SP6 Annual Compound Deliverable Year 2 (D6.3.1 – SGA2)

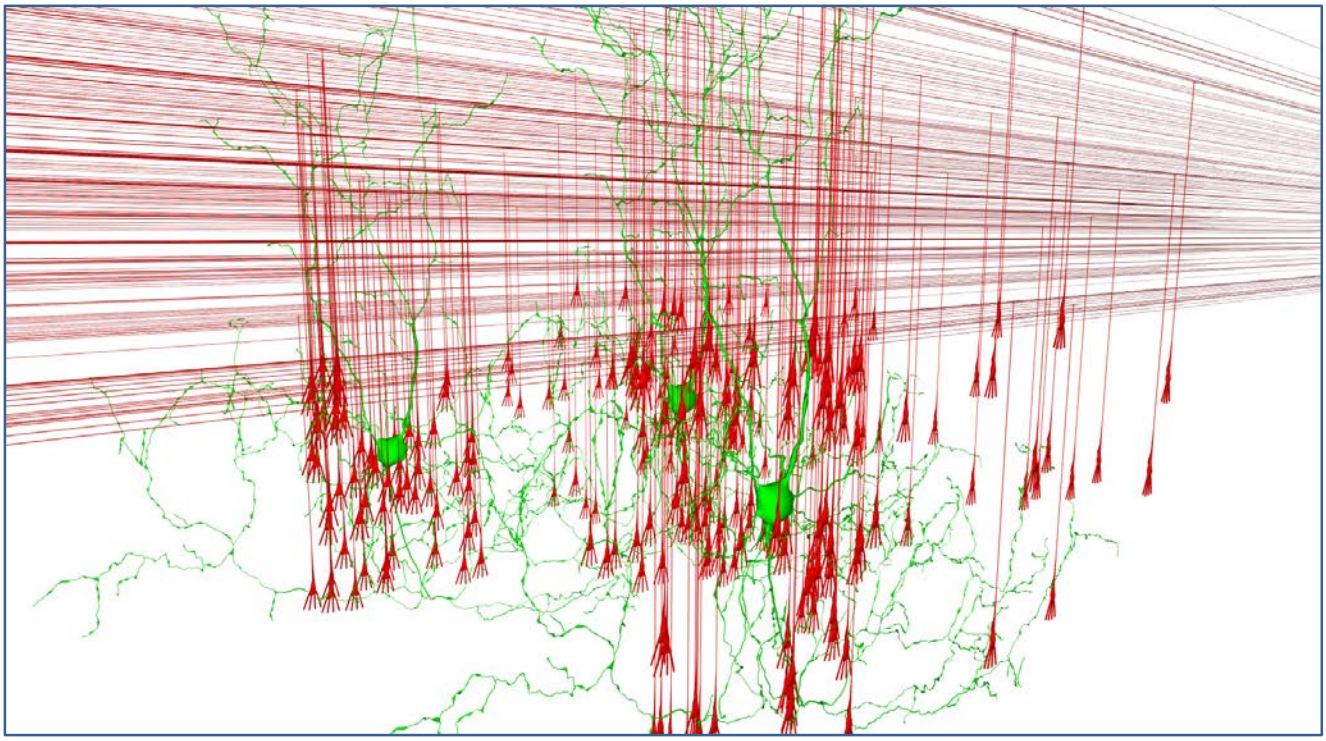

Figure 1: Detailed reconstruction of the cerebellar network[1] on the Brain Simulation Platform[2].

(Model by UNIPV, visualisation by URJC)

[1] https://collab.humanbrainproject.eu/#/collab/1655/nav/85477
[2] https://collab.humanbrainproject.eu/#/collab/1655/nav/28538

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Description in GA:	For consistent presentation of HBP results, SGA2 M24 Deliverables describing the accomplishments of an entire SP, WP or CDP have been prepared according to a standard template, which focuses on Key Results and the Outputs that contribute to them. Project management elements such as Milestones and Risks will be covered, as per normal practice, in the SGA2 Project Periodic Report.
Abstract:	This Deliverable is the annual compound of HBP deliveries and results (outputs and outcomes) from Subproject SP6 – Brain Simulation Platform. The complete live catalogue of HBP deliveries is accessible online at the HBP portal.
Keywords:	Brain Simulation Platform; co-design; data-driven; scaffold models; simulation neuroscience; Live Papers; multiscale models; community
Target Users/Readers:	(Potential) Platform users, computational neuroscience community and simulator tool users.

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1. Overview

To build, analyse and simulate data-driven models, in a collaborative manner and at multiple biological scales, is a key HBP goal. SP6 has led the effort to develop a user-centric Brain Simulation Platform (BSP), building on previous experience of letting users co-design the model building process, and thus drive needs for specific software, model reconstruction pipelines and simulation capabilities. This has resulted in a) the delivery of brain models going beyond anything made earlier by single labs, inside or outside Europe, and b) a mature infrastructure for automated model building and simulations that will provide an important part of EBRAINS in SGA3.

With regard to models, SP6 has created the most comprehensive, cellular level models of rodent cortical microcircuit, hippocampus (CA1), cerebellum and basal ganglia (striatum). Data from SP1 were important for this. Similarly, SP6 has continued to demonstrate that molecular level simulations can be used to constrain subcellular models, which in turn can be integrated into cellular level models. This bridging of scales is necessary for understanding phenomena such as plasticity and learning in the brain. The published models are being disseminated using “Live Papers”, and the data used for the models are registered in the Knowledge Graph.

In the process of generalising model building workflows using a co-design approach, the BSP has become more attractive to the community, as new software tools and standards for modelling at different biological scales have been developed and packaged as a set of online use cases and services. Such tools and use cases are attractive also for educational purposes, and the BSP has currently almost 700 external users. Users can test the online use cases on the available Fenix/ICEI infrastructure without having an HPC grant, thanks to integration and coordination between services provided by SPs 5, 6 and 7. The corresponding infrastructure for data-driven modelling is mature enough to attract many external users, and will represent an important functionality in SGA3.

