SP6 Annual Compound Deliverable Year 1 (D6.1.1 – SGA2)

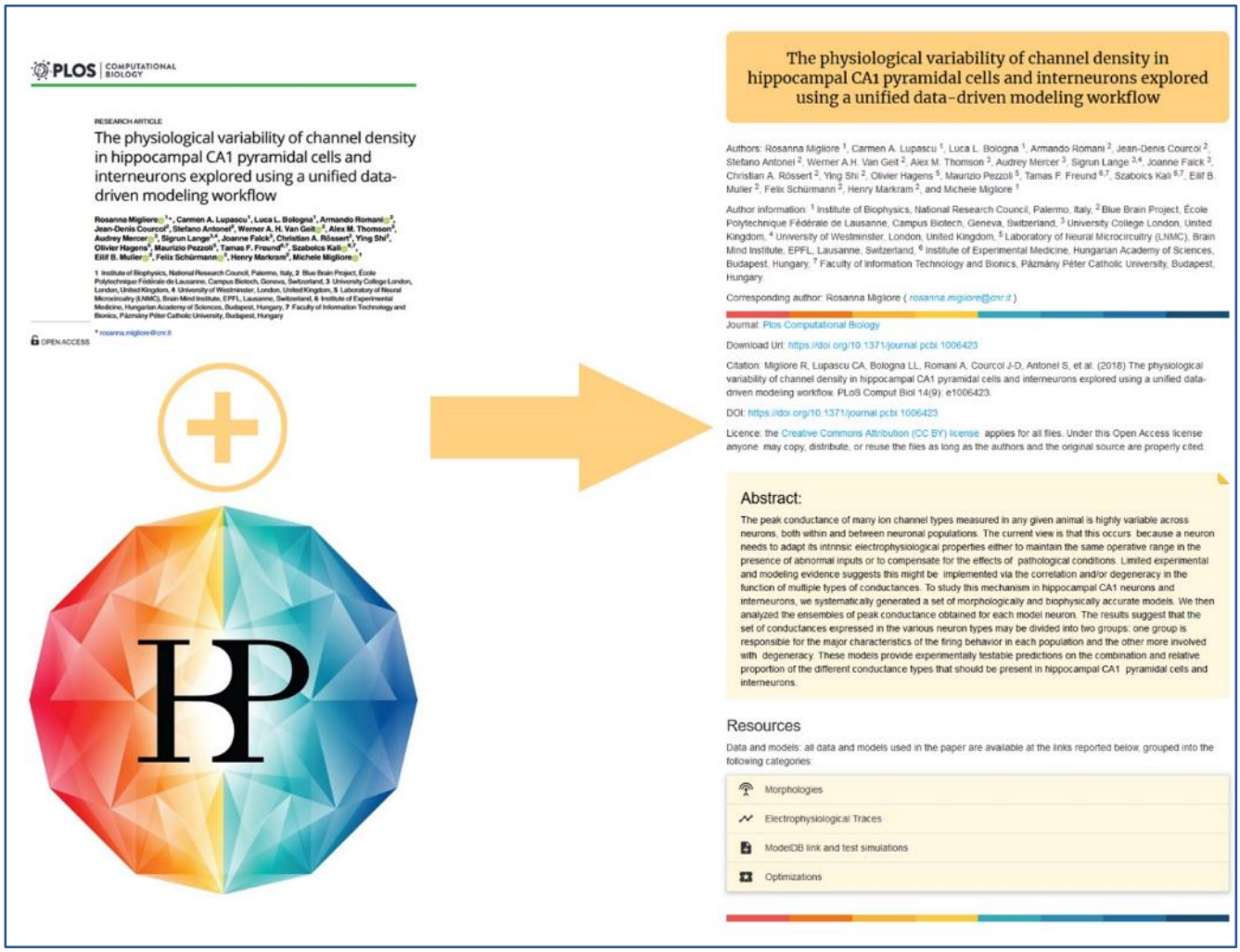

Figure 1: HBP Brain Simulation Platform "Live Papers" introduce a novel way to complement scientific publications on models.

A Live Paper provides links to the data underlying the paper. Moreover, it showcases the model outputs of the paper, using online services of the Brain Simulation Platform; for example, by allowing the execution of a simulation of the model in the browser.

Project Number:	785907	Project Title:	Human Brain Project SGA2

Document Title:	SP6 Annual Compound Deliverable Year 1
Document Filename:	D6.1.1 (D37.1 D20) SGA2 M12 ACCEPTED 190722
Deliverable Number:	SGA2 D6.1.1 (D37.1, D20)
Deliverable Type:	Report
Work Package(s):	WP6.1, WP6.2, WP6.3, WP6.4, WP6.5
Dissemination Level:	PU = Public
Planned Delivery Date:	SGA2 M12 / 31 Mar 2019
Actual Delivery Date:	SGA2 M12 / 25 Mar 2019; ACCEPTED 22 Jul 2019

Authors:	Henry MARKRAM, EPFL (P1), Felix SCHÜRMANN, EPFL (P1), Jeanette HELLGREN KOTALESKI, KTH (P39), Michele MIGLIORE, CNR (P12), Egidio D'ANGELO, UNIPV (P70)
Compiling Editors:	Suat SEVENCAN, KTH (P39); Jeanette HELLGREN KOTALESKI, KTH (P39)
Contributors:	Paolo CARLONI, JUELICH (P20), Ch. 3, 6; Antoine TRILLER, ENS (P17), Ch. 3; Sten GRILLNER, KI (P37), Ch. 3, 4; Eilif MULLER, EPFL (P1), Ch. 4; Szabolcs KÁLI, IEM HAS (P30), Ch. 4; Idan SEGEV, HUJI (P60), Ch. 4; Marc-Oliver GEWALTIG, EPFL (P1), Ch. 4; Jim KING, EPFL (P1), Ch. 5, Ch. 6; Markus DIESMANN, JUELICH (P20), Ch. 5; Jean-Denis COURCOL, EPFL (P1), Ch. 5, 6; Rebecca WADE, HITS (P26), Ch. 5; Andrew DAVISON, CNRS (P10), Ch. 6
SciTechCoord Review:	
Editorial Review:	Guy WILLIS, EPFL (P1)

Description in GA:	Overview of key results and impact achieved in M1-M12, tailored for presentation to the relevant audiences (research/industry/public). References to HBP/SP/CDP objectives and use cases for navigation between multiple Subprojects. Linkage of results to components/a set of component factsheets (lower-level information: component ownership, technology readiness level, performed quality control checks, etc.). (Note: For consistent presentation of HBP results, SGA2 M12 Deliverables describing the accomplishments of an entire SP or CDP have been prepared according to a standard template, which focuses on Key Results and the outputs that contribute to them. Project management elements such as Milestones and Risks will be covered, as per normal practice, in the SGA2 Year 1 Report.)
Abstract:	This Deliverable is the annual compound of HBP deliveries and results (outputs and outcomes) from Subproject SP6 – Brain Simulation Platform. Community Use cases and online training resources available at the HBP portal. The main deliveries from April 2018 to March 2019 are: • Multi-scale simulations relevant for understanding brain plasticity • Models of human and rodent neurons published as Live Papers • Advanced tools for data-driven modelling and simulations • Brain Simulation Platform - web accessible suite of highly integrated model building and simulation tools backed by HPC computing resources
Keywords:	Brain Simulation Platform; data-driven; scaffold models; Live Paper; simulation neuroscience; multiscale models; community
Target Users/Readers:	Scientists, companies and other potential users of HBP results.

Table of Contents

Table of Tables

Table of Figures

1. Overview

The ability to collaboratively build, simulate and analyse data-driven models of brain tissue is a core strategic strength of the HBP and a central capability of the HBP's Joint Platform efforts provided by SP6. Building on the previous success of having co-design science specifying new requirements, while developing and deploying a user-centric set of Brain Simulation Platform (BSP) capabilities attractive to the wider community, SP6 continued along those two lines in current funding phase.

Notably, on the scientific side, the most comprehensive models to date of rat neuron types in the hippocampal CA1 region have been published. Also, updated models of human pyramidal neurons have been released, adding active dendritic properties to the models previously published. Similarly, we have demonstrated, for the first time, that molecular level simulations can be used to inform kinetic models, representing a quantitative bridging of scales relevant for understanding processes such as plasticity and learning. The published results are being disseminated using "Live Papers". On the platform side, SP6 continued to make the BSP ever more attractive to the community. For example, several simulation software packages have been further optimised. Service accounts for access to high performance computing resources have been launched. Also, several standards for large-scale model specifications, as well as for both experimental data and model and simulation artefacts, have been released. In terms of direct community outreach and training, an HBP School on the BSP was held in Palermo in September 2018, giving first-hand training to users and complementing the success of SP6's earlier Massive Open Online Courses (MOOCs).

The plans for the next 12 months are to enhance and release several models, such as the microcircuits of hippocampal CA1 and striatum, as well as the cerebellar network. Also, initial attempts will be made to integrate plasticity or neuromodulation in all our microcircuit models. The aim is to bring the microcircuits to the exploitation phase and having a Live Paper representation thereof which makes use of the BSP's capabilities. In line with this goal, the tools and workflows of the platform will be further matured and developed to best support those Live Papers. At the same time, we will continue to train students and researchers in the opportunities the BSP offers, via specific dissemination activities such as the Erice School on Brain Modelling or a new MOOC on the BSP's capability.

2. Introduction

The goal of SP6 is to catalyse a global community effort to systematically integrate neuroscience knowledge through the construction of data-driven models of the brain at different levels of biological detail. To achieve this goal, SP6 is building the HBP BSP, which is made available through an online HBP Collaboratory, where researchers from within and outside the HBP can participate. The primary strategy for the BSP is to provide modularised workflows for model building and simulation that leverage state-of-the-art approaches and technologies for using neuroscience data to inform the construction and validation of the models. Many of the underlying technologies are developed by SP6 Partners as a form of matching support or as open-sourced technologies developed by researchers outside of the HBP, which are then customised and integrated into the BSP.

Activities over the last 12 months demonstrated that molecular level simulations can inform kinetic models. Several computational tools, from molecular dynamics and Brownian dynamics simulations to bioinformatics approaches, were combined to constrain a kinetic model of the adenylyl cyclase type 5 (AC5)-dependent signalling system in the striatum. A better understanding of this system is crucial when predicting which neuromodulatory signalling events will lead to synaptic plasticity, such as LTP or LTD in the corticostriatal synapse.

Similarly, the building of scaffold models at different biological scales has continued. The Life Cycle Model for Data-driven Models, introduced during the previous phase of the project, is used to track the maturation of the models. Several models have now reached the 'exploitation phase', which means that the publication of the models in scientific journals has been complemented with a Live Paper. The first Live Papers are now available at https://humanbrainproject.github.io/hbp-bsp-live-papers/index.html. They cover modelling of a) hippocampal neuron types; b) human pyramidal

neurons; and c) dopamine modulation of striatal principal neurons. Other models of the cortex, cerebellum, basal ganglia and hippocampus will follow this Live Paper approach as they reach the exploitation phase.

Those co-design drivers have continued to inform the refinement of the BSP that is aimed at integrating advanced software tools for the generation and simulation of models at different scales and to make this functionality available to the community. Where available, the BSP builds on best-in-class community software and contributes to its extension and maturation. The STEPS, CoreNeuron, Neuron and NEST simulation engines have all undergone new releases. Also, a new release of NEUROSHAPES, a collection of schemas for data and models, has been made, which allows standardised registration of data and model artefacts in the HBP Knowledge Graph. Furthermore, the SONATA standard for the definition of detailed and simplified network models has been further pursued together with the Allen Institute for Brain Science. This file format is the foundation of the circuit-level software ecosystem of the SP6 BSP and exchange with the community.

Lastly and perhaps most importantly, the usability and functionality of the BSP have been further improved. A first version of a "service account" for access to high-performance computing resources has been launched. This allows the use of compute-intensive workflows, such as synapse fitting, directly from the web-platform, without the need to apply separately for supercomputing time. Furthermore, the set of online use cases and services was significantly improved and extended in this period. All the model building and simulation tools present in the BSP are unique in the field. Examples of releases and improvements include: a) Features Extraction and Single Cell Modelling; b) Integration of hippocampus CA1 circuit into Brain Area Circuit for exploitation (https://collab.humanbrainproject.eu/#/collab/1655/nav/66856; c) simulation and visualisation stack; d) interactive tutorials; and e) import/export of SONATA format into/from PyNN.

3. Multi-scale models of plasticity (HBP Key Result KR6.1)

Plasticity over different spatial and temporal scales is crucial for learning, short- and long-term memory, homeostasis, etc. It allows the different brain microcircuits to adapt over a lifetime and recover from injuries or disease. As such, brain plasticity has far-reaching implications for understanding both the healthy and diseased brain. Plasticity typically depends on receptor-induced cascades controlled by network activity, including neuromodulatory systems, such as dopamine.

SP6's major accomplishments in this field in the first 12 months of the current phase of the Project rely on modelling and simulation over multiple scales: single molecules, signalling G-protein and calcium-dependent subcellular cascades and quantitatively detailed microcircuits. Also, these levels are being bridged, e.g., by integrating subcellular models into microcircuit models to simulate induction of plasticity, neuromodulation, etc. The different achievements are explained in more detail below.

In addition, all progress has been tracked using the "Life Cycle Model for Data-driven models", which were defined during the previous phase of the Project.

