurons, which match experimental EPSP's in these neurons. Thee synapses are located on realistic models of human dendritic spines. Paper in preparation. |
| SP2 - Morphological data of human neocortical pyramidal neurons | We completed new analysis of human neuron morphology; we found 2 L2/3 cell types in human. Paper under review in Cereb. Cortex |
| | |

| Downstream Component | Status |
|---|---|
| SGA2 - T6.1.3-C1 - Hodgkin-Huxley modelling of excitation-inhibition | The models are available at the HBP platform |
| SP6-T6.2.7-SGA1-Simplified brain models | The publication of the human neuron models could be used now for simplification efforts – for whole brain models |
| Template of morphing rules to translate pyramidal neuron function from rodent brain to microcircuits in the human brain | We found that human L2/3 neurons could not be morphed into mouse L2/3 neurons; as these morphologies are significantly (and importantly) different topologically |
| NEST code with abstracted neuron model representations | |
| complex to simplified models | |

## 3.6 T6.2.2 Models of Somatosensory Cortex

### *3.6.1 Key Personnel*

Task Leader: Javier DEFELIPE (UPM)

### *3.6.2 SGA1 DoA Goals*

The goal of this TZask is to coordinate community cellular-level modelling of the mouse somatosensory cortex, based on the detailed cellular somatosensory cortex model developed by the BBP before the start of the HBP, and further enhanced during the RUP (Markram et al, *Cell*, 2015). The focus is on validation and in *silico* experiments. Task 6.2.2 will thus be the first users of the CDP2, Product 6 '*In silico* experimentation lab on the example of the cellular-level neocortical model'. Validation and refinement is being performed in collaboration with BBP and with other HBP collaborators. The Task has access to the full set of models, tools and workflows developed by the BBP, which will be released as OSS, and made available through the BSP.

The original BBP model (Markram et al, 2015) is based on rat data. Task 6.2.2 will enhance the model for mouse, and compare the original and the enhanced versions. Models will use reconstruction data (layer heights and neural densities, neural composition, neuron morphologies, connectivity data, etc.) and validation data (voltage-sensitive dye and calcium imaging, *in vivo* multi-electrode recordings, optical stimulation experiments, etc.) coming from SP1 and from the community, integrated via the Neuroinformatics Platform. Model building and simulation will rely on high performance computing services provided by SP7. Models will use the NEURON simulator, relying on enhancements introduced by SP6.

Models will be compared in terms of validation experiments defined by the community. Validated models will contribute to *in silico* experiments for cognitive, behavioural, and clinical research, to be carried out in close collaboration with SP3, SP4 and with other SP6 Tasks. Simplified versions, developed in collaboration with T6.2.7, will feed into whole brain modelling in T6.2.6.

### *3.6.3 Task Achievement Summary*

During the last months we have processed brain material from 12 mice for electron microscopy and for immunocytochemistry for the neuronal marker NeuN and we have generated data regarding heights of the different cortical layers of the hindlimb somatosensory cortex. In this material we are currently in the process to estimate by stereological techniques the total neuronal density values in the different cortical layers. We have generated data regarding the total density and the distribution patterns of GABAergic interneurons in the somatosensory cortex of EGFP-GAD67 transgenic mice by

confocal microscopy and 3D automated particle counting methods. We have also measured the densities and distributions of GABAergic and glutamatergic punctate elements in the neuropil of every cortical layer by double immunofluorescence for vGlut1 and vGAT, confocal microscopy and 3D counting methods (Fiji software). In adjacent sections we have used FIB/SEM to estimate the number and distribution of excitatory and inhibitory synapses (in two animals) to validate the light microscope studies. Furthermore, in experiments with double immunostaining for vGAT and NeuN, and using image segmentation and 3D reconstruction techniques, we have released number and densities of GABAergic terminals around the cell bodies of pyramidal cells in different layers. Finally, we have digitalised 100 intracellularly injected pyramidal cells and performed 3D reconstructions of 30 cells across layers II-VI. All these quantitative data sets generated in the mouse brain are being used or will be used for enhancing and validating the original BBP model, based on rat data, for the simulation of the mouse neocortex performed by other groups of SP6.

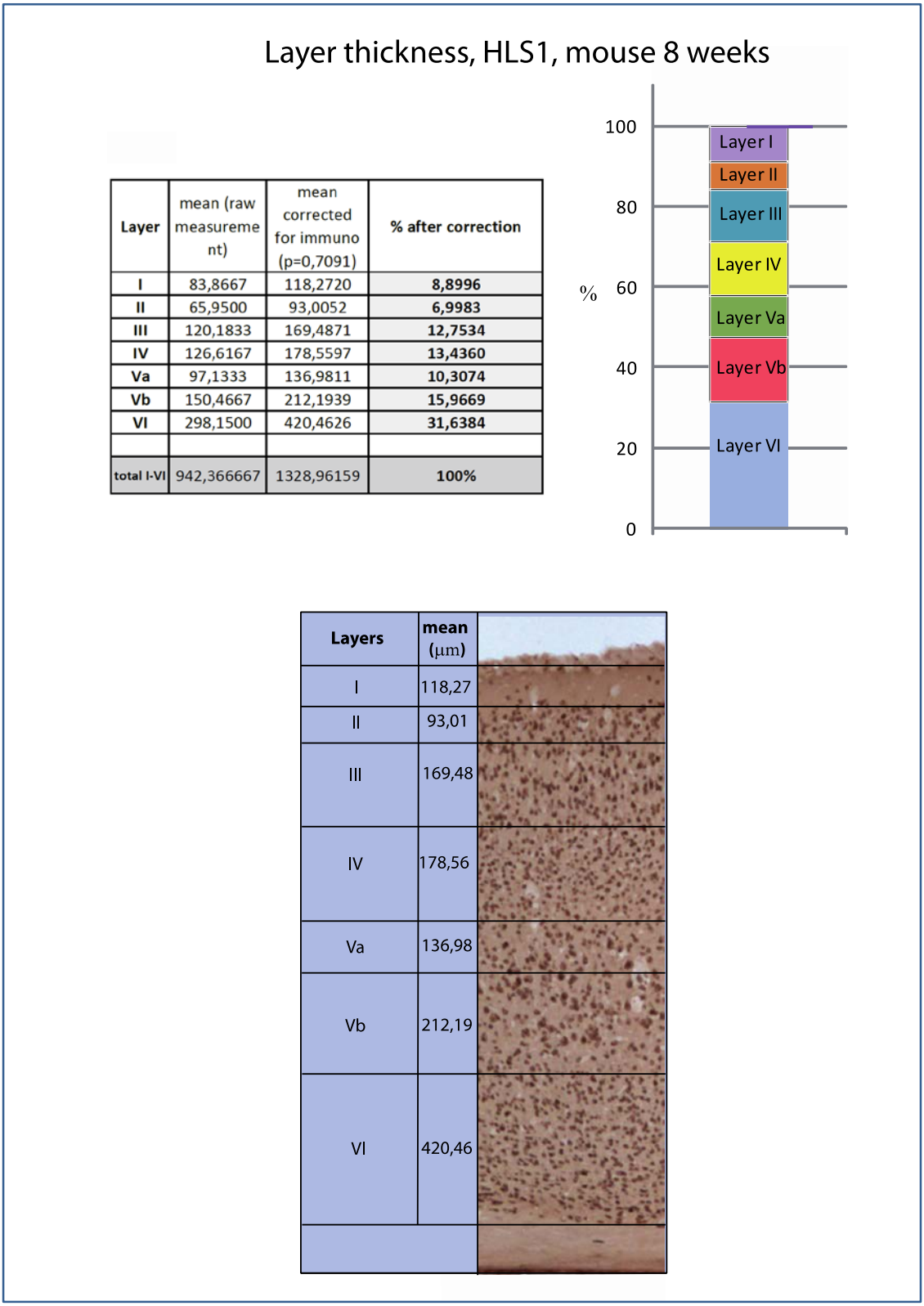


**Figure 6: Experimental results on layer structure of cortex in mouse.**

### *3.6.4 Component Progress*

#### 3.6.4.1 SP6-T6.2.2-SGA1-Initial model validation tests implemented to compare rat model with mouse data

Description of Component: Initial model validation tests implemented to compare rat model with mouse data.

Progress on Component: We have released data regarding layer heights, total density of interneurons and vGlut1 and vGAT punctate elements in all cortical layers. Furthermore, we have released number and densities of GABAergic terminals around the cell bodies of pyramidal cells in different layers. These data will be used for initial model validation.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.2-SGA1-Initial model validation tests implemented to compare rat model with mouse data** | |
|---|---|
| **Upstream Component** | **Status** |
| Immunocytochemical detection of excitatory an inhibitory terminals in the mouse neocortex (somatosensory cortex) by confocal microscopy. | Intermediate release. Essential data. |
| Nanoscale measurements of distributions of individual receptors and ion channels in cortical neurons | Received nothing: data will be provided by UCLM & IST. *Receptor and ion channel mapping strategy* has been achieved as planned (M12). Data is expected to be released from M12 to M24. Important data. |
| 3D reconstruction of thalamocortical projection neurons. | Received nothing: M12 release *Complete 3D datasets of single-cell somatosensory TC axons* is delayed until M18 due to the delay in hiring staff. Important data. |
| 3D reconstructions of 300 pyramidal neurons from the mouse somatosensory cortex across layers II-VI | Intermediate release. Essential data. |
| Whole-brain images of selected neuronal types. | Received nothing. Added value data. |
| Whole-brain maps of selected neuronal types | Received nothing. Added value data. |
| Images of neuronal activation of whole mouse brain | Received nothing. Added value data. |
| Maps of neuronal activation of whole mouse brain | Received nothing. Added value data. |
| Morphological categorization and clustering of synaptic coverage of GABAergic neuron subtypes | Received nothing: This Component is delayed due to the delay in the SGA1 signature and the effective work in T1.2.7 was starting in January 2017 consequently. In spite of this delay, M24 release *Synaptic coverage of GABAergic subtypes of cortical neuron* is expected to be achieved as planned. Essential data. |
| Quantitative electron microscopic (qEM) database of Synaptic Coverage of GABAergic Neuron Subtypes. | Received nothing: Part of the activities planned in this component is delayed (see the component above). M10 release *Immunostaining of GABAergic subtypes of cortical neuron* was not achieved but it has already started. In spite of this delay, the immunohistochemical characterisation of the GABAergic interneurons has started and the identification of three sub-types have been achieved. Data will be released from M12. Essential data. |
| Densities and 3D distributions of synapses using FIB/SEM imaging in the mouse neocortex (somatosensory cortex). | Intermediate release. Essential data. |

| | |
|---|---|
| New workflows for embedding exploratory analysis techniques into the early stages of the morphological data extraction and reconstruction processes. | Intermediate release. Report. |
| Tools for the early analysis of morphological data | Intermediate release. Essential software. |
| Association (co-clustering) of receptors and their effector ion channels in different neuronal compartments. | Received nothing: data is expected to be released from M12 to M24. Essential Data. |
| Nanoscale measurements of distributions of individual receptors and ion channels in cortical neurons | Received nothing. Essential Data. |
| SP1-T1.1.5-SGA1 K channel kinetic models including [K+]ext | Received nothing. Added value. |
| NEURON | Received nothing |
| | |
| **Downstream Component** | **Status** |
| SP3-Shrewbot++ robot platform | Provided nothing. Hardware added value |
| SP6-T6.2.7-SGA1-Simplified brain models. | Provided nothing. Model Important |

## 3.7 T6.2.3 Models of Cerebellum

### *3.7.1 Key Personnel*

Task Leader: Egidio D'ANGELO (UNIPV)

### *3.7.2 SGA1 DoA Goals*

Task 6.2.3 will develop a scaffold model of the mouse cerebellum, which will contribute to community-driven modelling in future SGAs. The work will include modelling of single cerebellar neurons and synapses, microcircuit modelling, development of full cerebellar network models, the use of these models to investigate integrated tissue functions (LFPs, neurovascular coupling), and (in conjunction with SP10) the application of network models to neurobotics. T6.2.3 will use mouse data (neural densities and composition, neuron morphologies, connectivity data, etc.) collected in SP1 and from the external community together with modelling tools developed in WP6.3 and tools integrated through WP6.4. T6.2.3 will play an essential role in the co-design of these tools, ensuring that they are of generic utility and applicability. Modelling and simulation will rely on high performance computing services provided by SP7. Models will use the NEURON simulator, and rely on enhancements introduced by SP6. Models will be compared in terms of validation experiments defined by the community and will be used for experiments in *in silico* electrophysiology and *in silico* behaviour (see SP3). Simplified versions of the model will be developed together with T6.2.7, feeding into whole brain modelling in T6.2.6. The results of the work in T6.2.3 will contribute the cellular level model of the cerebellum used in CDP2 Product 5: Cellular Level Cerebellar Model – generalisation strategies and integration in robotic systems.

### *3.7.3 Task Achievement Summary*

- During the first year of SGA1 we have proceeded along these fundamental streamlines:
- A framework for multi-scale modelling of the cerebellum has been established (D'Angelo et al., 2016; Alahmadi et al, 2017).

- The physiological investigation and biophysical modelling of single neurons has revealed an important new aspect (published in *Nature*: Dover et al., 2016), i.e. that the dogma of constant leaky axonal resistance does not hold in mammalian neurons. The analysis of the corresponding granule cell model is leading to a novel understanding of axonal spike generation and conduction.
- Optimisation of the Purkinje cell model and of the granule cell model. (In collaboration with EPFL we have refined procedures in the BSP to optimise the maximum conductance of the Purkinje cell model developed during the RUP. The results are encouraging and a full optimisation pipeline based on investigations carried out on neurons of the cerebellum has been completed and defined. One first paper was published in the RUP; the new one is under preparation.
- The optimisation of the granule cell model has been carried out and these models can predict electroresponsive properties like inward rectification, near-threshold oscillations, theta-frequency resonance and AP conduction velocity that were not set as features. These results indicate that the optimiser framework generates biophysically accurate models endowed with appropriate ionic mechanism, providing the basis for reconstructing large-scale neuronal networks operating with arbitrary firing patterns (Single Neuron Optimization as a Basis for Accurate Biophysical Modeling: The Case of Cerebellar Granule Cells, Masoli S, Rizza MF, Sgritta M, Van Geit W, Schürmann F, D'Angelo E., Front Cell Neurosci. 2017 Mar 15;11:71. doi: 10.3389/fncel.2017.00071. eCollection 2017).
- Cerebellar microcircuit scaffold models. At present, scaffold models for all the fundamental cerebellar neurons have been developed. These include granule cells, Golgi cells, Purkinje cells, stellate cells, unipolar brush cells, deep cerebellar nuclei cells, inferior olivary cells (the last three under development or in the validation process).
- Cerebellar microcircuit reconstruction. A scaffold model of the cerebellar microcircuit has been implemented using Brain Builder in collaboration with EPFL. The new model construction pipeline consists of first defining neuronal densities, locating them in space, generating appropriate morphologies of the all complement of axons and dendrites. The enforcement of proximity connectivity rules and the incorporation of active membrane and synaptic properties are the next steps. The paper is in preparation.

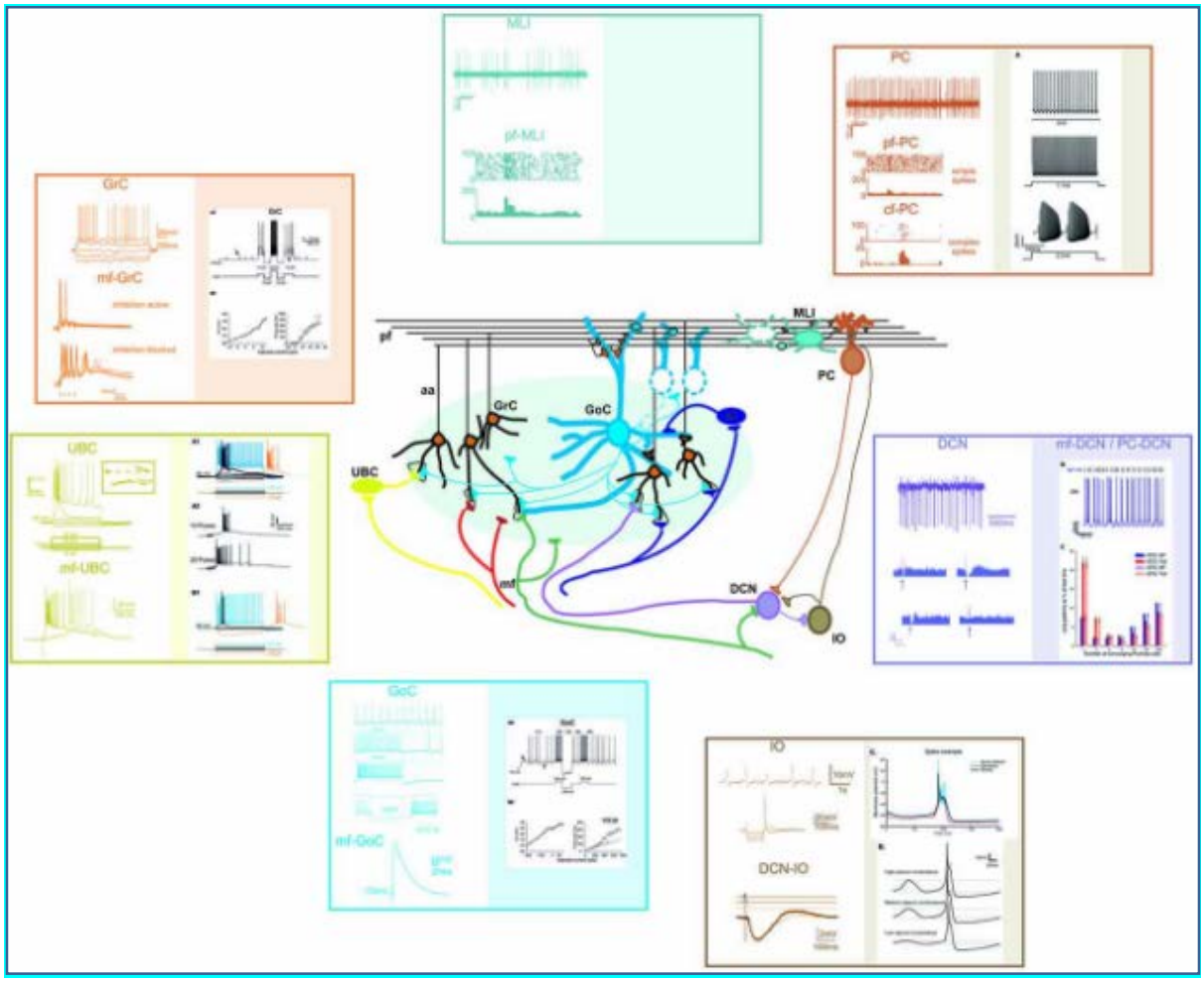


**Figure 7: The cerebellar microcircuit neuron models taken from D'Angelo et al., 2016. All neurons are currently developed or under development or in the validation process.**

### *3.7.4 Component Progress*

#### 3.7.4.1 Cerebellum electrophysiological pipeline

Description of Component: To compare models in terms of validation experiments defined by the community and use them for experiments in *in silico* electro-physiology and *in silico* behaviour.

CDP to which Component contributes: CDP2: The structural and functional basis of cerebellar dynamics and plasticity

Progress on Component: Models of the cerebellum have been reconstructed and validated against a large set of experimental data provided both from this laboratory and by the scientific community. In particular, the PC and GrC models have been reconstructed, optimised and validated (papers published). The procedure has been implemented as a pipeline on the Collab.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Cerebellum electrophysiological pipeline** | |
|---|---|
| **Upstream Component** | **Status** |
| Biological Signature of Healthy Ageing (model) | Have received nothing but we are planning to receive data for implementing changes imitating molecular/cellular pathology in the cerebellar network |

| | |
|---|---|
| Patch-clamp recordings from cerebellar neurons (data) T1.2.4 | Data are allowing reconstruction, optimisation and validation of cerebellar neuron models and microcircuit models |
| | |
| **Downstream Component** | **Status** |
| None | |

### 3.7.4.2 Cerebellum application model

Description of Component: To use models of Component 1 to investigate integrated tissue functions (LFPs, neurovascular coupling), and (in conjunction with SP10) the application of network models to neurorobotics.

CDP to which Component contributes: SGA2-SP1-UC03: The structural and functional basis of cerebellar dynamics and plasticity

Progress on Component: Models of Component 1 have been used to develop a module for LFP calculation as a fallout of PythonNEURON simulations. The module for neurovascular coupling is being developed following the results obtained in fMRI and imaging in brain slice recordings (paper published: Mapelli L, Gagliano G, Soda T, Laforenza U, Moccia F, D'Angelo EU. Granular Layer Neurons Control Cerebellar Neurovascular Coupling Through an NMDA Receptor/NO-Dependent System. *Journal of Neuroscience*. 2017;37(5):1340-1351).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Cerebellum application model** | |
|---|---|
| **Upstream Component** | **Status** |
| MIP - DATA > Reference Data > Quantitative MRI (qMRI) in vivo biomarkers of the microstructure of brain tissue - myelination, iron and water concentration (data) | MRI data provided through community collaborations |
| MODEL > Biological Signature of Healthy Ageing [essential] | Provided |
| Simulation of brain lesion and cortical bistability on complexity | No data provided yet but internal collaboration implemented |
| Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 | No data provided yet but internal collaboration implemented |
| eFEL | Provided |
| NEURON | Provided |
| Python | Provided |
| | |
| **Downstream Component** | **Status** |
| Simulation of brain lesion and cortical bistability on complexity | No data provided yet but internal collaboration implemented |
| Slow waves and complexity relationships explored by perturbations: definition of models, T3.2.2 | Will implement once relevant data will be received from upstream component |

### 3.7.4.3 Cerebellum scaffold models

Description of Component: To develop a scaffold model of the mouse cerebellum including single cerebellar neurons, synapses, microcircuits and full cerebellar network models.

CDP to which Component contributes: SGA2-SP1-UC03: The structural and functional basis of cerebellar dynamics and plasticity

Progress on Component: The cerebellum scaffold model is being developed. In detail we have progressed on circuit building implementing (i) cell placement in three-dimensional space according to density distribution of cerebellar cortical layers (ii) morphology assignment and three-dimensional spatial orientation. The code is written in Python and exploits brainbuilder, voxcellview and voxcell libraries to build and visualise the cerebellum cortical network. The connectome building operates now according to connectivity rules derived from experimental data. The notebook allows to visualise connectivity structure and to save the generated connectome as a .hdf5 file. At the moment, the notebook reconstructs the connectivity of the cerebellum granular layer.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Cerebellum scaffold models** | |
|---|---|
| **Upstream Component** | **Status** |
| coreneuron | Provided |
| NEURON | Provided |
| BrainBuilder Framework | Provided |
| BluePyOpt | Provided |
| NEST | Provided |
| Python | Provided |
| eFEL | Provided |
| coreneuron | Provided |
| Combined optogenetic, two-photon imaging and electrophysiological recordings from cerebellar neurons | Provided through SP1 |
| Patch-clamp recordings from cerebellar neurons | Provided through SP1 |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.7-SGA1-Simplified brain models | Ongoing through internal and external collaboration |

#### 3.7.4.4 TouchDetector (provided internally)

Description of Component: A library to compute neuron appositions in a detailed neuron circuit in an efficient and distributed way.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **TouchDetector** | |
|---|---|
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 5 upstream Components | Provided |

#### 3.7.4.5 Functionalizer (provided internally)

Description of Component: A library to compute synapse location and parameters in a detailed neuronal circuit model.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Functionalizer** | |
|---|---|
| **Upstream Component** | **Status** |

| | |
|---|---|
| 3 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |

## 3.8 T6.2.4 Models of Hippocampus

### *3.8.1 Key Personnel*

Task Leader: Szabolcs KÁLI (IEM HAS)

Other Researcher: Audrey MERCER (UCL)

Other Researcher: Michele MIGLIORE (CNR)

Other Researcher: Eilif MULLER (EPFL)

Other Researcher: Armando ROMANI (EPFL)

### *3.8.2 SGA1 DoA Goals*

Task 6.2.4 is a pilot project, which develops and tests strategies for fostering community convergence through data-driven reconstruction and simulation of the mouse hippocampus, providing feedback for the design of the Collaboratory, and of community collaboration tools. In addition, this Task explores the possibility of developing models of rat hippocampus and comparing these models to the mouse models. The work is guided by a task force of HBP partners who interface with the hippocampus community to develop community-driven models and tools. These include models of hippocampal neurons and synapses, cellular level models from the microcircuit to the whole hippocampus, simplified versions of models for use in *in silico* experimentation, and a validation suite for neurons, synapses and networks. A key goal is to create bridges allowing integration of data from HBP and community-based neuroinformatics resources.

### *3.8.3 Task Achievement Summary*

Significant progress has been made towards establishing an efficient workflow for data-driven modelling of hippocampal neurons and circuits. Models of rat hippocampal neurons were constructed through the use of reconstructed morphologies, recorded electrophysiological traces, and automated parameter optimisation. A database of optimised models has been internally organised and released. A set of tests comparing the electrophysiological behaviour of models of CA1 pyramidal neurons to experimental data was designed and implemented. This validation suite was applied to the automatically tuned models of CA1 pyramidal cells. Both the optimisation and the validation procedure can be run from the BSP.

Since the last stable release in June 2016, the network model of the rat CA1 region underwent a major revision that expanded the input data (morphology reconstructions and electrophysiological recordings), revised the model assumptions, and improved the toolchain to generate and simulate the model. In parallel, an increasing number of validations has been performed on the model to assess its validity and accordance with experimental evidences. A new release is planned for June 2017.

Substantial efforts were also devoted to bootstrapping community involvement. Results from this Task were described in detail at focused workshops and major conferences, emphasising the use of generic HBP tools and workflows. Feedback from researchers outside the HBP was generally positive, and there is an ongoing dialogue with some key members of the modelling community about their possible use of the HBP Platforms and contribution to the hippocampus community model. To facilitate further integration, we have organised a workshop on collaborative modelling of the hippocampus in collaboration with SP4, which will take place at the EITN in May 2017.

We note that work on some Components of this Task (including the provision of additional data on rat hippocampal neurons and the construction of mouse neuronal and network models) was substantially delayed due to the late availability of funding, but efforts have been increased to ensure that the Task objectives can be met by the end of SGA1.

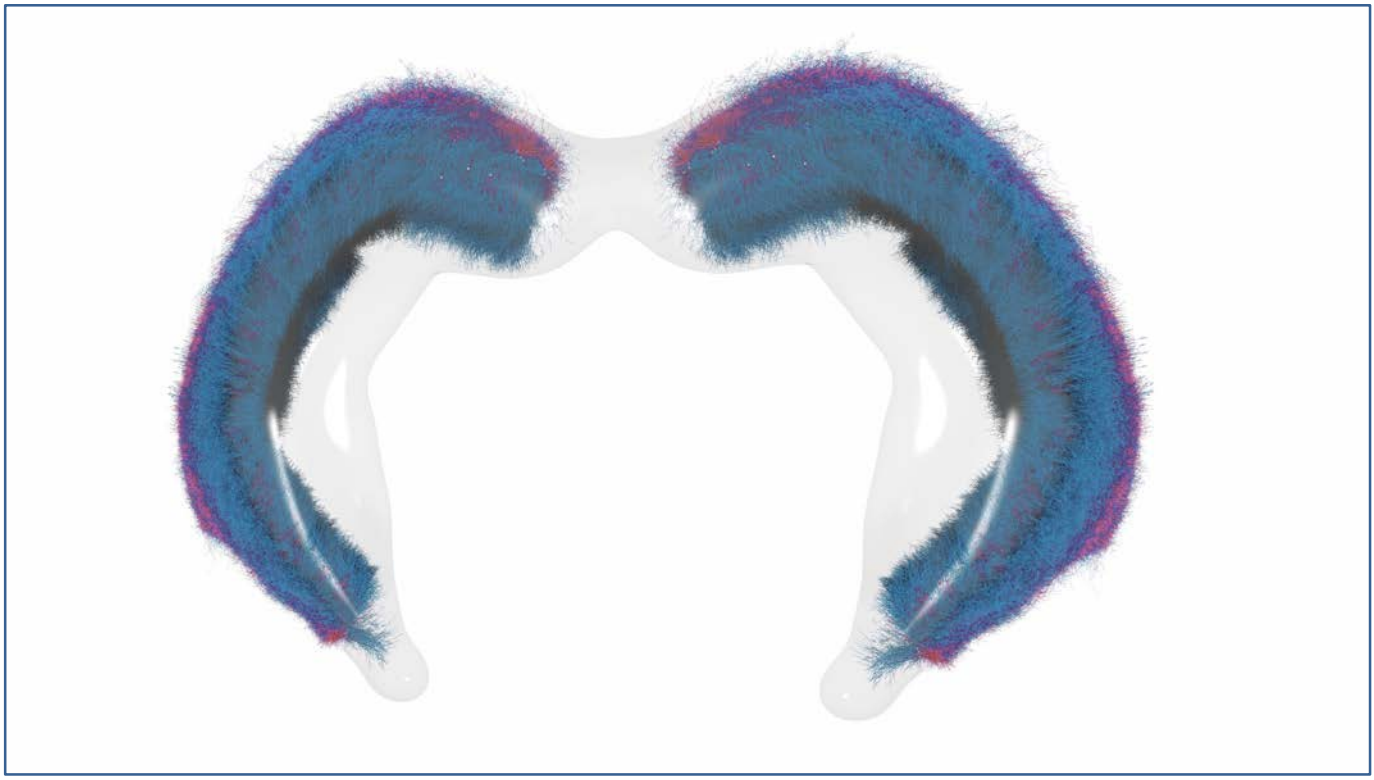

**Figure 8: The image shows the reconstruction of CA1 networks embedded in CA volume. Each CA1 contains 350,000 neurons, but only dendrites and a small percentage of the cells are shown for clarity. Blue, apical dendrites; red, basal dendrites.**

### *3.8.4 Component Progress*

#### 3.8.4.1 SP6-T6.2.4-SGA1-Models of rat hippocampal neurons

Description of Component: Detailed cellular models of different cell types in the rat hippocampus will be built using reconstructed morphologies and recorded electrophysiological data.