2. Introduction

In recent years, modelling and simulation of neurons and networks have converged on community use of a select set of open source simulation environments; in particular, NEST for large-scale networks of point neurons, NEURON for large scale networks of biophysically detailed cells, STEPS for biochemical models of individual cells and blocks of tissue. At the same time, the community has largely deposited published models into online resources, such as ModelDB, for others to inspect or use. Resources such as OpenSourceBrain have made selected models runnable in web browsers.

Since the start of the HBP, SP6 has looked beyond individual tools and resources, and aimed at an integrated ecosystem for modelling and simulation, co-designed with selected science drivers and integrating the best-in-class community software. Accordingly, SP6 organised its activities around 4 key results: Two focus on the scientific co-design drivers, namely KR6.1 Multi-scale models of plasticity, KR6.2 Scaffold models of brain regions/whole brain ready for community use. And two focus on the tools and the platform, namely KR6.3 Advanced tools for data-driven modelling and simulation and KR6.4 Brain Simulation Platform - web accessible suite of highly integrated model building and simulation tools backed by HPC computing resources.

There are now numerous key Outputs to support those Key Results. A central Output is a unique online platform for modelling and simulation, that is publicly accessible and used by external researchers supported by the HBP voucher programme and by learners around the world in massive open online courses built on top of this platform. Our Brain Simulation Platform is tightly integrated with advanced neuroinformatics resources, including a powerful knowledge graph capable of organising type-classified data and model artefacts, and supercomputing resources in leading European supercomputing centres. Parts are also integrated with the US Neuroscience Gateway.

Underlying this online platform are advanced software tools to which SP6 contributes. Specifically, SP6 has embraced the aforementioned main community simulation engines and contributed to their development; in particular, with respect to the size of achievable models and efficient use of modern high-performance computing systems. Furthermore, a unique and novel set of advanced model-

building workflows for single cell model building and *in silico* experimentation have been developed and made available to the community via open source and as a Service.

Those developments have been driven in co-design with some of the most advanced attempts to generate large-scale detailed brain tissue models, inspired by the foundational work of the Blue Brain Project (Markram *et al*., 2015). Thanks to HBP work, these have been generalised and applied to different areas of the rodent brain, namely basal ganglia, hippocampus CA1 and the cerebellum, and – recently - to human cortical cells. These developments not only leverage those models and the underlying tools and platform, but they also adhere to a novel life-cycle model for data-driven models, setting a new standard in data provenance. Collectively, those results are demonstrated in a new set of companion "Live Papers", powered by the Brain Simulation Platform and which feature online execution of the models and access to data.

Lastly, this set of new, biophysically-detailed, brain tissue models for selected regions has been leveraged for novel multi-scale studies of plasticity. On the one hand, SP6 used molecular dynamics simulations to derive parameters for subcellular models of plasticity. On the other hand, SP6 developed methods to simplify detailed models into networks of simplified models, to enable closed-loop experiments for robotics studies or execution on neuromorphic hardware.

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

Learning and plasticity are key characteristics of all structures in the vertebrate brain. To understand plasticity better will have far-reaching implications for the study of healthy and diseased brains. Plasticity depends on the interactions between intracellular processes and network activity, and is typically controlled by various neuromodulators (such as dopamine, acetylcholine, etc.). Therefore, one aim of this Key Result has been to bridge from the intracellular scale to the cellular/microcircuit scale, by building and simulating data-driven models at the subcellular level and to then integrate those models with whole neuron models. This typically requires that the cellular level models are sufficiently enhanced with, for example, improved calcium dynamics, dendritic spines, active dendrites and mechanisms for neuromodulation.

Modelling intracellular signalling is, however, a challenge, because some of the model parameters cannot be measured today, but fortunately molecular level simulations can contribute with important constraints regarding protein-protein interactions. Here, SP6 has thus provided molecular-level model components for constraining subcellular level models and also, as a next step, integrated subcellular models into enhanced models of the main neuron types in the hippocampus, cerebellum and striatum. The model components are provided as community resources, and some of the Outputs are highlighted as Live Papers. Also, the Outputs have been instrumental for the co-design of the molecular level use cases in KR6.4.

3.1 Outputs

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to this KR

Table 1: List of Outputs contributing to KR6.1.

Output	Name	Component ID
1	Predictions of ligand-receptors binding through multi-scale molecular simulations	C1661
2	Atomistic models of human muscarinic receptor	C2893
3	Proof of concept that multiscale simulations of protein dynamics and complexation can constrain models of plasticity	C1698
4	Scaffold plasticity model for multiscale integration	C3051

5	Feasibility analysis of semiconductor voltage nanosensors for neuronal membrane potential sensing	C3156
6	Cerebellar plasticity models	C3130
7	Hippocampus and plasticity	C1620
8	Enhanced model of striatal projection neurons	C3131

3.1.1.2 How Outputs relate to each other and the Key Result

Results from the first three Outputs (C1661, C2893, C1698) show that molecular simulations can predict important features of neuronal proteins. This information can be used, both to enhance the general understanding of proteins, receptors, etc., but also for drug discovery and when constraining subcellular level models (see Live Paper by Bruce et al., (2019), which was a collaboration between Tasks T6.1.1, T6.2.7 and T6.1.2).

The building of subcellular models (C3051) capitalises on results from the three first Outputs. Subcellular models of receptor induced signalling involved in synaptic plasticity and/or neuromodulation have been integrated into whole neuron models. This allows us to study, in a quantitative manner, the resulting effects on local membrane excitability or synaptic conductance. When such multiscale model components are integrated into a microcircuit model, one can investigate, for example, how plasticity results from ongoing network activity or how neuromodulation affects network behaviour. Thus, subcellular models at this level of detail are needed for Outputs 6, 7 and 8.