3.1 Outputs

3.1.1 Overview of Outputs

Table 1: List of Components contributing to the outputs of Key Result KR6.1

ID	Name
C1661	Applications of multi-scale molecular simulation of ligands binding to neuronal proteins
C1698	Multiscale simulations of protein dynamics and complexation
C2893	Atomistic models of human muscarinic receptor in natural mimic-like environment

3.1.2 Understanding receptors and protein interactions

Approaches have been developed to understand better receptors and interactions between proteins (Reille *et al.*, 2018) (C1661, C2893). Molecular level simulations are being used to study the binding of agonists and antagonists to muscarinic receptors (C2893). Such approaches will be important for providing a better understanding of how receptors are controlled by neuromodulators which are crucial for plasticity. This approach will also be useful for future facilitation of drug design.

3.1.3 Prediction of parameters for plasticity models

We have demonstrated that molecular level simulations can significantly enhance kinetic models of receptor-induced cascades, by providing crucial parameters which currently can't be measured (C1698). Here, several computational tools were combined, ranging from molecular dynamics and Brownian dynamics simulations to bioinformatics approaches, to inform and constrain a kinetic model of the adenylyl cyclase type 5 (AC5)-dependent signalling system in the striatum, which is crucial for LTP in the corticostriatal synapses. The simulations showed how the molecular properties of AC5, together with the stimulatory (Gaolf) and inhibitory (Gai) G-proteins, support supralinear/synergistic cyclic adenosine monophosphate (cAMP) production downstream of the receptors, in response to sub-second neuromodulatory transients. Results also provided insights into the computational capabilities of the different AC isoforms.

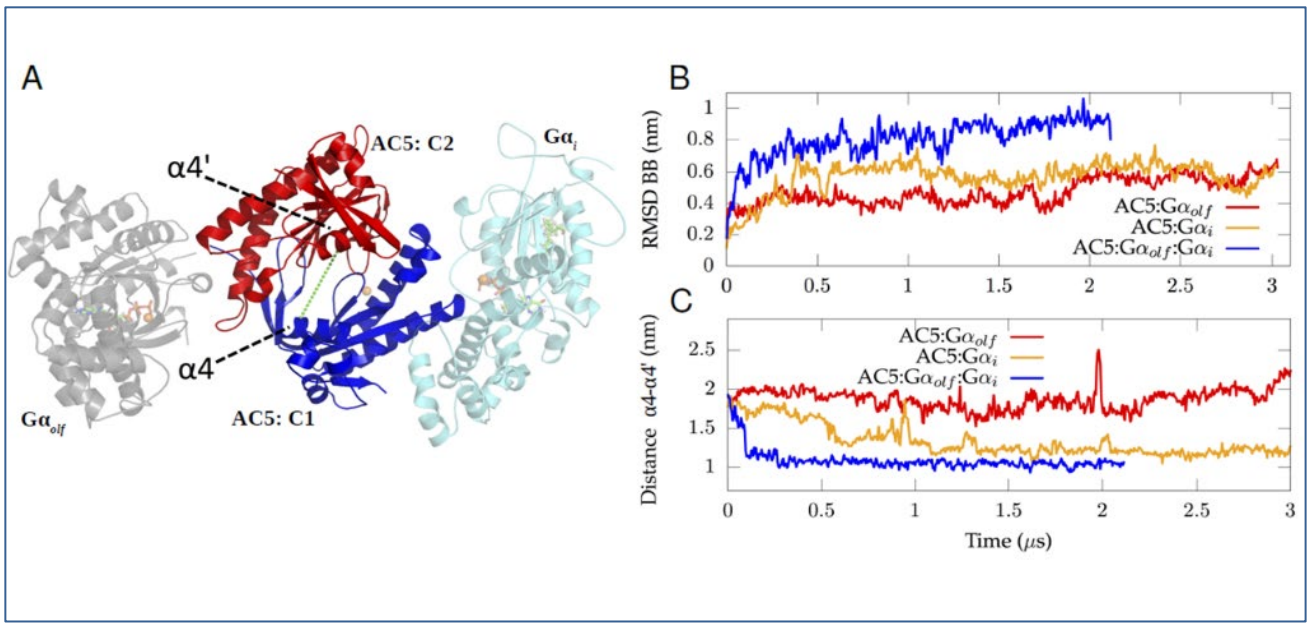

Figure 2: Stability analysis of the ternary complex.

A) Initial conformation of the ternary complex including Gαolf (gray), Gαi1 (cyan), C1 (blue), C2 (red). B) RMSD of the backbone of the protein complexes Gαolf AC5 Gαi1, AC5 Gαolf and AC5 Gαi1. C) Time evolution of the distance between Thr1007 and Ser1208 for the three simulated complexes (in apo form).

3.1.4 Bridging of scales

Models of receptor-induced cascades are being integrated into detailed neuron and microcircuits, to be able to investigate plasticity and neuromodulation in microcircuits.

A platform use case for simulating synaptic plasticity at a single cell level is under development, and published results (https://doi.org/10.3389/fncir.2018.00003) (C3051) have been integrated into the BSP in the form of a Live Paper: https://collab.humanbrainproject.eu/#/collab/44569/nav/306517.

In this Live Paper, one aim was to investigate the effects of dopamine in a biophysically detailed striatal principal neuron model. Dopaminergic afferents from the midbrain play a crucial role in striatal functions, such as initiation of movement. The effect on behaviour can be seen already within a few hundred milliseconds. This is surprisingly fast, as neuromodulation affects membrane excitability typically via phosphorylation of ion channels (e.g. Kv4.2 channels in direct pathway striatal projection neurons), and the resulting membrane effects are typically studied over tens of seconds or even minutes. One model prediction made to explain experimental data was that dopaminergic terminals activate excitatory ionotropic receptors to a significant degree and, interestingly, co-release of glutamate was recently reported to occur in the dorsal striatum (https://doi.org/10.7554/eLife.39786.001).

3.2 Validation and Impact

3.2.1 Actual Use of Output(s) / Exploitation

Experimental groups outside of the HBP have started to investigate subcellular model predictions developed within the HBP (Nair *et al.*, 2019) and further collaborations are expected. Also, the HBP Voucher Programme received successful applications proposing to integrate plasticity into microcircuit models using BSP tools and models built using the BSP.

3.2.2 Potential Use of Output(s)

The examples of models resulting from the work on bridging scales and simulating plasticity and neuromodulation is novel, and this approach is expected to have an increasingly strong influence on the field. It is important to support this work with corresponding BSP software tools during the last phase of the HBP. These services will be further disseminated through the MOOCs.

3.2.3 Publications

- Nair AG, Castro LRV, El Khoury M, Gorgievski V, Giros B, Tzavara ET, *et al*. The high efficacy of muscarinic M4 receptor in D1 medium spiny neurons reverses striatal hyperdopaminergia. Neuropharmacology. 2019;146:74-83, (C2893).
    - This publication provides an experimental verification that the predictions from the molecular level simulations can lead to fundamentally new insights. One key prediction was that the ternary complex Golf-AC5-Gi (see Section 3.1.3 above) can form but that this complex is inactive. In the Nair *et al*. paper, it was shown that blocking of the M4 receptor, which is linked to the activation of Gi, can indeed prevent cAMP production even if the Golf branch is significantly stimulated.
- Reille S, Garnier M, Robert X, Gouet P, Martin J, Launay G. Identification and visualization of protein binding regions with the ArDock server. Nucleic Acids Research. 2018;46(W1):W417-W22, (C1661, C2893).
    - In this publication, the ArDock server (ardock.ibcp.fr) is presented. ArDock is a structural bioinformatics web server for the prediction and the visualisation of potential interaction regions at protein surfaces. ArDock has a user-friendly interactive interface for the visualisation of annotated protein structures. Its modular architecture will support future extensions to include the calculation and interactive visualisation of additional amino acid properties (physicochemical or sequence-based).

3.2.4 Measures to Increase Impact of Output(s): Dissemination

Most Partners contributed to dissemination activities. For example, the multiscale integration efforts, as well as the subcellular level model building activities, were presented at the Erice school on The Neural Bases of Action (Dec 2018 in Sicily, Italy) (in collaboration with the HBP Education Programme), and at several workshops (e.g. CECAM, Neuroinformatics, SfN, OCNS, etc.).

Directly feeding into the highlights illustrated above were the following activities:

- Olivia ERIKSSON (KTH) presented and discussed how to use the workflow for the building of CaMKII models during INCOME2018, http://www.integrative-pathway-models.de/meetings/1st-income-symposium-and-hackathon/index.html
- Rebecca WADE (HITS) was an invited speaker at the 6th Annual CCPBioSim Meeting: Molecular Simulations in Drug Discovery and Development (http://www.ccpbiosim.ac.uk/ccpbiosim2018), as well as at the workshop "Challenges in Large-Scale Biomolecular Simulations" (http://www.biomath.nyu.edu/?q=biomath/conferences/Telluride2018/BiomolecularSimulations). She discussed and presented computationally efficient approaches to estimate kinetic parameters for binding. Such simulation-based methods are crucial for constraining subcellular level models (as illustrated above), as well as for drug design in the future.

4. Scaffold models of brain regions/whole brain ready for community use (HBP Key Result KR6.2)

An important goal of this Key Result (KR) is to improve and generalise the workflows for scaffold models of brain regions that were first developed for cortex. These are now being applied to other regions, namely the cerebellum, basal ganglia and hippocampus, to advance the whole-brain modelling workflow, and to implement and release them on the BSP and to the community. The different brain regions listed above have been selected because of their physiological and theoretical importance, and because they present different computational and modelling challenges. This KR contributes to developing multi-scale scaffold models of plasticity and neuromodulation by linking cellular level models of the rodent brain with subcellular/molecular models of receptors and signalling cascades.

The Life Cycle Model for Data-driven Models that was introduced during the previous phase of the Project is being used to track the maturation of the models, with the ultimate goal being to make them ready for community use by the end of the current phase.

4.1 Outputs

4.1.1 Overview of Outputs

Table 2: List of Components contributing to the outputs of Key Result KR6.2

ID	Name
C1646	Advanced cerebellar neurons and synapses construction, optimisation and validation
C1874	Whole brain scaffold
C2152	First iteration of community-driven neocortical model
C3057	Improved models of hippocampal neurons and circuitry in the mouse and the rat

4.1.2 Live Paper Concept – Make 1

The BSP is a unique online resource for advanced computational modelling and simulation. Through its integration with the HBP Neuroinformatics and HPAC Platforms, it allows interaction with data for building and validating models, as well as access to advanced computational resources. The newly introduced concept of a Live Paper packages and presents this functionality around a specific model publication. While the scientific paper content is published in regular scientific journals as before, the Live Paper idea complements that with an advanced resources page for this paper. On the one hand, it provides links to the data underlying the paper. On the other, it uses online services of the BSP to showcase the model outputs of the paper; for example, by allowing execution of a simulation of the model in the browser, or to rerun workflows that were used to produce the models in the first place. All of this can be done without having to install any software. Here, we announce "Make 1" of this concept and highlight the first modelling papers that have prepared such Live Paper companion sites. In the Life Cycle Model followed by the BSP, a Live Paper is essentially equivalent for a model to reach the community use phase ("Exploitation Phase"). Other models will use this Live Paper approach as they reach Exploitation Phase. (C1646, C2152) URL:https://collab.humanbrainproject.eu/#/collab/1655/nav/306845.

4.1.3 Live Paper: Migliore et al., 2018

In September 2018, HBP researchers published the PLoS Computational Biology paper Migliore *et al.*, The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modelling workflow (https://doi.org/10.1371/journal.pcbi.1006423). This paper uses the BSP's single cell modelling process to generate detailed models of hippocampal CA1 pyramidal cells and provided insight into two ion channel groups that have fundamentally different contributions to the cell's behaviour. One group seems responsible for major characteristics of the cell; the second group seems involved with the cell's degeneracy, (C3057). A Live Paper (see Figure 3) for this publication was created, marking the transition of these models to exploitation phase. The Live Paper gives access to the underlying data (morphologies, electrophysiological traces), provides access to the models and allows the models to be run in the Brain Simulations Neuron as a Service. The Live Paper is accessible here: https://collab.humanbrainproject.eu/#/collab/18565/nav/167297.

The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modeling workflow

Authors: Rosanna Migliore [1], Carmen A. Lupascu [1], Luca L. Bologna [1], Armando Romani [2], Jean-Denis Courcol [2], Stefano Antonel [2], Werner A.H. Van Geit [2], Alex M. Thomson [3], Audrey Mercer [3], Sigrun Lange [3,4], Joanne Falck [3], Christian A. Rössert [2], Ying Shi [2], Olivier Hagens [5], Maurizio Pezzoli [5], Tamas F. Freund [6,7], Szabolcs Kali [6,7], Eilif B. Muller [2], Felix Schürmann [2], Henry Markram [2], and Michele Migliore [1]

Author information: [1] Institute of Biophysics, National Research Council, Palermo, Italy, [2] Blue Brain Project, École Polytechnique Fédérale de Lausanne, Campus Biotech, Geneva, Switzerland, [3] University College London, United Kingdom, [4] University of Westminster, London, United Kingdom, [5] Laboratory of Neural Microcircuitry (LNMC), Brain Mind Institute, EPFL, Lausanne, Switzerland, [6] Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary, [7] Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, Budapest, Hungary.