CDP to which Component contributes: CDP2 (Mouse-based cellular cortical and sub-cortical microcircuit models); Use Cases: Single cell modelling, Multi-scale validation; Product 3: Community-based modelling strategy on the example of cellular-level hippocampus model

Progress on Component: Models of rat hippocampal neurons were constructed through the use of reconstructed morphologies, recorded electrophysiological traces, and automated parameter optimisation (CNR). A database of optimised models has been internally organised and released; models have been presented in scientific context. A set of tests comparing the electrophysiological behaviour of models of CA1 pyramidal neurons to experimental data was designed and implemented (IEM HAS). This validation suite was applied to the automatically tuned models of CA1 pyramidal cells (CNR+IEM HAS). Both the optimisation and the validation procedure can be run from the BSP.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.4-SGA1-Models of rat hippocampal neurons** | |
|---|---|
| **Upstream Component** | **Status** |

| | |
|---|---|
| single cell electrical model validation | High quality input has been received from all of the Tasks in the RUP, and some of the Tasks in SGA1. Further input is expected from intermediate releases in the near future. |
| single morphology validation | |
| hippocampus CA1 microcircuit model | |
| Electrophysiological recordings of primary neuron types of rat hippocampal CA1 | |
| Morphological reconstructions of primary neuron types of rat hippocampal CA1 | |
| Morphological reconstructions of primary neuron types of rat hippocampal CA1 | |
| BluePyOpt | |
| 3D reconstructions of 50 cells in rat hippocampal CA1 region | |
| NEURON | |
| STP model | |
| SP6-T6.2.4-SGA1-Database of morphologies and electrophysiological recordings from the rat hippocampus | |
| | |
| **Downstream Component** | **Status** |
| T3.3.4 (1) Temporal dynamics of rodent spatial memory | Intermediate results have been provided. |
| SGA2-T6.2.3 - Improved models of hippocampal neurons in the mouse and the rat | Intermediate results have been provided. |
| SGA2-T6.1.5-C3 Hippocampus microcircuit | Intermediate results have been provided. |
| SP6-T6.2.7-SGA1-Simplified brain models | Intermediate results have been provided. |
| Multi compartmental reconstructed cortical cells: their input-output transfer properties | Intermediate results have been provided. |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus | Intermediate results have been provided. |

### 3.8.4.2 SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons

Description of Component: Detailed cellular models of different cell types in the mouse hippocampus will be built using reconstructed morphologies and recorded electrophysiological data.

CDP to which Component contributes: CDP2 (Mouse-based cellular cortical and sub-cortical microcircuit models); Use Cases: Single cell modelling, Multi-scale validation; Product 3: Community-based modelling strategy on the example of cellular-level hippocampus model

Progress on Component: Work on this Component started only very recently, partly because of the delayed availability of funding (a postdoc at IEM HAS was hired for this job in November 2016), and partly because we have focused mainly on developing and validating the cellular reconstruction workflow using the rat data as an example (see component “SP6-T6.2.4-SGA1-Models of rat hippocampal neurons” above). Most of the work on this

Component has involved post-processing of the mouse hippocampal data (morphologies and electrophysiological traces) from IEM HAS to make them compatible with the existing modelling workflow. There were no releases planned for this Component in the current period.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons** | |
|---|---|
| **Upstream Component** | **Status** |
| Single cell electrical model validation | High quality input has been received from all of the Tasks in the RUP, and some of the Tasks in SGA1. Further input is expected from intermediate releases in the near future. |
| Single morphology validation | |
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models | |
| SP6-T6.4.5-SGA1-Brain Simulation Platform access | |
| SP6-T6.4.4-SGA1-Validation test repository | |
| SP6-T6.4.4-SGA1-Model validation browser app | |
| SP6-T6.4.4-SGA1-Model Validation Service | |
| SP6-T6.4.3-SGA1-Model representations for cellular and network models | |
| eFEL | |
| BluePyOpt | |
| 3D reconstructions of 50 cells in mouse hippocampal CA1 region | |
| Association (co-clustering) of receptors and their effector ion channels in different neuronal compartments | |
| Nanoscale measurements of distributions of individual receptors and ion channels in cortical neurons | |
| Database of all the major excitatory and inhibitory cell types of the mouse hippocampus, using a combination of morphological and electrophysiological classification | |
| Whole-cell recording and labelling of hippocampal neurons in vivo | |
| NEURON | |
| SP1-T1.1.5-SGA1 K channel kinetic models including [K+]ext | |
| STP model | |
| Morphological reconstructions of mouse hippocampal neurons | |
| | |
| **Downstream Component** | **Status** |

| | |
|---|---|
| Rule-based modelling incorporated in Brain Simulation Platform | Feedback on the data has been provided to data-collection tasks in SP1, but otherwise, no results have been released. |
| Morphological and electrophysiological characterization of hippocampal interneurons | |
| Models of state changes in the hippocampal network due to subcortical input | |
| SGA2-T6.2.3 - Improved models of hippocampal neurons in the mouse and the rat | |
| SGA2-T6.1.5-C3 Hippocampus microcircuit [essential] | |
| Database of all the major excitatory and inhibitory cell types of the mouse hippocampus, using a combination of morphological and electrophysiological classification | |
| SP6-T6.2.7-SGA1-Simplified brain models | |
| ModelManagement | |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | |

### 3.8.4.3 SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus

Description of Component: Circuit-level models of subfields of the rat hippocampus and the entire rat hippocampus will be constructed.

CDP to which Component contributes: CDP2 (Mouse-based cellular cortical and sub-cortical microcircuit models); Use Cases: *In silico* microcircuit experimentation, Multi-scale validation; Product 3: Community-based modelling strategy on the example of cellular-level hippocampus model

Progress on Component: After the last stable release in June 2016, the model underwent a major revision that expanded the input data (morphology reconstructions and electrophysiological recordings) (UCL, EPFL), revised the model assumptions, and improved the toolchain to generate and simulate the model (EPFL). In parallel, an increasing number of validations has been performed on the model to assess its validity and accordance with experimental evidences (EPFL). A new release is planned for June 2017.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus** | |
|---|---|
| **Upstream Component** | **Status** |
| JS Circuit Viewer | High quality input has been received from all of the Tasks in the RUP, and some of the Tasks in SGA1. Further input is expected from intermediate releases in the near future. |
| BrainBuilder Framework | |
| UNICORE | |
| Functionalizer | |
| TouchDetector | |
| ModelManagement | |
| Morphology Synthesizer | |
| Morphology repair and diversification framework | |
| NeuroM | |

| | |
|---|---|
| NEURON | |
| coreneuron | |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models | |
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
| STP model | |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons | |
| | |
| **Downstream Component** | **Status** |
| T3.3.4 (1) Temporal dynamics of rodent spatial memory | Intermediate results have been provided. |
| SGA2-T6.2.3 - Improved models of hippocampal circuitry in the mouse and the rat | |
| SP3-Shrewbot++ robot platform | |
| SP6-T6.2.7-SGA1-Simplified brain models | |

### 3.8.4.4 SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus

Description of Component: Circuit-level models of subfields of the mouse hippocampus and the entire mouse hippocampus will be constructed.

CDP to which Component contributes: CDP2 (Mouse-based cellular cortical and sub-cortical microcircuit models); Use Cases: *In silico* microcircuit experimentation, Multi-scale validation; Product 3: Community-based modelling strategy on the example of cellular-level hippocampus model

Progress on Component: Work on this Component has also been delayed due to the late availability of funding, particularly because this component depends strongly on Component "SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons" above. The plan is to optimise the toolchains to build, validate, and simulate the rat hippocampus model and apply the same workflow to the mouse hippocampus once more input data (mostly morphology reconstructions and electrophysiological recordings) will be available. This will be possible with minor changes in the model parameters and assumptions.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus** | |
|---|---|
| **Upstream Component** | **Status** |
| ModelManagement | High quality input has been received from all of the Tasks in the RUP, and some of the Tasks in SGA1. Further input is expected from intermediate releases in the near future. |
| JS Circuit Viewer | |
| BrainBuilder Framework | |
| Whole-brain maps of selected neuronal types | |
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models | |
| SP6-T6.4.5-SGA1-Brain Simulation Platform access | |

| | |
|---|---|
| SP6-T6.4.4-SGA1-Model validation browser app | |
| SP6-T6.4.4-SGA1-Validation test repository | |
| SP6-T6.4.4-SGA1-Model Validation Service | |
| SP6-T6.4.3-SGA1-Model representations for cellular and network models | |
| UNICORE | |
| Functionalizer | |
| TouchDetector | |
| Morphology Synthesizer | |
| Morphology repair and diversification framework | |
| Database of paired recordings in hippocampal slices which display in vivo-like activity levels and patterns | |
| Immunocytochemical detection of excitatory and inhibitory terminals in the mouse hippocampus (CA1) by confocal microscopy | |
| Densities and 3D distributions of synapses using FIB/SEM imaging in the mouse hippocampus (CA1) | |
| NEURON | |
| coreneuron | |
| STP model | |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons | |
| | |
| **Downstream Component** | **Status** |
| | |
| Morphological and electrophysiological characterization of hippocampal interneurons | Intermediate results have been provided. |
| Models of state changes in the hippocampal network due to subcortical input | |
| SGA2-T6.2.3 - Improved models of hippocampal circuitry in the mouse and the rat | |
| T3.3.3 Optogenetic manipulation of episodic encoding and retrieval in hippocampal, parahippocampal and mesencephalic dopamine cells | |
| T3.3.3 Decoded spike patterns of neural ensembles in cortex and hippocampus during multimodal scene representation | |
| T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1 | |

| | |
|---|---|
| Point-neuron model of the whole mouse brain | |
| Database of paired recordings in hippocampal slices which display in vivo-like activity levels and patterns | |
| SP6-T6.2.7-SGA1-Simplified brain models | |

#### 3.8.4.5 SP6-T6.2.4-SGA1-Database of morphologies and electrophysiological recordings from the rat hippocampus

Description of Component: Recordings from different cell types in rat hippocampal slices will be performed. The morphologies of recorded cells will be reconstructed using Neurolucida.

Progress on Component: Work on this Component has been delayed due to the late availability of funding. Two technicians are now working on Neurolucida reconstructions of CA2 neurones (starting date 01/03/2017) and new electrophysiological recordings were included into the database (UCL).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.2.4-SGA1-Database of morphologies and electrophysiological recordings from the rat hippocampus** | |
|---|---|
| **Upstream Component** | **Status** |
| NEURON | High quality input has been received from the NEURON component in the RUP |
| | |
| **Downstream Component** | **Status** |
| SGA2-T6.2.3 - Improved models of hippocampal neurons in the mouse and the rat | Intermediate results have been provided. |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons | Intermediate results have been provided. |

## 3.9 T6.2.5 Models of Basal Ganglia

### *3.9.1 Key Personnel*

Task Leader: Sten GRILLNER (KI)

Other Researcher: Alexander KOZLOV (KI), Shreyas SURYANARAYANA (KI)

### *3.9.2 SGA1 DoA Goals*

Goal: Development of single cell models of individual neuron types, reconstruction and simulation of the striatal microcircuit, reconstruction and simulation of microcircuits in the basal ganglia nuclei, reconstruction of input from cortex and thalamus. Scaffold versions of other basal ganglia nuclei will be simulated.

Given that the basal ganglia is a highly conserved structure, T6.2.5 will be able to use mouse data collected in SP1 as well as human data from SP2 and from the external community (neural densities and composition, neuron morphologies, connectivity data, etc.), together with modelling tools developed in WP6.3 and additional tools integrated through WP6.4. T6.2.5 will play an essential role in the co-design of these tools, ensuring that they are of generic applicability. Task 6.2.5 will develop a model of rodent basal ganglia, which will contribute to CDP2 Product 4: Cellular Level Basal Ganglia Model – Generalization Strategies.

### 3.9.3 Task Achievement Summary

Major progress towards the general framework of the basal ganglia circuitry outlined in (Grillner and Robertson, 2016; Grillner et al., 2016; Grillner, 2016) was achieved in single-cell modelling of the striatal neurons. This was possible due to detailed reconstructions of the morphology of the striatal neuronal subtypes and their membrane properties combined with utilizing the recently sequenced transcriptomes of striatal neurons from the mouse brain. Expression of ion channel genes of medium spiny neurons (MSN) based on the transcriptomes of 1208 single striatal cells from the mouse brain shown in the image below was extracted from the data by Gokce *et al.* (2016), Gene Expression Omnibus, accession number GEO82187. Similar data for all main types of striatal interneurons became available through external collaboration (publication pending). Single-cell models developed earlier (Du, 2017) were revised according to the newly available data and optimised using HBP tools, BluePyOpt, eFEL, and NeuroM.

Building striatal microcircuit according to the workflow adopted by HBP is being applied. Preliminary simulations of the basal ganglia circuitry using simplified neuron models were performed in order to establish the net effect of dopaminergic modulation of the basal ganglia function (Lindahl and Hellgren Kotaleski, 2017).

Two dissertations were defended during the report period (Lindahl, 2017; Du, 2017).

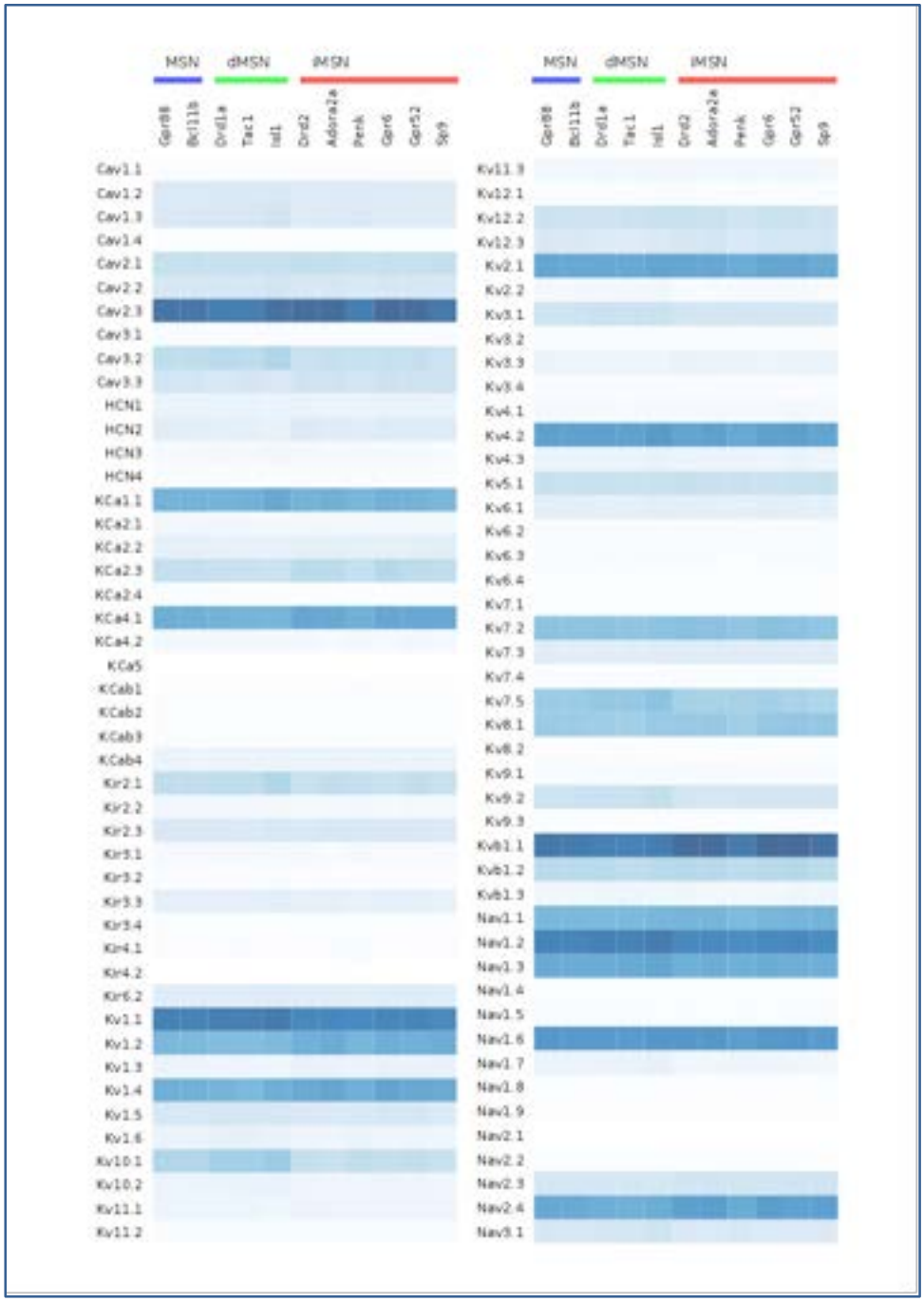


**Figure 9: Expression of ion channel genes in the medium spiny neurons of the mouse striatum.**

### *3.9.4 Component Progress*

#### 3.9.4.1 Functionalizer

Description of Component: A library to compute synapse location and parameters in a detailed neuronal circuit model.

CDP to which Component contributes: CDP2 - Mouse-Based Cellular Cortical and Subcortical Microcircuit Models (T6.2.5 will develop a model of rodent basal ganglia, which will contribute to CDP2 Product 4: Cellular Level Basal Ganglia Model – Generalization Strategies).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| Functionalizer | |
|---|---|
| **Upstream Component** | **Status** |
| TouchDetector (software) | Continuous contact with the developers. |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus | Continuous contact with the users. |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | Continuous contact with the users. |
| hippocampus CA1 microcircuit model | Continuous contact with the users. |

#### 3.9.4.2 SP6-T6.2.5-SGA1-Models of basal ganglia nuclei

Description of Component: Models of different types of interneurons and projection neurons in striatum are being built based on detailed morphology and membrane properties, distributed in geometrically defined populations. The model neurons will be synaptically connected via GABAergic synapses in the striatal microcircuit as shown experimentally. Scaffold versions of other basal ganglia nuclei will be simulated.

CDP to which Component contributes: CDP2 - Mouse-Based Cellular Cortical and Subcortical Microcircuit Models (T6.2.5 will develop a model of rodent striatum, which will contribute to CDP2 Product 4: Cellular Level Basal Ganglia Model – Generalization Strategies).

Progress on Component: The two types of projection neurons expressing dopamine receptors of the D1 and D2 type respectively have been simulated based on detailed morphology and electrophysiological data regarding membrane properties, and similarly the other main type of interneuron the FS (fastspiking) interneurons. These cells interact through GABAergic synapses. The synaptic properties of the interacting cells have also been simulated, as well as the cortical input synapses with AMPA and voltage-dependent NMDA synapses. The population of cells in striatum is randomly distributed within a specified volume, in which each cell is isolated but with a dendritic arbor, and synapses are formed with axon collaterals according to known connectivity patterns. Information regarding cellular properties in other basal nuclei is being analysed.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.2.5-SGA1-Models of basal ganglia nuclei | |
|---|---|
| **Upstream Component** | **Status** |
| NEURON | High-quality software products for single-cell analysis, modelling, simulation and validation were provided by upstream components. The open-source code and algorithm implementation support were available via HBP Collabs and GitHub. |
| BluePyOpt | |
| single cell electrical model validation | |
| single morphology validation | |
| Coreneuron | |

| | |
|---|---|
| Connectivity and morphology of neurons within striatum | Detailed experimental data on morphology and electrophysiology of striatal neurons was provided. Missing morphological reconstructions were supplemented by publicly available data after expert curation. Over 300 reconstructions of MSN cells, 70 FS cells and five cholinergic neurons were selected. |
| Cellular properties of neurons within striatum | |
| | |
| **Downstream Component** | **Status** |
| T3.5.5 (1) Mammalbot layered control architecture | Single-cell models, with properties, of the striatal neurons are available via HBP Collabs. Preliminary results of population dynamics usable for simplification and robot control have been reported. |
| SP3-Shrewbot++ robot platform | |
| SP6-T6.2.7-SGA1-Simplified brain models | |
| Motor control model | |

## 3.10 T6.2.6 Models of Whole Mouse Brain

### *3.10.1 Key Personnel*

Task Leader: Marc-Oliver GEWALTIG (EPFL)

Other Researcher: Csaba EROE (EPFL)

Other Researcher: Till SCHUMANN (EPFL)

### *3.10.2 SGA1 DoA Goals*

Develop data-driven scaffold models of the whole mouse brain, building on and successively integrating microcircuit and brain region models developed in T6.2.2-T6.2.5 and employing analysis of multimodal brain-scale anatomical datasets, and synthesis and transformation algorithms to complete a first-draft model of the whole mouse brain at a cellular-level of detail.

Simplified versions of these models (see T6.2.7 and SP4) will be used as brain models in the Neurorobotics Platform (SP10), enabling *in silico* experiments for behavioural, cognitive, and clinical research to be developed in collaboration with SP1, SP3, SP8, and SP10. Simplified mouse brain models will also be implemented in the Neuromorphic Computing Systems implemented in SP9.

The whole brain model developed in T6.2.6 will form the basis for the *in silico* experiments, planned in CDP1.

### *3.10.3 Task Achievement Summary*

In the reporting period, we performed an extensive literature study to obtain experimental reference values for densities and numbers of cells, glia, and neuron types in anatomically defined regions of the mouse brain. This study revealed that reliable data are available only for a small number of regions. Moreover, we have improved the classification of cells into glia, excitatory and inhibitory neurons, by adding additional gene expression datasets from the Allen Mouse Brain Atlas into our model. We analysed and manually re-aligned two more markers for glia cells (ALDH1L1 and TMEM119) and one marker for excitatory cells (Nrn1). A manuscript is in preparation.

A reduced-size version of the mouse brain model has been delivered to SP10-WP10.1 for use in the mouse rehabilitation experiment, as well as to SP9 for use on the SpiNNaker neuromorphic hardware.

With respect to simulating the mouse brain model at a full 74 million neuron scale, we have developed to generate and store a full-scale point neuron level mouse brain model on a distributed computer network. Different generation strategies and data storage layouts were tested to achieve the best performance.

### *3.10.4 Component Progress*

#### 3.10.4.1 Point-neuron model of the whole mouse brain

Description of Component: Point-neuron model of the whole mouse brain, based on staining and other imaging data.

CDP to which Component contributes: CDP1

Progress on Component: In the reporting period software and data formats were developed to generate and store a full-scale point neuron level mouse brain model on a distributed computer network. Different generation strategies and data storage layouts were tested to achieve the best performance.

Preliminary results of this work were presented at the First JARA Symposium, December 2016 in Julich.

The whole-brain model was improved by refining the cell-type identification by using additional gene expression data sets.

Reduced-size version of the mouse brain model has been delivered to SP10-WP10.1 for use in the mouse rehabilitation experiment.

Reduced version of the mouse brain model has also been delivered to SP9 (UMAN) for tests with SpiNNaker.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **6.2.6 Point-neuron model of the whole mouse brain** | |
|---|---|
| **Upstream Component** | **Status** |
| Fitting Generalized Integrate-and-FIre models | Ready for certain cell types. |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | Only exists in detailed version. |
| NEST - The Neural Simulation Tool | Main simulator used for point-neurons simulations. |
| SP6-T6.2.7-SGA1-Simplified brain models | No update |
| SP6-T6.3.5-SGA1-Prototype NEST simulation kernel with directed spike exchange | No update |
| Maps of neuronal activation of whole mouse brain | Simulation available, data still being analysed. |
| Whole-brain maps of selected neuronal types | Generated, and available via HBP Collab |
| Simplified EEG models | No EEG data has been provided |
| | |
| **Downstream Component** | **Status** |
| T3.3.3 Optogenetic manipulation of episodic encoding and retrieval in hippocampal, parahippocampal and mesencephalic dopamine cells | Data has not been provided yet. |
| T3.3.3 Decoded spike patterns of neural ensembles in cortex and | No release |

| | |
|---|---|
| hippocampus during multimodal scene representation | |
| T3.3.3 Multi-area recordings from visual and somatosensory cortices, perirhinal and entorhinal cortex and hippocampal CA1 | No release |
| Allen Mouse Atlas (AMA) based brain network | Network available via HBP Collab. Simulations and analysis of results are still in the works. |

## 3.11 T6.2.7 Simplification

### *3.11.1 Key Personnel*

Task Leader: Marc-Oliver GEWALTIG (EPFL)

Other Researcher: Christian RÖSSERT (EPFL)

Other Researcher: Eilif MULLER (EPFL)

Other Researcher: Willem WYBO (EPFL)

### *3.11.2 SGA1 DoA Goals*

Task 6.2.7 will develop automated approaches to simplify detailed brain models developed in T6.2.1-T6.2.5 to point neuron representations which are compatible with the NEST simulator and with the neuromorphic computing systems developed in SP9.

The fidelity of simplified models will be assessed using the same suite of validations developed for Quality Assurance during the development of high-fidelity reference models. The validation suite will be executed using the validation framework developed in WP6.4.

The long-term goal for future SGAs is to integrate simplified models into higher-level models (e.g. integration of phenomenological representations of sub-cellular models into models of single neurons).

### *3.11.3 Task Achievement Summary*

In the reporting period, we improved the neuron simplification pipeline in several ways. The simplification pipeline, presented for the end of the RUP has been further refined as follows. Dendritic filters used to correct for displacement of synapses to the soma can now be directly extracted from a few recordings. To enable a NEST implementation, and dramatically reduce runtimes of the simplified networks, a clustering approach has been developed to define groups of synaptic populations which can be linearly superposed. The manuscript describing the semi-automatic simplification workflow has been updated accordingly and is available at: https://arxiv.org/abs/1604.00087

### *3.11.4 Component Progress*

#### 3.11.4.1 SP6-T6.2.7-SGA1-Simplified brain models

Description of Component: Will use theoretical insights from SP4 to simplify detailed brain models developed in T6.2.1-T6.2.5 to point-neuron representations which are compatible with the NEST simulator and with the neuromorphic computing systems developed in SP9.

CDP to which Component contributes: CDP1

Progress on Component: The manuscript describing the semi-automatic simplification workflow has been updated accordingly and is available at: https://arxiv.org/abs/1604.00087

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.2.7-SGA1-Simplified brain models | |
|---|---|
| **Upstream Component** | **Status** |
| Multi compartmental reconstructed cortical cells: their input-output transfer properties | Ready for certain cell types. |
| NEST Support for Modellers | No update |
| NEST - The Neural Simulation Tool | |
| SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations | No update |
| SP6-T6.3.6-SGA1-Tool for LFP recording in NEST simulations | No update |
| SP6-T6.2.5-SGA1-Models of basal ganglia nuclei | No update |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons | No update |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons | No update |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus | No update |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | No update |
| Cerebellum scaffold models | No update |
| SP6-T6.2.2-SGA1-Initial model validation tests implemented to compare rat model with mouse data | No update |
| SP6-T6.2.1-SGA1-models of nonlinear human neurons | No update |
| SP6-T6.2.1-SGA1-Models of human dendritic spines | No update |
| SP6-T6.2.1-SGA1-Modelling synaptic inputs to human dendritic spines | No update |
| SP6-T6.2.1-SGA1-Detailed passive models of human neurons | No update |
| | |
| **Downstream Component** | **Status** |
| T3.5.5 (1) Mammalbot layered control architecture | No release |
| Point-neuron model of the whole mouse brain | No release |
| Model simplification service (neuromorphic) | No release |
| SP6-T6.4.3-SGA1-Model representations for synaptic plasticity | No release |
| SP6-T6.4.3-SGA1-Model representations for cellular and network models | No release |
| SP6-T6.3.5-SGA1-Prototype NEST simulation kernel with directed spike exchange | No release |

| | |
|---|---|
| NEURON | No release |

# 4. WP6.3 Reconstruction and Simulation Tools

## 4.1 Key Personnel

Work Package Leader: Felix SCHÜRMANN (EPFL)

## 4.2 WP Leader's Overview

The goal of Work Package 6.3 is to build a suite of tools and workflows for data-driven reconstruction and simulation of brain models at different levels of biological organisation, exploiting programmatic access to data made available through the Neuroinformatics Platform (SP5). The foundation to this Work Package comes from work performed by SP6 in the RUP, as well as partners' background brought into the HBP as well as community tools such as STEPS, NEURON and NEST. These tools provide the foundation for the online platform developed in WP6.4.

The development paths for the individual tools are guided by the input from the science drivers in WP6.1 and WP6.2 as well as the work coordinated by CDP1 and CDP2, and from feedback from WP6.4. As some of those tasks connect to wider communities as well as from the feedback of WP6.4, also input from the community is being incorporated into the development plans. Furthermore, a very tight collaboration has been established with all partners in WP6.3 in order to deliver this functionality through the online platform and to improve the user experience for the average user as recommended by the review of the end of the ramp-up phase.