Output 5 (C3156) is a step in the direction of being able to measure voltage fluctuations with high spatial and temporal accuracy, which is needed as an input for synaptic plasticity models, as well as for the enhancement of whole neuron models, since quantification of calcium cascades triggered by depolarisation events are necessary constraints. Thus, this Output is important for Outputs 4, 6, 7 and 8.

Results from Outputs 6, 7 and 8, (C3130, C1620 and C3131) allow users to predict how neuronal activity shapes plasticity.

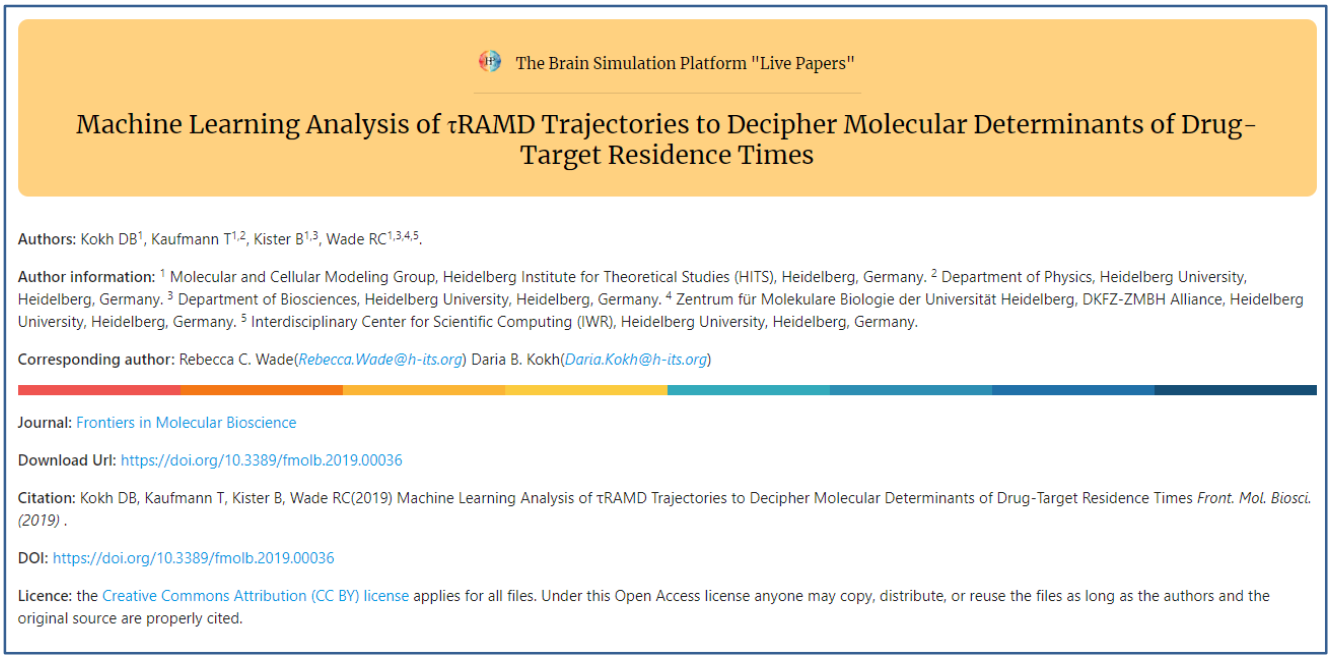
All Outputs can also be used by the community, either as model components, or as informative "data" objects.

3.1.2 Output 1: Predictions of ligand-receptors binding through multi-scale molecular simulations

Table 2: KR6.1 Output 1 links.

Component	Link to	URL
C1661	Model Repository	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/kokh_et_al_2019/kokh_et_al_2019.html
	Technical Documentation	https://www.frontiersin.org/articles/10.3389/fmolb.2019.00036/full
	User Documentation	https://www.frontiersin.org/articles/10.3389/fmolb.2019.00036/full

Here SP6 has developed and used a molecular-dynamics based approach for the systematic analysis of protein-ligand binding contacts in ligand dissociation trajectories, estimation of ligand unbinding rate constants, and deciphering molecular determinants that affect protein-ligand residence times. The approach will assist in studying drug-target binding kinetics and the derivation of parameters for systems neuropharmacology. The method was evaluated for ligands binding a soluble protein (a large set of 94 compounds of the heat shock protein 90 (HSP90)) and applied to a transmembrane protein in two model membranes: the muscarinic receptor M2. The work is illustrated in a Live Paper (Kokh *et al.*, 2019), see Figure 2.



The Brain Simulation Platform "Live Papers"

Machine Learning Analysis of τRAMD Trajectories to Decipher Molecular Determinants of Drug-Target Residence Times

Authors: Kokh DB[1], Kaufmann T[1,2], Kister B[1,3], Wade RC[1,3,4,5].

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Journal: Frontiers in Molecular Bioscience

Download Url: https://doi.org/10.3389/fmolb.2019.00036

Citation: Kokh DB, Kaufmann T, Kister B, Wade RC(2019) Machine Learning Analysis of τRAMD Trajectories to Decipher Molecular Determinants of Drug-Target Residence Times *Front. Mol. Biosci. (2019)* .

DOI: https://doi.org/10.3389/fmolb.2019.00036

Figure 2: Screenshot of Live Paper[3] Kokh *et al.*, 2019.

3.1.3 Output 2: Atomistic models of human muscarinic receptor

Table 3: KR6.1 Output 2 links.