Corresponding author: Rosanna Migliore (*rosanna.migliore@cnr.it*)

Journal: Plos Computational Biology

Download Url: https://doi.org/10.1371/journal.pcbi.1006423

Citation: Migliore R, Lupascu CA, Bologna LL, Romani A, Courcol J-D, Antonel S, et al. (2018) The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modeling workflow. PLoS Comput Biol 14(9): e1006423.

DOI: https://doi.org/10.1371/journal.pcbi.1006423

Abstract:

The peak conductance of many ion channel types measured in any given animal is highly variable across neurons, both within and between neuronal populations. The current view is that this occurs because a neuron needs to adapt its intrinsic electrophysiological properties either to maintain the same operative range in the presence of abnormal inputs or to compensate for the effects of pathological conditions. Limited experimental and modeling evidence suggests this might be implemented via the correlation and/or degeneracy in the function of multiple types of conductances. To study this mechanism in hippocampal CA1 neurons and interneurons, we systematically generated a set of morphologically and biophysically accurate models. We then analyzed the ensembles of peak conductance obtained for each model neuron. The results suggest that the set of conductances expressed in the various neuron types may be divided into two groups: one group is responsible for the major characteristics of the firing behavior in each population and the other more involved with degeneracy. These models provide experimentally testable predictions on the combination and relative proportion of the different conductance types that should be present in hippocampal CA1 pyramidal cells and interneurons.

Resources

Data and models: all data and models used in the paper are available at the links reported below, grouped into the following categories:

- Morphologies
- Electrophysiological Traces
- ModelDB link and test simulations
- Optimizations

Figure 3: Screenshot of the Live Paper on hippocampal neurons in the BSP.

Clicking on the Resources links at the lower part of the screen provides access to the data and to running the models directly in the BSP.

4.1.4 Live Paper: Eyal et al., 2018

In 2016, HBP researchers published the eLife paper Eyal *et al.*, Unique membrane properties and enhanced signal processing in human neocortical neurons (https://doi.org/10.7554/eLife.16553.001). This paper used the BSP's single cell modelling process to generate initial detailed models of human pyramidal cells and provided insight into their unique membrane properties. In 2018, these models were extended to cover active properties of the cells, such as excitatory synaptic properties, spine characteristics and channel-based somatic/ axonal spiking mechanisms. With the help of those models, conditions for cells behaviour such as dendritic NMDA spikes and axo-somatic sodium spikes are explored, providing a detailed account of the information-processing implications (https://doi.org/10.3389/fncel.2018.00181), (C1627, C1628, C1629, C1630). A Live Paper (see Figure 4) for this publication has been created: https://collab.humanbrainproject.eu/#/collab/47206/nav/324090

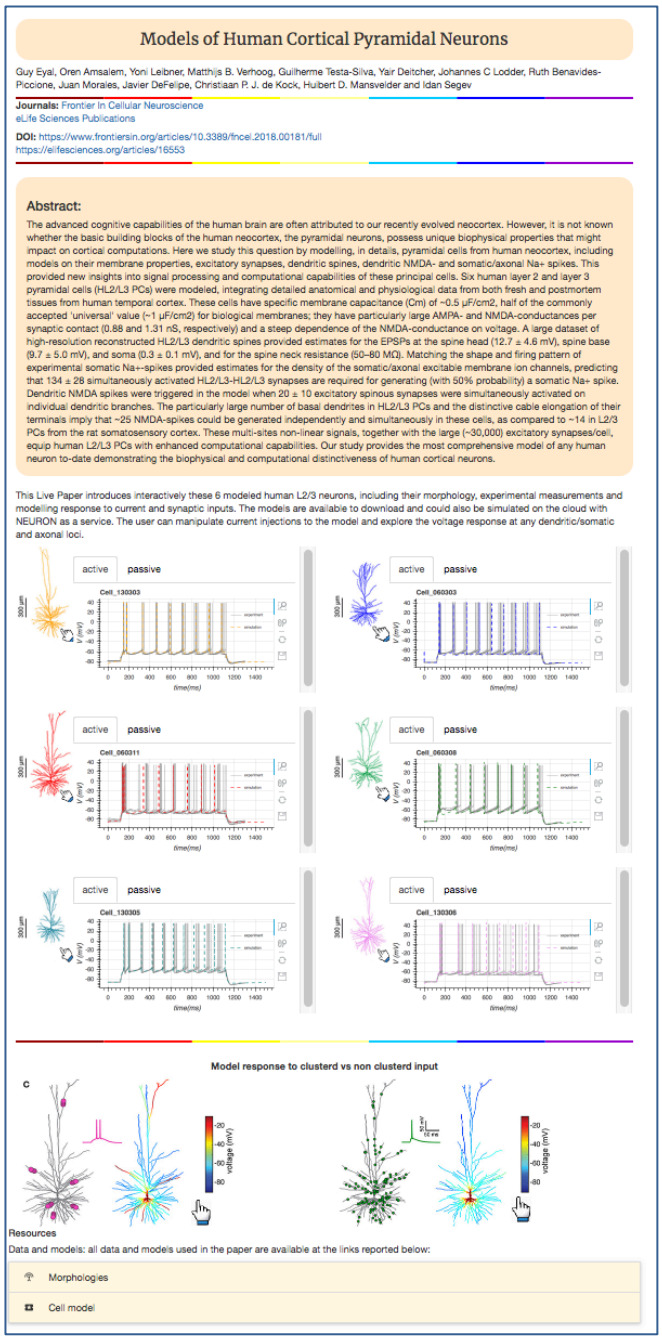

Figure 4: Screenshot of the Live Paper on human pyramidal neurons in the BSP.

Clicking on the Resources links at the lower part of the screen provides access to the data and to running the models directly in the BSP.

4.1.5 Live Paper: Lindroos et al., 2018

In 2018, HBP researchers published the Frontiers in Neural Circuits paper Lindroos *et al.*, Basal Ganglia Neuromodulation Over Multiple Temporal and Structural Scales-Simulations of Direct Pathway MSNs Investigate the Fast Onset of Dopaminergic Effects and Predict the Role of Kv4.2 (doi:10.3389/fncir.2018.00003). This paper is a proof-of-concept of multiscale simulations, namely how a model of a dopamine receptor-induced cascade was integrated with a detailed neuron model of a striatal principal neuron. A Live Paper (see Figure 5) for this publication has been created: https://collab.humanbrainproject.eu/#/collab/44569/nav/306517.

Figure 5: Screenshot of the Live Paper on a multiscale model of a striatal neuron with subcellular cascades in the BSP.

Clicking on the Resources links at the lower part of the screen provides access to the data and to running the models directly in the BSP.

4.1.6 Advancements of Models not yet in the Exploitation Phase

- **Scaffold Somatosensory Cortex Microcircuit** - In order to support automatic model validation and reproducibility, this model was used as a driver to develop HBP Knowledge Graph schemas for the various artefacts that are required for building and simulating such models. In particular, atlas-derived datasets have been addressed. The schemas are accessible as part of the Neuroshapes repository: https://github.com/INCF/neuroshapes.
- **Scaffold Cerebellum** - The scaffold model of the cerebellum microcircuit is complete https://www.biorxiv.org/content/10.1101/532515v1. The Purkinje cell model is being updated to reflect the availability of 21 new morphologies of mice neurons (https://collab.humanbrainproject.eu/#/collab/1655/nav/66852). The embedding of simplified E-GLIF cerebellar neurons in the scaffold is almost complete and is being pursued through a collaboration with the HBP Partnering Project cerebNEST: (https://collab.humanbrainproject.eu/#/collab/1655/nav/66853).
- **Scaffold Hippocampus CA1** - A new, improved version of the rat CA1 circuit model has been constructed and validated, and is now used to run *in silico* experiments involving hippocampal population dynamics. Detailed validations have been run on thousands of variants of the model neurons used in the circuit model. New and updated morphological and electrophysiological data on mouse hippocampal neurons have been received, and are used to build optimised model neurons.
- **Scaffold Basal Ganglia -** The striatum scaffold model is being updated to reflect connection probabilities matching experimental counts (https://collab.humanbrainproject.eu/#/collab/1655/nav/66853). Cell morphologies which best comply with microcircuit constraints have been selected and used in single cell optimisations (https://collab.humanbrainproject.eu/#/collab/1655/nav/66852).
- **Scaffold Whole Brain Network Level Model for mouse** – Automation and modularity of the building workflows have been improved. In particular, HBP Knowledge Graph schemas for simplified networks and networks of point neurons models have been developed and are accessible as part of the Neuroshapes repository: https://github.com/INCF/neuroshapes.

4.2 Validation and Impact

4.2.1 Actual Use of Output(s)

The Life Cycle Model for Data-driven models developed earlier are now well applied. Accordingly, different uses can be attributed depending on the maturity of the models. Importantly, several models that were previously in the Structured Phase have now been published and have achieved Exploitation Phase status (hippocampal neurons, human neurons, multiscale models of striatal neurons). This is manifested in several Live Papers for those models that are now available in the BSP and that allow any person with an HBP Community account to access the underlying data, access the models and use BSP online services to interact with the models.

Models that are still in the Structured Phase of the Life Cycle have been the basis for proposals from the community to exploit the HBP Voucher Programme, which is intended to allow external laboratories to use the HBP Platforms to advance their scientific investigations. Launched during this reporting period and just activated, the Voucher Programme has received over 50 applications for 15 funded proposals. Out of these, 7 directly involve the BSP (two for the cerebellum and five for the hippocampus).

4.2.2 Potential Use of Output(s)

With the continuation of current funding phase, more models will reach the Exploitation Phase and will become widely available. This will allow the models pursued by the HBP to be further used in several ways. We are planning to involve external groups via the Voucher Programmes (see Section 4.2.1 above), FLAG-ERA projects (two submitted on cerebellum modelling and two on hippocampus modelling), ETN projects (one submitted on cerebellum modelling). These groups will exploit the HBP platform system for modelling aspects related to fundamental physiological research, biomedical applications, neuro-engineering and robotics.

4.2.3 Publications

- Migliore R, Lupascu CA, Bologna LL, Romani A, Courcol J-D, Antonel S, *et al*. The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modeling workflow. PLOS Computational Biology. 2018;14(9):e1006423, (C3057).
    - This paper shows that automatic optimisation procedures developed in the HBP can capture salient properties of neuronal firing, e.g. their differentiated discharge properties within physiological variability ranges. This approach will open a more extensive application of the technique. The models have been extended into a White Paper on the Brain Simulation Platform.
- Suryanarayana SM, Hellgren Kotaleski J, Grillner S, Gurney KN. Roles for globus pallidus externa revealed in a computational model of action selection in the basal ganglia. Neural Networks. 2019;109:113-36, (output Scaffold Basal Ganglia).
    - This paper reports the reconstruction of the scaffold model of the basal ganglia, one of the main microcircuit models required in SGA2. The model has been used to investigate how the circuit may operate during action selection, in particular through the involvement of the globus pallidus externa. The scaffold of basal ganglia will be further developed and used in the Brain Simulation Platform for brain circuit reconstruction and simulations.
- Geminiani A, Casellato C, Locatelli F, Prestori F, Pedrocchi A, D'Angelo E. Complex Dynamics in Simplified Neuronal Models: Reproducing Golgi Cell Electroresponsiveness. Frontiers in Neuroinformatics. 2018;12(88). (output Scaffold Cerebellum).
    - This paper reports an advanced procedure for model simplification that has been applied to a cerebellar model for testing. This procedure is needed to reconstruct microcircuit models with simplified single point neurons in SGA2 and beyond. The model will be used to investigate the cerebellar microcircuit in pyNEST and embed it into robots. The pipeline will be made available through the Brain Simulation Platform.

4.2.4 Measures to Increase Impact of Output(s): disseminations

SFN 2018 (3-7 November 2018, San Diego)

This KR was showcased at the annual neuroscience meeting; many of the results obtained were presented through nanosymposia or poster presentation. One example is given for the cerebellum by the nanosymposium entitled Cerebellum: Local and Long-Range Functions. The richness of cerebellar granule cell firing properties captured by modelling optimisation procedures from Tognolina M, Masoli S, D'Angelo E.

2nd HBP Curriculum workshop series, neuroscience for ICT: Applications to computation and robotics (4-6 July 2018, Berlin)

The work carried out for the hippocampus was shown in many occasions; one was the summer school in which Carmen Lupascu presented Bridging the gaps: Computation and neuroscience - neuroscience and computation II.

11th FENS Forum of Neuroscience (7-11 July 2018, Berlin)

This KR was showcased at the annual neuroscience meeting; of the ten-plus abstracts presented, one was on the basal ganglia brain region.

Investigating action selection in the basal ganglia – computational approaches at different levels of biological description, Suryanarayana SM, Kozlov A, Hjorth J, Hellgren Kotaleski J, Gurney K, Grillner S.

5. Advanced tools for data-driven modelling and simulation (HBP Key Result KR6.3)

The BSP is based on a variety of advanced software tools for the generation and simulation of models at different scales. Where available, the BSP builds on best-in-class community software and contributes to their extension and maturation. At the same time, a major contribution of the BSP is to provide a tightly integrated ecosystem of workflows, allowing end-to-end modelling at scale. In addition, necessary functionality not found in community software is being co-developed with the science drivers. These tools and standards are made available through the BSP and benefit the computational neuroscience community in multiple ways.