Even though some partners have been affected by the late start of SGA1, the Work Package has achieved all its Milestones and work is overall progressing well. The outcomes of this Work Package contribute directly to the success of the modelling work done in the HBP at the molecular, subcellular, cellular and network level.

Progress by Task:

T6.3.1 Tools for molecular dynamics-based simulations – Based on the work of the RUP, the first part of SGA1 worked towards a first draft release of tools for molecular dynamics based simulations. Several partners have worked on this and achieved Milestone MS6.3.1. For example, partner HITS has released a new feature of their tool SDA to represent crowding molecules with an adaptive resolution.

T6.3.2 Tools for Reaction-Diffusion Simulations – The collaboration between Partner EPFL and affiliated Partner OIST on the STEPS simulator is progressing well. The main goal is a scalable parallel implementation of the reaction-diffusion simulator making subcellular simulations at scale feasible. After having addressed the fundamental mathematics of parallelising the Gillespie algorithm during the RUP, in this reporting phase the algorithm has been implemented and shown to scale to about 2000 processors. Similarly, the scalability of the eField solver has been addressed and shown to scale to 4000 processors. Milestone MS6.3.2 has been achieved.

T6.3.3 Tools for cellular reconstruction – Tightly coupled with the science driver of WP6.2 as well as co-design project CDP2, this Task matures and enriches the model building toolchain developed during the RUP. In particular, work in this reporting phase has been invested into the single cell model building toolchain including morphology analysis, morphology repair, feature extraction and model optimisation. A particular need from the Hippocampus community modelling task has been addressed, namely generalising and maturing the management of electrical cell models at scale.

T6.3.4 Tools for Cellular-Level Simulations – Work on this Task builds on the success of coreNeuron, which was a major outcome of the RUP and which a simulator engine for extreme scale parallelism with a factor 7 memory reduction. During the first part of SGA1 the Task focused on maturing the interface between NEURON and coreNeuron. As a result,

a well-defined interface facilitating model exchange between the community simulator NEURON and coreNeuron has been implemented. This first interface is file-based and Milestone MS6.3.4 has been reached.

T6.3.5 Tools for Network Simulation – During the RUP the network simulator (NEST) has been proven to scale to extreme levels of parallelism, and the range of models it can solve had been widened. During the first phase of SGA1 this task explored how the simulator can embrace highly parallel threading. The results are presented in a report and the corresponding milestone MS6.3.5 has been achieved.

T6.3.6 Whole brain level *in silico* instrumentation, services and apps (point neuron models) – Due to the delayed signing of the SGA1, the partners involved in this Task only could start their work with a delay. Nevertheless, the milestone MS6.3.7 on an early prototype for configuring stimulation and recording in NEST has been achieved. However, the work on LFP recording in NEST had to be postponed and is planned to be pursued at full pace during the second period.

## 4.3 Priorities for the remainder of the phase

For the remainder of SGA2, the Work Package will continue on maturing the tools as well as implementing features as required by the users towards the goal of a whole rodent brain. Particular focus will be on the milestones and deliverables in support of CDP1 and CDP2 supporting network-level models and cellular-level models respectively and their ease of use/ease of adoption by external users. Furthermore, in tight collaboration with the respective simulator and user communities, longer-term technology work on the simulator engines will be pursued in order to ensure scalability for HBP use cases in subsequent phases as well as readiness for future architectures as provided by SP7.

## 4.4 Milestones

**Table 3: Milestones for WP6.3 - Reconstruction and Simulation Tools**

| MS No. | Milestone Name | Leader | Task(s) involved | Expected Month | Achieved Month | Comments |
|---|---|---|---|---|---|---|
| MS6.3.1 | First draft release of tools | JUELICH | T6.3.1 | MAR 2017 | MAR 2017 | The Brownian dynamics simulation software SDA uses all-atom molecular structures to simulate the diffusional motion of biomolecules. This method has been extended to allow these all-atom molecules to interact with crowding molecules represented with an adaptive-resolution simulation model. In this scheme, the interactions between the molecules of interest, and between these molecules and crowder molecules, are represented with the all-atom model, while crowder-crowder interactions use a simple spherical model. This allows for a reduction of computational cost while retaining the higher-level representation in the important regions of the simulation. This newly-released feature is the first step towards a model for predicting association rate constants under crowded cellular conditions, to investigate what effect molecular crowding has on the association rate constants that have been calculated in T6.1.1. The updated code is available to HBP researchers via from HITS' git server, and is recorded in the HBP software catalogue (https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,SDA ) with instruction for accessing and installing the code. The software has been successfully downloaded, installed and used by Master's students in both the Physics and Molecular Biotechnology departments at Heidelberg University. |
| MS6.3.2 | Simulator capable of handling entire dendrite of a principal neuron | EPFL | T6.3.2 | MAR 2017 | MAR 2017 | STEPS eField can now execute up to 4096 cores which allows supporting an entire dendrite of a neuron. The code is released under STEPS 3.0 and 3.1. A paper has been published on the parallelisation of the reaction-diffusion solver (Chen W, De Schutter E (2017). Parallel STEPS: Large Scale Stochastic Spatial Reaction-Diffusion Simulation with High Performance Computers. Front. Neuroinform. 11:13. doi: 10.3389/fninf.2017.00013. (Parallelisation) Article, Simulation Scripts). An internal report is describing the parallelisation of the eField solver. Means of verification: 1) Software test checked in to simulator's repository: http://steps.sourceforge.net/STEPS/download.php (STEPS 3.0 and 3.1) 2) Internal report available at: https://flagship.kip.uni-heidelberg.de/jss/FileExchange?hbpUsID=166 |

| | | | | | | |
|---|---|---|---|---|---|---|
| MS6.3.3 | Internal release of prototype and open-source release of mature cellular tools | EPFL | T6.3.3 | SEP 2017 | | |
| MS6.3.4 | Well-defined interface between NEURON and coreNeuron implemented | EPFL | T6.3.4 | MAR 2017 | MAR 2017 | NEURON and CoreNeuron are now interfaced through files. The interface is the file data layout which is checked in the github repository. Means of verification: Tutorial: https://github.com/nrnhines/ringtest Code download: https://github.com/BlueBrain/CoreNeuron, 07179b9e67b39140390fc4287151b8c2b187a7db Interface documentation: https://github.com/BlueBrain/CoreNeuron/blob/master/doc/README.md |
| MS6.3.5 | Report on design of a simulator architecture for highly parallel threading | JUELICH | T6.3.5 | MAR 2017 | MAR 2017 | Report on design of a simulator architecture for highly parallel threading; internal report available at: https://flagship.kip.uni-heidelberg.de/jss/FileExchange?hbpUsID=166 |
| MS6.3.6 | Early prototype implementation of tool supporting stimulation and recording (spikes, voltages) | NMBU | T6.3.6 | MAR 2017 | MAR 2017 | Early prototype implementation of tool achieved to solicit user feedback to guide further development. Tool "NEST Connection App" registered in HBP Software catalog. Software available from https://github.com/compneuronmbu/NESTConnectionApp/releases, tag v0.1; requires NEST simulator version tagged "External/TopologySelectNodes" or later for full functionality. Successfully tested by project scientist as JUELICH, T4.2.1. |
| MS6.3.7 | Readiness evaluation of all components | EPFL | T6.3.1, T6.3.2, T6.3.3, T6.3.4, | NOV 2017 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | for release in Brain Simulation Platform under D6.5.2 | | T6.3.5, T6.3.6 | | | |

Note: The numbering of the Milestones follows that of the SGA1 Amendment 1

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## 4.5 T6.3.1 Tools for molecular dynamics-based simulations

### *4.5.1 Key Personnel*

Task Leader: Paolo CARLONI (JUELICH)

Other Researcher: Richard LAVERY (CNRS)

Other Researcher: Rebecca WADE (HITS)

Other Researcher: Ursula RÖTHLISBERGER (EPFL)

Other Researcher: Modesto OROZCO (IRB/JUELICH)

### *4.5.2 SGA1 DoA Goals*

Task 6.3.1 will develop web-based multi-scale molecular modelling and simulation tools for estimating kinetic and thermodynamic parameters for molecular interactions and enzymatic activity, and for understanding molecular events in neuronal cascades. The tools, which will be developed in a co-design process with the molecular modelling team in T6.1.1, will cover scales ranging from the quantum mechanical level to coarse-grained modelling. Support will be provided for bioinformatics-based high-throughput structural predictions to assess similarities between protein variants and isoforms.

T6.3.1 relies on model-development activities in WP6.1 to drive the model-development process, and to validate tools, and will collaborate closely with SP7 to optimise use of HPC resources.

T6.3.1 is essential for the development of molecular-level models, and thus, indirectly for subcellular, and single neuron models that incorporate such models.

### *4.5.3 Task Achievement Summary*

The molecular simulation tools being used in T6.1.1 are being further developed to allow for more accurate predictions, including modifications that allow the highly crowded cellular environment to be better represented.

Calculating association rate constants of interacting biomolecules via Brownian dynamics simulations is a well-established technique, however it requires that many reactive trajectories are sampled to provide reliable statistics. In dilute conditions, this is easily tractable, however modelling molecular crowding in simulations results in significantly increased computational requirements. To account for this, we have developed a new solute model in which the associating biomolecules, and crowding molecules with which they interact, are represented in atomic resolution detail, while other crowding molecules are treated using a lower resolution spherical model. Preliminary testing of this model in T6.1.1 suggests that it is able to reproduce the concentration-dependent diffusional behaviour of higher resolution protein models, while using less than 10% of the computational resources. This approach is currently being developed into a workflow for estimating rate constants under crowding conditions.

Two novel tools have been developed for predicting the structure and stability of protein-protein interactions. The first uses molecular docking with a small set of arbitrary proteins to predict the most likely binding sites on the surface of a target protein. The second uses data from molecular dynamics simulations to estimate binding stability. A faster version of the latter tool, under development, should enable estimates of binding strength to be obtained within hours, providing crucial data for the construction of reliable models of neuronal signalling cascades.

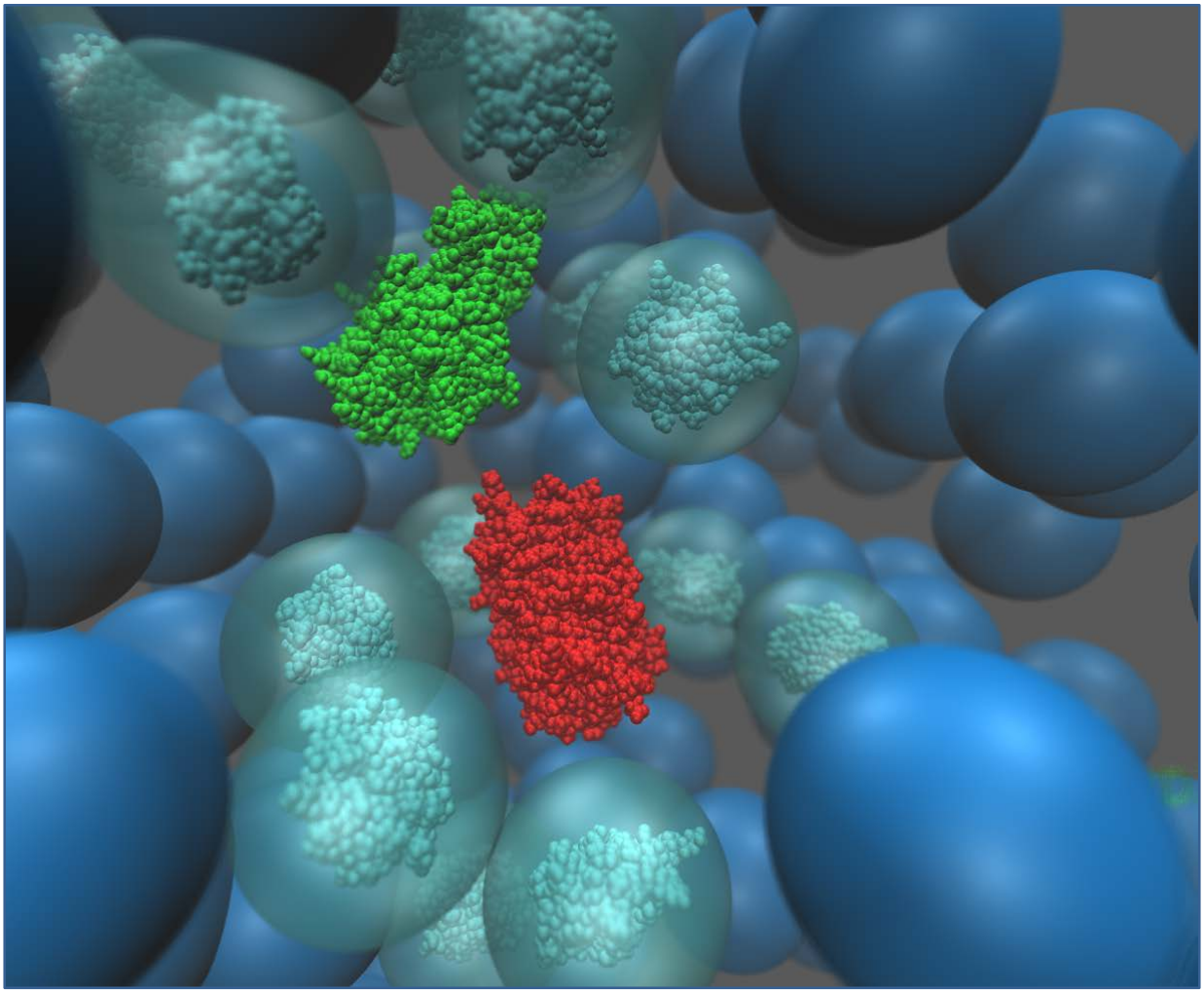

**Figure 10: Diagram of the adaptive resolution Brownian dynamics solute model developed in SDA.**

**The diffusional association of two proteins (red and green) is simulated in a background of crowding proteins (blue). All interactions between the associating proteins, and between these proteins and crowding proteins, are modelled in atomic detail, while interactions between crowding proteins are modelled using a coarse-grained spherical representation.**

### *4.5.4 Component Progress*

#### 4.5.4.1 SP6-T6.3.1-SGA1-Tools for Brownian dynamics simulations

Description of Component: Development of SDA software, and associated tools, for Brownian dynamics simulation

Progress on Component: (**HITS**) The Brownian dynamics simulation software SDA uses all-atom molecular structures to simulate the diffusional motion of biomolecules. This method has been extended to allow these all-atom molecules to interact with crowding molecules represented with an adaptive-resolution simulation model. In this scheme, the interactions between the molecules of interest, and between these molecules and crowder molecules, are represented with the all-atom model, while crowder-crowder interactions use a simple spherical model. This allows for a reduction of computational cost while retaining the higher-level representation in the important regions of the simulation. This newly-released feature is the first step towards a model for predicting association rate constants under crowded cellular conditions, to investigate what effect molecular crowding has on the association rate constants that have been calculated in T6.1.1.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.3.1-SGA1-Tools for Brownian dynamics simulations | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.1-SGA1-Brownian dynamics simulations | Updated software containing coarse-grained and adaptive-resolution solute models delivered for validation. |

#### 4.5.4.2 SP6-T6.3.1-SGA1-Python scripts for MD analysis

Description of Component: Development of Python scripts to analysis different properties along MD trajectories.

Progress on Component: The scripts allow to compute different quantities along the MD trajectories: for example, the accessible surface area, the protein volume, the gap index, distances, internal variables. These scripts are also used to compute the binding energy between a pair of proteins from MD simulations (CNRS).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.3.1-SGA1-Python scripts for MD analysis | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics | We have received the trajectory of protein AC and complex AC:Gai. (complete). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | We are providing the scripts to analyse the MD trajectory of protein AC and complex AC:Gai (partial release). |

#### 4.5.4.3 SP6-T6.3.1-SGA1-Internal Normal Mode Calculator

Description of Component: Internal Normal Mode Analysis on protein and protein complexes

Progress on Component: (**CNRS**) The Internal Normal Mode Analysis, iNMA, improves the treatment of protein flexibility. The method involves the calculation of the normal modes that represent the intrinsic vibrational characteristics of a macromolecule using internal coordinates (i.e. bond angles and bond torsions), enabling the accurate representation of large conformational movements without expensive computations. INMA calculator can be also used to predict the vibrational entropy and enthalpy of a protein or a complex.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.3.1-SGA1-Internal Normal Mode Calculator | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.1.1-SGA1-All Atom Molecular Dynamics (model) | We have received the trajectory of protein AC and complex AC:Gai. (complete). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | We have provided the flexibility and the conformation change of protein AC. We provided the conformational entropy of the protein AC (complete). |

#### 4.5.4.4 SP6-T6.3.1-SGA1-Coarse-grain solvent model

Description of Component: Corse-grain solvent model

Progress on Component: (**CNRS**) The solvation energy has a significant contribution to affinities. The tool allows computing the solvation energy using implicit solvent model for a given protein.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.3.1-SGA1-Coarse-grain solvent model** | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.3.1-SGA1-PaLaCe coarse-grain protein model | We will provide the protein-solvent interaction of protein Gai or complex AC:Gai (not released). |

#### 4.5.4.5 SP6-T6.3.1-SGA1-PaLaCe coarse-grain protein model

Description of Component: PaLaCe is a protein coarse-grain model with an implicit representation of the solvent

Progress on Component: (**CNRS**) We are now working on replacing the all-atom representation with a coarse-grain model (PaLaCe II) and the molecular dynamics trajectory with either stochastic dynamics or Monte Carlo sampling, using experimental or homology derived protein structures and profiting from the interface prediction "arbitrary docking server" described in our report on M 6.3.1 (First draft release of tools). The tool will allow to compute the binding energy between a pair of protein and it will be coupled to our existing web server.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.3.1-SGA1-PaLaCe coarse-grain protein model** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Coarse-grain solvent model | We will receive the new coarse-grain solvent model of proteins AC and Gai (not released). |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations | We will provide the result of the docking experiment for the protein Gai and AC or/and the stochastic dynamic of protein Gai and AC. (not released). |

#### 4.5.4.6 SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations

Description of Component: Web-based multi-scale molecular modelling and simulation tools for estimating kinetic and thermodynamic parameters for molecular interactions and enzymatic activity, and for understanding molecular events in neuronal cascades. The tools will cover scales ranging from the quantum mechanical level to coarse-grained modelling. Support will be provided for bioinformatics-based high-throughput structural predictions to assess similarities between protein variants and isoforms.

Progress on Component: See Task Achievement Summary.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.3.1-SGA1-Tools for Molecular Dynamics-based simulations** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.3.1-SGA1-Python scripts for MD analysis | We are receiving the scripts to analyse the MD trajectory of protein AC and complex AC:Gai (partial release). |

| | |
|---|---|
| SP6-T6.3.1-SGA1-Internal Normal Mode Calculator | We have received the flexibility and the conformation change of protein AC. We provided the conformational entropy of the protein AC (complete). |
| SP6-T6.3.1-SGA1-PaLaCe coarse-grain protein model | We will receive the result of the docking experiment for the protein Gai and AC or/and the stochastic dynamic of protein Gai and AC. (not released). |
| HPC systems at JSC | We have received supercomputing time (complete). |
| HPC systems at BSC | We have received supercomputing time (complete). |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | We have provided monthly progress updates to the SP6 group. |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis | We have provided monthly progress updates to the SP6 group. |
| Position paper on the workflows and strategies for intracellular and synaptic modelling | We have provided monthly progress updates to the SP6 group. |
| SP6-T6.1.1-SGA1-Ligand design for brain imaging | We have provided monthly progress updates to the SP6 group. |
| SP6-T6.1.1-SGA1-QM/MM simulations for prediction of reaction kinetics | We have provided monthly progress updates to the SP6 group. |
| SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters | We are progressing with our highly scalable QM/MM, in a collaboration lead by Prof. Ursula ROETHLISBERGER. |

## 4.6 T6.3.2 Tools for Reaction-Diffusion Simulations

### *4.6.1 Key Personnel*

Task Leader: Fabien DELALONDRE (EPFL)

Other Researcher: Aleksandr OVCHARENKO (EPFL)

### *4.6.2 SGA1 DoA Goals*

Task 6.3.2 will develop methods and implementations for the scalable execution of parallel reaction-diffusion simulations of biochemical processes and voltage-gated processes in brain cells, using up to a thousand processors. The implementation, which relies on the scalable parallel spatial Gillespie, will extend the current version of the STEPS simulator (which incorporates HBP contributions from the RUP) to support the modelling of reaction diffusion in populations of molecules. Work in this Task will contribute to modelling efforts in Tasks 6.1.2-4. The new parallel implementation will be tested first on neuron compartments and subsequently on an entire neuron.

### *4.6.3 Task Achievement Summary*

During this period the Task was able to achieve its main goal, which was to simulate reaction-diffusion of biochemical processes on up to a thousand processors. A new splitting of the Gillepsie algorithm allows scaling the resolution of reaction-diffusion with linear scaling up to 1,500 cores. In addition, we were able to generate water tight 3D meshes of the entire dendritic tree of a Purkinje cell as shown in the figure below. All of those improvements are either already released in STEPS 3.0 or will soon be released in the upcoming 3.1 release, planned for September 2017. The next steps will focus on demonstrating the possibility to solve a reaction-diffusion.

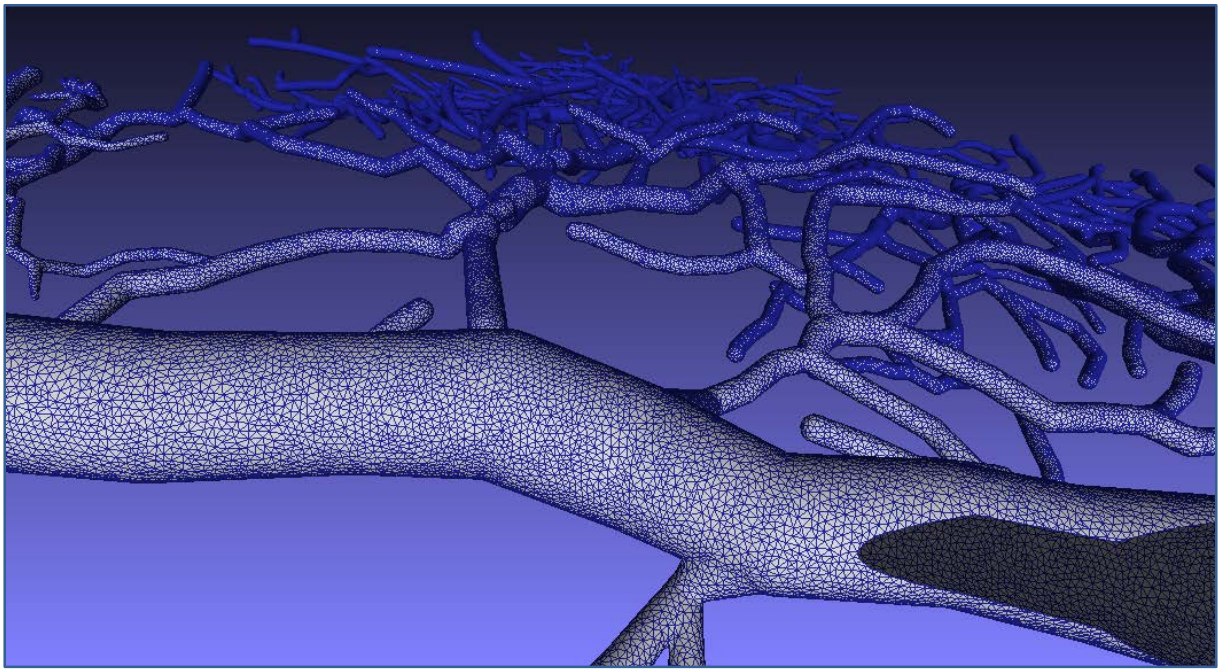

**Figure 11: 3D watertight mesh of Purkinje Cell dendritic tree.**

### *4.6.4 Component Progress*

#### 4.6.4.1 STEPS

Description of Component: STochastic Engine for Pathway Simulation developed by OIST University in collaboration with the Blue Brain Project. STEPS public website can be found here: http://steps.sourceforge.net/STEPS. A public release of a new version is in progress and will be released on the HBP HPC platform, accessible through the Collaboratory.

Progress on Component: EPFL developments focused on two main items. A new meshing library based on the Cgal open-source library has been developed. It allows building watertight 3D mesh models of the full Purkinje cell using less than a million vertices. On the simulator side, the PETSc library has been fully integrated to the STEPS simulator. This allows scaling up the eField solver to support meshes that include up to 2 million vertices (8 million elements) on 4k Blue Gene/Q processors which is twice the size of the full Purkinje cell model. Finally, new releases of STEPS (3.0 and 3.1) that includes both parallel reaction-diffusion and eField are available on the STEPS website: http://steps.sourceforge.net/STEPS/download.php

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **STEPS** | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.1.4-SGA1- Integration of Subcellular Models in Single Neuron Models [essential] | Tool has been available for users |
| SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis [essential] | |

| | |
|---|---|
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades [essential] | |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [essential] | |
| SP6-T6.1.2-SGA1-Data-Driven Modelling of G Protein-Coupled Receptor-Dependent Cascades [important] | |

## 4.7 T6.3.3 Tools for Cellular Reconstruction

### *4.7.1 Key Personnel*

Task Leader: Jean-Denis COURCOL (EPFL)

### *4.7.2 SGA1 DoA Goals*

Task 6.3.3 will provide tools for cellular-level reconstruction in WP6.2 and in CDP2. The work to be carried out includes development of tools for the analysis and validation of neuron morphologies, a validation framework and an experiment builder. These tools, together with work to further mature the "optimiser framework" (the multi-constraint optimisation framework used to fit electrical neuron models to their observed behaviour) will be released as open-source Software.

Tools will be developed in a co-design process with Tasks developing scaffold models in WP6.2.

The tools developed in T6.3.3 will build on tools developed in the RUP and also will make use of APIs provided by SP5. SP6 will collaborate with SP5 and other consumers of Neuroinformatics data in the co-design of these interfaces.

T6.3.3 is essential for the development of cellular level models, and thus, indirectly for all SPs and community users, using such models (SP1-4, SP8-10), as well as for CDP2.

### *4.7.3 Task Achievement Summary*

NeuroM, an open-source tool for morphology analysis has been extended with a set of analysis available for the community such as z-jump check, sholl analysis, section tortuosity analysis. This tool is also easily accessible through the Collaboratory as a Brain Simulation Platform use case, where the end user can select this use case, the model to be analysed and have a Jupyter notebook with a predefined set of analysis in the user's own collab:

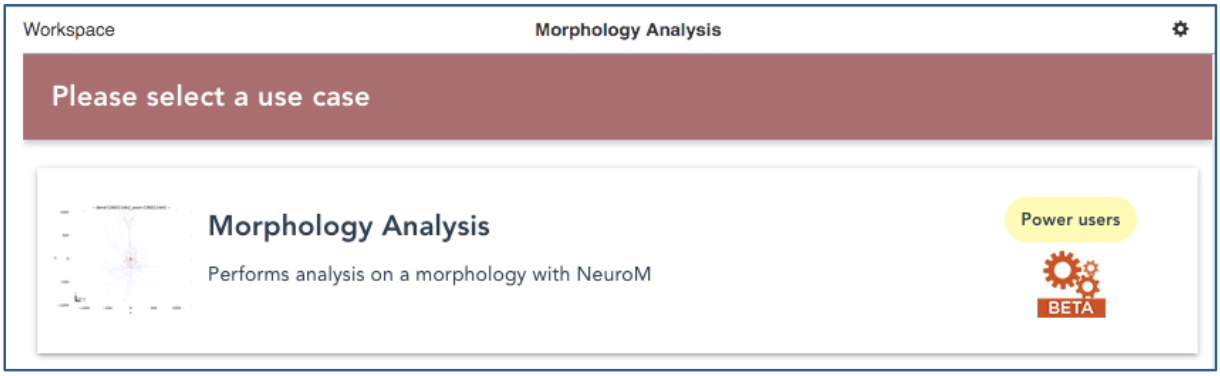


**Figure 12: Selection of the use case.**

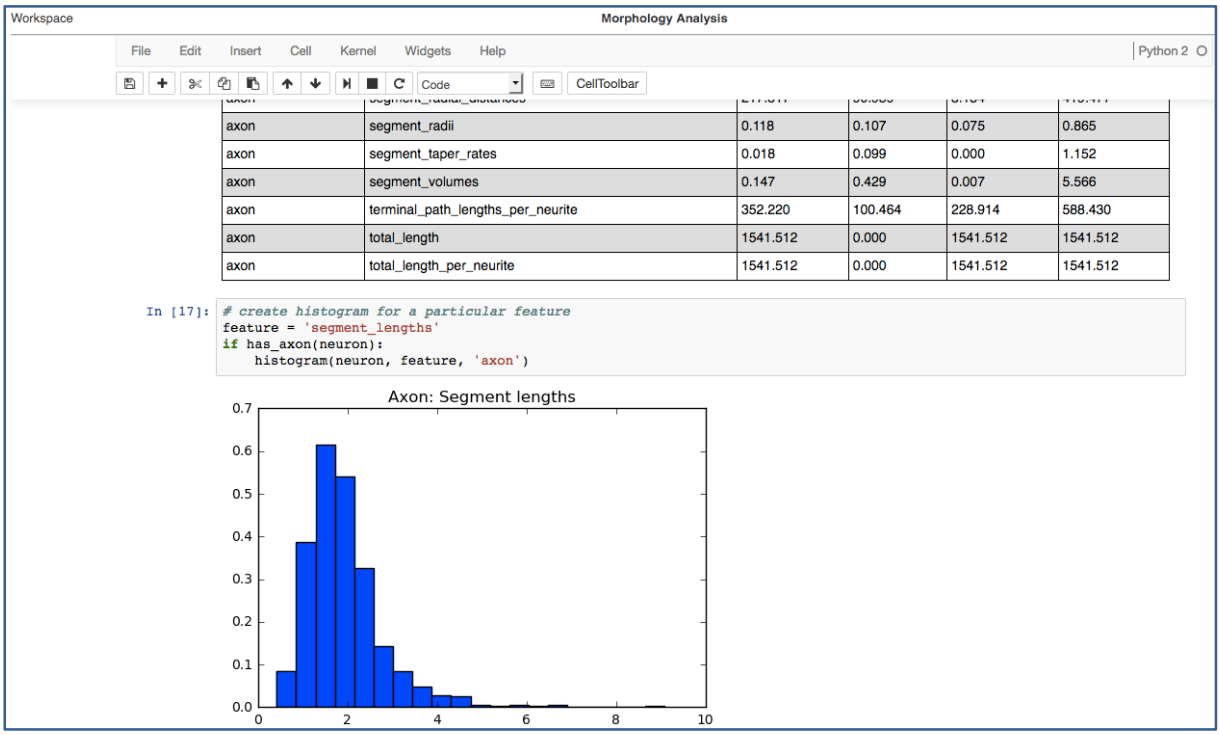


**Figure 13: A Jupyter notebook automatically created with a set of NeuroM analysis.**

BluePyOpt, a open-source tool for electrical model parameter optimisation has been improved to support point processes. It has been engineering to ensure compatibility with BluepyMM, a new tool being developed to generalise electrical cell model and validate the generalisation. Efforts have been made so that generalisation can be applied on various brain regions.