Component	Link to	URL
C2893	Model Repository	https://kg.ebrains.eu/search/instances/Model/19873bd656c4c82d25ed20da04f56df4
	Technical Documentation	https://www.plumed.org/doc-master/user-doc/html/_syntax.html
	User Documentation	https://www.plumed.org/doc-master/user-doc/html/tutorials.html

A molecular dynamics-based approach was developed and used for the systematic analysis of protein-ligand binding contacts in ligand dissociation trajectories, estimation of ligand unbinding rate constants, and deciphering molecular determinants that affect protein-ligand residence times. The approach will assist in studying drug-target binding kinetics and the derivation of parameters for systems neuropharmacology.

We computed the full free-energy landscape of the binding/unbinding process of iperoxo with M2 muscarinic receptor in a neuronal membrane, using non-equilibrium simulation technique (Ratchet and Pawl MD) and enhanced sampling methods (Well-tempered metadynamics). This protocol can be ideally applied to any kind of protein/membrane protein interaction. We also computed the unbinding constant for the same system via infrequent metadynamics (paper in preparation to be continued in SGA3).

This work provides and demonstrates new molecular dynamics-based simulation approaches to computing molecular parameters and properties that can be used in subcellular mathematical modelling e.g. of signalling cascades.

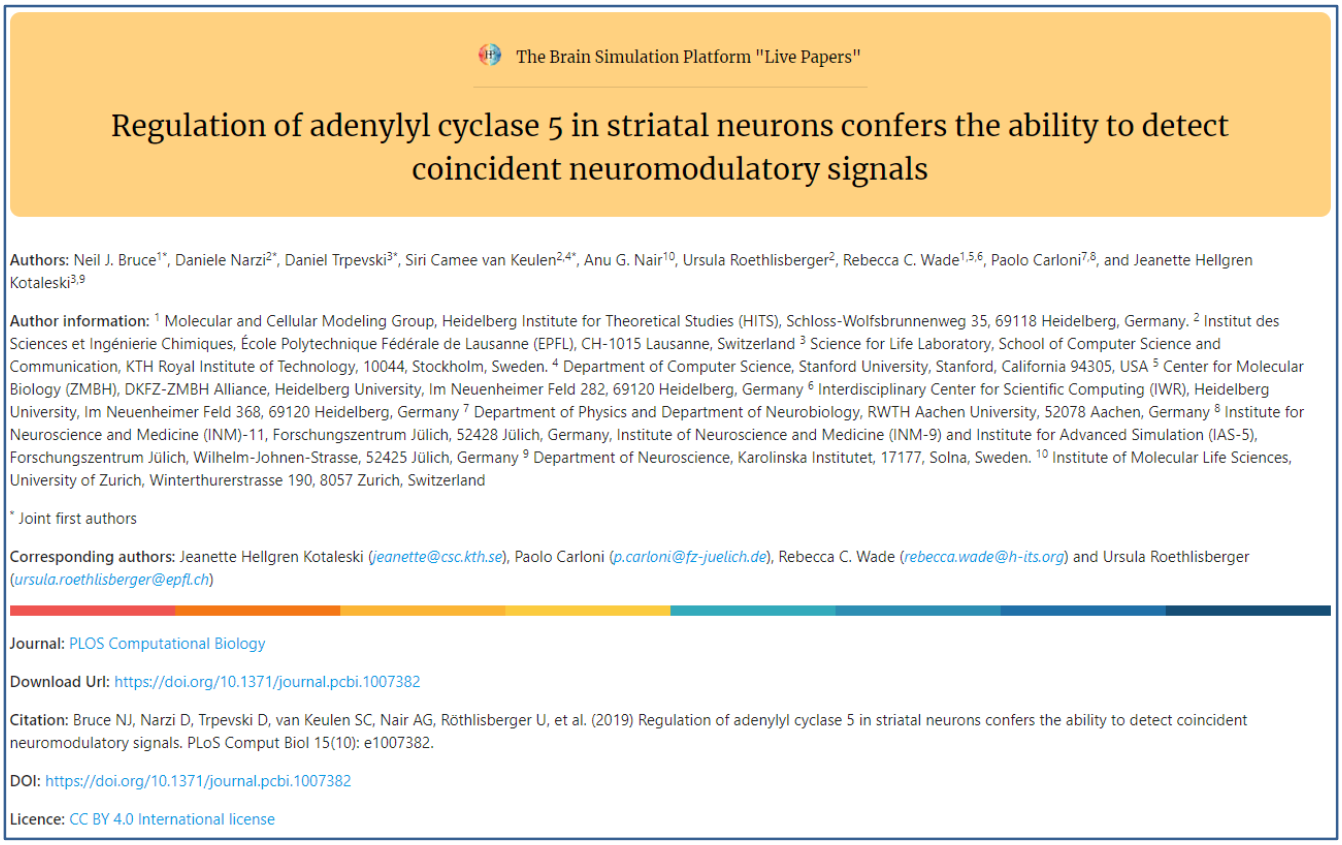
[3] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/kokh_et_al_2019/kokh_et_al_2019.html

3.1.4 Output 3: Proof of concept that multiscale simulations of protein dynamics and complexation can constrain models of plasticity

Table 4: KR6.1 Output 3 links.

Component	Link to	URL
C1698	Model Repository	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/bruce_et_al_2019/bruce_et_al_2019.html
	Technical Documentation	https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1007382
	User Documentation	https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1007382

Stability and activity of the complex of Gαolf, Gαi, and AC5 have been determined using protein structure-based molecular dynamics simulations and their association rate constants were computed using Brownian dynamics simulations (SDA software Task T6.3.7). Rate constants were then employed for building a kinetic model of the AC5-dependent signalling system. Results are illustrated in a Live Paper (Bruce *et al.*, 2018), see Figure 3.