5.1 Outputs

5.1.1 Overview of Outputs

Table 3: List of Components contributing to the outputs of Key Result KR6.3

ID	Name
C1667	Implementation of directed communication in NEST
C1669	Fitting of single cell electrical model
C1714	Optimising execution on next generation hardware
C1715	Strong scaling of NEURON framework
C2729	Provide description of simplified circuits
C3059	Subcellular parameter optimization

5.1.2 Community simulation engines

These were co-developed as part of the BSP and cover various scales of models. They have all undergone new releases. These simulators are available as part of the BSP, but can also be obtained from the simulators' public community pages:

- STEPS 3.4.1 - Nov 20, 2018 - https://github.com/CNS-OIST/STEPS. Simulator for reaction-diffusion models at the subcellular level. The STEPS 3.4.1 release includes optimisations of the non-spatial deterministic solver and performance improvements for large models.

- CoreNEURON 0.13 - Oct 4, 2018 - https://github.com/BlueBrain/CoreNeuron. Memory and performance optimised simulator for large-scale networks of detailed neurons. The CoreNEURON 0.13 release now makes it possible for CoreNEURON to be run as a library, so that it can be linked to NEURON and run directly after model setup via the hoc interface. Further improvements relate to better support for checkpoint/restore simulations. A manuscript preprint describing CoreNEURON has been made available on arXiv https://arxiv.org/abs/1901.10975, (C1714, C1715).
- NEURON 7.6.5 - Jan 13, 2019 - https://github.com/neuronsimulator/nrn. Simulator for biophysically detailed neurons and networks thereof. The primary focus in the 7.6.5 release of the NEURON simulator is on simplified interoperability with the optimised CoreNEURON simulation engine. For example, CoreNEURON can now be used directly within NEURON.
- NEST 2.16.0 - Aug 21, 2018 - https://github.com/nest/nest-simulator. Simulator for large-scale networks of simple neurons. The NEST 2.16.0 release includes the new simulation kernel based on the technology described in Jordan *et al*. 2018. Major work went into making the technology compatible with the feature set of NEST and assuring overall performance, (C1667).

5.1.3 NEUROSHAPES community data schemas

NEUROSHAPES community data schemas that are relevant to simulation neuroscience have been further extended. These schemas allow the standardised registration of data and model artefacts in the HBP Knowledge Graph (powered by the Blue Brain Nexus software) and subsequent provenance tracking (see Figure 6). The publically available schema definitions are available under https://github.com/INCF/neuroshapes and the 1.0.3RC release (5 Feb 2019) includes schemas for:

- Experiments (whole cell patch, sharp electrode, brain slices)
- Morphologies (stained slice, annotated slice, reconstruction, mesh)
- Simulation (feature extraction from experimental traces, morphologies single cell models, detailed circuit, simplified circuit, simulation), (C1669, C2729).

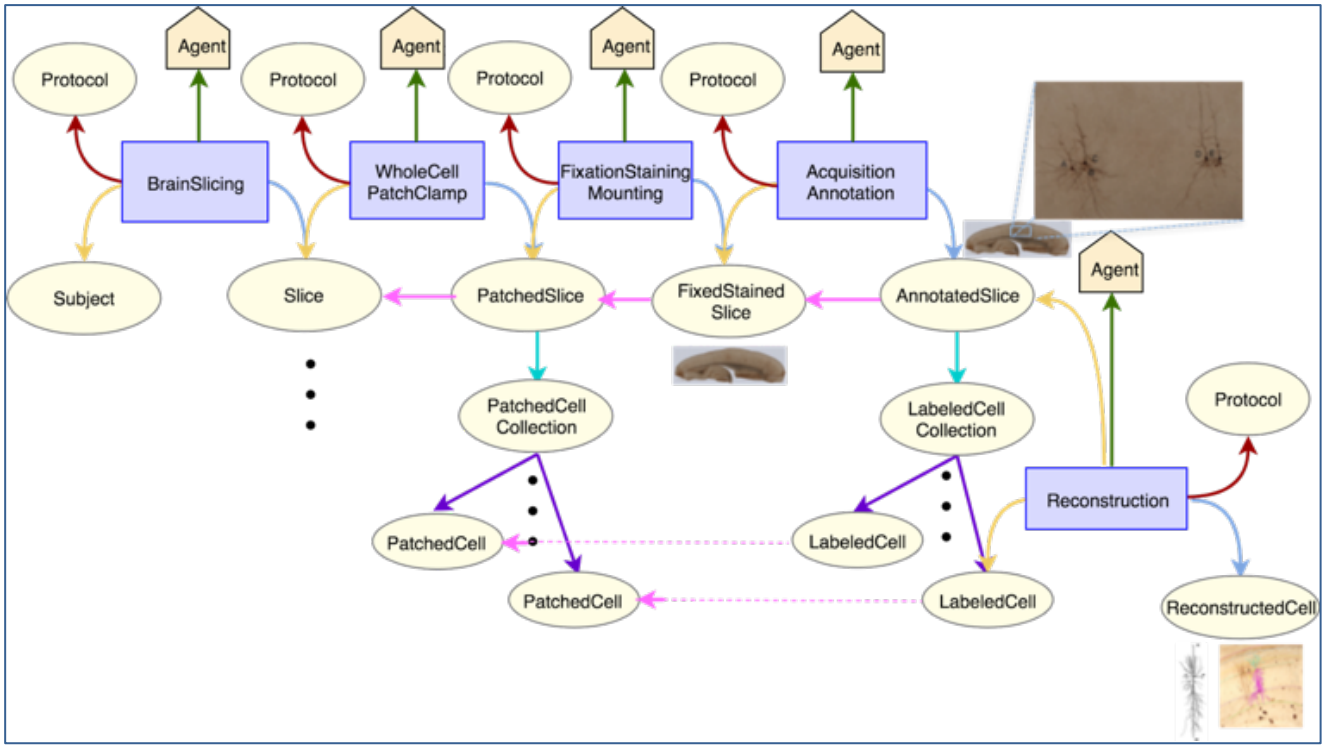

Figure 6: Diagram illustrating the entities & provenance relations for morphology reconstruction

(as defined in the Neuroshapes repository and as available in the HBP KnowledgeGraph)

5.1.4 SONATA community model file format

Development of SONATA has continued, in partnership with the Allen Institute for Brain Science and EPFL/BBP, for the definition of detailed and simplified network models and simulations. This file format is the foundation of the circuit-level software ecosystem of the BSP and exchange with the community. The file format is publicly available under https://github.com/AllenInstitute/sonata and a manuscript is in preparation. Support for this file format has already successfully been implemented in the recently open sourced RTNeuron software for interactive visualisation of detailed network models and simulations (https://github.com/BlueBrain/RTNeuron) and the PyNN network definition language (https://github.com/NeuralEnsemble/PyNN), (C2729).

5.1.5 Deep integration of single cell modelling tools with HBP Knowledge Graph

Integration has been accomplished. In particular, software tools such as BluePyOpt (https://github.com/BlueBrain/BluePyOpt), relevant pre- and post-processing steps, and Neuron as a Service (https://blue-naas.humanbrainproject.eu) now allow the input and output of artefacts that are described by schemas in the Knowledge Graph. This will make it possible for the HBP Neuroinformatics Platform to track provenance with fine-grained detail. Figure 7 already shows a tighter integration between the HBP Model Catalog and services of the BSP.

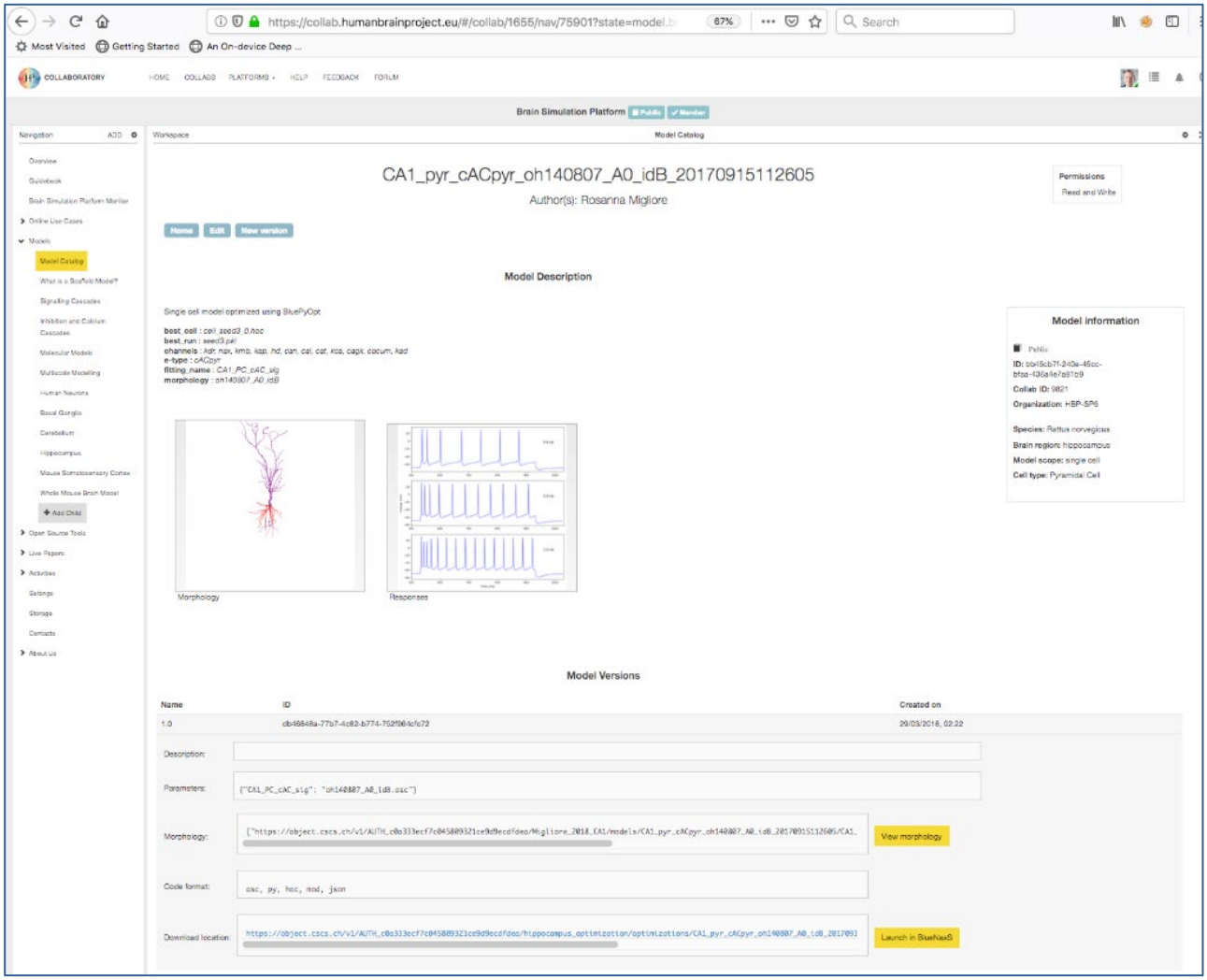

Figure 7: Screen shot of the HBP Model Catalog showing a registered single cell model.

It is now possible to directly invoke services on this model, such as loading it into Neuron as a Service for simulation or for viewing the morphology (see yellow links towards the bottom of the screen shot).

5.1.6 Parameter estimation workflow

The workflow illustrated below (Figure 8) was developed to better constrain subcellular models. This new method combines approximate Bayesian computation (ABC) with global sensitivity analysis (GSA) in order to give better informed predictions; it points out weaker parts of the model that are important targets for further experiments, as well as giving guidance on parameters that are essential for distinguishing different qualitative output behaviours. (Eriksson *et al.*, 2018). The source code is freely available at: https://github.com/alexjau/uqsa.

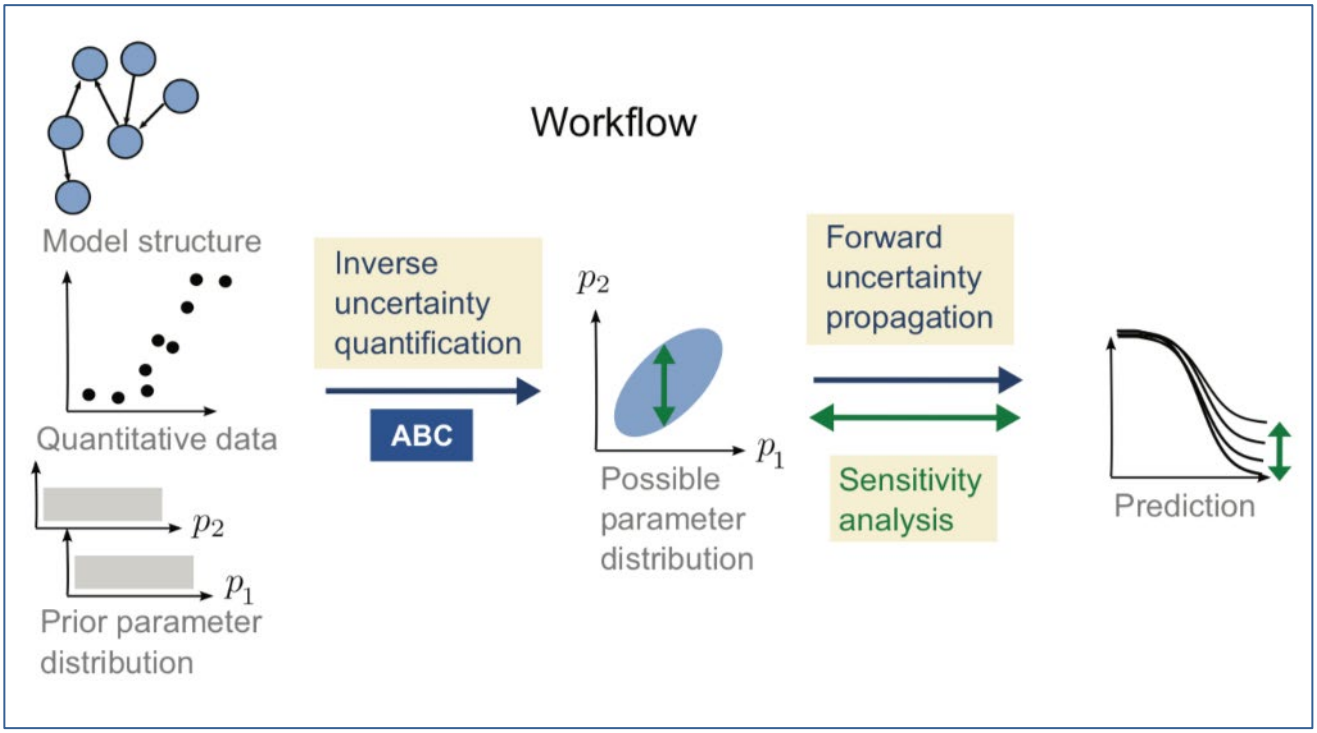

Figure 8: Parameter estimation workflow using approximate Bayesian computation (ABC) and global sensitivity analysis (GSA) as published in Eriksson *et al.*, 2018.