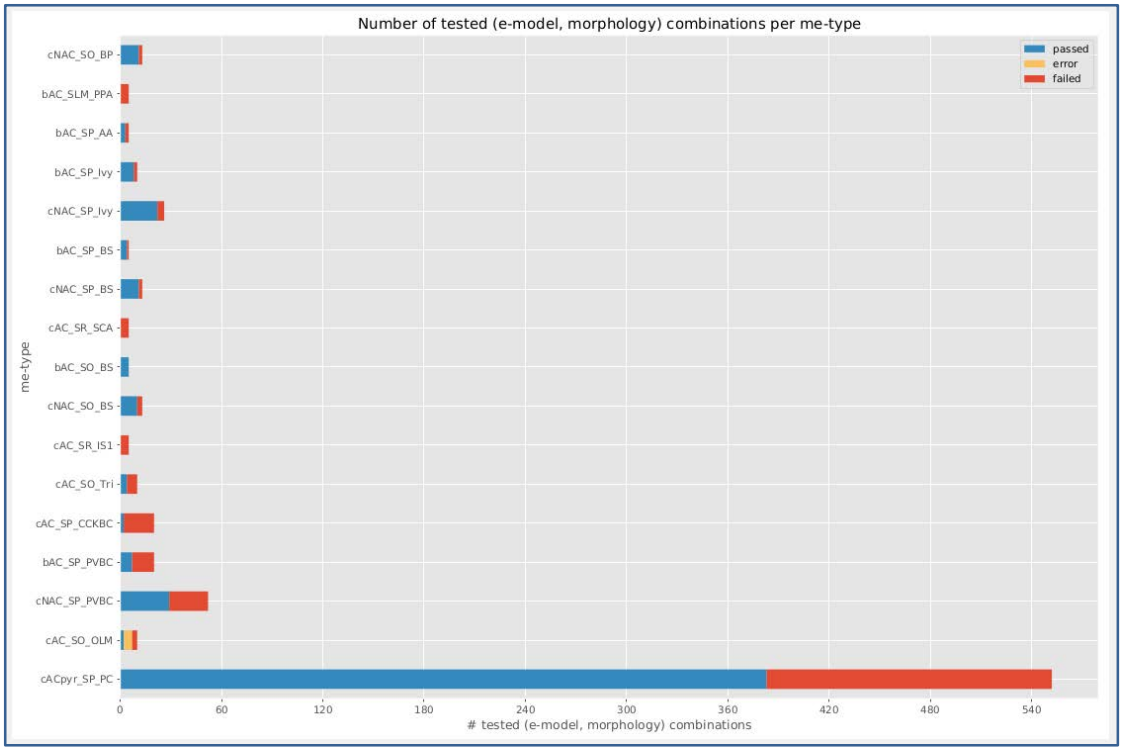


**Figure 14: A validation of the generalisation of electrical models on the hippocampus CA1.**

The Morphology Repair toolchain improvements have been focused around the flexibility of the pipeline and apical point detection.

### *4.7.4 Component Progress*

#### 4.7.4.1 NeuroM

Description of Component: A python package library for neuron morphology analysis.

CDP to which Component contributes: CDP2

Progress on Component:

Release of V1.0.0, v1.1.1, v1.2.0, v1.2.1, v1.3.0, v1.4.0

- New feature: Z-jump check implemented
- New feature: Zero radius dection
- New feature: Get number of terminations
- New feature: Section tortuosity
- New feature: configurable statistics tool
- New feature: get number of multifurcation
- New feature: get meander angle
- New feature: support for python 3+
- New feature: neuronal density
- New feature: support for sholl analysis
- Improvement: plotting speed improved
- Improvement: SWC soma support

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| NeuroM | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| single morphology validation [essential] | Delivered internally |
| Morphology Synthesizer [essential] | Delivered internally |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus [important] | Delivered internally |
| Morphology repair and diversification framework [added value] | Delivered internally |

#### 4.7.4.2 eFEL

Description of Component: The Electrophys Feature Extraction Library (eFEL) allows neuroscientists to automatically extract features from time series data recorded from neurons (both in vitro and *in silico*). Examples are the action potential width and amplitude in voltage traces recorded during whole-cell patch clamp experiments. The user of the library provides a set of traces and selects the features to be calculated. The library will then extract the requested features and return the values to the user.

CDP to which Component contributes: CDP2

Progress on Component: Release of v2.11

- New feature: option to compute all eFeatures only during stimulus interval
- New feature: support for Windows

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| eFEL | |
|---|---|
| **Upstream Component** | **Status** |
| Electrophysiological recordings of primary neuron types of rat hippocampal CA1 | Delivered internally |
| | |
| **Downstream Component** | **Status** |
| Single cell electrical model validation [essential] | Delivered internally |
| SP6-T6.2.1-SGA1-models of nonlinear human neurons [important] | Delivered internally |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons [important] | Ongoing collaboration |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons [essential] | Delivered internally |
| Microcircuit Modelling tools [essential] | Delivered internally |

| | |
|---|---|
| Cerebellum electrophysiological pipeline [essential] | Delivered internally |
| Cerebellum application model [essential] | Ongoing collaboration |
| Cerebellum scaffold models [essential] | Delivered internally |
| BluePyOpt [essential] | Stable and open-sourced |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models [essential] | Support effective |

#### 4.7.4.3 BluePyOpt

Description of Component: BluePyOpt is an open-source tool that can be used by neuroscientist for parameter optimisations.

CDP to which Component contributes: CDP2

Progress on Component:

- New feature: support of NEURON point processes (synapses, point neuron models)
- New feature: allow for customisation of delete axon method
- New feature: generate HOC code for models defined in BluePyOpt
- New feature: compatibility with Python 3
- Improvement: increase test code coverage to >90%
- Improvement: load morphology from HOC files

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **BluePyOpt** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [important] | Delivered internally |
| feel [essential] | Stable and open-sourced |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.1-SGA1-models of nonlinear human neurons [important] | Delivered internally |
| SP6-T6.2.5-SGA1-Models of basal ganglia nuclei [essential] | Ongoing collaboration |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons [important] | Ongoing collaboration |
| T6.4.2 Microcircuit level services [essential] | Delivered internally |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons [essential] | Delivered internally |
| Microcircuit Modelling tools [essential] | Delivered internally |
| Cerebellum scaffold models [essential] | |
| ModelManagement [essential] | Stable. To be replaced by BluePyMM |

| | |
|---|---|
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models [essential] | Delivered internally |
| SP6 Tool to fit electrical models of neurons to data [essential] | Delivered with BluePyOpt |

#### 4.7.4.4 ModelManagement

Description of Component: Model Management implements a workflow to reuse an existing etype and apply it to a series of morphologies. This etype must have been produced by the Optimizer Framework to fit it to an exemplar morphology. MM will apply it to other potentially compatible morphologies and will filter the combinations that present erroneous behaviour.

CDP to which Component contributes: CDP2

Progress on Component:

- Complete rewrite of the pipeline to make it extensible for other brain region than Somatosensory Cortex
- The pipeline relies on the same protocols definition than BluePyOpt to ensure compatibility between generalisation and optimisation pipelines
- Models that come out of the MM pipeline can now be run as standalone HOC templates
- Write code to analyse the results of MM
- Testing MM on hippocampal models

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **ModelManagement** | |
|---|---|
| **Upstream Component** | **Status** |
| Single cell electrical model validation [essential] | Delivered internally |
| Morphology repair and diversification framework [essential] | Delivered internally |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [important] | Delivered internally |
| Morphological reconstructions of mouse hippocampal neurons [added value] | Delivered internally |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons [added value] | Delivered internally |
| BluePyOpt [essential] | Stable and open-sourced |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus [essential] | Delivered internally |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus [important] | Delivered internally |
| BrainBuilder Framework [essential] | Delivered internally |

#### 4.7.4.5 Morphology Repair and diversification framework

Description of Component: A framework to enable morphology reconstruction and diversification of a population of morphologies.

CDP to which Component contributes: CDP2

Progress on components, including:

- New feature: support for subtyping of morphological types
- New feature: improved support for apical point detection
- New feature: expansion and exclusion capabilities
- New feature: support for parallisation
- Improvement: test pipeline with hippocampus morphologies

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Morphology repair and diversification framework** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [important] | Delivered internally |
| SP6-T6.5.1-SGA1-Brain Simulation Platform - Results for SGA1 Period 1 [important] | Delivered internally |
| NeuroM [added value] | Stable and open-sourced |
| | |
| **Downstream Component** | **Status** |
| ModelManagement [essential] | Stable. To be replaced by BluePyMM |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus [important] | Delivered internally |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus [important] | Delivered internally |
| BrainBuilder Framework [important] | Delivered internally |

## 4.8 T6.3.4 Tools for Cellular-Level Simulations

### *4.8.1 Key Personnel*

Task Leader: Fabien Delalondre (EPFL)

Other Researcher: James King (EPFL)

### *4.8.2 SGA1 DoA Goals*

Task 6.3.4 will research technologies providing better scaling and increased simulation speed for cellular-level simulation, including concepts for upcoming exascale computer systems (in collaboration with SP7). T6.3.4 will enhance the coreNEURON simulator to support memory-efficient and high-performance simulation of models developed in WP6.2. To facilitate scientific users, T6.3.4 will develop an efficient interface between NEURON and CoreNeuron simulators, offering users the flexibility to define model specifications using NEURON, and to efficiently simulate large-models using CoreNeuron. The interface will also make it possible to use CoreNeuron as a library for the NEURON simulator. The tools produced in

T6.3.4 will provide the simulation support needed for cellular-level modeling in CDP2 (products 3-6).

### *4.8.3 Task Achievement Summary*

During this period of time, the Task has achieved the full interfacing of NEURON and CoreNeuron through a binary file interface. At this point in time, CoreNeuron is not yet built as a library that can directly be addressed by the NEURON code as this software engineering task proved to be more tedious than anticipated (requiring more effort and time). However, the Task was able to deliver versions of CoreNeuron (with 7x memory reduction compared to NEURON) to the community accessible via github which can now scale up to the 48 racks of Argonne MIRA Blue Gene/Q (3.1 Million concurrent threads). Several algorithmic improvements have been made in CoreNeuron to accelerate the strong scaling of the code (multisend algorithms).

### *4.8.4 Component Progress*

#### 4.8.4.1 Neurodamus, NEURON and CoreNeuron

Description of Component: Neurodamus - High-level interface used to drive NEURON simulator. NEURON - Simulator for empirically-based simulations of neurons and networks of neurons. CoreNeuron - Optimised version of NEURON simulator used for empirically-based simulations of neurons and networks of neurons.

Progress on Component: NEURON and CoreNeuron are now fully interfaced. The model specification is done in NEURON in an embarrassingly parallel way which supports the building of arbitrary size of models. Each piece of the model is then written to persistent memory or disk. The data is then loaded in CoreNeuron using a memory efficient implementation (7x less data) and reassembles to start the efficient modelling of neural network activity. During this period, EPFL's efforts focused on modifying Neurodamus, NEURON and CoreNeuron to support application specific checkpoint/restart mechanism. Such an implementation has been successfully tested on up to 8eight racks of IBM Blue Gene/Q. As part of this effort a number of issues in the multisplit algorithm implementation have been fixed. Finally, to increase the strong scaling of CoreNeuron, the multisend functionality implemented in NEURON has been added to CoreNeuron.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Neurodamus** | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [essential] | Tool has been available for users |
| Coreneuron [important] | |
| NEURON [essential] | |

| **NEURON** | |
|---|---|
| **Upstream Component** | **Status** |
| Plasticity: STDP for a multi-compartment model with NMDA spikes (Algo STDPbackprop) [important] | Continuous contact with the developers. |

| | |
|---|---|
| SP6-T6.2.7-SGA1-Simplified brain models [important] | Continuous contact with the developers. |
| Neurodamus [essential] | Continuous contact with the developers. |
| Js Simulation Configuration [added value] | Continuous contact with the developers. |
| Neuron with enabled malleability [added value] | Continuous contact with the developers. Feature has been implemented and tested. Results of implementation have been demonstrated to developers. |
| | |
| **Downstream Component** | **Status** |
| PyNN [essential] | Tool has been available for users |
| SP6-T6.4.3-SGA1-Model representations for cellular and network models [essential] | |
| STP model [essential] | |
| Graphical User Interface (GUI) to configure the procedure to fit synaptic events [essential] | |
| SP6 Tool to fit electrical models of neurons to data [essential] | |
| T10.1.1 Closed Loop Simulation of treadmill locomotion [important] | |
| T10.1.1 Closed Loop Simulation of locomotion overground [important] | |
| Improved LFP model with quasi-active conductances [essential] | |
| Simplified EEG models [essential] | |
| post simulation task workflow [added value] | |
| Cerebellum application model [essential] | |
| Cerebellum electrophysiological pipeline [important] | |
| Microcircuit Modelling tools [essential] | |
| HBP PCP CoreNeuron data set [essential] | |
| Coreneuron [important] | |
| Bluepy service [important] | |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [essential] | |
| Plasticity: STDP for a multi-compartment model with NMDA spikes (Algo STDPbackprop) [essential] | |
| SP6-T6.2.5-SGA1-Models of basal ganglia nuclei [essential] | |
| Cerebellum scaffold models [essential] | |
| SP6-T6.2.1-SGA1-Detailed passive models of human neurons [essential] | |

| | |
|---|---|
| SP6-T6.2.1-SGA1-Modelling synaptic inputs to human dendritic spines [essential] | |
| SP6-T6.2.1-SGA1-Models of human dendritic spines [essential] | |
| SP6-T6.2.1-SGA1-models of nonlinear human neurons [essential] | |
| SP6-T6.2.2-SGA1-Initial model validation tests implemented to compare rat model with mouse data [essential] | |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus [essential] | |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus [essential] | |
| SP6-T6.2.4-SGA1-Database of morphologies and electrophysiological recordings from the rat hippocampus [essential] | |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons [essential] | |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons [essential] | |
| T6.4.2 Microcircuit level services [essential] | |
| SP1-T1.1.5-SGA1 K channel kinetic models including [K+]ext [essential] | |
| Study of malleability options in NEST and Neuron [essential] | |

| **coreneuron** | |
|---|---|
| **Upstream Component** | **Status** |
| Neurodamus [important] | Continuous contact |
| NEURON [important] | |
| SP6-T6.4.5-SGA1-Brain Simulation Platform access [important] | |
| | |
| **Downstream Component** | **Status** |
| T6.4.2 Microcircuit level services [essential] | Tool has been available for users |
| Cerebellum scaffold models [essential] | |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models [essential] | |
| Bluepy service [important] | |
| HBP PCP CoreNeuron data set [essential] | |

| | |
|---|---|
| SP6-T6.2.5-SGA1-Models of basal ganglia nuclei [important] | |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus [essential] | |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus [essential] | |
| Cerebellar microcircuit model [essential] | |

# 5. T6.3.5 Tools for Network Simulation

## 5.1 Key Personnel

Task Leader: Markus DIESMANN (JUELICH)

Other Researcher: Tammo IPPEN (JUELICH/NMBU)

Other Researcher: Jochen M. EPPLER (JUELICH)

Other Researcher: Hans Ekkehard PLESSER (NMBU)

## 5.2 SGA1 DoA Goals

Task 6.3.5 will research technologies providing better scaling and increased simulation speed for network-level simulation, including the development and testing of concepts for upcoming exascale computer systems (in collaboration with SP7). T6.3.5 will focus on the core simulator code, without developing new features, or operating simulation as a service. The work performed in this Task will contribute to simulation of whole brain models used in CDP1.

## 5.3 Task Achievement Summary

Task 6.3.5 has made significant advances towards the fast and efficient construction of brain-scale networks of point neurons. Thread-based parallelisation of network construction is essential for this purpose, since a purely MPI-based parallelisation incurs and unacceptable memory overhead. We found that two independent bottlenecks in the existing simulation kernel led to significant scaling issues with thread-based parallelism. One bottleneck was due to massive thread contention while allocating and de-allocating many small objects in memory during network construction. The other bottleneck was traced back to inefficient loop structures in the code constructing the network. The found that we could address the first issue by using modern thread-aware memory allocators (jemalloc, tcmalloc) and the second issue by selecting appropriate loop structures depending on network parameters. With these improvements, a random network of the size of the rat brain (200 million neurons, 2 trillion synapses) could be constructed in just 20 seconds on over 900,000 threads on JUQUEEN. The changes in the simulation kernel are included in current NEST release (2.12), which is publicly available on GitHub.

Publication: Ippen T, Eppler JM, Plesser H and Diesmann M. (2017) Constructing neuronal network models in massively parallel environments. *Frontiers in Neuroinformatics,* 11:30. doi:10.3389/fninf.2017.00030

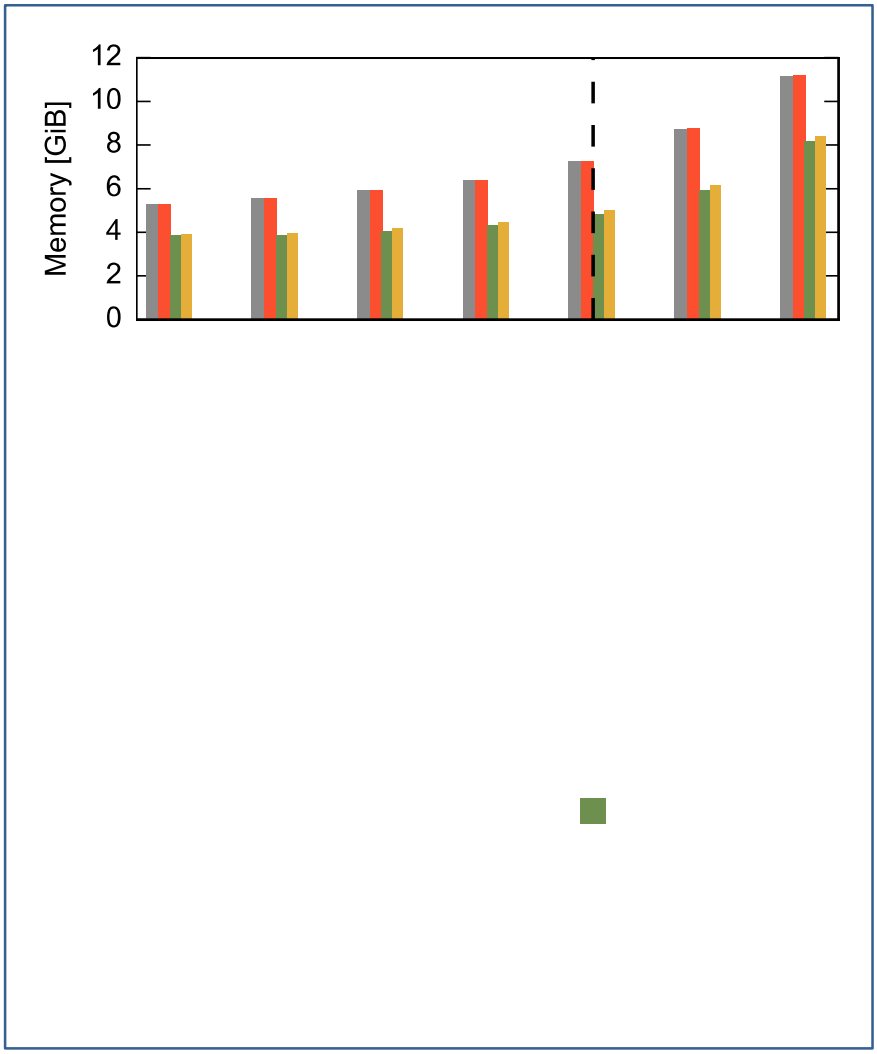


**Figure 15: Combined effect of improved memory allocation and loop order on construction time and memory consumption for a brain-scale neuronal network.**

**(A) Memory consumption at the end of and (B) time required for construction of a random network of 200 million neurons and 2.25 trillion synapses on JUQUEEN (dry-run mode); the horizontal axis specifies the number of threads per MPI process. Gray bars/curve indicate the original implementation, while red indicates results with modified loop order but standard memory allocator. The green and yellow bars/curves combine the modified loop order with the memory allocators tcmalloc and jemalloc, respectively. The black curve in (B) indicates ideal scaling. The dashed vertical line indicates the number of physical cores available on a compute node. From Ippen et al, 2017.**

## 5.4 Component Progress

### *5.4.1 Prototype NEST simulation kernel with directed spike exchange*

Description of Component: Research technologies providing better scaling and increased simulation speed for network-level simulation, including the development and testing of concepts for upcoming exascale computer systems.

CDP to which Component contributes: CDP1-CDP3

Progress on Component: Task 6.3.5 has successfully achieved completion of Milestone MS 6.3.5 "Report on design of a simulator architecture for highly parallel threading". Results have been published (Ippen et al, 2017) and the changes in the simulation kernel are included in current NEST release (2.12), which is publicly available on GitHub. Work has been performed by JUELICH with contributions by NMBU. For details, please see the Task Achievement Summary for Task 6.3.5, Section 20.3.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| Prototype NEST simulation kernel with directed spike exchange | |
|---|---|
| **Upstream Component** | **Status** |
| "SP6-T6.2.7-SGA1-Simplified brain models" (T6.2.7) | We have received high quality input. |
| "NEST Requirements Management" (T7.5.5) | We have received high quality service. |
| "NEST - The Neural Simulation Tool" (many contributing tasks) | The NEST-2.12 software was released and continues to be a high quality input to this component. |
| | |
| **Downstream Component** | **Status** |
| The component has 6 downstream components from different tasks | The prototype NEST simulation kernel component is due M24 and is developed in tight coordination with the future users. Internal report on design of simulator architecture for highly parallel threading is available (MS3.6.5 M12 [achieved]). |

## 5.5 T6.3.6 Whole brain level *in silico* instrumentation, services and apps (point neuron models)

### *5.5.1 Key Personnel*

Task Leader: Hans Ekkehard PLESSER (NMBU)

### *5.5.2 SGA1 DoA Goals*

Task 6.3.6 will develop tools to that will allow domain specialists to configure complete *in silico* experiments on point-neuron based whole-brain models by connecting stimulation and recording devices to specific neuron populations. For stimulation, the tools will allow the user to select target populations from ontologies, atlases or using graphical tools, and will configure spike- or current- injecting stimulation devices to the target populations. For recording, the tools will allow the user likewise to select populations of interest and will provide not only spike and membrane voltage recordings, but also the local field potential (LFP). The tools developed in T6.3.6 will thus allow validation of models against a broader set of experiments, particularly *in vivo* studies. They will also allow the integration of whole brain models with neurorobotics systems.

The tools to be developed in T6.3.6 will be built on tools that have been developed during the RUP, but will also depend on further theoretical developments in modelling of LFP signals in SP4 and HPC technology developed in SP7.

TP6.3.6 is essential for validation of whole brain models in WP6.2, for *in silico* experiments using whole brain models in CDP1 and for SPs using such models (e.g. SP3, SP9, SP10).

### *5.5.3 Task Achievement Summary*

T6.3.6 has developed an early prototype of the *NEST Connection App* for graphically selecting parts of a neuronal network model for connection of stimulation or recording devices, implemented in Python. T6.3.6 has also made necessary modifications to the NEST simulator to allow the creation of connections to/from selected neurons in the simulator. The prototype has been presented to potential users in SP4 and SP10 and we have received useful feedback for further development. The prototype is available through the HBP Software Catalogue and on Github.

T6.3.6 is also in close contact with T4.1.4, the task developing theory and underlying methodology and tools for LFP modelling, to prepare for work on a tool supporting users in

configuring LFP recordings. In view of the delayed start of this task due to the later signing of SGA1, and the fact that the delivery of this component is due only in M24, we have prioritised work on Component "Tools for configuring stimulation and recording in NEST simulations".

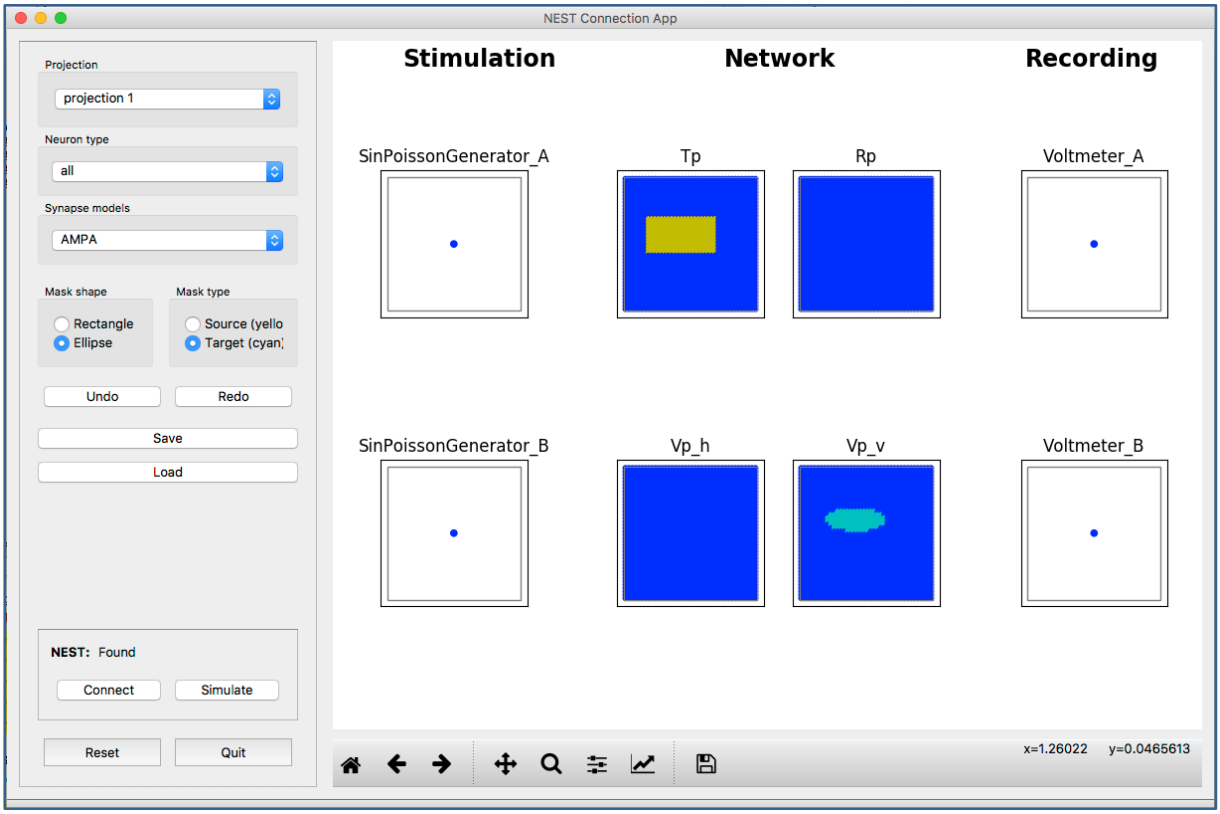


**Figure 16: NEST Connection App prototype screen shot. Users can configure projections from Stimulation devices (left) to a network or from the network to recording devices (right) by selecting rectangular or elliptical areas in populations of network neurons.**

### *5.5.4 Component Progress*

Commencement of work on T6.3.6 has been delayed, as staff for this Task could only be hired after the HBP SGA1 was signed.

#### 5.5.4.1 Tools for configuring stimulation and recording in NEST simulations

Description of Component: Tools will allow users to select target populations from ontologies, atlases or using graphical tools, and will configure spike- or current-injecting stimulation devices to the target populations. Tools will also allow the user to select populations of interest and will provide not only spike and membrane voltage recordings.