The Brain Simulation Platform "Live Papers"

Regulation of adenylyl cyclase 5 in striatal neurons confers the ability to detect coincident neuromodulatory signals

Authors: Neil J. Bruce[1*], Daniele Narzi[2*], Daniel Trpevski[3*], Siri Camee van Keulen[2,4*], Anu G. Nair[10], Ursula Roethlisberger[2], Rebecca C. Wade[1,5,6], Paolo Carloni[7,8], and Jeanette Hellgren Kotaleski[3,9]

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Journal: PLOS Computational Biology

Download Url: https://doi.org/10.1371/journal.pcbi.1007382

Citation: Bruce NJ, Narzi D, Trpevski D, van Keulen SC, Nair AG, Röthlisberger U, et al. (2019) Regulation of adenylyl cyclase 5 in striatal neurons confers the ability to detect coincident neuromodulatory signals. PLoS Comput Biol 15(10): e1007382.

DOI: https://doi.org/10.1371/journal.pcbi.1007382

Figure 3: Screenshot of Live Paper[4] Bruce *et al.*, 2019.

[4] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/bruce_et_al_2019/bruce_et_al_2019.html

3.1.5 Output 4: Scaffold plasticity model for multiscale integration

Table 5: KR6.1 Output 4 links.

Component	Link to	URL
C3051	Model Repository	https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=237653#tabs-1
	Technical Documentation	https://collab.humanbrainproject.eu/#/collab/44569/nav/306517
	User Documentation	https://collab.humanbrainproject.eu/#/collab/44569/nav/306517

SP6 integrated a dopamine-dependent signalling cascade (C3051) into a direct pathway striatal projection neuron model carrying dopamine type I receptors (C3131). The goal was to better understand the cellular mechanisms involved in dopamine neuromodulation, as well as the role of dopamine transients seen in experimental settings during onset of movements. The resulting prediction was that, most likely, the dopamine axon terminals are co-releasing glutamate. Another prediction was that dopamine probably decreases the Kv4.2 conductance in the dendrites. This type of multiscale modelling work, still in its infancy, is quite unique in the computational field. Typically, only excitatory glutamatergic and inhibitory GABAergic synapses are represented in models, while experiments suggest that neuromodulatory systems are crucial for shaping the behavioural repertoire. These types of approaches are now being integrated in the construction of the full striatal microcircuit, where all different neuron types can be modulated with dopamine mimicking experimental data, where available. This is further demonstrated in the striatal Live Paper highlighted under KR2 (Hjorth *et al.*, 2020).

3.1.6 Output 5: Feasibility analysis of semiconductor voltage nanosensors for neuronal membrane potential sensing

Table 6: KR6.1 Output 5 links.

Component	Link to	URL
C3156	Software Repository	https://github.com/pabloserna/Nanorods
	Technical Documentation	https://github.com/pabloserna/Nanorods
	User Documentation	https://github.com/pabloserna/Nanorods

We have reported the development of lipid-coated semiconductor voltage-sensitive nanorods (vsNRs) that self-insert into the neuronal membrane. We described a workflow to detect and process the photo-luminescent signal of vsNRs after wide-field time-lapse recordings. We also presented data indicating that vsNRs are feasible for sensing membrane potential in neurons at a single-particle level. The state of the art for voltage sensors are voltage dyes and voltage proteins. These probes lack the spatial accuracy needed to address the voltage fluctuations near synaptic inputs where the plasticity occurs, e.g., spines. NRs do have an extremely good spatial accuracy, but their response is very noisy. We went beyond the state of the art, by developing a protocol to identify them and obtain their response in neurons. These results can lead to further developments in voltage sensors in addition to the direct use for modelling.

3.1.7 Output 6: Cerebellar plasticity models

Table 7: KR6.1 Output 6 links.

Component	Link to	URL
C3130	Model Repository	https://collab.humanbrainproject.eu/#/collab/9136/nav/69078
	Technical Documentation	https://collab.humanbrainproject.eu/#/collab/9135/nav/69070

	User Documentation	https://collab.humanbrainproject.eu/#/collab/9135/nav/69070

A cerebellar model was built in NEURON 7.8. It uses the reaction and diffusion module to simulate internal calcium handling, and activation of calmodulin and nitric oxide synthase (NOS). This protein generates NO which diffuses into the extracellular matrix and controls the presynaptic release probability. The connection between the pre and post synaptic sides is simulated with a synapse build with the Tsodyks and Markram framework. This approach was employed in only a few cases, because of its intrinsic difficulty in finding the data and its high computational power requirement. The model reproduces the experimental recording of STDP and is generic enough to be used by other neurons depending on NO for their synaptic plasticity.

3.1.8 Output 7: Hippocampus and plasticity

Table 8: KR6.1 Output 7 links.

Component	Link to	URL
C1620	Model Repository	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/solinas_et_al_2019/solinas_et_al_2019.html
	Technical Documentation	https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1006975
	User Documentation	https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1006975

A detailed computational model that accounts for previously published experimental results of plasticity that is dependent on Brain Derived Neurotrophic Factor (BDNF) or independent on it. The model explains the magnitude and time course of both transient forms of LTP (t-LTP) and allows predicting t-LTP properties that result from an altered BDNF turnover. Since BDNF levels are typically decreased in dementia patients, understanding the function of BDNF in memory processes is important for counteracting neurodegenerative diseases.

3.1.9 Output 8: Enhanced MSN model

Table 9: KR6.1 Output 8 links.