5.2 Validation and Impact

5.2.1 Actual Use of Output(s)

The outputs listed above are of fundamental importance for the BSP, i.e. the web-accessible online platform for modelling and simulation in the HBP Collaboratory.

For example, the NEST simulation engine is being used within the HBP for the network-level cortical multi-area model with point neurons, which is being developed by researchers in SP4 (see https://inm-6.github.io/multi-area-model and Schmidt *et al.*, 2018). Similarly, the CoreNEURON simulator is used to simulate network-level versions (with detailed neurons) of the Hippocampus CA1 model developed by SP6 researchers (https://www.humanbrainproject.eu/en/brain-simulation/hippocampus/) and the Mouse cortical microcircuit (https://www.humanbrainproject.eu/en/brain-simulation/mouse-sscx/), while the NEURON simulator is the foundation of the single cell modelling MOOC (https://www.edx.org/course/simulation-neuroscience-epflx-simneurox). It is deployed via Spack on SP7 HPAC Platform systems. All simulators are furthermore used by communities outside of the HBP; for specific details, we refer to the reference tracking done by the respective simulator owners. However, for example, we have seen substantial attention being paid by the community and media to a paper about NEST's new simulation kernel developed in a previous phase (Jordan *et al.*, 2018). This article is now in the top 1% for that journal, ranked by number of views, and in the top 7%,

ranked by number of downloads. The work described in Jordan *et al.*, 2018 was mentioned in the media more than 20 times.

Outputs related to the NEUROSHAPES community data-schemas and the deep integration of single cell modelling with the HBP Knowledge Graph are used in connection with the single cell modelling workflows implemented in the BSP and the MOOC on single cell modelling (https://www.edx.org/course/simulation-neuroscience-epflx-simneurox). Similarly, the definitions for simplified circuits are facilitating the interoperation of the BSP with the HBP Neurorobotics Platform. Outputs related to the SONATA community model file format are being used by the Allen Institute for Brain Science, which is co-developing this format.

5.2.2 Potential Use of Output(s)

After the resounding success of the first MOOC "Simulation Neuroscience: reconstruction of a single neuron" which linked the edX.org platform with the BSP for interactive use, a second MOOC on simulating circuits is in the final stages of preparation. The definition of standardised data schemas for circuits and simulations, as well as the definition of a high-performance file system for network models, around which a tool ecosystem can flourish, are key elements for circuit level functionality within the BSP. Those outputs are being complemented with the work on the CoreNEURON simulation engine, as well as refinements of platform use cases for the configuration, simulation and analysis of circuit models. It is planned to release this MOOC in 2019.

Similarly, the definition by the BSP and the Allen Institute for Brain Science of a joint data format (SONATA) for detailed and simplified network models will allow exchange of models and tools with the Allen Institute and the community at large. This new file format makes interactions with large-scale models tractable, which previously was not practical with more verbose community standards such as NeuroML. It is thus expected that this format will form an important pillar for integration of community models.

5.2.3 Publications

- Schmidt M, Bakker R, Shen K, Bezgin G, Diesmann M, van Albada SJ. A multi-scale layer-resolved spiking network model of resting-state dynamics in macaque visual cortical areas. PLOS Computational Biology. 2018;14(10): e1006359.
  - This publication concerns use of the NEST Simulator (C1667).
- Eriksson O, Jauhiainen A, Maad Sasane S, Kramer A, Nair AG, Sartorius C, *et al*. Uncertainty quantification, propagation and characterization by Bayesian analysis combined with global sensitivity analysis applied to dynamical intracellular pathway models. Bioinformatics. 2018;35(2):284-92.
  - This publication describes the parameter estimation workflow for subcellular models (C3059).
- Kumbhar PS, Delalondre F, Hines ML, Ovcharenkov A, Schürmann F. CoreNEURON - An Optimized Compute Engine for the NEURON Simulator.
  - This manuscript is in submission but has already been shared with the community as a preprint under http://arxiv.org/abs/1901.10975; it describes CoreNEURON and how it can be used by the community (C1714, C1715).

5.2.4 Measures to Increase Impact of Output(s): disseminations

Organisation of and participation in hackathons for specific tools, as well as the overall integration with other parts of the HBP platform ecosystem, were important for disseminating work in this area. For example, a hackathon focusing on parallel data io for NEST simulation output was held in Ås

(Norway) in June 2018 (C1667). Another example was a hackathon for bringing models to the Exploitation Phase of the Model Life Cycle that was held in Geneva, January 2019 (C1669). During this event, schemas for simplified network models were also built that will facilitate interoperability with the HBP Neurorobotics Platform (C2729).

This work was also presented at the HBP School in Palermo, 17-21 September 2018. Multiple presentations were given and tutorials conducted to introduce participants to the underlying concepts of the BSP and specifics of the tools and formats (C1669, C1714). Similarly, NEST tutorials were held at the CNS conference, Seattle, July 2018 and tutoring provided at OCNC Okinawa, July 2019 (C1667).

Lastly, following the success of the first MOOC "Simulation Neuroscience: reconstruction of a single neuron", EPFL/BBP has led the preparations for the next MOOC in this series, focusing on *in silico* experimentation on network models. The technical integration work with the BSP, recording of lectures and definition of exercises is quite advanced and a release of this MOOC is planned later in 2019.

6. Brain Simulation Platform - web accessible suite of highly integrated model building and simulation tools backed by HPC computing resources (HBP Key Result KR6.4)

The set of online use cases, tools, and services on the BSP has been significantly improved and extended in this period. Here, we think it is important to report on the BSP usage, for a general audience.

At the time of writing, there were 24 active use cases online on the BSP, spanning different model levels. Of these 24 use cases, 3 were related to subcellular models, 14 to single cells, and 4 to brain circuits. A group of 365 unique users, external to HBP, were running these use cases and had created 769 new collabs to carry out their work. Furthermore, there were 3 MOOCs linked to the BSP use cases; 386 students are actively using the Platform and have created so far 1,823 Collabs to carry out their educational plan.

All the model building and simulation tools present in the BSP are unique in the field. There are no similar platforms or similar tools available in the neuroscience community. These tools are also unique in allowing users to run use cases using computing resources on a variety of HPC systems, using a variety of access procedures. Use cases can now run on several HPC systems where simulation engines have been installed and software stacks deployed. The HPC systems that can be used via the BSP are at CSCS (Lugano, Switzerland), JSC (Jülich, Germany), CINECA (Bologna, Italy), and NSG (San Diego, USA). Individual users can access the systems to run their simulations through their PRACE grants; entry-level users can run simulations without a computing grant, thanks to a service account using a general purpose computing allocation granted to the HBP by the ICEI project. All jobs are executed using secure UNICORE rest APIs. For a typical example of access through the service account by running the synaptic events fitting use case at, go to: https://collab.humanbrainproject.eu/#/collab/1655/nav/66850.

6.1 Outputs

6.1.1 Overview of Outputs

Table 4: List of Components contributing to the outputs of Key Result KR6.4

C ID	C Name
C1614	C1 Platform administration and operations
C1615	Deploy simulation and circuit building software on SP7 platform using Nix and Docker
C1634	C1 Simulation engines apps for the Platform
C1636	Install first version of production-ready SP6 Brain Simulation Platform on 2 HBP computing systems
C1718	Model-representation conversion and interoperability tools

6.1.2 New GUI for Features Extraction and Single Cell Model Building tools

The Features Extraction and Single Cell Model Building tools have been equipped with new GUI capabilities for data fetching/selection/visualisation, and improved back-end processing with new statistical analysis settings and output generation (C1634).

6.1.3 Integration of hippocampus CA1 circuit into Brain Area Circuit

The latest internal HBP release of the hippocampus CA1 circuit has been integrated into the Brain Area Circuit *in silico* experiment use case GUI; this can be seen at: https://collab.humanbrainproject.eu/#/collab/1655/nav/66856 (C1615).

6.1.4 Deployment of simulation and visualization stack

The deployment of simulation stack was updated to use optimising compilers and mpi libraries provided by each HPC site. This is now achieved by using Spack package manager for the deployment on the HPC systems at Jülich, Cineca and CSCS. With the Nix package manager, visualisation stacks have been also deployed on the Jülich and Cineca systems (C1636).

6.1.5 Interactive tutorials

Interactive video tutorials for each use case on the BSP are progressively being added online. To see how they work, use the "Interactive tutorial" button here: https://collab.humanbrainproject.eu/#/collab/1655/nav/66850. Users are guided step-by-step with a graphical and detailed explanation of the different choices available during a use case execution (C1614).

6.1.6 Implementation of service account

A first version of the service account has been implemented; it allows any user to submit jobs to remote HPC systems without requiring HPC authentication. Job submission through a service account is currently available for the NeuroScience Gateway (USA) and the Piz Daint system (CSCS, Switzerland). During the second funding phase of the Project it will be progressively integrated into other use cases. (C1614) Its application to the synaptic events fitting use case can be seen at: https://collab.humanbrainproject.eu/#/collab/1655/nav/66850.

6.1.7 Import/export of SONATA format into/from PyNN

A module for the import/export of the SONATA format into/from PyNN has been developed, and is available in PyNN v0.9.4 (released in March 2019, see: http://neuralensemble.org/docs/PyNN/releases/0.9.4.html). This allows point-neuron network models in SONATA format to be loaded by PyNN, simulated with NEST, NEURON, SpiNNaker, etc., then the results saved in the SONATA data report format. It also allows models and simulation plans defined as a PyNN script to be exported in SONATA format and hence simulated using any SONATA-supporting simulation pipeline (C1718).

6.2 Validation and Impact

6.2.1 Actual Use of Output(s)

The outputs are being systematically used by platform users internal and external to the HBP. An indicative and independent measure of the actual use of BSP outputs can be obtained through external tools as Google Analytics. Since we begin to collect page statistics (June 2017), the BSP has accumulated almost 90,000 page views and more than 34,000 sessions. Another important indicator of the interest of the external community in using BSP outputs is the success of the Voucher Programme. The programme was initiated to attract external laboratories interested in using any of the HBP Platform outputs for their scientific investigations without being directly funded by the HBP. Launched during this reporting period and just activated, the Voucher Programme received many proposals specifically interested in using the BSP. Of the 15 proposals which were accepted to receive HBP support, seven directly involve the BSP.

6.2.2 Potential Use of Output(s)

The primary use of the outputs so far is for educational and training purposes, with an increasing portion for scientific investigations. However, it is still too early to see scientific papers published by external groups acknowledging the BSP. It should be stressed that building a user community is not something that can be done in a short period of time. It requires a set of robust and attractive tools, supported by intense, systematic dissemination and training activities. In the previous phase, many use cases were built and improved; during SGA2 Year 1, the TRLs for many of them have significantly increased, relative to their values at the end of the previous phase, and will continue to increase to TRL 9 before the end of the current phase. The use for scientific publication of the outputs can thus be expected to systematically increase with time.

6.2.3 Publications

- Migliore R, Lupascu CA, Bologna LL, Romani A, Courcol J-D, Antonel S, *et al*. (2018) The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modeling workflow. PLoS Comput Biol 14(9): e1006423 (C1614).
    - In this paper, we study the phenomenon of degeneracy in hippocampal CA1 neurons and interneurons. Using BSP tools and apps, we systematically generated a set of morphologically and biophysically accurate models, and analysed the ensembles of peak conductance obtained for each model neuron. Analysis of the model neurons suggests several experimentally testable predictions related to the combination and relative proportion of the different conductances that should be expressed on the membrane of different types of neurons for them to fulfil their role in the hippocampus circuitry. The full set of model and experimental files are available online in the BSP as a Live Paper at: https://collab.humanbrainproject.eu/#/collab/18565/nav/167297.