CDP to which Component contributes: CDP 1, CDP1-P3 A virtual imaging lab app

Progress on Component: T6.3.6 has developed an early prototype of the *NEST Connection App* for graphically selecting parts of a neuronal network model for connection of stimulation or recording devices, implemented in Python, especially through Jupyter notebooks. Integration into the Collaboratory is in progress. T6.3.6 has also made necessary modifications to the NEST simulator to allow the creation of connections to/from selected neurons in the simulator. All work on this component has been performed by partner NMBU.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.3.6-SGA1-Tools for configuring stimulation and recording in NEST simulations | |
|---|---|
| **Upstream Component** | **Status** |
| Multi-area model of cortical network at neuronal resolution [added value] | No update |
| NEST - The Neural Simulation Tool [essential] | + T7.5.5 + close contact and collaboration + regular code updates received + excellent |
| | |
| **Downstream Component** | **Status** |
| Laminar single-area model generating cortical slow waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 [essential] | + T3.2.5 + contact established and support provided + good |
| Single-area non-laminar model generating cortical slow waves - NEST flavour - WaveScalES SP3 SGA1 T3.2.5 [important] | + T3.2.5 + contact established and support provided + good |
| SP3 - Synaptic plasticity in Slow Wave Activity simulations as specified by CDP5 [essential] | + T3.6.2 + contact established and support provided + good |
| Multi-area model of cortical network at neuronal resolution [added value] | + T4.2.1 + contact established and information exchanged + good |
| Analysis of network-level mechanisms constraining the in vivo implementation of learning rules and implementing integration, encoding and recall of multisensory memories [important] | + T3.6.3 + contact established and information provided + satisfactory |
| Modelling of network-level mechanisms from T3.6.3a [important] | + T3.6.3 + contact established and information provided + satisfactory |
| NEST in situ framework [added value] | + contact established and requirements discussed + good |
| Large-scale modelling of TMS/EEG-PCI [important] | + contact established and support provided + good |
| SP6-T6.2.7-SGA1-Simplified brain models [important] | + T6.2.7 + contact established + satisfactory |
| T3.6.1 NEST/NRP eye movement simulation [essential] | + T3.6.1 + contact established + satisfactory |
| SP3.3.4 Multisensory integration for spatial navigational and episodic memory [added value] | + T3.3.4 + no delivery so far |
| SP3-T3.6.4-SGA1-Neuromodulation and plasticity mechanisms [important] | + T3.6.4 + contact established and support provided + good |
| NEST-simulated spatial-point-neuron data visualisation [added value] | + T7.3.1 + contact established and requirements discussed + good |

### 5.5.4.2 Tool for LFP recording in NEST simulations

Description of Component: Provide tool that allows LFP recordings from NEST simulations.

Progress on Component: T6.3.6 is in close contact with T4.1.4, the Task developing theory and underlying methodology and tools for LFP modelling, to prepare for work on this tool. In view of the delayed start of this task due to the later signing of SGA1, and the fact that the delivery of this component is due only in M24, we have prioritised work on Component "Tools for configuring stimulation and recording in NEST simulations".

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.3.6-SGA1-Tool for LFP recording in NEST simulations** | |
|---|---|
| **Upstream Component** | **Status** |
| Multi-area model of cortical network at neuronal resolution [added value] | No update |
| Simplified EEG models [essential] | + T4.1.4 + contact established + good |
| Improved LFP model with quasi-active conductances [essential] | + T4.1.4 + contact established + good |
| Simplified model of local field potentials [essential] | + T4.1.4 + contact established + good |
| NEST - The Neural Simulation Tool [essential] | + T7.5.5 + close contact and collaboration + regular code updates received + excellent |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.7-SGA1-Simplified brain models [important] | + T6.2.7 + contact established + satisfactory |
| Modelling of network-level mechanisms from T3.6.3a [important] | + T3.6.3 + contact established and information provided + satisfactory |
| Analysis of network-level mechanisms constraining the in vivo implementation of learning rules and implementing integration, encoding and recall of multisensory memories [important] | + T3.6.3 + contact established and information provided + satisfactory |
| Multi-area model of cortical network at neuronal resolution [added value] | + T4.2.1 + contact established and information exchanged + good |

# 6. WP6.4 Brain Simulation Platform

## 6.1 Key Personnel

Work Package Leader: Michele MIGLIORE (CNR)

## 6.2 WP Leader's Overview

The goal of WP6.4 is to design, implement and operate the HBP Brain Simulation Platform (BSP), which is accessible to users via the Collaboratory. All Tasks have consistently worked for this purpose, in most cases without any major delays or blocking issues. Most of the effort has been focused on model and validation of single cell tools and apps. The implementation of model circuits is proceeding as planned. Several use cases, specifically oriented toward the average user, have been implemented, tested, and made publicly available in the new release of the Platform. For a quick and intuitive access, they have been grouped in "Trace Analysis", "Single Cell building", "Morphology", "Circuit Building", and "*in silico* experiments" for single cell, small circuit, and brain area circuits. Their use is being monitored through Google Analytics tools and demonstrated by a number of teams different from developers, both internal and external to HBP. Because of its potentially high visibility in the Neuroscience Community the work done can be expected to have a major impact in the field.

A few Use Cases, and in particular those tightly connected to the availability of experimental data and those related to model circuits, are suffering some delay and limitations because: a) all upstream Components from the Neuroinformatics Platform are still missing, b) there are important weaknesses and limitations of core Collaboratory functionality that reduce user friendliness or hinder access and functionalities, and c) the BSP has not been given institutional access to HPC resources to test the development, deployment, and use of the microcircuit models. All these problems have been bypassed so far in different ways, thanks to the additional, unplanned, effort dedicated by all involved WP partners. For example, the data that other partners have decided to make visible for internal/external users are currently stored in a local server and fetched through custom code; Jupyter notebooks use terse and simplified GUIs; the model circuit for the hippocampus is being developed mostly using custom developed tools outside the Collaboratory, and run relying on personal HPC allocations independently granted to the CDP2 Implementation Leader.

- T6.4.1 Cellular Level Apps. The two components of this Task are progressing as planned, with GUI for simulating single cell model, and an IPython Widget that allows displaying neuron morphology in the context of a notebook.
- T6.4.2 Microcircuit Level Services. The planned Python library is being developed. An initial version of Jupyter notebooks for microcircuits have been integrated in the Collaboratory.
- T6.4.3 Model representation and standards. Work on the Components in this Task has been severely delayed by the extended SGA1 contract negotiations; however, the planned report will be released internally at the end of Month 12.
- T6.4.4 Validation Framework Services and Apps. A prototype of the Model Validation Service has been developed, deployed, and made available internally to members of SP6. It is being been used for initial validations of hippocampus neuron models.
- T6.4.5 Technical Support for Community Model Building and Validation. All Components have released the planned Collaboratory Apps to support data-driven models and to simplify access to the Platform. The relative entries have been added to the HBP Software Catalog, and tested by users different from developers, internal and external to HBP.

- T6.4.6 Platform Administration and Operations. The service planned by this Task for M12 has been achieved. It allows to host in a local server the data that other partners would like to be visible to internal/external users, and includes the setup and management of a virtual machine and a server used to deploy and host user-specific apps and data.

## 6.3 Priorities for the remainder of the phase

For the reminder of the phase, priority will be given to activities able to increase the number of users, internal/external community engagement, and scientific dissemination (reports, papers, etc.). For this purpose, we will consolidate and extend use case number and functionality, model validation and analysis, and single cell and circuit *in silico* experimentation.

## 6.4 Milestones

**Table 4: Milestones for WP6.4 - Brain Simulation Platform**

| MS No. | Milestone Name | Leader | Task(s) involved | Expected Month | Achieved Month | Comments |
|---|---|---|---|---|---|---|
| MS6.4.1 | Collaboratory integrated morphology and single cell building workflows | EPFL | T6.4.1 | SEP 2017 | | |
| MS6.4.2 | Initial version of microcircuit webservices integrated with ipython in the Collaboratory | UNIPV | T6.4.2 | MAR 2017 | MAR 2017 | Two different Jupyter notebooks are available as web-services on the Cerebellum Collaboratory:<br>• Circuit building - cell placement in three-dimensional space, according to density distribution of cerebellar cortical layers. Morphology assignment and three-dimensional spatial orientation. The code is written in Python and exploits brainbuilder, voxcellview and voxcell libraries to build and visualise the cerebellum cortical network.<br>• Connectome building - connect cells according to connectivity rules derived from experimental data. The notebook allows to visualise connectivity structure and to save the generated connectome as a .hdf5 file. At the moment, the notebook reconstructs the connectivity of the cerebellum granular layer.<br>Achieved 1. Both web services are available through Collaboratory as Jupyter notebooks running Python code 2. Possibility to place cells in three-dimensional space according to specific densities 3. Possibility to assign and visualise cells morphologies and their orientation in three-dimensional space 4. Possibility to generate realistic microcircuit connectome according to explicit connectivity rules 5. Possibility to visualise and store connectome data |
| S6.4.3 | Report on the adequacy of model representations standards for community models | CNRS | T6.4.3 | MAR 2017 | MAR 2017 | Version 1.0 of the report has been distributed to other researchers in SP6, and uploaded to the Collaboratory and at: https://flagship.kip.uni-heidelberg.de/jss/FileExchange?hbpUsID=166 for access by the Project reviewers. |

| | | | | | | |
|---|---|---|---|---|---|---|
| MS6.4.4 | Initial version of open-source tools to build data-driven models is released | CNR | T6.4.4 | MAR 2017 | MAR 2017 | Planned release achieved. Entry in the HBP Software Catalog created. Apps and Jupyter notebooks have been released in the Collaboratory and integrated in the BSP. The relative code is included in several Use Cases related to subcellular and single cell model and simulation. It allows Collaboratory users to access the Neuroscience Gateway Portal through REST APIs, and UNICORE access to JSC and CINECA HPC systems. Internal and external use is monitored and demonstrated by Google Analytics. As a representative example, the usage monitoring of the "Feature Extraction Graphical User Interface" web application, developed for providing engineering support to build data-driven model, resulted in the following statistics, collected as of 12 February, 2017 to date: 32 new users, 131 sessions (64% of which comprised multi-page visits), 84% of users not being part of the development team. |
| MS6.4.5 | Initial version of web applications for platform configuration and deployment services is released | CNR | T6.4.5 | MAR 2017 | MAR 2017 | Planned release achieved. Entry in the HBP Software Catalog created. Apps and Jupyter notebooks have been released into the Collaboratory, and they are already in use on the BSP. The service provided allows to host in a local server the data that other partners would like to be visible to internal/external users. This includes the setup and management of a virtual machine and a server used to deploy and host user-specific apps and data. Next release is expected at M24 and will include hosting more user apps, and an initial installation of an umbrella user to access the Neuroscience Gateway. This will greatly facilitate internal/external users in their initial approach with the BSP use cases. Internal and external use is monitored and demonstrated by Google Analytics. As a representative example, the usage monitoring of the "Feature Extraction Graphical User Interface" web application, developed for providing engineering support to build data-driven model, resulted in the following statistics, collected as of 12th February, 2017 to date: 32 new users, 131 sessions (64% of which comprised multi-page visits), 84% of users not being part of the development team. |
| MS6.4.6 | Release of initial version of web applications for model validation | CNRS | T6.4.6 | JUN 2017 | | |
| MS6.4.7 | Readiness evaluation of all components for release in Brain | CNR | T6.4.1, T6.4.2, T6.4.3, T6.4.4, | NOV 2017 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Simulation Platform under D6.5.2 | | T6.4.5, T6.4.6 | | | |

Note: The numbering of the milestones follows that of the SGA1 Amendment 1.

## 6.5 T6.4.1 Cellular Level Apps

### *6.5.1 Key Personnel*

Task Leader: Jean-Denis COURCOL (EPFL)

### *6.5.2 SGA1 DoA Goals*

T6.4.1 will develop Apps providing a user-friendly graphics interface to cellular-level modeling tools developed in T6.3.3, based on use cases from WP6.1 and WP6.2. These will include the cellular level optimiser framework (the tool used to fit electrical models of neurons to their observed electrical behaviour), the morphology pipeline (the tool used to analyse and validate neuron morphologies); and the validation of single cell models.

T6.4.1 depends on the development of tools and APIs in WP6.4.2-4 and prototype work in WP6.1 and WP6.2.

The Apps developed in T6.4.1 will make a fundamental contribution to community driven modeling in T6.2.2 and T6.2.4, and will encourage community-driven app development.

### *6.5.3 Task Achievement Summary*

A new application for Single Cell *in silico* experiment has been developed so that any end user can run a virtual experiment on the available cell models. This application has been made available as a use case in the BSP:


**Figure 17: Selection of the use case.**

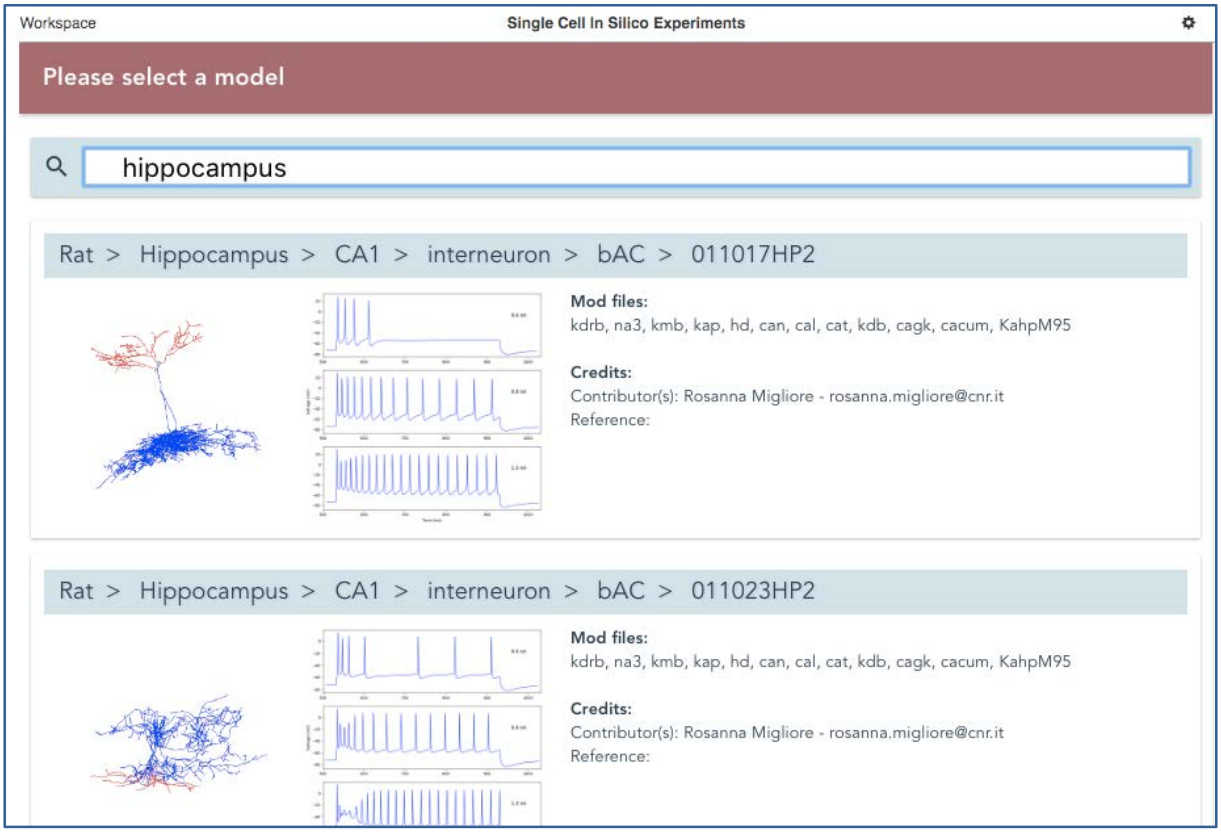


**Figure 18: Selection of the model.**

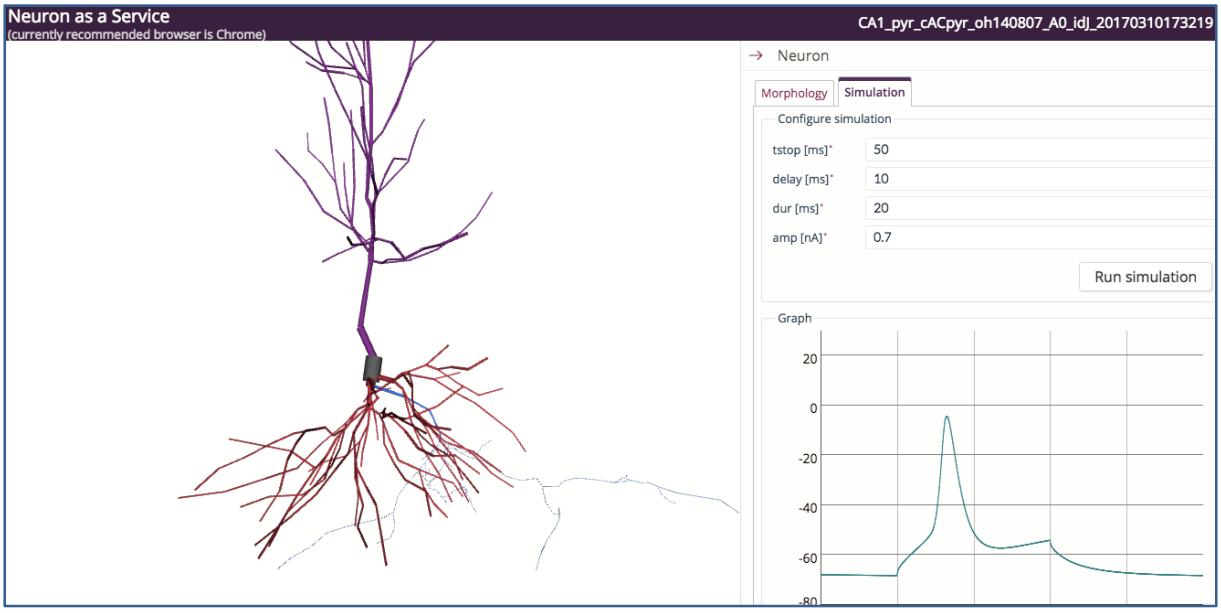


**Figure 19: Configuration and execution of the virtual experiment.**

A morphology viewer application has been provided as an HTML page but also has a Jupyter Notebook widget to display any of the morphology models provided as a python object or as a file.

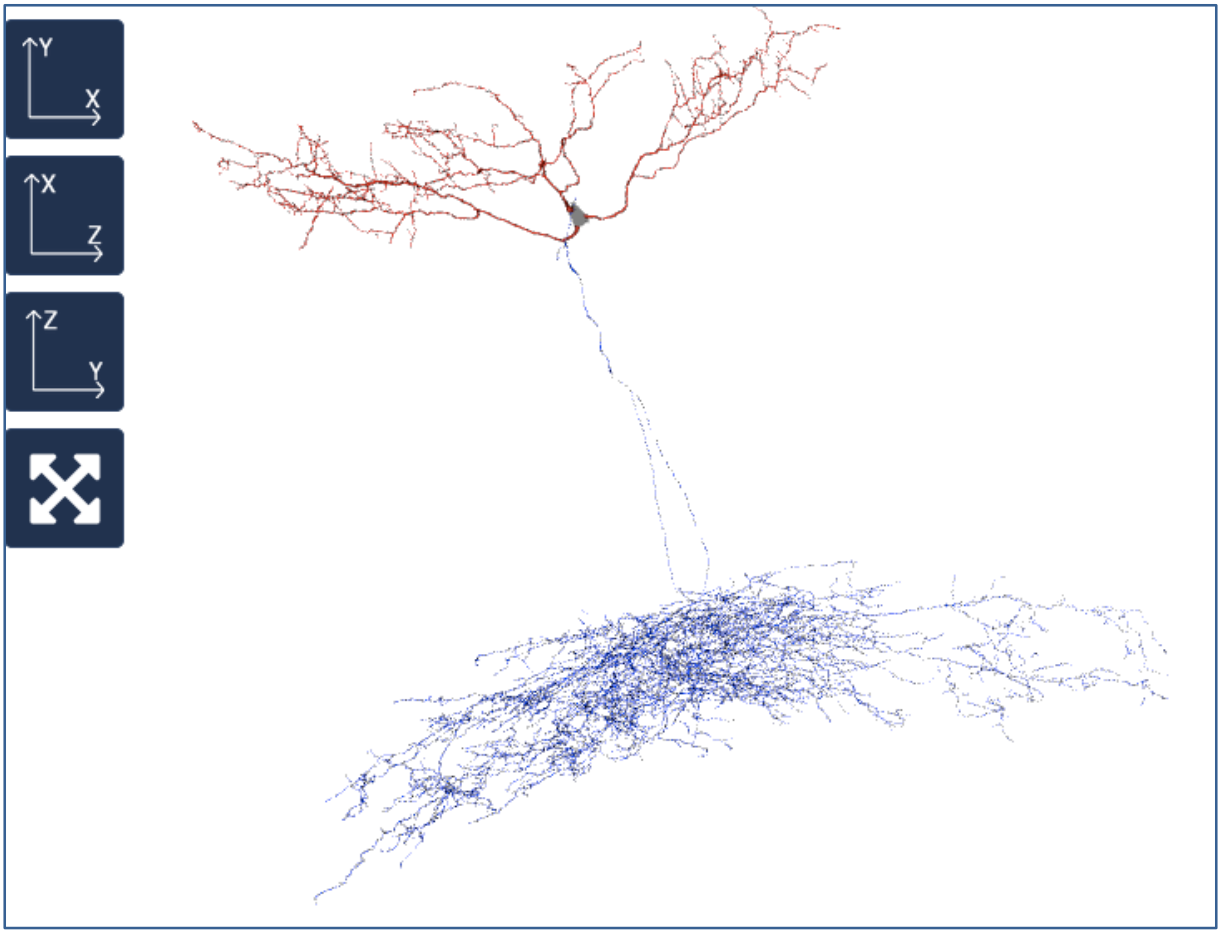


**Figure 20: A morphology visualisation from within the Collab.**

### *6.5.4 Component Progress*

#### 6.5.4.1 A GUI for simulating single cell model

Description of Component: A web application that allows defining stimulus on neuron, define the location of reporting activity using Neuron simulator.

CDP to which Component contributes: CDP2

Progress on Component: The back-end build on top of OpenShift has been prototyped so as a set of REST API. This can scale horizontally to support a large number of users.

The GUI that will trigger and consume this API will be built during year 2 of SGA1.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **GUI for single cell model simulation** | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| N.A | |

#### 6.5.4.2 A Widget to display morphology in notebooks

Description of Component: An IPython Widget that allows displaying neuron morphology in the context of a notebook.

CDP to which Component contributes: CDP2

Progress on Component:

- Improvement: Integration with neuroma 0.018+
- New Feature: display closest point position under mouse
- New Feature: display specified segment, section id
- New feature: display soma as a plane with transparency
- Improvement: upgrade to ipywidget 5.2.2

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| A Widget to display morphology in notebooks | |
|---|---|
| **Upstream Component** | **Status** |
| N.A | |
| | |
| **Downstream Component** | **Status** |
| Mouse hippocampus model | Provided internally |
| SP6-T6.2.4-SGA1-Models of rat hippocampal neurons | Provided internally |
| SGA2 - T6.4.3 - convert/extend/maintain circuit building pipeline in the form of Jupyter notebooks. | Provided internally |
| SP6 Morphology pipeline | Provided internally |
| Morphology repair and diversification framework | Provided internally |

## 6.6 T6.4.2 Microcircuit Level Services

### *6.6.1 Key Personnel*

Task Leader: Egidio D'ANGELO (UNIPV)

Other Researcher: Jean-Denis COURCOL (EPFL)

### *6.6.2 SGA1 DoA Goals*

T6.4.2 will take microcircuit level modelling tools, including tools developed by the Blue Brain Project prior to the start of the HBP, additional tools developed during the RUP, as well as technologies prototyped by WP6 partners, and make them available for consumption through remote access. This work contributes to modelling of the cerebellum (T6.2.3), the hippocampus (T6.2.4) and the basal ganglia (T6.2.5) all essential Components of CDP2. Insights from this co design process will contribute to work in later phases of the HBP.

The services provided by T6.4.2 are essential for the development of microcircuit models in WP6.2 and CDP2 and thus, indirectly for SPs using such models (e.g. SP3, SP9, SP10).

### *6.6.3 Task Achievement Summary*

The BrainBuilder framework has been improved to support the latest needs for hippocampus and cerebellum circuit models.

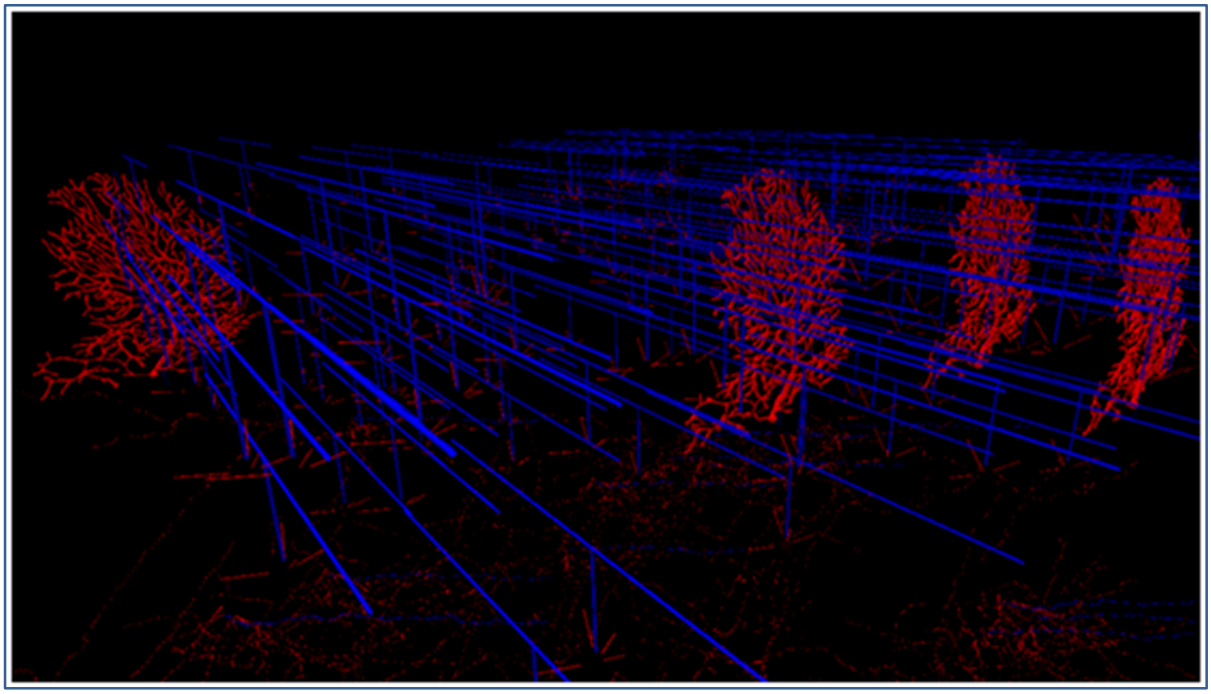

**Figure 21: Custom cell orientations and loading of morphologies in the debugging viewer applied to cerebellum.**

For cerebellum, two different Jupyter notebooks are available as web-services on the Cerebellum Collaboratory and the related M12 Milestone has been achieved.

The granular layer of the Cerebellum (GL) includes two main types of cells; the granule cells (GrCs) and the Golgi cells (GoCs). Both are stimulated by the pontine mossy fibers (mfs); synaptic contacts among GrCs /GoCs and mfs are called glomeruli (Gloms).

In order to reconstruct the microcircuit connectivity of the GL, we proceeded as follows:

- Cell spatial placement according to respective densities; in our "Connectome building" notebook, this procedure is implemented in pure Python code.
- According to (i) connectivity ratios and (ii) basic geometrical properties of axonal/dendritic trees estimated from experiments (see "Cerebellum data center" in the collab for details), we derived a simple set of connectivity rules
- In the program file, we first connect GoCs axons to Gloms, given that GoCs inhibit GrCs within the Gloms. Exact shape and dimension of GoC axonal plexus are still unknown; however, it is known that its spatial extension is anisotropic and orthogonal to parallel fibres, the T-shaped axons of GrCs
- Then, GoCs dendrites are connected to Gloms, according to a simple, isotropic distance-rule (i.e., Gloms with a distance below a given threshold will connect to a given GoC)
- GrCs dendrites are then connected to Gloms; even though computationally expensive, given the high amount of GrCs in GL, GrCs are known to have few (~4) and short (~13.6 micron) dendrites; moreover, a single GrC will never send more than one dendrite to the same Glom
- Finally, connect GoCs axonal plexus to GrCs (inside Gloms).
- The last part of the program saves connectivity data as Python dictionaries in h5 files

The viewers have been enhanced for analysis of the properties and connectivity of the cells.