Component	Link to	URL
C3131	Model Repository	https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.1.6/msn-model-2020Q1.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.1.6/msn-optim-2019Q3.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.1.6/msn-ephys-2019Q3.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.1.6/msn-morph-2019Q3.zip
	Technical Documentation	https://senselab.med.yale.edu/modeldb/ShowModel.cshtml?model=237653#tabs-1; https://collab.humanbrainproject.eu/#/collab/376/nav/42864; https://collab.humanbrainproject.eu/#/collab/376/nav/42863;
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/lindroos_et_al_2018/lindroos_et_al_2018.html (Live Paper)

Single-cell models of the striatal projection neurons (SPN; or medium spiny neurons, MSN) were fitted to individual neurons using electrophysiological recordings from *ex-vivo* experiments. Ion channels for the models were selected based on gene expression pattern from single-cell RNA-seq experiments. This is the first attempt to make SPN models based on scRNA-seq and patch-clamp electrophysiological data. Finally, the models were enhanced with dopamine neuromodulation, by affecting the corresponding membrane conductances. In an alternative variant of this model, a

dopamine cascade directly affected some of the conductances (see C3051). Results are shown in a Live Paper (Hjorth *et al.*, 2020) under KR2.

3.2 Validation and Impact

3.2.1 Actual and Potential Use of Output(s)

All Outputs from this Key Result are released in the form of model components deposited on the Knowledge graph as well as via other resources such as ModelDB, Biomodels, github, etc. Thus, these models can be reused by the community in other contexts. Also, insights gained by the molecular level simulations can be used by the pharmacological industry Furthermore, this work under KR1 has been conducted in a co-design process with KR3 and KR4 (especially KR4, Output 5). Thus, during SGA3 the EBRAINS model building pipelines will be further enhanced based on the experience gained so far, and additional User Cases will enable users to perform e.g. molecular dynamics simulations and make analyses for other systems. Also, two of SGA3 vouchers related to hippocampal and striatal plasticity will contribute to the strengthening of modelling services at this level, thus aiming at facilitating the building of multiscale models of phenomena such as plasticity and neuromodulation.

Some of the Outputs from this Key Result have been highlighted in the form of Live Papers, thus the impact is expected to increase further.

3.2.2 Publications

- Output 1 - Predictions of ligand-receptors binding through multi-scale molecular simulations (C1661): P2008 Kokh *et al.*, 2019. Machine Learning Analysis of τRAMD Trajectories to Decipher Molecular Determinants of Drug-Target Residence Times. Frontiers in Molecular Biosciences.
    - Significance: A molecular dynamics-based approach for the analysis of protein-ligand binding contacts in ligand dissociation trajectories, estimation of ligand unbinding rate constants, and deciphering molecular determinants that affect protein-ligand residence times is important when studying e.g. drug-target binding kinetics.
- Output 2 - Atomistic models of human muscarinic receptor (C2893): P2032 Capelli *et al.*, 2019. Exhaustive Search of Ligand Binding Pathways via Volume-Based Metadynamics. The Journal of Physical Chemistry Letters.
    - Significance: This approach provides and demonstrates new molecular dynamics-based simulation approaches to computing molecular parameters and properties that can be used in subcellular mathematical modelling e.g. of signalling cascades.
- Output 3 - Proof of concept that multiscale simulations of protein dynamics and complexation can constrain models of plasticity (C1698): P2205 Bruce *et al.*, 2019. Regulation of adenylyl cyclase 5 in striatal neurons confers the ability to detect coincident neuromodulatory signals. PLOS Computational Biology. (Also highlighted as a Live Paper).
    - Significance: Here it is demonstrated how modelling of receptor induced signalling can use insights and data from molecular simulations at multiple scales.
- Output 4 - Scaffold plasticity model for multiscale integration (C3051): P749 Lindroos *et al.*, 2018. 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. Frontiers in Neural Circuits (Live Paper). Also proof of concept how to model neuromodulation in a multiscale manner is illustrated in Hjorth *et al.*, 2020, compare Output 8.
    - Significance: Here it is demonstrated how multiscale modelling, bridging between the intracellular level and the whole cell level, can enhance our understanding of neuromodulation and give rise to new hypotheses.

- Output 5 - Feasibility analysis of semiconductor voltage nanosensors for neuronal membrane potential sensing (C3156): P2317 Ludwig *et al.*, 2020. Feasibility analysis of semiconductor voltage nanosensors for neuronal membrane potential sensing. bioRxiv.
  - Significance: The results can lead to further developments in voltage sensors in addition to the direct use for predicting parameters for modelling.
- Output 6 - Cerebellar plasticity models (C3130): No publication yet.
- Output 7 - Hippocampus and plasticity (C1620): P1866 Solinas *et al.*, 2019. A kinetic model for Brain-Derived Neurotrophic Factor mediated spike timing-dependent LTP. PLOS Computational Biology.
  - Significance: This modelling approach allows the prediction of transient forms of synaptic plasticity depending on BDNF turnover. Since BDNF levels are typically decreased in dementia patients, understanding the function of BDNF in memory processes is important for counteracting neurodegenerative diseases.
- Output 8 - Enhanced MSN model (C3131): P2489 (*in press* – SGA3 publication) Hjorth *et al.*, 2020. The microcircuits of striatum *in silico*. Proceedings of the National Academy of Sciences of the United States of America.
  - Significance: This is the first attempt to make SPN models based on scRNA-seq and patch-clamp electrophysiological data. Also, a generic way to model dopamine neuromodulation is demonstrated.

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

4.1 Outputs

4.1.1 Overview of Outputs

An important goal of this Key Result is to improve and generalise the workflows for scaffold models of different brain regions (cortex, cerebellum, basal ganglia and hippocampus) and to release them on the BSP and to the community. The scaffold models are also intended to provide a basis for implementing the whole-brain modelling workflow. A first set of Live Papers (papers that are "replicable" with the Live Paper packages on the BSP) was delivered at the end of the first year of SGA2 (March 2019) and now we have six new Live Papers and two additional preliminary Live Papers linked to the different brain regions. The maturation of the models is tracked by the Life Cycle Model (https://collab.humanbrainproject.eu/#/collab/1655/nav/368782) for data-driven models, to help make them ready for community use. The Live Papers are available at this link on the BSP (https://collab.humanbrainproject.eu/#/collab/1655/nav/306845).