6.2.4 Measures to Increase Impact of Output(s): disseminations

- Organisation and execution of the first HBP School on the BSP (Palermo, 17-21 September 2018). (C1614, C1615).
  - The School introduced the participants to the BSP, with the main aim to train users on how to exploit the possibilities offered by the Platform to implement cellular level computational models, to use High-Performance Analytics and Computing Platform systems to configure and run a simulation, and to visualise/analyse the results. Through tutorials and hands-on activities, attendees learnt how to interact with the BSP to carry out their own research, to set up and manage a data-driven collaborative project, or to use the BSP to interact with the HBP Neuroinformatics Platform.
- Organisation and execution of the 9th CodeJam Workshop (Palermo, 26-28 November 2019). (C1614).
  - The goal was to catalyse open-source, collaborative software development in computational and systems neuroscience and neuroinformatics, by bringing together researchers, students and engineers to share ideas, present their work, and write code together. The theme of this 9th instalment was "co-design": scientists, students and engineers from different disciplines collaborating to build a research infrastructure for computation-based neuroscience, and to use this infrastructure to model brain circuits, behaviour and learning, develop novel bio-inspired computing systems
- Organisation of EITN Workshop on hippocampus modelling (January 28-29, 2019) (C1614, C1615, C1636).
  - The intent this workshop was to form a group of HBP Partners interested in shaping a product focused on the hippocampus. The idea was centred on having, by the end of the next phase, a fully-fledged, full-scale, data-driven, cellular-level model ready to be used by the community for a variety of scientific explorations.

7. Conclusion and Outlook

During the previous funding phase of the HBP, the BSP was developed to provide a modular and easy-to-use set of online functionalities for modelling and simulation of neural tissue. These efforts were complemented by outreach and training events, such as the Massive Open Online Course on “Simulation Neuroscience: reconstruction of a single neuron”, training students and interested researchers in these novel tools and guiding them to the use of resources offered by the HBP.

Another aspect of the BSP comprises the modelling efforts pursued within the HBP as co-design drivers of the functionality of the platform. In order to better convey the maturity of those components and signal when they are ready for community uptake and contribution, a Life Cycle Model for Data-Driven models ways introduced in the previous phase.

During the last 12 months, work on both axes has pushed forward.

7.1 Improved usability and functionality of the platform

Part of the usability improvements happened “under the hood” of the BSP and relate to better deployment of software on the various HPC systems of HBP’s HPAC Platform, as well as advanced integration with the HBP’s Neuroinformatics Platform. Importantly, we have managed to put in place a first version of a service account for certain HPC systems, substantially lowering the threshold for the access to high performance computing resources. For example, this now allows the invocation of compute-intensive workflows, such as synapse fitting, directly from the web-platform without the need to apply separately for supercomputing time. Other usability improvements are on the surface

of the platform and relate to improved UIs for online use cases such as Feature Extraction, Single Cell Model Building tool or the *in silico* experiment use case for brain circuits.

At the same time, the HBP continued to improve the capabilities of the tools underlying the BSP. Notably, all simulators supported by the platform have undergone feature extensions and scalability improvements and are available in the BSP, but can similarly be accessed via the public source code repositories of the simulators' community pages for use outside the HBP. The definition of data schemas for inputs and outputs relevant for advanced modelling workflows is another contribution triggered by the goal to create a tightly knit ecosystem of tools and workflows that transcends the platform. Specifically, schemas for the HBP Neuroinformatics Platform have been defined for data that is used for single cell model building or circuit simulation and made publicly available. These schemas can be reused by anybody using the data management solution that underlies the HBP Knowledge Graph. Similarly, the definition of a high-performance file format for large-scale models has been pursued by EPFL/BBP and the Allen Institute and provides an anchor point for the software ecosystem developed by the HBP and beyond. In particular, this file format now provides a practical way to integrate external models into the BSP or to have external users immediately benefit from HBP software compatible with this format.

Those platform improvements were complemented by additional training and outreach events. These ranged from specific and focused hackathons, through improved online training material, to the first HBP School on the BSP held in Palermo, 17-21 September 2018, that provided in-depth training on BSP tools and workflows.

7.2 Improved Models and Model Availability

While a number of the models pursued by the HBP are still in the Structured Phase of the Product Life Cycle, others have been published and reached the Exploitation Phase; i.e., the models and underlying data are made available to the community. Importantly, these also show how users can benefit from the advanced capabilities of an online platform. In the last 12 months, several models have reached this Exploitation Phase: 1) Migliore *et al.*, 2018 on hippocampal neurons, 2) Eyal *et al.*, 2018 on first ever active human neurons, and 3) Lindroos *et al.*, 2018 on striatal neurons with subcellular cascades. On the one hand, these models provide novel scientific insights. On the other, publication of the models in scientific journals has been complemented by publishing what we call Live Papers. These Live Papers can be thought of as companion resource sites, providing easy access to the data and model, and at the same time, where BSP services can be applied to them; for example, to run a simulation of the model through the web browser. We believe that this is a major step forward in how models can be shared with and made reusable by the community. Additional models are being prepared for Exploitation Phase release and will be added as soon as their publications are accepted.

For new models to be added, they have to reach a maturity level that makes them viable for the community. Similarly, the BSP capabilities need to be scheduled to provide the required Live Paper support. In particular, we plan to make an Exploitation Phase release within the next 12 months for all models currently being developed by SP6. Accordingly, progress has been made in maturing models on the subcellular and network levels. For example, a scaffold model of the cerebellum has been submitted for review. Together with the simplification of multi-compartmental cerebellar models, this also has been embedded into robotic controllers for closed-loop simulations (Antonietti *et al.*, 2018; Geminiani *et al.*, 2018). These activities are generating new neurophysiological concepts about the mechanisms of function of the cerebellum and are providing an innovative workflow to simulate motor control and its pathologies. Similarly, model components for the hippocampus CA1 and striatum have been improved to increase the fidelity of the network models and, eventually, enable attainment of the Exploitation Phase.

Dissemination of those modelling activities have been pursued through a variety of channels, such as the EITN Workshop on Hippocampus modelling (28-29 January 2019). The outcome of the HBP Voucher Programme showed the interest of the community in these models and paves the way for an early on-boarding of additional external users.

Outlook

The activities for the next 12 months are well defined and have a strong focus on further maturing the models, with the aim to bring them to Exploitation Phase and having a Live Paper representation thereof which makes use of the BSP's capabilities. In line with this goal, the tools and workflows of the platform will be matured and developed to best support those Live Papers.

At the same time, we will continue to train students and researchers in the opportunities the BSP offers, via specific dissemination activities, such as the Erice school on Brain Modelling or a new MOOC on the BSP's capability as an *in silico* experimentation facility, focusing on the example of the hippocampus.

Annex A: Component Details

Component Field	Data
ID	C1614
Component Title	C1 Platform administration and operations
Component Type	Service
Component Leader	Michele MIGLIORE
Component Description	SGA2 - T6.4.6-C1 will generate tools allowing internal or external users to carry out their projects on the Platform. This includes the development and management of umbrella accounts for collaborative projects, and tools to host and maintain web applications, to allow a smooth integration with the other platforms, to access and use HPC systems through UNICORE and REST APIs from the Platform, and to effectively use the FEDAPP infrastructure.
Latest Release	BrainSimulationPlatformServiceAccount_v0.1
Release date	2019-02-28
Release URL	https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,bsp_service_account

Component Field	Data
ID	C1615
Component Title	Deploy simulation and circuit building software on SP7 platform using Nix and Docker
Component Type	Software
Component Leader	James Gonzalo KING
Component Description	The production ready software of the BSP will be installed on at least 3 HBP computing platforms. The deployment will be based on Nix and delivered via a Docker image.
Latest Release	Version 0.6
Release date	2019-01-07
Release URL	https://github.com/BlueBrain/spack/releases/tag/v0.6

Component Field	Data
ID	C1627
Component Title	Modelling the spiking activity of L2/3 pyramidal neurons in human temporal cortex
Component Type	Model
Component Leader	Idan Segev
Component Description	We have recently developed the Multiple Objective Optimisation (MOO) evolutionary algorithm that enables one to extract electrical features of the spiking activity of neurons (e.g., spike shape, rate, adaptation index, etc.) and use these for building realistic electrical

	model of the cell in question. We have somatic recordings for ~30 L2/3 pyramidal neurons in response to a range of depolarizing step/brief currents from in human temporal cortex. These spiking activities and the MOO algorithm will enable us to build the first-ever detailed models for human L2/3 spiking activity (for various types/amplitudes of somatic inputs).
Latest Release	Eyal *et al.*
Release date	2019-03-21
Release URL	https://collab.humanbrainproject.eu/#/collab/47206/nav/324090

Component Field	Data
ID	C1628
Component Title	Modelling L2/3 dendritic spines in human temporal cortex
Component Type	Model
Component Leader	Idan Segev
Component Description	We have high-resolution LM as well as EM data on dendritic spines from human L2/3 pyramidal cells. These include spine head/neck area and dimensions. This data will enable us to construct detailed models of human dendritic spines, which are rather elongated and come with large number ~15,000 - 30,000 spines/neuron. Questions such as charge transfer from spine head to spine base (and vice versa) and the expected dendritic voltage as a function of the number of local activated dendritic spines could be explored as part of this component.
Latest Release	Eyal *et al.*
Release date	2019-03-21
Release URL	https://collab.humanbrainproject.eu/#/collab/47206/nav/324090

Component Field	Data
ID	C1629
Component Title	Modelling L2/3-L2/3 synaptic connection
Component Type	Model
Component Leader	Idan Segev
Component Description	We have already several recordings from pairs of connected L2/3 pyramidal neurons in human temporal cortex. We also have the putative locations of these (multi-contact) synapses. This data, and based on the above two Components) will enable us to build detailed models of these pyramidal-to-pyramidal excitatory synapses, including estimates of the underlying synaptic conductance change and its temporal (depressive) dynamics. Integrating these synaptic properties into the full 3D models of these cells will provide first estimated as to how many E-E synapses is required to fire L2/3 pyramidal neurons and will enable to start building an I/O landscape for these cells.
Latest Release	Eyal *et al.*
Release date	2019-03-21
Release URL	https://collab.humanbrainproject.eu/#/collab/47206/nav/324090

Component Field	Data

ID	C1630
Component Title	Modelling NMDA spike in L2/3 pyramidal neurons in human temporal cortex
Component Type	Model
Component Leader	Idan Segev
Component Description	We have initial results, via high-frequency somatic stimulation, demonstrating that human L2/3 neurons could generate long-lasting dendritic NMDA spike. This is also supported by extracellular focal dendritic stimulation and simultaneous somatic recordings using AMPA/NMDA blockers in the human cortical slice. Via our modelling efforts, this data and additional experimental data to be obtained in the near future, we will be able to build initial models for human NMDA spikes. These models will be later validated via direct dendritic recordings (in SGA3).
Latest Release	Eyal *et al*.
Release date	2019-03-21
Release URL	https://collab.humanbrainproject.eu/#/collab/47206/nav/324090

Component Field	Data
ID	C1634
Component Title	C1 Simulation engines apps for the Platform
Component Type	Software
Component Leader	Michele MIGLIORE
Component Description	This component will generate open source tools for the community that uses the BSP to configure, run, visualise, and analyse data-driven cellular models. This will include support for modellers and experimentalists at different levels, from those interested in using the Platform's infrastructure and facilities using GUIs and public HPC resources (such as the Neuroscience Gateway and Cloud Computing), to more expert users engaged in collaborative projects using their own HPC grants on one of the supercomputer centres supporting BSP activities. Tools will be either Jupyter notebooks or web applications, and will be included into the software catalogue.
Latest Release	SynapticEventsFittingV1.1
Release date	2019-01-01
Release URL	https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Synaptic%20events%20fitting

Component Field	Data
ID	C1636
Component Title	Install first version of production-ready SP6 Brain Simulation Platform on 2 HBP computing systems
Component Type	Software
Component Leader	James Gonzalo KING
Component Description	We will install production-ready software of the SP6 Brain Simulation Platform on at least 2 HBP computing systems. The installation will be based on Nix deployment packaging.
Latest Release	Version 0.6

Release date	2019-01-07
Release URL	https://github.com/BlueBrain/spack/releases/tag/v0.6

Component Field	Data
ID	C1646
Component Title	Advanced cerebellar neurons and synapses construction, optimisation and validation
Component Type	Model
Component Leader	Egidio D'ANGELO
Component Description	Following generation of SGA1 neuron scaffolds, the models of cerebellar neurons (granule cells, PCs, DCN cells, molecular layer interneurons, inferior olivary neurons) and synapses require completion, update and refinement. Moreover, they need to be extensively tested for advanced validation and prediction of emerging patterns of activity in relation to the output generated by network activity (partly shared with Component 2). This process will include the following. (1) Neuron models extended validation toward optogenetically controlled input patterns in vitro and in vivo. This will be done primarily for granule cells, PCs, DCN cells and will allow to verify the effective connectivity patterns. (2) Upgrade models to incorporate realistic neuronal morphologies, that will be substituted to SGA1 synthesized equivalents. This will be made possible through CDP1 data and through external collaborations and databases. (3) Improved representation of the spike generating mechanism in the axon initial segment and axon, that imposes critical constraints to neuronal firing both in granule cells, Purkinje cells, and inferior olivary cells. (4) Incorporation of initial models of plasticity rules in granular layer synapses (shared with T6.1.4) and testing of their impact on neuronal responsiveness.
Latest Release	GrC_PC_GoC_SC_v0.9
Release date	2019-02-28
Release URL	Available to reviewers upon request (simona.tritto@unipv.it)