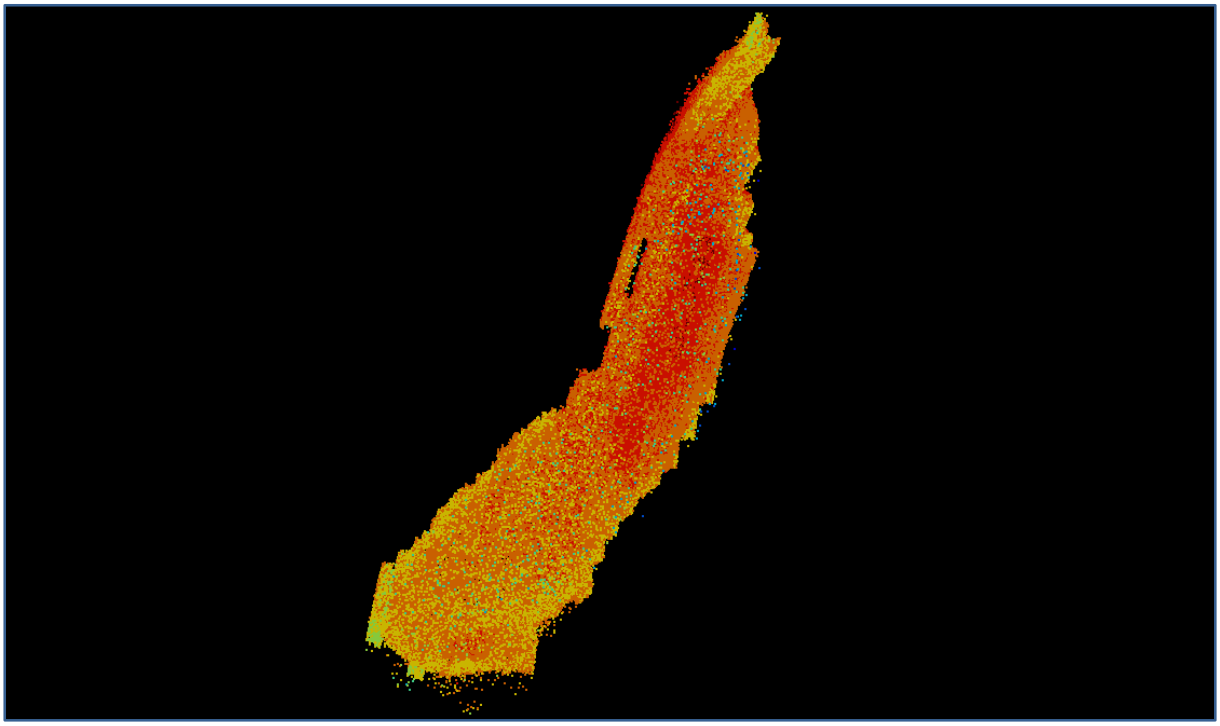

**Figure 22: Displaying the number of connections per cells during building in the hippocampus CA1.**

### *6.6.4 Component Progress*

#### 6.6.4.1 BrainBuilder Framework

Description of Component: A python modularisable library to build brain region based on voxel data properties.

CDP to which Component contributes: CDP2

Progress on Component:

- Support of orientation definition for the cerebellum model
- Debugging viewer that shows a subset of the neurons morphologies in the context of the circuit in Jupyter notebooks
- Support of colour map for cell properties viewer
- Support of volumetric query for cell properties viewer
- API to query segment Id to voxel Id
- Integration of atlas hierarchy into circuit file format for cell properties
- Support for region in cell properties viewer
- Support for slicing of brain region
- Support for validation of segment volume per brain region
- Support for Cell placement in hippocampus as a Jupyter notebook in the Collaboratory

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **BrainBuilder Framework** | |
|---|---|
| **Upstream Component** | **Status** |
| 5 upstream Components | Provided |
| | |

| Downstream Component | Status |
|---|---|
| 8 downstream Components | Provided |

### 6.6.4.2 Other components

The Task has another 13 Components belonging to different Tasks that contribute to the Microcircuit Level Services Task. All the Components are software and we have received Components from the majority of them.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Automated task GUI generation and document storage GUI** | |
|---|---|
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |
| | |
| | |
| **UNICORE** | |
| **Upstream Component** | **Status** |
| 4 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 16 downstream Components | Provided |
| | |
| | |
| **TouchDetector** | |
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 5 upstream Components | Provided |
| | |
| | |
| **Task Manager Framework** | |
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |
| | |
| | |
| **SP6-T6.4.2-SGA1-RTNeuron** | |
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 5 downstream Components | Provided |
| | |
| | |
| **post simulation task workflow** | |

| Upstream Component | Status |
|---|---|
| 3 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 2 downstream Components | Provided |
| | |
| | |
| **ModelManagement** | |
| **Upstream Component** | **Status** |
| 7 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 5 downstream Components | Provided |
| | |
| | |
| **mesobuilder** | |
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 5 downstream Components | Provided |
| | |
| | |
| **SP6-T6.4.2-SGA1-Livre** | |
| **Upstream Component** | **Status** |
| 2 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 4 downstream Components | Provided |
| | |
| | |
| **JS Provenance Viewer** | |
| **Upstream Component** | **Status** |
| 3 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |
| | |
| | |
| **Js Simulation Configuration** | |
| **Upstream Component** | **Status** |
| 3 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |
| | |
| | |
| **Functionalizer** | |
| **Upstream Component** | **Status** |
| 3 upstream Components | Provided |

| | |
|---|---|
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |
| | |
| | |
| **BlueBuilder** | |
| **Upstream Component** | **Status** |
| 5 upstream Components | Provided |
| | |
| **Downstream Component** | **Status** |
| 3 downstream Components | Provided |

## 6.7 T6.4.3 Model Representation and Standards

### *6.7.1 Key Personnel*

Task Leader: Andrew P. DAVISON (CNRS)

Other Researcher: B. Lungsi SHARMA (CNRS)

Other Researcher: Shailesh APPUKUTTAN (CNRS)

Other Researcher: Pedro E. GARCIA-RODRIGUEZ (CNRS)

### *6.7.2 SGA1 DoA Goals*

T6.4.3 will work with community partners and with model developers in T6.2.2-T6.2.6 to adopt and/or develop standards for representing brain models, and for sharing them. Specifically, T6.4.3 will develop open APIs for morphology analysis, classification, conversion, and manipulation; establish open standards for performant, interoperable model representations (from the cellular-level to the point neuron levels); develop open APIs to access information on models; and work with SP4 and CDP5 to create representations for models of synaptic plasticity. The Task will work with SP7 and SP9 to ensure that the APIs and model representations are consistent with high performance on both traditional HPC and neuromorphic computing systems (cf T9.1.4). As far as possible T6.4.3 will use and/or extend existing community standards (e.g. NeuroML, NineML, PyNN).

### *6.7.3 Task Achievement Summary*

We have performed a census and comparative analysis of the most widely used model representation formats in HBP and in the wider computational neuroscience community. Based on this analysis we wrote a report comparing the requirements for model representation formats for large-scale, data-driven modelling and simulation to the capabilities of existing formats, with recommendations for the future evolution and standardisation of model representation in neuroscience. The report, entitled '*Model descriptions in computational neuroscience: supercomputers and standardisation*' was made available within SP6, and is also available to reviewers.

### *6.7.4 Component Progress*

Please note that hiring of personnel to work on the Components in this Task was severely delayed by the extended SGA1 contract negotiations; as a consequence most of the effort in this Task will take place in the second year of SGA1.

#### 6.7.4.1 Model representations for cellular and network models

Description of Component: This is an umbrella Component for the set of neuronal network model representation formats used in HBP and the wider community. Following the completion of the report on the adequacy of existing model representations for current and

future needs in large-scale, data-driven modelling and simulation, we will define a number of software Components needed for conversion between formats.

CDP to which Component contributes: CDP2

Progress on Component: We have performed a census and comparative analysis of the most widely used model representation formats in HBP and in the wider computational neuroscience community. A report on this work was made available at the end of Month 12 (see below).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Model representations for cellular and network models** | |
|---|---|
| **Upstream Component** | **Status** |
| "Simplified brain models" (T6.2.7) | This Component is needed to help define the requirements for model representation formats. As of Month 12, no input has been received beyond what was achieved in the RUP. |
| Brion (external) | A C++ library for read and write access to Blue Brain data structures, including BlueConfig/CircuitConfig, Circuit, CompartmentReport, Mesh, Morphology, Synapse and Target files. This stable, well-tested library is now distributed as open-source software. |
| NineML (external) | A modular model description language developed by an INCF working group. Version 1.0 of the specification was released in 2015. A number of software tools have some level of support for NineML. (see http://incf.github.io/nineml/software/) |
| NeuroML (external) | An XML-based model description language developed by an active community. Version 2.0beta4 of the specification was released in 2016. A large number of software tools have support for NeuroML (https://neuroml.org/tool_support) and a growing number of models are available in this format (see http://www.opensourcebrain.org). |
| NEURON (T6.3.4) | NEURON is a well-established, widely used and high-quality simulator developed primarily outside HBP. It uses several languages for model specification (NMODL, Hoc, Python). |
| NEST (T7.1.1, T7.1.3, T7.1.4, T7.4.1) | NEST 2.10.0 was released shortly before the end of the Ramp-Up Phase (31/12/2015). NEST 2.12.0 was released on 1 March 2017. NEST is a well-established, widely used and high-quality simulator with a large development community both inside and outside HBP, which is highly responsive to bug reports. It uses Python, C++ and two custom languages (sli, NESTML) for model specification. |
| | |
| **Downstream Component** | **Status** |
| "Models of mouse hippocampal neurons" (T6.2.4), "Circuit model of the mouse hippocampus" (T6.2.4), "STP model" (T1.1.4) | Nothing has yet been delivered. |

### 6.7.4.2 Model representations for synaptic plasticity

Description of Component: This is an umbrella Component for the set of synaptic plasticity model representation formats used in HBP, including NeuroML/LEMS and NineML.

CDP to which Component contributes: CDP2

Progress on Component: We have performed a census and comparative analysis of the most widely used model representation formats in HBP and in the wider computational neuroscience community for models of synaptic plasticity. A report on this work was made available at the end of Month 12 (see below).

Quality Control (Note: includes only scientific/technical components and not those of the coordination Tasks, WP6.5):

| **Model representations for synaptic plasticity** | |
|---|---|
| **Upstream Component** | **Status** |
| "Simplified brain models", NineML, NeuroML | See above. |
| "Integration of Subcellular Models in Single Neuron Models" (6.1.4) | Deliverable expected at Month 12. |
| "Position paper on the workflows and strategies for intracellular and synaptic modelling" (T1.1.6, T6.1.4) | Expected Month 18. |
| "Plasticity: STDP for structural plasticity" (T4.3.1) | Preprint available at: http://arxiv.org/abs/1609.05730 (Deger et al. 2016) |
| "STP model" (T1.1.4) | Expected Month 24. |
| "NEST code with abstracted neuron model representations" (T7.1.3) | Work is underway, but not yet released (expected Month 24). |
| | |
| **Downstream Component** | **Status** |
| "Position paper on the workflows and strategies for intracellular and synaptic modelling" (T1.1.6, T6.1.4) | Expected Month 18. |
| "STP model" (T1.1.4) | Expected Month 24. |
| "Neuromorphic code generation feasibility study" (T9.1.4), "pyNN.neuroml" (T9.1.4) | Nothing has yet been delivered. |

### 6.7.4.3 PyNN

Description of Component: PyNN (pronounced 'pine') is both a simulator-independent Python API for building neuronal network models and a Python package that implements this API for the NEST, NEURON and Brian simulators. It is developed using an open-source community model. CNRS (P10) is one of the major contributors and the project administrator.

Progress on Component: Three minor releases were made during the reporting period:

- Version 0.8.1 – 25/05/2016 – support for NEST 2.10.0, bug fixes. Release notes: http://neuralensemble.org/docs/PyNN/releases/0.8.1.html
- Version 0.8.2 – 06/12/2016 – new spike source models, minor enhancements, bug fixes. Release notes: http://neuralensemble.org/docs/PyNN/releases/0.8.2.html
- Version 0.8.3 – 08/03/2017 – support for NEST 2.12.0, NeuroML v2. Release notes: http://neuralensemble.org/docs/PyNN/releases/0.8.3.html

During this period, we began tracking the NEST master branch in a specific development branch of PyNN, which allowed us to reduce the time needed to release a compatible PyNN release following a NEST release from 6 months with NEST 2.10 to 7 days with NEST 2.12.

CDP to which Component contributes: CDP5

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| PyNN | |
|---|---|
| **Upstream Component** | **Status** |
| "NEURON" (T6.3.4), "NEST" (7.1.1, 7.1.3, 7.1.4, 7.4.1) | See above. |
| "pyNN.neuroml" | A new version of the pyNN.neuroml module, supporting NeuroML v2, was developed, primarily by Dr Padraig GLEESON (UCL). This was released as part of PyNN 0.8.3. |
| Plasticity models (T4.3.1, T4.3.2) | The plasticity models developed in WP4.3 will be used when reviewing the PyNN API for synaptic plasticity modelling, in the second year of SGA1. |
| "MUSIC library" (T9.1.2) | The PyNN/MUSIC interface, which makes it possible to set up MUSIC co-simulations in an easy and friendly way from within PyNN, currently has a bug. This needs to be resolved and the interface integrated into the PyNN master branch. |
| "Neo" (T5.7.1, T5.7.2) | Neo 0.4.0 was released on 07/07/2016, Neo 0.4.1 was released on 03/08/2016. Neo is a stable and well-tested Python package with a medium-to-large development community both inside and outside HBP. (Over the past twelve months, 16 developers contributed to Neo [source: https://www.openhub.net/p/python-neo]). |
| | |
| **Downstream Component** | **Status** |
| "Neuromorphic Visual motor coordination" (T10.2.3, T10.4.3), "SP9 Neuromorphic Benchmarks repository" (T9.1.3), "Sensory-motor maps" (T10.1.2), "Workflow for comparison of spiking neuron data obtained from NEST and SpiNNaker simulation" (T9.1.5), "Sensory models" (T10.1.2), "Robot Demonstrator – Mobile platform" (T10.4.3), "Biomimetic learning control architecture for modular robots" (T10.4.4), "Laminart with segmentation and retina into the NRP" (T10.2.1), "Model of spinal chord using reservoir computing for real-time control" (T10.4.5), "SP9 Neuromorphic Job Queue Service" (T9.1.1), "pyNN.neuroml" (T9.1.4) | PyNN 0.8.0 has been available to downstream components since the beginning of SGA1. Three further releases of PyNN have taken place during the first 12 months of SGA1. |

#### 6.7.4.4 Report on the adequacy of model representation standards for community models

Description of Component: A report comparing the requirements for model representation formats for large-scale, data-driven modelling and simulation to the capabilities of existing formats, with recommendations for the future evolution and standardisation of model representation in neuroscience.

CDP to which Component contributes: CDP2

Progress on Component: The report was released internally at the end of Month 12.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| Report on the adequacy of model representation standards for community models | |
|---|---|
| **Upstream Component** | **Status** |
| "Model representations for synaptic plasticity", "Model representations for cellular and network models" (T6.4.3) | See above. These Components have fed into this report and future work will be informed by this report. |
| | |
| **Downstream Component** | **Status** |
| "Model representations for synaptic plasticity", "Model representations for cellular and network models" (T6.4.3) | See above. These Components have fed into this report and future work will be informed by this report. |

## 6.8 T6.4.4 Validation Framework Services and Apps

### *6.8.1 Key Personnel*

Task Leader: Andrew P. DAVISON (CNRS)

Other Researcher: B. Lungsi SHARMA (CNRS)

Other Researcher: Shailesh APPUKUTTAN (CNRS)

Other Researcher: Pedro E. GARCIA-RODRIGUEZ (CNRS)

### *6.8.2 SGA1 DoA Goals*

T6.4.4 will develop services and apps facilitating community model-building and community validation of models developed in T6.2.1-6, and use them to perform preliminary validations of these models. The work to be performed includes enhancements of the existing validation framework in collaboration with corresponding WP6.3 tasks; tools facilitating web access to validation experiments and their results; and outreach activities. In addition, T6.4.4 will work actively to build community support with a special emphasis on validation experiments coming from the community. The apps developed in T6.4.4 will make a fundamental contribution to community-driven modelling in CDP2 and in T6.2.4, and will encourage community-driven app development.

### *6.8.3 Task Achievement Summary*

A prototype of the Model Validation Service has been developed and made available to HBP users. The Service can be accessed through a web browser (see figures below) or through a Python client, and allows users to find validation tests that are relevant to a given species, cell type, and brain region, register the results of running validation experiments, and view the validation results. A small library of tests is already available, focused mostly on validation of models of neurons from hippocampus CA1. Use of the Python client is documented in the BSP Guidebook.

### *6.8.4 Component Progress*

Please note that hiring of personnel to work on the Components in this Task was severely delayed by the extended SGA1 contract negotiations; as a consequence most of the effort in this Task will take place in the second year of SGA1.

#### 6.8.4.1 Model Validation Service

Description of Component: The Model Validation Service REST API will allow modellers to: (i) find validation tests that are suitable for the species, structure (single cell, brain region, etc.) and spatial/temporal scale being modelled; (ii) define and upload new validation test

definitions (iii) register/upload the results of running validation experiments; and, (iv) query the database of validation results**.**

CDP to which Component contributes: CDP2

Progress on Component: Following a period of requirements gathering and evaluation of related open-source tools (e.g. the SciUnit framework), a prototype of the Model Validation Service has been developed, deployed, and made available internally to members of SP6. It has been used for initial validations of hippocampus neuron models.

On the basis of feedback from internal users, the service will be extended and improved in the second year of SGA1, in particular through a deeper integration with the HBP Neuroinformatics Platform: experimental reference data will all be registered with the KnowledgeGraph and Neural Activity Resource, and database queries will make use of the ontologies developed in SP5. A first public release is planned for Month 15.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Model Validation Service** | |
|---|---|
| **Upstream Component** | **Status** |
| "Workflow for comparison of spiking neuron data obtained from NEST and SpiNNaker simulation" (T9.1.5) | This is an important use case for the Validation Service, but modification of the workflow to use the Service has not yet been implemented. |
| Workflow for comparison of electrophysiological and simulated data" (T4.5.1) | This example workflow is expected to be an important driver of the design of the Model Validation Service, but work on modifying the workflow to use the Service has not yet been implemented. |
| "Knowledge Graph Service" (T5.5.1) | Registration of experimental reference data with the Knowledge Graph is currently possible. Extensions to the Knowledge Graph Service required for tracking modelling workflow provenance have not yet been implemented. |
| Validation test repository (T6.4.4) | See below. |
| | |
| **Downstream Component** | **Status** |
| "Models of mouse hippocampal neurons" and "Circuit model of the mouse hippocampus" (T6.2.4) | Existing validation tests for hippocampal pyramidal and interneurons were used as a test case in developing the prototype of the Validation Service. The prototype has been made available to the hippocampus modelling team. No hippocampus circuit validations have yet been registered with the Service, but this is in progress. |
| "Engineering support to build data-driven models" and "Support of open-source tools for configuration of data-driven models" (T6.4.5) | A preliminary version of documentation for the Model Validation Service prototype has been provided to Task 6.4.5. |
| Model validation browser app (T6.4.4) | See below. |

### 6.8.4.2 Validation test repository

Description of Component: A repository of validation test definitions, accessible via an API implemented in the Model Validation Service. As much as possible, the test definitions will refer to experimental data registered with the KnowledgeGraph, and use ontologies developed by the Neuroinformatics Platform.

CDP to which Component contributes: CDP2

Progress on Component: A small number of validation test definitions, building on work by the hippocampus modelling team, have been incorporated in the prototype test repository. We have begun a census of all model validation activities in HBP (SP2, SP3, SP4, SP6, SP9, SP10).

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Validation test repository** | |
|---|---|
| **Upstream Component** | **Status** |
| "single morphology validation" (T6.3.3) | Tools for morphology validation have not yet been incorporated in the validation framework. |
| "single cell electrical model validation" (T6.3.3) | Tools for validation of single cell electrical activity have been incorporated into the validation framework, and several of the validation tests currently in the repository use this software. |
| "Analysis and Validation tasks for Circuit and Simulation" (RUP T6.5.1) | A number of validation tests were implemented during the RUP using the Task Framework. This Framework is not being further developed during SGA1, and the existing tests will be migrated to the new repository. Work on this has not yet begun. |
| | |
| **Downstream Component** | **Status** |
| As for Model Validation Service | See above. |

### 6.8.4.3 Model Validation app

Description of Component: A Collaboratory app for searching, browsing and viewing the results of model validation experiments.

CDP to which Component contributes: CDP2

Progress on Component: A prototype web browser-based graphical interface has been developed, deployed, and made available to members of SP6. The current version is not deeply integrated into the Collaboratory (except for authentication), and can be used either within the Collaboratory or as a standalone website (see screenshots).

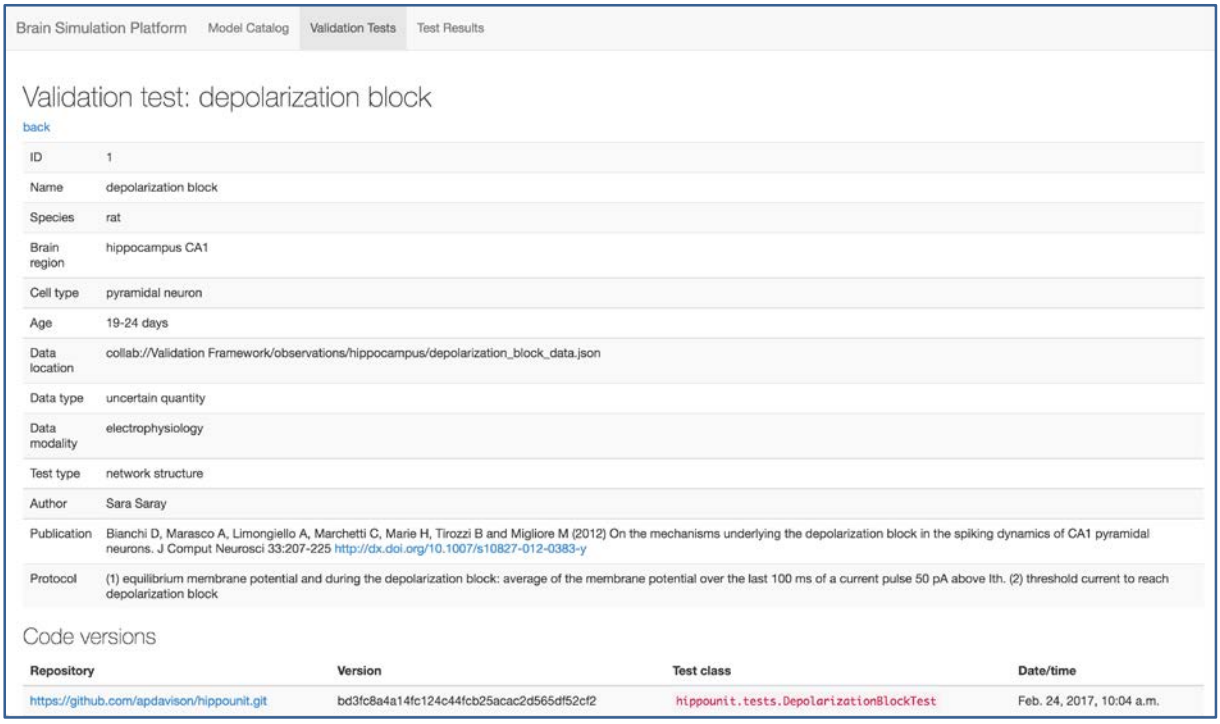


**Figure 23: Prototype Model Validation app showing an example validation test definition**

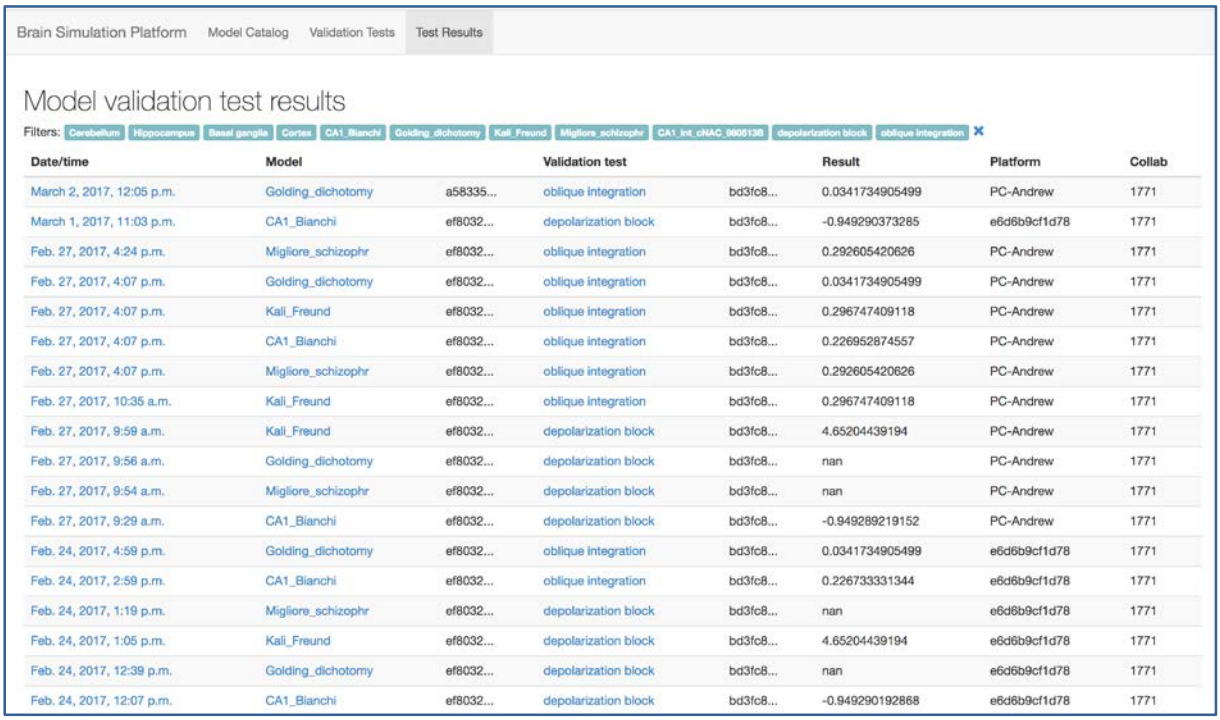


**Figure 24: Prototype Model Validation app displaying a list of validation test results**

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **Model Validation app** | |
|---|---|
| **Upstream Component** | **Status** |
| As for Model Validation Service | See above. |
| | |
| **Downstream Component** | **Status** |

| | |
|---|---|
| As for Model Validation Service | See above. |

## 6.9 T6.4.5 Technical Support for Community Model Building and Validation

### *6.9.1 Key Personnel*

Task Leader: Michele MIGLIORE (CNR)

Other Researcher: Rosanna MIGLIORE (CNR)

Other Researcher: Luca Leonardo BOLOGNA (CNR)

### *6.9.2 SGA1 DoA Goals*

To provide engineering support to the community which uses HBP tools to build and validate data-driven models. This will include maintenance and support of open-source tools for data-driven model building along with developer support for community groups using and extending the tools. This effort will contribute to fostering a self-sustaining community around some of the tools needed for data-driven modelling efforts.

### *6.9.3 Task Achievement Summary*

The main achievement of this Task consists of the design and implementation of web applications and Jupyter notebooks for data-driven model building, setup around three sets of use cases: 1) electrophysiological features extraction, allowing to select raw experimental data (provided by HBP members and/or external contributors), extract feature of interest from selected traces, and generate a set of output files the final; 2) an ensemble of Jupyter notebooks to fit synaptic events using data and models from either the Neuroinformatics Platform (NIP), or user own; 3) Jupyter notebooks to configure and run a cell parameter optimisation, choosing from HBP data for morphology, channel kinetics, features, and parameters. Guidebook entries have been written and constantly updated; they describe the applications in details and guide the users through their functionalities.