4.1.1.1 List of Outputs contributing to this KR

Table 10: List of Outputs contributing to KR6.2.

Output	Name	Component ID
1	Live Paper Amsalem *et al.*, 2020[5]. P2295	C3135
2	Live Paper Martinello *et al.*, 2019[6]. P2110	C3133

[5] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/amsalem_et_al_2020/amsalem_et_al_2020.html
[6] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/martinello_et_al_2019/martinello_et_al_2019.html

3	Live Paper Masoli *et al.*, 2020[7]. P1878	C3129
4	Live Paper Casali *et al.*, 2019[8]. P1877	C3129
5	Live Paper Geminiani *et al.*, 2019[9]. P2023	C3128
6	Live Paper, Hjorth *et al.*, 2020[10]. P2489	C3134
7	Live Papers, Sáray *et al.*, 2020 (in prep), Romani *et al.*, 2020 (in prep).	C3133

4.1.1.2 How Outputs relate to each other and the Key Result

These Outputs all contribute to whole brain modelling and community engagement, and can be considered in the "Exploitation Phase". The codes are publicly available and the simulations can be run as use cases of the BSP. The availability of the models to the outside community has promoted 23 applications to the Voucher Programme, resulting in 13 funded proposals, eight of which directly involved the BSP (three on cerebellum modelling, three on hippocampus modelling and two on subcellular modelling). These activities will be part of SGA3.

4.1.2 Output 1: Live Paper, Amsalem et al., 2020.

Table 11: KR6.2 Output 1 links.

Component	Link to	URL
C3135	Software Repository	https://github.com/orena1/neuron_reduce
	Technical Documentation	https://github.com/orena1/neuron_reduce
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/amsalem_et_al_2020/amsalem_et_al_2020.html

Neuron_Reduce is a new analytical approach to reducing the morphological complexity and computational time of non-linear neuron models. It enables realistic simulations of neural networks at unprecedented scale, including networks emerging from micro-connectomics efforts and biologically-inspired "deep networks". This uses highly realistic brain simulations to explore the emergence of neurological disease (e.g. epileptic seizures) in specific neuronal networks (see Figure 4).

[7] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/masoli_et_al_2020/masoli_et_al_2020.html
[8] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html
[9] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/geminiani_et_al_2019/geminiani_et_al_2019.html
[10] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/hjorth_et_al_2020/hjorth_et_al_2020.html

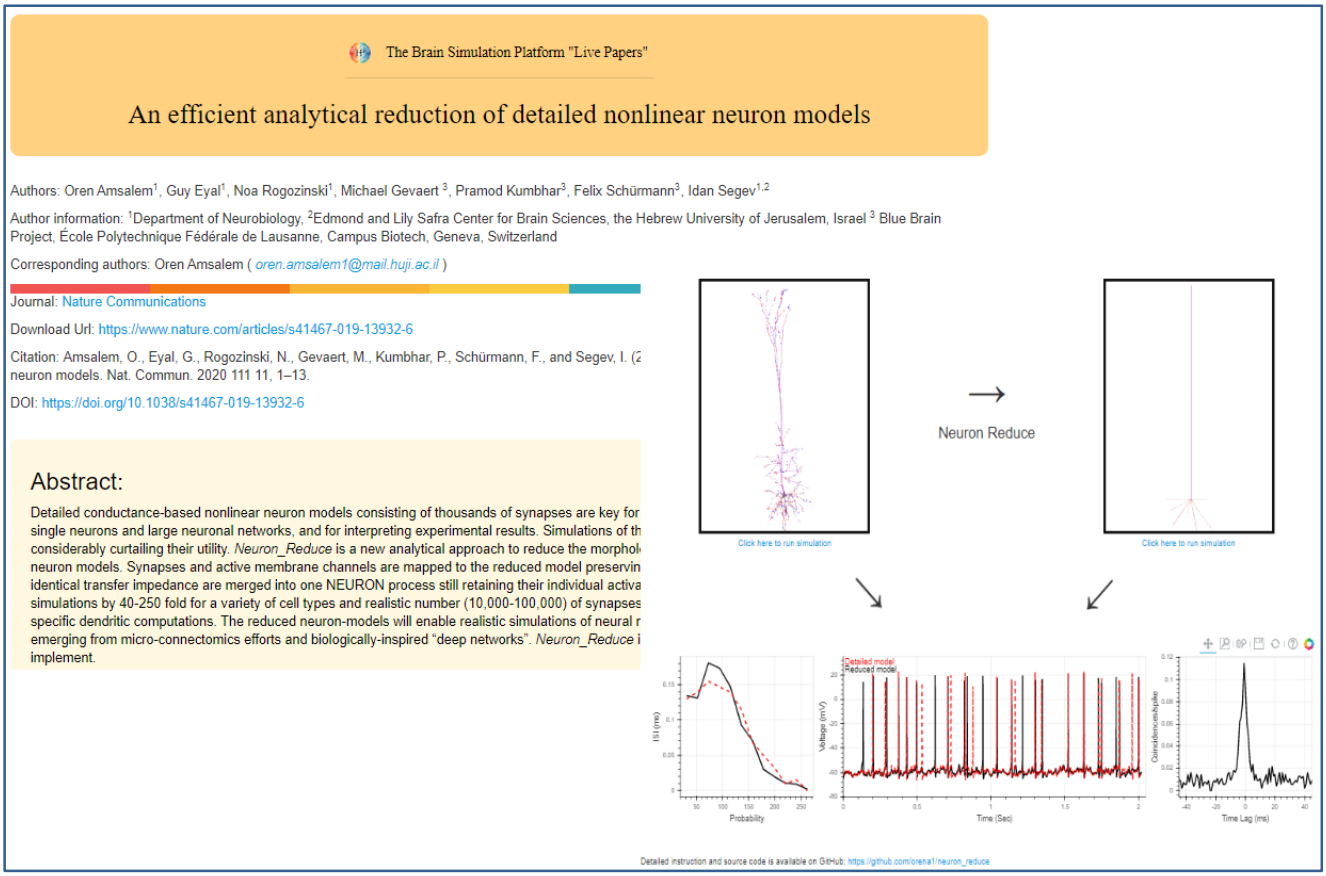

Figure 4: Screenshot of the Live Paper[11] on neuron reduction.