Component Field	Data
ID	C1661
Component Title	Applications of multi-scale molecular simulation of ligands binding to neuronal proteins
Component Type	Model
Component Leader	Paolo CARLONI
Component Description	A multiscale approach using QM, all-atom and coarse-grain simulations and free energy calculations will be used for characterising ligand binding to a variety of proteins. These will include: (1) radiolabelled allosteric modulators of neuronal receptors to improve brain imaging and help characterizing the distribution of different neuroreceptors in different regions of the human brain for SP2 and CDP3 (JUELICH). (2) Characterization of allosteric mechanisms associated with ligand binding to enzymes and receptors (EPFL). For example, a novel metadynamics-based type of MD simulation will be used to compute off-rates of ligands in presence and absence of different allosteric modulators to understand the allosteric modulation of the residence times of the agonists or antagonists in neuroreceptors (JUELICH). Collaboration with CDP6 on computational drug design and SP1 is planned.
Latest Release	tauRAMD simulations of muscarinic receptor M2
Release date	2019-02-01

Release URL	Available to reviewers upon request (daria.kokh@h-its.org)

Component Field	Data
ID	C1667
Component Title	Implementation of directed communication in NEST
Component Type	Software
Component Leader	Markus DIESMANN
Component Description	In the simulation kernel of NEST, the compute-node unspecific communication of spike data is replaced by directed communication.
Latest Release	NEST 2.16.0
Release date	2018-08-21
Release URL	http://www.nest-simulator.org/download/#releases

Component Field	Data
ID	C1669
Component Title	Fitting of single cell electrical model
Component Type	Software
Component Leader	Jean-Denis COURCOL
Component Description	Reconstruction of cell electrical model, based on parameter optimisation. Investigate new techniques for cell optimisation. Improve extensibility.
Latest Release	Version 1.8
Release date	2019-02-19
Release URL	https://github.com/BlueBrain/BluePyOpt/tree/1.8

Component Field	Data
ID	C1698
Component Title	Multiscale simulations of protein dynamics and complexation
Component Type	Model
Component Leader	Daniele NARZI
Component Description	We will use coarse-grained and atomic-detail models to perform simulations to generate kinetic and thermodynamics parameters, to compute protein-protein docking modes and inform kinetic modelling in T6.1.2 We will use these models to investigate the effects of protein dynamics on protein function and computed parameters which can feed into kinetic models. Procedures for predicting protein binding sites and protein-protein docking rescoring will be validated for a significant number of known interacting protein pairs (CNRS). Coarse-grained (CG) discrete (dMD) and co-evolutionary data will be combined for the prediction of functional dynamics and interactions (IRB). Enhanced sampling molecular dynamics (MD) simulations will be performed to compute binding free energies and rates of ligand association and dissociation (EPFL). Brownian dynamics simulations and MD simulations will be performed to compute kinetic parameters

	(HITS). Methodology will be developed and validated to compute the influence on kinetic parameters of cellular crowding and confinement. This will be implemented in the SDA software, validated on a range of experimental data and then applied to signalling cascades important for plasticity and crowded cellular spaces such as the postsynaptic density or the synaptic cleft.
Latest Release	MD simulations of AC5:Gi complexes – 2018
Release date	2019-02-19
Release URL	https://collab.humanbrainproject.eu/#/collab/45194/nav/310542

Component Field	Data
ID	C1714
Component Title	Optimising execution on next generation hardware
Component Type	Software
Component Leader	James Gonzalo KING
Component Description	CoreNeuron execution will be optimised on next-generation hardware.
Latest Release	CoreNEURON 0.14
Release date	2019-03-01
Release URL	https://github.com/BlueBrain/CoreNeuron/releases/tag/0.14

Component Field	Data
ID	C1715
Component Title	Strong scaling of NEURON framework
Component Type	Software
Component Leader	James Gonzalo KING
Component Description	Methods will be investigated to support strong scaling of NEURON that may require exposing a higher level of parallelism.
Latest Release	NEURON 7.7.0
Release date	2019-01-15
Release URL	https://github.com/neuronsimulator/nrn/releases/tag/7.7.0

Component Field	Data
ID	C1718
Component Title	Model-representation conversion and interoperability tools
Component Type	Software
Component Leader	Andrew DAVISON
Component Description	A Python package providing tools to interconvert between Brain Simulation Platform model representations and community representations, for example NeuroML.

Latest Release	PyNN v0.9.4
Release date	2019-03-22
Release URL	http://neuralensemble.org/docs/PyNN/releases/0.9.4.html

Component Field	Data
ID	C1874
Component Title	Whole brain scaffold
Component Type	Other
Component Leader	Marc-Oliver GEWALTIG
Component Description	Meta-Component to group all Components related to the whole brain scaffold. Downstream Components will generally refer to this meta-Component to address the whole brain scaffold, rather than listing all parts of it.
Latest Release	Version 10.
Release date	2019-03-01
Release URL	https://collab.humanbrainproject.eu/#/collab/1655/nav/75901?state=model.07a61338-2b63-45f8-b790-cf0ab533070f

Component Field	Data
ID	C2152
Component Title	First iteration of community-driven neocortical model
Component Type	Service
Component Leader	Eilif MULLER
Component Description	Bootstrap and run a first iteration for a community process for defining and developing of a data-driven neocortical model using the collaborative HBP platform.
Latest Release	Enabling component - NEUROSHAPES 1.0.3RC release
Release date	2019-02-05
Release URL	https://github.com/INCF/neuroshapes/

Component Field	Data
ID	C2729
Component Title	Provide description of simplified circuits
Component Type	Model
Component Leader	Genrich IVASKA
Component Description	This Component will provide a pipeline to implement the simplified synapses and neurons in the NEURON/Neurodamus simulator. Furthermore, it will provide a function to generate a complete description of the simplified circuits at various levels of abstraction that can be used in other simulators, e.g. point-neuron simulators and neuromorphic hardware.

Latest Release	Version 0.1.0
Release date	2019-02-28
Release URL	https://github.com/INCF/neuroshapes/commit/db9fda3d43f522941e54279c84b79699fb1e613a

Component Field	Data
ID	C2893
Component Title	Atomistic models of human muscarinic receptor in natural mimic-like environment
Component Type	
Component Leader	Paolo CARLONI
Component Description	We focus on the M2 receptor, belonging to the family of Muscarinic Acetylcholine Receptors (mAchR), a sub-class of G-Protein Coupled Receptors found abundantly throughout the central and peripheral nervous system [1]. Their activation may inhibit the deposition of Î²-amyloid peptide, a key pathological feature of Alzheimer's Disease [2]. Targeting selectively such receptor is particularly challenging since their orthosteric site is very similar across the family (70% of sequence identity). Moreover, their endogenous ligand, acetylcholine, also targets nicotinic a4/b2 receptor [3]. The structure of M2 receptor is well-characterised: The X-ray structures with the agonist Iperoxo (4-(4,5-dihydro-1,2-oxazol-3-yloxy)-N,N,N- trimethylbut-2-yn-1-aminium) (4mqs [4]), with the agonist and the allosteric modulator LY2119620 (3-amino-5-chloro-N-cyclopropyl-4-methyl-6[2-(4-methylpiperazin-1-yl)-2oxoethoxy]thieno[2,3-b]pyridine-2-carboxamide) (4mqt [4]) and in complex with an antagonist QNB ((3R)-1-azabicyclo[2.2.2]oct-3-yl hydroxy(diphenyl)acetate) (3uon [5]) are available. Atomistic models of the receptors will be built based on available crystallographic structures and embedded in membranes resembling the effective composition of the physiological membrane in which they are expressed. Then, microsecond timescale MD simulations will be performed to relax the receptor's conformation and examine the stability of the ligands inside of the binding pocket. Critical intra- and intermolecular interactions corresponding to allosteric ligand will be evaluated in C2. 1. Thiele, Alexander. Muscarinic signalling in the brain. Annual review of neuroscience 36 (2013): 271-294. 2. Eglen, Richard M. Muscarinic receptor subtype pharmacology and physiology. Progress in medicinal chemistry 43 (2005): 105-136. 3. Wang, Hong, *et al*. Nicotinic acetylcholine receptor Î±7 subunit is an essential regulator of inflammation. Nature 421.6921 (2003): 384-388. 4. Kruse, Andrew C., *et al*. Activation and allosteric modulation of a muscarinic acetylcholine receptor. Nature 504.7478 (2013): 101-106. 5. Haga, Kazuko, *et al*. Structure of the human M2 muscarinic acetylcholine receptor bound to an antagonist. Nature 482.7386 (2012): 547-551.
Latest Release	Ratchet&Pawl and Metadynamics input files
Release date	2019-02-05
Release URL	Available to reviewers upon request (r.capelli@fz-juelich.de)

Component Field	Data
ID	C3051
Component Title	Scaffold plasticity model for multiscale integration
Component Type	Model
Component Leader	Jeanette HELLGREN KOTALESKI

Component Description	Here we will package selected receptor-induced cascades involved in plasticity and neuromodulation in main types of neurons. Dopaminergic, cholinergic and glutamate receptor induced cascades are of special interest.
Latest Release	Live Paper: Basal Ganglia Neuromodulation - Lindroos *et al.*, 2018
Release date	2018-02-06
Release URL	https://collab.humanbrainproject.eu/#/collab/44569/nav/306517

Component Field	Data
ID	C3057
Component Title	Improved models of hippocampal neurons and circuitry in the mouse and the rat
Component Type	Model
Component Leader	Szabolcs KALI
Component Description	The database of morphologically and biophysically detailed models of neurons in the mouse and the rat hippocampus constructed in the previous phases will be extended by including new cell classes. Models of all cell types will be improved by taking advantage of newly available morphologies, physiological characterisation, ion channel distributions or kinetics, better parameter optimization methods, etc. The detailed cellular-level models of hippocampal circuitry developed in the previous phases will be extended and refined by including new data on cell numbers, distributions, connectivity, synaptic parameters, etc., by incorporating the new cell models, and by taking advantage of improved circuit-building tools developed in the project. New experimentally-based validations of the cellular and circuit models will be implemented. Special emphasis will be given to the detailed comparison of analogous data and models from the mouse and the rat to explore possible strategies for inter-species generalisation.
Latest Release	Live Paper: Migliore *et al.*, 2018 (v1)
Release date	2018-09-18
Release URL	https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/migliore_et_al_2018/migliore_et_al_2018.html

Component Field	Data
ID	C3059
Component Title	Subcellular parameter optimization
Component Type	Software
Component Leader	Jeanette HELLGREN KOTALESKI; Olivia ERIKSSON
Component Description	Software for subcellular model parameter estimation will be developed to allow: i) a quantification of the uncertainty in the model parameters given prior information, data and model structure, ii) an investigation how this uncertainty is propagated to predictions from the model and iii) a characterization of how the model behaviour depend of subsets of parameters. As a first attempt, the calcium dependent signalling cascade leading to CaMKII activation will be used. Subsequently, the model will be generalised to GPCR cascades.
Latest Release	Version 0.1
Release date	2019-01-15
Release URL	https://github.com/alexjau/uqsa

Annex B: Summary of Dissemination Status of SP6 SGA2 Model Components

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Signalling Cascades (C3051, C1709, C1710) - https://www.humanbrainproject.eu/en/brain-simulation/signalling-cascades/						
Basal ganglia	n/a	D1 MSN	Intracellular reaction network model	Exploitation	Nair *et al.*, 2016	Public
Basal ganglia	n/a	D1 MSN	Computational form of the model (ODEs)	Exploitation	Nair *et al.*, 2016	Public
General	n/a	General	Endocanabinoid cascade	Incubator	Unpublished	HBP internal
Generic	n/a	MSN	Intracellular reaction network model	Incubator	Unpublished	HBP internal
General	n/a	General	CaMKIIs intracellular reaction network model	Incubator	Unpublished	HBP internal
General	n/a	General	CaMKIIs computational form of the model (ODEs)	Incubator	Unpublished	HBP internal
Basal ganglia	n/a	MSN	MGluR intracellular reaction network model	Incubator	Unpublished	HBP internal
Basal ganglia	n/a	MSN	MGluR computational form of the model (ODEs)	Incubator	Unpublished	HBP internal
Inhibition and Calcium Cascades (C1781, C1782, C1784) - https://www.humanbrainproject.eu/en/brain-simulation/inhibition-and-calcium-cascades/						
General	General	General	Dendritic spine model with inhibition (python)	Structured/Exploitation pending	Unpublished	HBP Internal
General	General	General	Dendritic spine model with inhibition (NEURON)	Structured/Exploitation pending	Unpublished	HBP Internal
General	General	General	Spine morphometry estimator	Structured/Exploitation pending	Unpublished	HBP Internal
General	Mouse	General	Simplified Ca-dependent cascade model	Incubator	Unpublished	HBP Internal
General	Mouse	General	Full Ca-dependent cascade model	Incubator	Unpublished	HBP Internal
Molecular Signalling Cascades (SGA1 C559, SGA1 C1046, SGA1 C948, C1698) - https://www.humanbrainproject.eu/en/brain-simulation/molecular-signalling-cascades/						
General	Rat	General	Predicted association rate constants of G proteins to AC5 complexes	Structured/Exploitation pending	Unpublished	HBP Internal
General	Rat	General	MD Trajectories of AC5 - G protein complexes	Structured/Exploitation pending	Unpublished	HBP Internal
General	Rat	General	MD simulation models of AC5 G-protein complexes	Structured/Exploitation pending	Unpublished	HBP Internal
General	Rat	General	BD simulation association models of AC5 G-protein complexes	Structured/Exploitation pending	Unpublished	HBP Internal