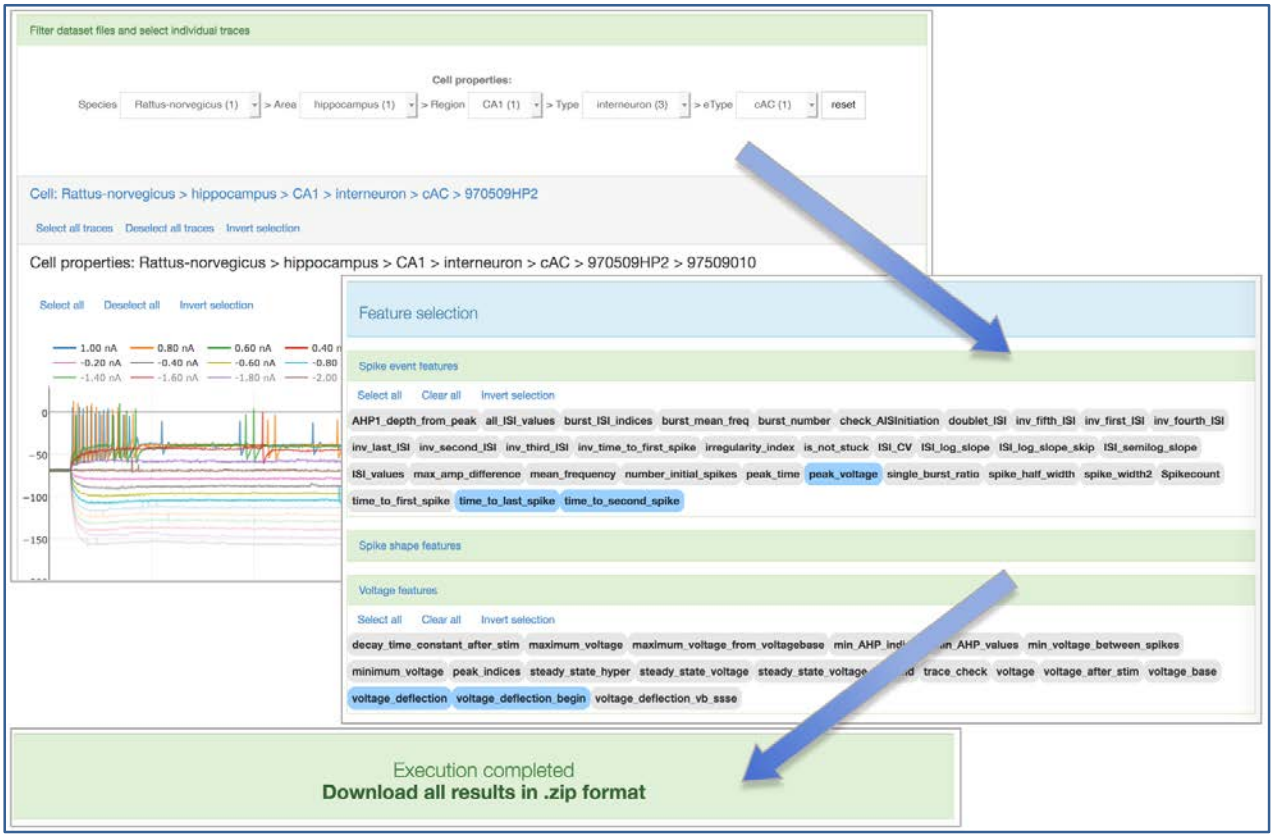


**Figure 25: Screenshots displaying the use of the Feature Extraction Graphical User Interface.**

#### 6.9.3.1 Engineering support to build data-driven models

Description of Component: This Component provides a user-friendly interface to allow users to perform an easy extraction of electrophysiological activity features, needed for data-driven model construction.

CDP to which Component Contributes: CDP2, Mouse-Based Cellular Cortical and Subcortical Microcircuit Models; CDP2-UC-001: Single cell modelling

Progress on Component: Planned release achieved. Entry in the HBP Software Catalog created. Partner CNR has released the Component, and it is already in use on the BSP. The relative App is available in the public Collab:

https://collab.humanbrainproject.eu/#/collab/1655/nav/15470

The next release is planned for M20 and will include additional functionalities, such as integration with the Allen Institute Brain Atlas, the possibility to read different file formats, and functions for selection of specific groups of traces.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.4.5-SGA1-Engineering support to build data-driven models** | |
|---|---|
| **Upstream Component** | **Status** |
| SP6-T6.4.4-SGA1-Model Validation Service | We have received high quality Components from most of them. There were no major problems in the implementation process. However, all upstream components from the Neuroinformatics Platform are still missing. To ameliorate this problem, the data that other partners have decided to |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models | |

| | |
|---|---|
| SP6-T6.4.4-SGA1-Validation test repository | make visible to internal/external users are currently stored in a local server and fetched through custom code. |
| STP data | |
| UNICORE | |
| Neo | |
| HPC systems at JSC | |
| HPC systems at Cineca | |
| Electrophysiological recordings of primary neuron types of rat hippocampal CA1 | |
| eFEL | |
| Collaboratory Storage UI | |
| Collaboratory Storage Service | |
| HPAC Authentication & Autorisation Infrastructure Services | |
| Collaboratory Web UI | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons | As of 12 February 2017, internal and external use is monitored and demonstrated by Google Analytics tools and other tools developed in the other Component of this Task: the number of new users who accessed the application to date is 32, for an overall number of 131 sessions, 64% of which comprised multi-page visits. The percentage of users accessing the web application who were not part of the developers' team was 84%. |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | |
| Technical coordination SP6 | |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus | |
| Collaboratory Storage UI | |
| Collaboratory Web UI | |
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
| BlueBuilder | |

### 6.9.3.2 Brain Simulation Platform access

Description of Component: A Collaboratory app for providing a user-friendly interface to access BSP services.

CDP to which Component Contributes: CDP2, Mouse-Based Cellular Cortical and Subcortical Microcircuit Models; CDP2-UC-001: Single cell modelling

Progress on Component: Planned release achieved. Component has been released by Partner CNR, it is integrated in the BSP and the relative code is included in several Use Cases related to subcellular and single cell model and simulation. It allows Collaboratory users to access the Neuroscience Gateway Portal through REST APIs, and UNICORE access to JSC and CINECA HPC systems. Examples of its use are:

https://collab.humanbrainproject.eu/#/collab/1655/nav/15470

https://collab.humanbrainproject.eu/#/collab/1655/nav/16442

https://collab.humanbrainproject.eu/#/collab/1655/nav/17359

https://collab.humanbrainproject.eu/#/collab/1655/nav/16708

https://collab.humanbrainproject.eu/#/collab/1269/nav/13763

The code is available in the HBP Software Catalog, and it has been developed in collaboration with T6.4.6. The next release is expected at M24 and will include more features, such as integration with the NIP and access to the cellular level microcircuit models.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.4.5-SGA1-Brain Simulation Platform access | |
|---|---|
| **Upstream Component** | **Status** |
| HBP Identity Service | We have received high quality Components from all of them. There were no major problems in the implementation process. However, important weaknesses and limitations of the Collaboratory, especially those related to the use of Jupyter notebooks, reduce user friendliness and limit functionality. |
| Collaboratory Service | |
| Collaboratory Web UI | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons | Using or will be using this component. |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | |
| Technical coordination SP6 | |
| coreneuron | |
| Collaboratory Service | |
| Collaboratory Web UI | |

### 6.9.3.3 Support of open-source tools for configuration of data-driven models

Description of Component: This component will provide a user-friendly interface to configure and launch optimisation processes on remote HPC systems.

CDP to which Component Contributes: CDP2, Mouse-Based Cellular Cortical and Subcortical Microcircuit Models; CDP2-UC-001: Single cell modelling

Progress on Component: Planned release achieved. Component has been released by Partner CNR, and is already integrated into several use cases on the BSP. It allows the configuration and launch, from the Platform, of the optimisation procedure on the Cineca MARCONI supercomputer systems, and on the Neuroscience Gateway Portal.

The code is available in the HBP Software Catalog, as a part of a number of Collabs using it.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
|---|---|
| **Upstream Component** | **Status** |
| SP5 - HPC workflow to analyse HCP data | We have received high quality Components from all of them. There were no major problems in the implementation process. |
| HBP Software Engineering and Quality Assurance Approach | |
| SP6-T6.4.4-SGA1-Model Validation Service | |
| SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models | |

| | |
|---|---|
| SP6-T6.4.4-SGA1-Validation test repository | |
| HBP Identity Service | |
| HPC systems at JSC | |
| HPC systems at Cineca | |
| Collaboratory Web UI | |
| BluePyOpt | |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons | Using or will be using this Component. |
| SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus | |
| SP5 - Registration of HCP dataset | |
| HBP Software Engineering and Quality Assurance Approach | |
| Technical coordination SP6 | |
| SP6-T6.2.4-SGA1-Circuit model of the rat hippocampus | |
| Collaboratory Web UI | |

## 6.10 T6.4.6 Platform Administration and Operations

### *6.10.1 Key Personnel*

Task Leader: Michele MIGLIORE (CNR)

Other Researcher: Luca Leonardo BOLOGNA (CNR)

### *6.10.2 SGA1 DoA Goals*

To provide deployment, monitoring and updating of the common services that sit behind the Platforms. This includes the support of configuration and deployment services, and the hosting of web applications. It also includes some operations support for the developers of the Platforms.

### *6.10.3 Task Achievement Summary*

The main achievements of this Task consists of the backend configuration, hosting, setting and deployment of the applications developed to build and validate data-driven models. Web applications have been configured to be tracked for usage statistics through the Google Analytics platform and backend logging (see Fig. 2-A). A service for configuring HPC resources to launch fitting and optimisation procedures for model building has been developed, leveraging the Rest APIs provided by the HPC systems (i.e. Unicore and NSG access service). Additionally, a complementary service to monitor the status of the jobs launched on the remote systems and to fetch the output has been implemented and a graphical user interfaces provided. Finally, two datasets for managing electrophysiological raw data and cell parameter optimisation results have been created and are currently hosted and updated on private backend servers and github public repository.

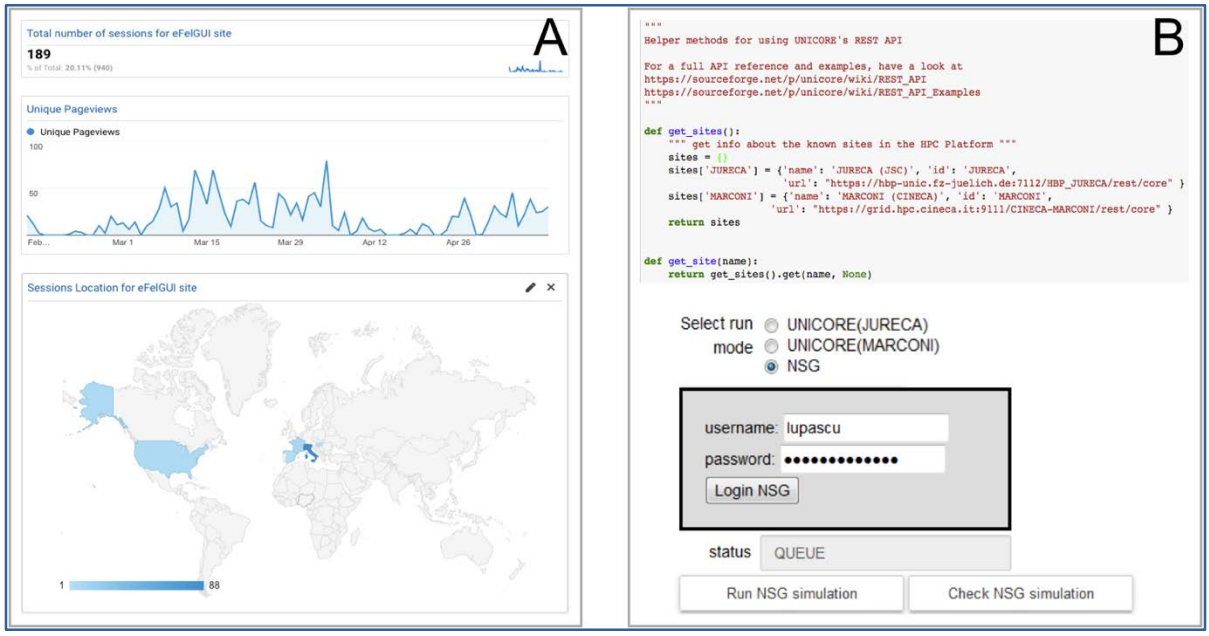


**Figure 26: Brain simulation platform common services.**

**A) App statistics as monitored via Google Analytics; B) Python code and user interface for launching and monitoring processes on HPC systems.**

#### 6.10.3.1 Web hosting, deployment, monitoring and updating of platform services for data-driven models

Description of Component: This component provides the services needed to deploy, monitor, update and host the web applications developed for support to data-driven models.

CDP to which Component Contributes: CDP2, Mouse-Based Cellular Cortical and Subcortical Microcircuit Models; CDP2-UC-001: Single cell modelling

Progress on Component: Planned release of service achieved. Entry in the HBP Software Catalog created. The Component has been released by Partner CNR, and it is already in use on the BSP. The service provided by this Component, allowed to host in a local server the data that other partners would like to be visible to internal/external users. This includes the setup and management of a virtual machine and a server used to deploy and host user-specific apps and data. The next release is expected at M24 and will include hosting more user apps, and an initial installation of an umbrella user to access the Neuroscience Gateway. This will greatly facilitate internal/external users in their initial approach with the BSP Use Cases. Internal and external use is monitored and demonstrated by Google Analytics and other tools developed in the other Component of this Task. As a representative example, the usage monitoring of the "Feature Extraction Graphical User Interface" web application, developed for providing engineering support to build data-driven model, resulted in the following statistics, collected as of 12 February 2017 to date: 32 new, 131 sessions (64% of which comprised multi-page visits), 84% of users not being part of the development team.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.4.6-SGA1-Web hosting, deployment, monitoring and updating of platform services for data-driven models** | |
|---|---|
| **Upstream Component** | **Status** |
| HBP Software Engineering and Quality Assurance Approach | We have received high quality Components from most of them. There were no major problems in the implementation process. However, important weaknesses and limitations of |
| NEST - The Neural Simulation Tool | |

| | |
|---|---|
| STEPS | the Collaboratory, especially related to the use of Jupyter notebooks, reduce user friendliness and limit deployment and functionality. |
| NEURON | |
| Neurodamus | |
| coreneuron | |
| SP6-T6.4.4-SGA1-Validation test repository | |
| SP6-T6.4.4-SGA1-Model Validation Service | |
| HPAC Authentication & Autorisation Infrastructure Services | |
| Collaboratory Web UI | |
| Python | |
| | |
| **Downstream Component** | **Status** |
| SP6-T6.4.5-SGA1-Engineering support to build data-driven models | Many of them are already using this Component |
| SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models | |
| BlueBuilder | |
| BluePyOpt | |
| BrainBuilder Framework | |
| JS Circuit Viewer | |
| JS Provenance Viewer | |
| Js Simulation Configutation | |
| ModelManagement | |
| Morphology repair and diversification framework | |
| Technical coordination SP6 | |
| HBP Software Engineering and Quality Assurance Approach | |
| Single cell electrical model validation | |
| Single morphology validation | |

#### 6.10.3.2 A software package to help developers collect statistics on Collaboratory apps

Description of Component: A software package to help developers collect statistics on Collaboratory apps.

CDP to which Component Contributes: CDP2, Mouse-Based Cellular Cortical and Subcortical Microcircuit Models; CDP2-UC-001: Single cell modelling

Progress on Component: Under development. A release is expected at M20 and will include a package to collect statistics for Collabs using the Neuroscience Gateway, and HPC systems at the JSC and CINECA.

Quality Control (Note: includes only scientific/technical Components and not those of the coordination Tasks, WP6.5):

| **SP6-T6.4.6-SGA1-Software package for collecting Collaboratory apps statistics** | |
|---|---|
| **Upstream Component** | **Status** |
| Collaboratory | We have received high quality Components from all of them. There were no major problems in the implementation process. |
| SP6-T6.4.4-SGA1-Validation test repository | |

| | |
|---|---|
| SP6-T6.4.4-SGA1-Model Validation Service | |
| HBP Identity Service | |
| Collaboratory Service | |
| Python | |
| | |
| **Downstream Component** | **Status** |
| Graphical User Interface (GUI) to configure the procedure to fit synaptic events | Using or will be using this Component. |
| Collaboratory Web UI | |

# 7. WP6.5. Coordination and Community Outreach

## 7.1 Key Personnel

Work Package Leader: Jeanette Hällgren KOTALESKI (KTH)

## 7.2 WP Leader's Overview

The SP monthly meetings have worked very well with status updates from every Task. This has enabled the researchers increased opportunities to keep track of the progress from other groups that they need to collaborate with or whose work they depend on. Furthermore, a regular backlog planning of groups involved in the Platform development has been established, allowing a tight alignment of the technical work between different groups.

The work in this Work Package has enabled the SP to progress smoothly and keep track of upcoming reporting, etc. and has improved the collaborations with the other SPs, for example via the SP6 data specification document which has enabled data-providing SPs to, at an early stage, incorporate this into their SGA2 planning.

Information flow from HBP central management and timeliness of SIB decisions have been challenging at times leading to unnecessarily short deadlines and unnecessary uncertainty.

## 7.3 Priorities for the remainder of the phase

This Task will for the remainder of SGA1 continue with the successful monthly SP meetings, representing SP6 at management meetings/science coordination meetings, as well as coordinate the planning of SGA2 and the reporting from SGA1.

## 7.4 Milestones

**Table 5: Milestones for WP6.5 - Coordination and Community Outreach**

| MS No. | Milestone Name | Leader | Task(s) involved | Expected Month | Achieved Month | Comments |
|---|---|---|---|---|---|---|
| MS6.5.1 | SP6 roadmap for SGA2 | KTH | ALL SP6 | APR 2017 | APR 2017 | The SGA2 work plan was uploaded into EMDESK. |

## 7.5 T6.5.1 Scientific Coordination and Support

### *7.5.1 Key Personnel*

Task Leader: Jeanette Hällgren KOTALESKI (KTH)

Other Researcher: Daniel VARE (KTH)

Other Researcher: Felix SCHÜRMANN (EPFL)

Other Researcher: Katrien VAN LOOK (EPFL)

### *7.5.2 SGA1 DoA Goals*

- Coordinate the Subproject reporting and writing of Deliverables
- Monitor scientific progress within the Subproject
- Organise SP-wide meetings
- Coordinate with the External Relations Team on issues related to innovation
- Coordinate with the Ethics Manager and with SP12 on issues related to ethics
- Provide support to Partners for administration, innovation, training and ethics
- Act as a point of contact with the Project Coordination Office

### *7.5.3 Task Achievement Summary*

The SP6 scientific coordination and support for the period has performed according to expected and has coordinated the SPs monthly scientific updates, has created Task progress sheets that have been regularly updated and distributed to the related researchers at the monthly meetings. In addition, this Component has been the contact point between SP6 and the Project Coordination Office in respect of SP management and scientific coordination. This Task was also involved in arranging the HBP summit 2016.

### *7.5.4 Component Progress*

#### 7.5.4.1 SP6-T6.5.1-SGA1-Brain Simulation Platform - Results for SGA1 Period 1

Description of Component: WPs involved: WP6.1, WP6.2, WP6.3, WP6.4 & WP6.5

- Brain Simulation Platform v2: This Deliverable will consist of the second formal release of the BSP and related documentation. The Platform, accessible to end-users via the HBP Collaboratory, will provide access to tools, apps and services developed in WP6.3 and WP6.4 (based on co-design drivers from WP6.1 and WP6.2, as well as CDP1 and CDP2).
- Scaffold model Collabs release v2: This Deliverable will expose the latest releases of models and simulations of the scaffold modelling activities of WP6.1 and WP6.2 in their respective Collabs, and showcase the underlying workflows of the BSP.
- CDP2 Collab release v2: CDP2 Deliverable: This Deliverable will expose the models and simulations of CDP2 in the respective Collab and showcase the underlying workflows of the BSP and other platforms.

Progress on Component: This Component is the M12 Deliverable.

#### 7.5.4.2 SP6-T6.5.1-SGA1-Brain Simulation Platform - Results for SGA1 Period 2

Description of Component: WPs involved: WP6.1, WP6.2, WP6.3, WP6.4 & WP6.5

Progress on Component: This Component starts at M13.

## 7.6 T6.5.2 Technical Coordination and Support

### *7.6.1 Key Personnel*

Task Leader: Egidio D'ANGELO (UNIPV)

Other Researcher: Simona TRITTO (UNIPV)

Other Researcher: Felix SCHÜRMANN (EPFL)

Other Researcher: Jean-Denis COURCOL (EPFL)

Other Researcher: Michele MIGLIORE (CNR)

### *7.6.2 SGA1 DoA Goals*

T6.5.2 will be responsible for technical coordination within the Subproject, and for coordination with other SPs and will lead technical implementation work for CDP2. This work will involve: coordination of Platform testing; standardisation of data formats, terminology and development processes; coordination of documentation and dissemination of standards; coordination of software development; coordination of user engagement and training; and representation of SP6 on the SP Technical Coordinators Committee.

### *7.6.3 Task Achievement Summary*

During this reporting period the technical coordinator has followed up the new BSP release with regular meetings with the Partners involved (CNR, EPFL, UNIPV, KTH and CNRS) and setting up the new BSP Collaboratory. Importantly, a weekly SP6 development meeting has been set up, which provides a forum for fine-grained alignment and prioritisation of activities between members of the various groups that contribute to SP6 tool and Platform goals. All ongoing activities and blocking items are tracked in a common Kanban-like worksheet. Researchers from different Partners visited each other for extended periods for deep technical discussions.

One input to the new BSP release is the coherent use of classifying workflows of the Platform as "everybody", "power user" and "expert" (see Figure 26). These labels are meant to help give a more consistent experience to the platform users. For example, "everybody" will indicate an easy to use workflow with a predefined user interface; "power user" may imply that the workflow is exposed as a Jupyter notebook, allowing the user to customise the workflow; "expert" exposes the full capability of the Platform, e.g. allowing the user to redirect to different backends. These labels are also used in the development process to decide which target technology is to be used to expose a functionality.

The Neuroinformatics Platform (NIP) and High Performance Analytics and Computing (HPAC) Platform are critical dependencies for the BSP. As pointed out in the risk overview, due to the restructuring following the DPIT process of SP5, joint interface work between NIP has been delayed. SP6 therefore has approached SP5 to set up regular meetings to align respective work plans. The focus is to maximise SP5 support for the revised BSP. Similarly, SP6 has approached SP7 for regular interactions to advance technical integration on aspects such as containers and Jupyter notebooks.

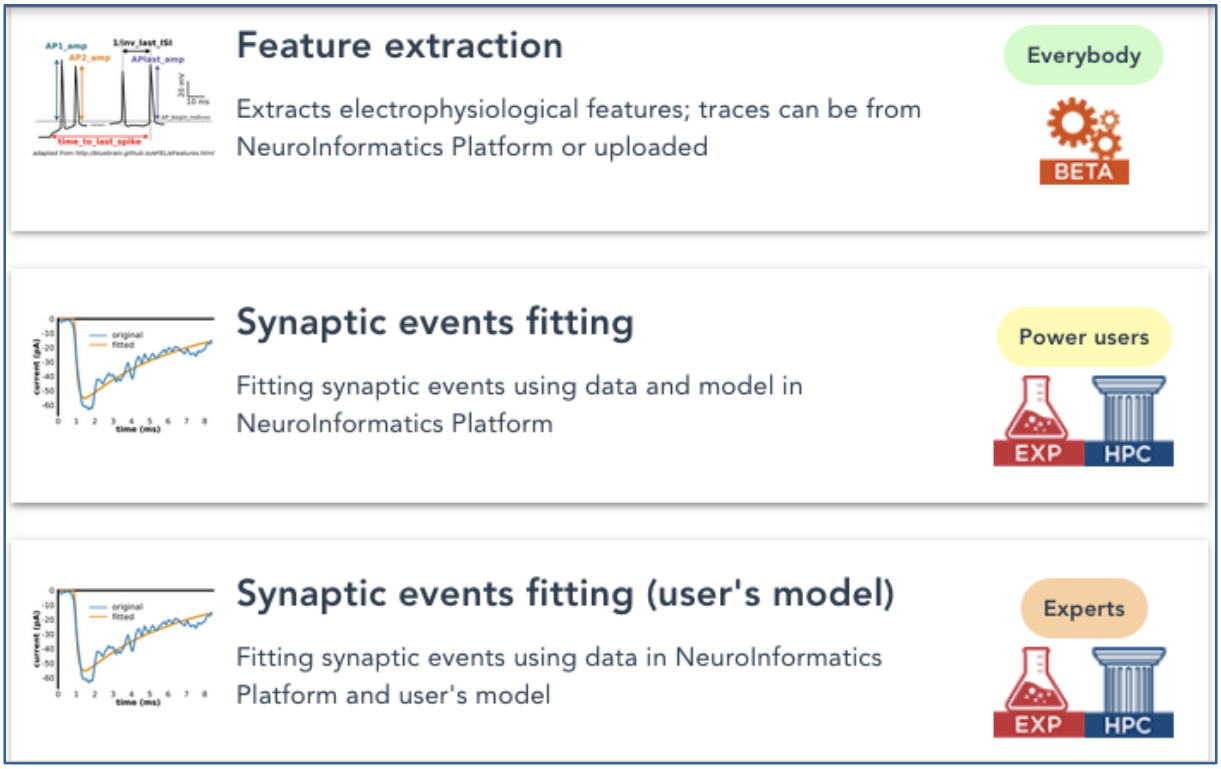


**Figure 27: Labels used in the new Brain Simulation Platform to indicate ease of use of workflows.**

SP6 furthermore is planning a Hackathon on June 6-9 in Geneva with members from SP5, SP6 & SP7 with the focus on Single Cell modelling.

All these activities are reported in the related collabs:

(https://collab.humanbrainproject.eu/#/collab/1622/nav/14347; https://collab.humanbrainproject.eu/#/collab/332/nav/2763).

CDP2 has been included in the SGA2 proposal; the technical coordinator follows up on Component and Task dependencies.

### *7.6.4 Component Progress*

No component to report, contributes to component: HBP Software Engineering and Quality Assurance Approach.

## 7.7 T6.5.3 Community Coordination and Support

### *7.7.1 Key Personnel*

Task Leader: Eilif MULLER (EPFL)

Other Researcher: Michele MIGLIORE (CNR)

Other Researcher: Egidio D'ANGELO (UNIPV)

Other Researcher: Szabolcs KÁLI (IEM HAS)

Other Researcher: Armando ROMANI (EPFL)

Other Researcher: Katrien VAN LOOK (EPFL)

Other Researcher: Hans Ekkehard PLESSER (NMBU)

### 7.7.2 SGA1 DoA Goals

The Task will be responsible for supporting community activities in the SP. This work will include community engagement and outreach to grow the community of users of the BSP, such as participation in and organisation of workshops and training, site visits to work with early adopters, catalysing success stories and development of scalable dissemination strategies. The Task will act as a point of contact between the SP and community users and coordinate communications towards participating communities.

### 7.7.3 Task Achievement Summary

In this period, we have been involved with organising the HBP booth at FENS (2-6 July 2016), at the INCF annual conference (3-4 September 2016) and at the Society for Neuroscience (SfN, 12-16 November 2016). At these conferences we engaged with potential users of the Platform and performed short demonstrations at the FENS and SfN conference booths. At FENS we also organised a technical workshop "Introduction to the Human Brain Project Collaboratory" and participated in a satellite event workshop "Cells, Circuits and Computation: Expanding the Horizons of Big Data Analysis", co-organised with the Allen Institute. This event provided hands-on training of novel analysis tools from the Platform and from the Allen Institute. At SfN 2016, Marc-Oliver GEWALTIG, Eilif MULLER, Jeff MULLER, David LESTER and Andrew DAVISON, representing SP6, SP9, SP10 and SP12, co-organised a satellite workshop "Collaborative Neuroscience and Enabling Infrastructure" (https://www.humanbrainproject.eu/sfn-2016-satellite), and SP6 participated in the satellite workshop “Using the Neuroscience Gateway Portal for Parallel Simulations”.

Several members of SP6 participated, and presented talks and posters (Szabolcs KÁLI, Michele MIGLIORE, Armando ROMANI, Andrew DAVISON, Eilif MULLER), in a workshop “Collaborative Development of Data-Driven Models of Neural Systems” on the Janelia Research Campus (18-21 September 2016). This was a very productive workshop with stimulating discussions on topics such as, approaches to enable collaborative modelling, tools for morphological reconstruction and model validation, and standards for model representation.

SP6 and the BSP were also represented in the HBP delegation which participated in the US Brain Initiative Summit (12-14 December 2016) in Washington DC. An HBP booth with projection system was organised and several presentations on the BSP were given by Egidio D’ANGELO, Eilif MULLER and Marc-Oliver GEWALTIG. Marc-Oliver GEWALTIG (SP6 and SP10) presented a short summary of the BSP in the meeting’s main track. Participation in the US Brain Summit was very productive; to meet US Brain Initiative counterparts and establish links and contacts for further interactions.

Organisation for a follow-up meeting to the community engagement workshop “HBP HippocampCA1: Collaborative and Integrative Modeling of Hippocampal CA1” is underway in collaboration with SP4, with the meeting due to be held 23-24 May 2017 at the EITN in Paris. The meeting will again be focused on growing a user and development community of the collaborative data-driven models of hippocampus being developed using the HBP BSP.

Work is underway, on a series of open online courses tightly coupled to the HBP BSP to teach students to use the BSP to model neurons, networks, and simulate them. The first such online course, focused on neuron modelling, is on track to be launched in June 2017. This work is in collaboration with the EPFL Center for Digital Education, and benefits from additional funding from sources external to the HBP.

Other workshops and courses where SP6 work was represented to the community include:

- NEST user workshop (3-4 November 2016)
- School of Brain Cells & Circuits “Camillo Golgi” (1-5 December 2016)
- 3rd Human Brain Project School, Future Neuroscience (28 November-4 December 2016)

- 1st HBP Open Day (12 October 2016) that took place before the HBP Summit.

### *7.7.4 Component Progress*

#### 7.7.4.1 SP6-SGA1-Community coordination

Description of Component: Provide coordination to build the community via workshops and training, and provide support via various communication channels and activities.

CDP to which Component contributes (if relevant): CDP2

Progress on Component: This period saw active participation at selected conferences (FENS, SfN), the organisation of and participation in a number of workshops (FENS, SfN, Janelia Research Campus), and the organisation and involvement in training/education workshops (NEST user workshop, "Camillo Golgi" School, HBP School). Work is underway on a first open online course to teach students Simulation Neuroscience of neurons using the HBP BSP to build morphologically detailed data-driven neuron models, and is on track to be launched in June 2017.