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Molecular Signalling Cascades (C1709) - https://www.humanbrainproject.eu/en/brain-simulation/molecular-signalling-cascades/						
Basal ganglia	Mouse/rat	D1R MSN	Model of AC signalling cascade	Structured/Exploitation pending	Unpublished	HBP Internal
Molecular Modelling (C2893, C1661) - https://www.humanbrainproject.eu/en/brain-simulation/molecular-models/						
General	General	General	PLUMED scripts	Incubator	Unpublished	HBP Internal
General	General	General	MD model of M2 with POPC membrane	Incubator	Unpublished	HBP Internal
General	General	General	MD model of M2 with mixed membrane	Incubator	Unpublished	HBP Internal
Multiscale (SGA1 C766) - https://www.humanbrainproject.eu/en/brain-simulation/multiscale-modelling/						
Striatum	Mouse	Medium Spiny Neuron	Morphology dMSN, cell WT-P270-20	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	n/a	Medium Spiny Neuron	Ion channel models MSN	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	n/a	Medium Spiny Neuron (dMSN)	Single cell electrophysiological model	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	n/a	Medium Spiny Neuron (dMSN)	Subcellular cascade D1R/AC5/cAMP/PKA	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Multiscale (C3051) - https://www.humanbrainproject.eu/en/brain-simulation/multiscale-modelling/						
Basal ganglia	n/a	MSN	Subcellular plasticity model	Incubator	Unpublished	HBP Internal
Human Neurons (SGA1 C1029) - https://www.humanbrainproject.eu/en/brain-simulation/human-neurons/						
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 0603Cell03	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 0603Cell08	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 0603Cell11	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 1303Cell03	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 1303Cell05	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Passive model HL2/3 1303Cell05	Exploitation	Eyal *et al.*, 2016	Public; Live Paper
Human Neurons (C1627, C1628, C1629, C1630) - https://www.humanbrainproject.eu/en/brain-simulation/human-neurons/						
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 0603Cell03	Exploitation	Eyal *et al.*, 2018	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 0603Cell08	Exploitation	Eyal *et al.*, 2018	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 0603Cell11	Exploitation	Eyal *et al.*, 2018	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 1303Cell03	Exploitation	Eyal *et al.*, 2018	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 1303Cell05	Exploitation	Eyal *et al.*, 2018	Public; Live Paper
Cortex	Human	L2/3 Pyramidal cell	Active model HL2/3 1303Cell06	Exploitation	Eyal *et al.*, 2018	Public; Live Paper

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Basal Ganglia (SGA1 972) - https://www.humanbrainproject.eu/en/brain-simulation/basal-ganglia/						
Striatum	Mouse	SPN, INTs	Scaffold striatum	Structured	Unpublished	HBP Internal
Striatum	Mouse/rodent	SPN	Medium spiny neuron	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Basal Ganglia (C1621, C1622, C1623, C1778, C1780) - https://www.humanbrainproject.eu/en/brain-simulation/basal-ganglia/						
Striatum	Mouse/rodent	SPN	MSND1	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	MSND1 full	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	Ion channels	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	MSND1 full	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	MSND1 fixed half	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	MSND1 fixed full	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	MSND1 dynamic	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse/rodent	SPN	Signalling cascades	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper
Striatum	Mouse	SPN, INT	Connectivity	Structured	Unpublished	HBP Internal
Striatum	Mouse	SPN, INT	Simulation	Structured	Unpublished	HBP Internal
Cerebellum (SGA1 C3023) - https://www.humanbrainproject.eu/en/brain-simulation/cerebellum/						
Cerebellum	Rat	Granule cell mono compartmental	Granule cell - Mono compartmental	Exploitation	Masoli *et al.*, 2017	Public
Cerebellum	Rat	Granule cell mono compartmental	Granule multi morphology	Exploitation	Masoli *et al.*, 2017	Public
Cerebellum	Rat	Granule cell mono compartmental	Granule cell - Multi compartmental	Exploitation	Masoli *et al.*, 2017	Public
Cerebellum	Mouse	Purkinje cell multi compartmental	Purkinje cell - Multi compartmental	Exploitation	Masoli *et al.*, 2015	Public
Cerebellum (C1646, C1616, C1646, C1647) - https://www.humanbrainproject.eu/en/brain-simulation/cerebellum/						
Cerebellum	Rat	Granule cells	Granule cells	Incubator	Unpublished	HBP Internal
Cerebellum	Mouse	Purkinje cells	Purkinje cells	Incubator	Unpublished	HBP Internal
Cerebellum	Mouse	Stellate cells	Stellate cells	Incubator	Unpublished	HBP Internal
Cerebellum	Rat/mouse	Granule cells	Plasticity glomerulus	Incubator	Unpublished	HBP Internal
Cerebellum	Rat/mouse	n/a	Cerebellum network model with point-neurons	Structured	Unpublished	HBP Internal
Cerebellum	Rat/mouse	n/a	Cerebellum network model with detailed single cell models	Incubator	Unpublished	HBP Internal

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Cerebellum	Rat/mouse	Granule cells, Purkinje cells, Stellate cells	Morphological detailed single cell models	Incubator	Unpublished	HBP Internal
Hippocampus (C1620, C3057) - https://www.humanbrainproject.eu/en/brain-simulation/hippocampus/						
Hippocampus CA1 (mouse or rat)	Rat/mouse	PC, INTs	Synaptic plasticity models	Incubator	Unpublished	HBP Internal
Hippocampus (CA1)	Rat	PC, INTs	Single cell models	Exploitation	Migliore *et al.*, 2018	Public; Live Paper
Hippocampus (CA1)	Rat	PC, INTs	Network model 20180309	Structured	Unpublished	HBP Internal
Hippocampus (CA1, CA3, DG)	Mouse	PC, INTs	Hippocampal cell models (mouse)	Structured	Unpublished	HBP Internal
Hippocampus (CA1, CA3, DG)	Mouse	PC, INTs	Hippocampal network models of sub regions (mouse)	Incubator	Unpublished	HBP Internal
Somatosensory Cortex (C2152, C2153) - https://www.humanbrainproject.eu/en/brain-simulation/mouse-sscx/						
Somatosensory cortex	Mouse	n/a	Mouse SSCx circuit network model	Structured	Unpublished	HBP Internal
Whole Mouse Brain (C1874, C1875, C1876, C1877, C3033, C3034) - https://www.humanbrainproject.eu/en/brain-simulation/whole-mouse-brain-model/						
Whole mouse brain	Mouse	n/a	Whole mouse brain cell densities	Exploitation	Erö *et al.*, 2018	Public
Whole mouse brain	Mouse	n/a	Whole mouse brain point neuron network scaffold	Structured	Unpublished	HBP Internal

Annex C: Summary of Data Use in SP6 SGA2 Model Components

Model Name	Data Use in Model	Data Source	HBP Funded
Signalling Cascades (C3051, C1709, C1710)			
Intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No
CaMKIIs intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No
MGluR intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No
Inhibition and Calcium Cascades (C1781, C1782, C1784)			
Dendritic spine model with inhibition	Spine reconstruction data and morphometry from somatosensory cortex L2/3 pyr neurons	ENS	No
Molecular Signalling Cascades (SGA1 C559, SGA1 C1046, SGA1 C948, C1698)			
Predicted association rate constants of G proteins to AC5 complexes	AC5, G protein and complex electrostatic potential grid files	SGA1, T6.1.1; SGA2, T6.1.1	Yes
	Structures of AC5 - G protein complexes	SGA1, T6.1.1; SGA2, T6.1.1	Yes
Molecular Signalling Cascades (C1709)			
Model of AC signalling cascade	Rate constants for G protein association	SGA1, T6.1.1; SGA2, T6.1.1	Yes
Molecular Modelling (C2893, C1661)			
Homology structural models	Modelled adenylyl cyclase (AC) isoform structures	SGA1, T6.1.1;	Yes
	AC isoform electrostatic potential grid files	SGA1, T6.1.1	Yes
Multiscale (SGA1 C766)			
Single cell electrophysical model including a subcellular cascade	Validation data (dendritic); Ca transient (fluorescent)	SGA1, T6.1.4	Yes
	Validation data (somatic); Electrophysiology (FI)	SGA1, T6.1.4	Yes
	Subcellular cascade D1R/AC5/cAMP/PKA	SGA1, T6.1.2	Yes
	Conversion recipe (DataSpace)	SGA1, T6.1.4	Yes
Human Neurons (SGA1 C1029)			
Passive model	Morphology	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
	Electrophysiology - passive transients	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes

Model Name	Data Use in Model	Data Source	HBP Funded
	Spine data	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
Human Neurons (C1627, C1628, C1629, C1630)			
Active model	Electrophysiology – single cell recordings	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
	Electrophysiology pair recordings	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
	Electrophysiology extracellular stimulations	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
	Electrophysiology spike trains	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes
Basal Ganglia (SGA1 972)			
Scaffold striatum	Atlas	Allen Institute	No
	Cell densities	Literature	No
Basal Ganglia (C1621, C1622, C1623, C1778, C1780)			
Enhanced MSN model	Morphology	Neuromorpho SGA2, T6.1.6 (derived)	No Yes (derived data)
Multi-scale MSN scaffold model	Morphology	Neuromorpho SGA2, T6.1.6 (derived)	No Yes (derived data)
Simulation of the microcircuits of striatum	Morphology	Neuromorpho SGA2, T1.2.4 SGA2, T6.1.6 (derived)	No Yes Yes (derived data)
	Connectivity	Literature SGA2, T6.1.6 (derived)	No Yes (derived data)
Simulation of the integrated function of the basal ganglia	Long-range axons	Janelia	No
Cerebellum (SGA1 C3023)			
Granule cells	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4; Literature	Yes
	Granule mono morphology	SGA1, T1.2.4, T6.2.4; Literature	Yes
Purkinje cells	Purkinje cell p43 mouse morphology	RUP, T6.4.5; Literature	Yes
Golgi cells	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4; Literature	Yes
Cerebellum (C1646, C1616, C1646, C1647)			
Granule cells	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes
Purkinje cells	Electrophysiology	SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes
Stellate cells	Electrophysiology	SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes

Model Name	Data Use in Model	Data Source	HBP Funded
Cerebellum network model with point-neurons	Cell densities	Literature	No
	Layers width	Literature	No
	Connectivity ratios (convergence and divergence)	Literature	No
	Functional simulation parameters	Literature	No
Cerebellum network model with detailed single cell models	Cell densities	Literature	No
	Layers width	Literature	No
	Connectivity ratios (convergence and divergence)	Literature	No
	Functional simulation parameters	Literature	No
Hippocampus (C1620, C3057)			
Network model 20180309	Atlas	Literature	No
	Cell densities	Literature	No
	Cell type composition	Literature	No
	Morphology reconstructions	RUP, T6.4.4; SGA1, T6.2.4; SGA2, T6.2.3	Yes
	Bouton density	Literature	No
	Number of synapses per connection	Literature	No
	Synaptic parameters	SGA1, T1.2.6; Literature	Yes
Hippocampal cell models (mouse)	Morphological reconstructions	RUP, T1.2.4; SGA1, T1.2.1, T1.2.5; SGA2, T1.2.2	Yes
	Single neuron electrophysiological recordings	RUP, T1.2.4; SGA1, T1.2.5; SGA2, T1.2.2	Yes
Hippocampal network models of subregions (mouse)	Atlas	Literature	No
	Cell densities	Literature	No
	Cell type composition	Literature	No
	Synaptic bouton density	Literature	No
	Synaptic parameters	SGA1, T1.2.6; Literature	Yes
Somatosensory Cortex (C2152, C2153)			
Mouse SSCx circuit network model	Cell densities needed for network generation (new data)	SGA1, T6.2.2	Yes
	Layer thickness	SGA1, T6.2.2	Yes
	Density of all neurons, used for circuit building	SGA1, T6.2.2	Yes

Model Name	Data Use in Model	Data Source	HBP Funded
	Density of interneurons, used for validations	SGA1, T6.2.2	Yes
	Synaptic density, used for validations	SGA1, T6.2.2	Yes
Whole Mouse Brain (C1874, C1875, C1876, C1877, C3033, C3034)			
Whole mouse brain	Mouse whole voxel-brain for cell density	Literature	No
	Region annotation descriptor	Literature	No
	Region annotated brain volume	Literature	No
	Mouse whole voxel-brain for depth according to pia	Literature	No
	Cell numbers and densities from literature table	Literature	No
	Cortex recipe (cell type distribution and connection types)	Blue Brain Project	No
	Thalamus recipe (cell type distribution and connection types)	Blue Brain Project	No
	Hippocampus recipe (cell type distribution and connection types)	SGA2, T6.2.3	Yes
	Cerebellum recipe (cell type distribution and connection types)	SGA1, T6.2.3	Yes
	Basal ganglia recipe (cell type distribution and connection types)	Literature	No
	Adaptive exponential integrate and fire parameters	Literature	No
	Viral tracers injections experiments	Literature	No
	Mouse whisker input and cutaneous input projections on SSCx	Literature	No
	Whole brain model parameters	SGA2, T6.2.6	Yes