Quality Control:

| **SP6-SGA1-Community coordination** | |
|---|---|
| **Upstream Component** | **Status** |
| This Component/Task works closely with the Subproject's Scientific Soordination (T6.5.1) and Technical Coordination (T6.5.2). | Ongoing |
| | |
| **Downstream Component** | **Status** |
| This Component/Task works closely with the Subproject's Scientific Coordination (T6.5.1) and Technical Coordination (T6.5.2). | Ongoing |
| Report on Collaborations and Partnerships, T11.4.4 | Milestone due in M15 (MS11.4.4) |

# 8. CDP2 Mouse-based Cellular Cortical and Sub-Cortical Microcircuit Models

## 8.1 Key Personnel

CDP Science Leader: Egidio D'ANGELO (UNIPV)

CDP Implementation Leader: Michele MIGLIORE (CNR)

## 8.2 CDP Leader's Overview

CDP2 is on schedule or ahead of schedule on some of its activities.

- What went particularly well?

The activity of CDP2 developed along the three use cases.

In Use Case1 we have performed optimisation of granule cells (paper published) and of stellate cells, Golgi cells and Purkinje cells (papers in preparation). In all cases we have used the OptimizerFramework or BluePyOpt and optimisations have been successful. All these cases have posed specific technical and scientific questions, which have been faced providing substantial feedback to refine the BluPyOpt software and its accessibility by general users through the BSP. The optimisation pipeline for granule cell optimisation is now available in Jupiter Notebook on the Collaboratory.

In Use Case2, the development of pipelines for brain microcircuits models is in progress along with the tools required for their implementation. We have been dealing with the cerebellum, basal ganglia and hippocampus, which have posed specific technical and scientific questions, which have been critical to provide effective feedback to generalise tools in the BSP. In particular, new pipelines have been developed for these microcircuits allowing 3D orientation of neuronal processes and providing the basis for extended and flexible connectivity rules. New brain builder pipelines for cerebellum and hippocampus are now available in Jupiter Notebook on the Collaboratory. Papers are in progress.

In Use Case2, we are also proceeding along the simplification process of neuron models and the construction of simplified large-scale networks. This is leading to implement a full cerebellum network into the brain model developed in collaboration with CDP1. Abstracts submitted to OCNS.

In Use Case 3, the simulation of local field potentials from 3D microcircuits has progressed considerably. A new computational module for NEURON has been developed and tested and is now freely available. The paper has been published.

- What didn't go according to plan?

The availability of HPC resources for running simulations is a risk due to the fact the users will have to individually ask for allocations that may or may not be granted. The relevance of this problem is expected to increase with the size and scale of simulations and the number of users.

- Impact of work done

The impact of work done is measurable in terms of tool development and pipeline implementation in the Collaboratory. Some of corresponding papers are already published and others are in progress. Moreover, the attractiveness of this activity for the internal and external community is increasing. We are on schedule for Milestone delivery at M18.

## 8.3 Use Case Progress

### 8.3.1 CDP2-UC-001 - single cell modelling

Use Case Description: Allow users to upload and/or select morphologies and electrical traces from the Neuroinformatics Platform, and use those in an easy-to-use neuron builder that will output a ready-to-run NEURON compatible simulation package.

Use Case Leader: Egidio D'ANGELO (UNIPV)

Contributing Tasks & Components

T6.3.4 (SGA1) Tools for cellular-level simulation

T7.5.2 (SGA1) Data Services

T7.5.3 (SGA1) Low-level Infrastructure Services

T9.1.4 (SGA1) Model and experiment descriptions

T11.3.2 (SGA1) Collaboratory and Research Infrastructure Integration Web Services

T6.4.1 (SGA1) Cellular level apps

T6.3.3 (SGA1) Tools for cellular reconstruction

T4.1.2 (SGA1) Input-output transfer functions of morphologically detailed neuronal models

T4.5.1 (SGA1) Comparing models with mouse and human brains

T7.5.1 (SGA1) HPC and Cloud Services

**Components**

BluePyOpt (software)

Collaboratory Jupyter Notebook (service)

Golgi cell model optimization (model)

Granule cell model optimization (model)

NEURON (software)

Purkinje cell model optimization (model)

## 8.4 Progress summary

### 8.4.1 CDP2-UC-002 - Multi-scale validation

Use Case Description: Validate the cellular level model behaviour against experiments at different scales, for example spiking behaviours at the single cell and microcircuit levels. Start building the bridge to behaviour with simplified representations of the microcircuit level models.

Use Case Leader: Egidio D'ANGELO (UNIPV)

Contributing Tasks & Components:

T7.5.2 (SGA1) Data Services

T7.4.1 (SGA1) Co-design of applications to enable dynamic resource management

T4.1.1 (SGA1) Simplified dendritic neuron models

T7.5.3 (SGA1) Low-level Infrastructure Services

T7.1.4 (SGA1) Massively parallel methods for network construction from rules and data

T4.1.4 (SGA1) Models of brain signals

T7.1.3 (SGA1) Code generation for neuron and synapse models for software and neuromorphic backends

T7.1.1 (SGA1) Integration methods for continuous-time population models

T7.5.6 (SGA1) Platform Integration Services

T6.3.4 (SGA1) Tools for cellular-level simulation

T7.5.1 (SGA1) HPC and Cloud Services

T6.4.1 (SGA1) Cellular level apps

T6.3.3 (SGA1) Tools for cellular reconstruction

T6.4.2 (SGA1) Microcircuit level services

Components:

Cerebellar microcircuit model (model)

Golgi cell model optimization (model)

Granule cell model optimization (model)

Mouse hippocampus model (model)

Purkinje cell model optimization (model)

Simplified model of local field potentials (model)

Simplified neuron models (model)

STDP (data)

### *8.4.2 4.3.3 CDP2-UC-003 In silico microcircuit experimentation*

Use Case Description: The microcircuit model already built by the BBP (Product 6), or the scaffold models (Products 3-5) will be made available as a framework for *in silico* experimentation (using Product 2). For example, together with CDP5, plasticity rules building on calcium signalling together with neuromodulation can be plugged in and tested in our models.

Use Case Leader: Michele MIGLIORE (CNR)

Contributing Tasks & Components:

T1.2.4, T6.2.2, T6.2.3, T6.2.4, T6.2.5, T6.3.3, T6.3.4, T6.4.2, T6.4.4, T6.5.2 (from GA)

Progress summary: The Use Case is under development. We are using Components from most of the involved Tasks. To date, we foresee no major problems or blocking issues in the implementation process. However, it should be noted that: a) all upstream Components from the Neuroinformatics Platform are still missing, b) there are important weaknesses and limitations of the Collaboratory that reduce user friendliness or hinder access, and c) the BSP has not been given institutional access to resources to test the development, deployment, and use of the microcircuit models. To bypass this problem, the development of this Use Case is currently proceeding mostly using custom developed and deployed tools outside the Collaboratory, and HPC allocations granted to the CDP2 Implementation Leader.

## 8.5 Priorities for the remainder of the phase

As noted above, we are on schedule. For the remainder of the phase, the priorities are:

- complete neuron construction, optimisation and validation for cerebellum, hippocampus and basal ganglia, along with corresponding tools and pipelines.
- complete the scaffold network reconstruction in brain builder for cerebellum, hippocampus and basal ganglia, along with corresponding tools and pipelines

- complete neuron simplification in brain builder for cerebellum along with corresponding tools and pipelines.

# 9. Publications

## 9.1 Publications that acknowledge the HBP

Amsalem O, Van Geit W, Muller E, Markram H, Segev I. (2016). From Neuron Biophysics to Orientation Selectivity in Electrically Coupled Networks of Neocortical L2/3 Large Basket Cells. *Cereb Cortex*;26(8):3655-68. doi: 10.1093/cercor/bhw166. Epub 9 June 2016.

Antonietti A, Casellato C, D'Angelo E, Pedrocchi A. (2016). Model-Driven Analysis of Eyeblink Classical Conditioning Reveals the Underlying Structure of Cerebellar Plasticity and Neuronal Activity. *IEEE Trans Neural Netw Learn Syst*; [Epub ahead of print]

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Berthet P, Lindahl M, Tully PJ, Hellgren-Kotaleski J, Lansner A. (2016). Functional Relevance of Different Basal Ganglia Pathways Investigated in a Spiking Model with Reward Dependent Plasticity. *Front Neural Circuits*;10:53. doi: 10.3389/fncir.2016.00053. eCollection 21 July 2016.

Brocke E, Bhalla US, Djurfeldt M, Hellgren Kotaleski J, Hanke M. (2016). Efficient Integration of Coupled Electrical-Chemical Systems in Multiscale Neuronal Simulations. *Front Comput Neurosci*;10:97. doi: 10.3389/fncom.2016.00097. eCollection 12 September 2016.

Casasnovas R, Limongelli V, Tiwary P, Carloni P, Parrinello M. (2017). Unbinding Kinetics of a p38 MAP Kinase Type II Inhibitor from Metadynamics Simulations. *J Am Chem Soc*; doi: 10.1021/jacs.6b12950. [Epub ahead of print]

- T6.1.1
- Components: SP6-T6.1.1-SGA1-Ligand design for brain imaging; SP6-T6.1.1-SGA1-All Atom Molecular Dynamics; SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters

Cellot G, Maggi L, Di Castro MA, Catalano M, Migliore R, Migliore M, Scattoni ML, Calamandrei G, Cherubini E. (2016). Premature changes in neuronal excitability account for hippocampal network impairment and autistic-like behavior in neonatal BTBR T+tf/J mice. *Sci Rep*;6:31696. doi: 10.1038/srep31696.

- T1.1.4, T6.4.5, T6.4.6
- Components: Report on functional in vivo interaction data between synaptic proteins of the neuroligin and the neuroxin families, and their use for the computational modeling of trans-synaptic signalling

D'Angelo E, Antonietti A, Casali S, Casellato C, Garrido JA, Luque NR, Mapelli L, Masoli S, Pedrocchi A, Prestori F, Rizza MF, Ros E. (2016). Modeling the Cerebellar Microcircuit: New Strategies for a Long-Standing Issue. I;10:176. doi: 10.3389/fncel.2016.00176. eCollection 8 July 2016. Review.

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Dover K, Marra C, Solinas S, Popovic M, Subramaniyam S, Zecevic D, D'Angelo E, Goldfarb M. (2016). FHF-independent conduction of action potentials along the leak-resistant cerebellar granule cell axon. *Nat Commun*;7:12895. doi: 10.1038/ncomms12895.

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Eyal G, Verhoog MB, Testa-Silva G, Deitcher Y, Lodder JC, Benavides-Piccione R, Morales J, DeFelipe J, de Kock CP, Mansvelder HD, Segev I. (2016). Unique membrane properties and enhanced signal processing in human neocortical neurons. *Elife*. 6 October 2016;5. pii: e16553. doi: 10.7554/eLife.16553.

Garrido JA, Luque NR, Tolu S, D'Angelo E. (2016). Oscillation-Driven Spike-Timing Dependent Plasticity Allows Multiple Overlapping Pattern Recognition in Inhibitory Interneuron Networks. *Int J Neural Syst*;26(5):1650020. doi: 10.1142/S0129065716500209. Epub 15 April 2016.

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Grillner S, Robertson B. (2016). The Basal Ganglia Over 500 Million Years. *Curr Biol*;26(20):R1088-R1100. doi: 10.1016/j.cub.2016.06.041. Review.

- T1.2.3, T5.8.2, T5.8.3, T6.2.5
- Components: Cellular properties of neurons within striatum, Connectivity and morphology of neurons within striatum, Integrated data sources, Cell type ontologies, Models of basal ganglia nuclei

Gulyás AI, Freund TF, Káli S. (2016). The Effects of Realistic Synaptic Distribution and 3D Geometry on Signal Integration and Extracellular Field Generation of Hippocampal Pyramidal Cells and Inhibitory Neurons. *Front Neural Circuits*;10:88. doi: 10.3389/fncir.2016.00088.

- T1.2.5, T6.2.4
- Components: Database of all the major excitatory and inhibitory cell types of the mouse hippocampus, using a combination of morphological and electrophysiological classification; SP6-T6.2.4-SGA1-Models of rat hippocampal neurons; SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons

Ippen T, Eppler JM, Plesser H and Diesmann M. (2017). Constructing neuronal network models in massively parallel environments. *Front. Neuroinform*;11:30. doi:10.3389/fninf.2017.00030

- T6.3.5, T7.1.4
- Components: Prototype NEST simulation kernel with directed spike exchange (T6-3-5); Rule- and data-based connectivity generation in NEST (T7.1.4).

Kohus Z, Káli S, Rovira-Esteban L, Schlingloff D, Papp O, Freund TF, Hájos N, Gulyás AI. (2016). Properties and dynamics of inhibitory synaptic communication within the CA3 microcircuits of pyramidal cells and interneurons expressing parvalbumin or cholecystokinin. *Journal of Physiology*;594:3745-3774. doi: 10.1113/JP272231.

- T1.2.5, T1.2.6, T6.2.4
- Components: Database of all the major excitatory and inhibitory cell types of the mouse hippocampus, using a combination of morphological and electrophysiological classification; Protocol for paired recordings in hippocampal slices which display in

vivo-like activity levels and patterns; Database of paired recordings in hippocampal slices which display in vivo-like activity levels and patterns; SP6-T6.2.4-SGA1-Models of mouse hippocampal neurons; SP6-T6.2.4-SGA1-Circuit model of the mouse hippocampus

Lindahl M, Hellgren Kotaleski J. (2017). Untangling Basal Ganglia Network Dynamics and Function: Role of Dopamine Depletion and Inhibition Investigated in a Spiking Network Model. *eNeuro*;3(6). pii: ENEURO.0156-16.2016. doi: 10.1523/ENEURO.0156-16.2016. eCollection 12 January 2017.

- T1.2.3, T5.8.2, T5.8.3, T6.2.5
- Components: Cellular properties of neurons within striatum, Connectivity and morphology of neurons within striatum, Integrated data sources, Cell type ontologies, Models of basal ganglia nuclei

Lupascu CA, Morabito A, Merenda E, Marinelli S, Marchetti C, Migliore R, Cherubini E, Migliore M. A General Procedure to Study Subcellular Models of Transsynaptic Signaling at Inhibitory Synapses. Front Neuroinform. 2016 Jun 30;10:23. doi: 10.3389/fninf.2016.00023. eCollection 30 June 2016.

- T1.1.4, T6.4.5, T6.4.6
- Components: STP model, Graphical User Interface (GUI) to configure the procedure to fit synaptic events, Report on functional in vivo interaction data between synaptic proteins of the neuroligin and the neuroxin families, and their use for the computational modelling of trans-synaptic signalling, SP6-T6.4.5-SGA1-Support of open-source tools for configuration of data-driven models

Masoli S, Rizza MF, Sgritta M, Van Geit W, Schürmann F, D'Angelo E. (2017). Single Neuron Optimization as a Basis for Accurate Biophysical Modeling: The Case of Cerebellar Granule Cells. *Front. Cell. Neurosci*;11:71. doi: 10.3389/fncel.2017.00071

Nair AG, Bhalla US, Hellgren Kotaleski J. (2016). Role of DARPP-32 and ARPP-21 in the Emergence of Temporal Constraints on Striatal Calcium and Dopamine Integration. *PLoS Comput Biol*;12(9):e1005080. doi: 10.1371/journal.pcbi.1005080. eCollection 1 September 2016.

Parasuram H, Nair B, D'Angelo E, Hines M, Naldi G, Diwakar S. (2016). Computational Modeling of Single Neuron Extracellular Electric Potentials and Network Local Field Potentials using LFPsim. *Front Comput Neurosci*;10:65. doi: 10.3389/fncom.2016.00065. eCollection 28 June 2016.

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Sgritta M, Locatelli F, Soda T, Prestori F, D'Angelo EU. (2017). Hebbian Spike-Timing Dependent Plasticity at the Cerebellar Input Stage. *J Neurosci*;37(11):2809-2823. doi: 10.1523/JNEUROSCI.2079-16.2016. Epub 10 February 2017.

- T6.2.3
- Components: Cerebellum electrophysiological pipeline, Cerebellum application model, Cerebellum scaffold models

Tong R, Wade RC, Bruce NJ. (2016). Comparative electrostatic analysis of adenylyl cyclase for isoform dependent regulation properties. *Proteins*;84(12):1844-1858. doi: 10.1002/prot.25167. Epub 24 October 2016.

- T6.1.1

- Components: SP6-T6.1.1-SGA1-Brownian dynamics simulations, SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters, SP6-T6.1.1-SGA1-Homology structural models

Van Geit W, Gevaert M, Chindemi G, Rössert C, Courcol JD, Muller EB, Schürmann F, Segev I, Markram H. (2016). BluePyOpt: Leveraging Open Source Software and Cloud Infrastructure to Optimise Model Parameters in Neuroscience. *Front Neuroinform*;10:17. doi: 10.3389/fninf.2016.00017. eCollection 7 June 2016.

## 9.2 Publications submitted and in preparation

Frezza E, Martin J, Lavery R. Structural and mechanistic insights into G-protein alpha activation of adenylyl cyclase 5 using all-atom molecular dynamics. *Biophys. J.* 2017 submitted.

- T6.1.1
- Components: SP6-T6.1.1-SGA1-Coarse-grain protein model; SP6-T6.1.1-SGA1-Homology structural models; SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters

Colizzi F, Sfriso P, Orozco M. The regulation of adenylyl cyclase by G-protein from coevolution-driven molecular simulations. Manuscript in preparation.

- T6.1.1
- Components: SP6-T6.1.1-SGA1-Coarse-grain protein model

Van Keulen SC, RothlisbergerU. Exploring the inhibition mechanism of adenylyl cyclase type 5 by N-terminal myristoylated Gαi1:GTP. 2017, submitted.

- T6.1.1
- Components: SP6-T6.1.1-SGA1-All Atom Molecular Dynamics

Rodriguez PC, Almeida LG, Triller A. Continuous rearrangement of the postsynaptic gephyrin scaffolding domain: a super-resolution quantified and energetic approach. Submitted.

- T6.1.3
- Component: SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis

Ranft J, Almeida LG, Rodriguez PC, Triller A, Hakim V. An Aggregation-Removal Model for the Formation and Size Determination of Post-Synaptic Scaffold Domains. In revision, *PLOS Computational Biology*.

- T6.1.3
- Component: SP6-T6.1.3-SGA1-Data-driven modelling of Ca2+ dependent cascades controlling synaptic signalling and homeostasis

## 9.3 Other publications of interest (not specifically acknowledging the HBP)

V Breton-Provencher, K Bakhshetyan, D Hardy, R Bammann, F Cavarretta, M Snapyan, D Coté, M Migliore, Saghatelyan A. (2016). Principal cell activity induces spine relocation of adult-born interneurons in the olfactory bulb, *Nature Comm*;7:12659. doi: 10.1038/ncomms12659.

Cavarretta F, Marasco A, Hines ML, Shepherd GM and Migliore M. (2016). Glomerular and mitral-granule cell microcircuits coordinate temporal and spatial information processing in the olfactory bulb, *Front Comput Neurosci*;10:67; doi: 10.3389/fncom.2016.00067

Chen W, **De Schutter** E. (2017). Parallel STEPS: Large Scale Stochastic Spatial Reaction-Diffusion Simulation with High Performance Computers. *Front Neuroinform*;11:13. doi: 10.3389/fninf.2017.00013. eCollection 10 February 2017.

- T6.3.2

Du K. (2017). Nonlinear synaptic integration on dendrites of striatal medium spiny neuron – a computational study. Thesis of the Karolinska Institute 2017:1-60. (ISBN 978-91-7676-527-2)

- T1.2.3, T5.8.2, T5.8.3, T6.2.5
- Components: Cellular properties of neurons within striatum, Connectivity and morphology of neurons within striatum, Integrated data sources, Cell type ontologies, Models of basal ganglia nuclei

Grillner S, Ip N, Koch C, Koroshetz W, Okano H, Polachek M, Poo MM, Sejnowski TJ. (2016). Worldwide initiatives to advance brain research. *Nat Neurosci*;19(9):1118-22. doi: 10.1038/nn.4371.

- T1.2.3, T5.8.2, T5.8.3, T6.2.5
- Components: Cellular properties of neurons within striatum, Connectivity and morphology of neurons within striatum, Integrated data sources, Cell type ontologies, Models of basal ganglia nuclei

Grillner S. (2016). Commentary on F1000 article by Vogelstein entitled "Grand challenges for global brain sciences" *F1000Research*;5:2873 (doi: 10.12688/f1000research.10025.1)

- T1.2.3, T5.8.2, T5.8.3, T6.2.5
- Components: Cellular properties of neurons within striatum, Connectivity and morphology of neurons within striatum, Integrated data sources, Cell type ontologies, Models of basal ganglia nuclei

Hepburn I, Chen W, **De Schutter** E. (2016). Accurate reaction-diffusion operator splitting on tetrahedral meshes for parallel stochastic molecular simulations. *J Chem Phys*;145(5):054118. doi: 10.1063/1.4960034.

- T6.3.2

Marasco A, De Paris A, Migliore M. (2016). Predicting the response of olfactory sensory neurons to odor mixtures from single odor response, *Sci Rep*;6:24091.

McDougal RA, Morse TM, Carnevale T, Marenco L, Wang R, Migliore M, Miller PL, Shepherd GM, Hines ML. (2017). Twenty years of ModelDB and beyond: building essential modeling tools for the future of neuroscience. *J Comput Neurosci*;42(1):1-10. doi: 10.1007/s10827-016-0623-7. Epub 15 September 2016.

Migliore R, De Simone G, Leinekugel X, Migliore M. (2016). The possible consequences for cognitive functions of external electric fields at power line frequency on hippocampal CA1 pyramidal neurons, *Eur. J. Neurosci*; doi: 10.1111/ejn.13325.

Neymotin SA, Suter BA, Dura-Bernal S, Shepherd GM, Migliore M, Lytton WW, J. (2017). Optimizing computer models of corticospinal neurons to replicate in vitro dynamics *Neurophysiol*;117(1):148-162. doi: 10.1152/jn.00570.2016. Epub 19 October 2016.

van Keulen SC, Rothlisberger U. (2017). Effect of N-Terminal Myristoylation on the Active Conformation of Gα(i1)-GTP. Biochemistry;56(1):271-280. doi: 10.1021/acs.biochem.6b00388. Epub 29 December 2016.

- T6.1.1

- Components: SP6-T6.1.1-SGA1-All Atom Molecular Dynamics; SP6-T6.1.1-SGA1-Homology structural models; SP6-T6.1.1-SGA1-Estimates of kinetic and thermodynamic parameters

# 10. Dissemination

Please find below a selected list of participation at important external conferences and events by SP6 members.

Satellite Symposium, Society for Neuroscience Meeting, 12 November 2016: Using the Neuroscience Gateway Portal for Parallel Simulations, Michele MIGLIORE (CNR), Carmen LUPASCU (CNR), T6.4.5, T6.4.6

Felix SCHÜRMANN co-organised (with Markus DIESMANN, SP6) a mini-symposium on "Level of Detail in Brain Modeling: Common Abstractions and their Scientific Use" at the PASC16 conference with multiple speaker of partner JUELICH and EPFL/BBP on SP6 simulation technology and science in Lausanne, 8-10 June 2016.

Felix SCHÜRMANN organised a session "Neuroscience & Supercomputing: The Human Brain Project & Other International Efforts" at the ISC High Performance Conference 2016 in Frankfurt, 19-23 June 2016.

Felix SCHÜRMANN gave a talk at the Royal Society Meeting „Applying computational modelling to clinical neuroscience" in Buckinghamshire on 6-7 April 2016 entitled "Reconstruction and Simulation of Neocortical Microcircuitry" which is the foundation of the HBP Brain Simulation Platform.

Felix SCHÜRMANN gave an HBP overview lecture at the Keystone conference "State of the Brain" in Alpbach on 23 May 2016.

Sten GRILLNER organised a Keystone conference on the "State of the Brain" in Alpbach, 22-26 May 2016 with participation among others of the EU director Thomas Skordas and the head of NINDS Walter Koroshetz.

H.E. PLESSER. The Human Brain Project Research Infrastructure. Technologies for Digital Life Workshop, Centre for Digial Life Norway, Bergen, Norway, 21 October 2016.

Janelia workshop "Collaborative Development of Data-Driven Models of Neural Systems": talk by S. KÁLI, posters by MIGLIORE, ROMANI, KÁLI (Task 6.2.4).

KUNKEL S., PLESSER H.E. (2016) NEST: Current developments – Simulation code for supercomputers; Talk at NEST User Workshop, Karlsruhe, Germany.

JORDAN J., KUNKEL S., IPPEN T., HELIAS M., DIESMANN M., MORRISON A. (2016) NEST 5g: a simulation kernel for the exascale; Talk at SMHB General Assembly 2016, Juelich, Germany.

Neil BRUCE. MolModel2016: School on Molecular Modelling for Life Sciences, 6-10 June 2016, Pula, Sardinia, Italy. *Simulating macromolecular recognition through diffusional Brownian dynamics* (Invited Oral Contribution).

CECAM Workshop: Reaction Coordinates from Molecular Trajectories, Leiden (The Netherlands) 29 August – 2 September 2016, *Understanding protein-ligand unbinding kinetics from metadynamics simulations*, R. CASASNOVAS PERERA, V. LIMONGELLI, P. TIWARY, P. CARLONI, M. PARRINELLO (Oral Contribution).

PLUMED Meeting, Trieste, 22-27 May 2017. F. COLIZZI, P. SFRISO, M. OROZCO. Chasing the regulation of adenylyl cyclase by G-protein with coevolution-driven molecular simulations (Oral Contribution).

E. FREZZA, J. MARTIN, R. LAVERY. Structural Biology meets Biophysics – French Biophysics Meeting - December 2016, Obernai, France *Insights on flexibility and mechanics of adenylyl cyclase bound to G proteins from molecular dynamics simulations* (Oral Contribution).

Felix SCHÜRMANN presented the HBP to a delegation of the Chinese Academy of Science visiting EPFL on 12 July 2016.

Sten GRILLNER Took part in the Rockefeller meeting, New York, on Coordinating Brain Projects across the Globe on 19 September 2016 and provided the "wrap up" concluding the meeting.

Sten GRILLNER took part in the "International Brain Initiative meeting at UN, New York on 27 February 2017.

Sten GRILLNER. Discussion with The Swedish Minister of Research regarding Neuroinformatics and HBP on 15 February 2017.

# 11. Education

Members of SP6 were very actively involved, as presenters and participants, in the following events organised in this period by the HBP Education Programme:

- FENS Satellite workshop – a joint workshop between the Allen Institute and HBP. Cells, Circuits and Computation: Expanding the Horizons of Big Data Analysis, Denmark, July 2016
    - Eilif MULLER, Werner VAN GEIT and Christian ROESSERT gave presentations and tutorials
- 3rd HBP Education School on Future Neuroscience, the Multiscale Brain: from Genes to Behaviour, Austria, November/December 2016
    - Werner VAN GEIT, Michael REIMANN and Armando ROMANI gave numerous tutorials, and Csaba EROE gave a presentation
- Young Researchers' Event, Simulation on Different Scales of Space and Time, Hungary, April 2016
    - Srikanth RAMASWAMY gave a presentation in the Plenary Session and Werner VAN GEIT gave two tutorials.

The 2016 Course of the School of Brain Cells and Circuits "Camillo Golgi" was dedicated to the cerebellum and Egidio D'ANGELO was one of the Course Directors. The Course, held in December in Erice, Italy, started with a series of presentations covering the cellular and molecular biophysics of the cerebellar neurons and circuits, up to integrative aspects of cerebellar functioning. Interactive workshops then enabled the participants to apply the fundamental knowledge on cerebellar functioning to the analysis of the brain pathologies in animal models and humans, ranging from hereditary ataxias to multiple sclerosis, neurodegenerative diseases and autism. The Course gathered around 80 scientists from different disciplines in a lively and interactive training scheme.

# 12. Ethics

The two ethics rapporteurs during this period were Robert LINDROOS and Daniel KELLER. There were several types of ethics rapporteur activities during this period: we attended ethics rapporteur conferences, participated in regular teleconference calls with SP12, wrote reports for SP12, and interacted with SP6 members regarding ethics. The ethics rapporteur attended the Ethic Rapporteur conference in Bristol on 28-29 March 2017. We attended the ethics rapporteur Teleconference on 7 December 2016. We participated in the call on Ethics and Society on 1 February 2017 and advertised the opportunities for collaboration with SP12 members. Furthermore, we raised awareness in SP6 of ethics issues and invited SP6 members to bring ethics issues to our attention. Additionally, we prepared a description of ethical issues in SP6 for SP12, and update this report yearly. There are several ethical issues of particular interest to SP6: safeguarding the privacy of individual subjects, vetting data that

goes into the Platform to ensure that it was collected ethically and humanely, assigning proper credit to collaborative work, managing public expectations, and avoiding potential misuse/dual use of the Platform.

# 13. Innovation

In the case of simulator engines where the HBP decided to connect to larger community projects such as STEPS, NEURON, and NEST, all contributions from Partners of the HBP have been made available according to the open-source license terms of the community projects. Furthermore, previously open-sourced software such as eFEL, NeuroM, BluePyOpt continued to be developed as open-source and all contributions of this phase have been released. Some developments such as the new version of the model management have not yet been released as open-source but will go through the open sourcing process of the respective partner.

Partner EPFL has successfully created a start-up company on the EPFL background IP and EPFL sole foreground IP.