4.1.3 Output 2: Live Paper, Martinello et al., 2019.

Table 12: KR6.2 Output 2 links.

Component	Link to	URL
C3133	Data and model Repository	https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/bsp-lp-martinello-et-al-2019/Fig_3_Traces.zip https://senselab.med.yale.edu/modeldb/ShowModel.cshtml?model=245417#tabs-1
	Technical Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/martinello_et_al_2019/martinello_et_al_2019.html
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/martinello_et_al_2019/martinello_et_al_2019.html

Little is known about the properties and function of ion channels that affect synaptic terminal-resting properties. In this Live Paper (see Figure 5), the electrophysiological recordings together with computational modelling, demonstrated that the Kv7 current was active at rest in adult hippocampal mossy fibre synaptic terminals and enhanced their membrane conductance. This is a distinctive mechanism by which KV7 channels influence hippocampal neuronal excitability and synaptic plasticity.

[11] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/amsalem_et_al_2020/amsalem_et_al_2020.html

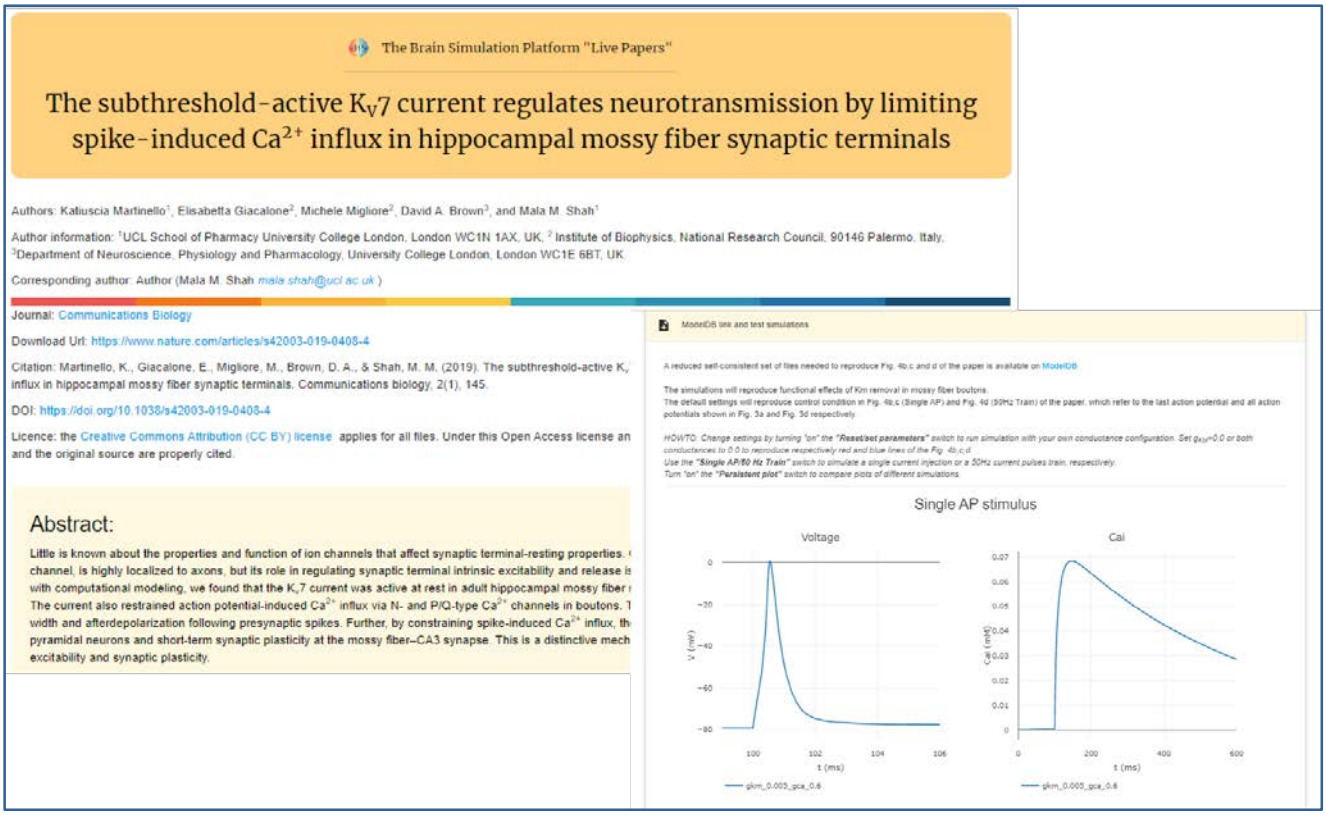

Figure 5: Screenshot of the Live Paper[12] on spike-induced CA2+ influx.

4.1.4 Output 3: Live Paper, Masoli et al., 2020.

Table 13: KR6.2 Output 3 links.

Component	Link to	URL
C3129	Model Repository	https://kg.ebrains.eu/search/instances/Model/9d75be374c1ef7b7c912d00b455591eb https://kg.ebrains.eu/search/instances/Model/39fe56b528600a3b6ce0562cdc54cadf https://kg.ebrains.eu/search/instances/Model/4af000106729670820a52a21fd13a5f9 https://kg.ebrains.eu/search/instances/Model/31465cac31e598aebe9abaad48acc6f7
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/single_cell_building/cerebellum/opt_gc_axon_collab/opt_gc_axon_collab.html
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/single_cell_building/cerebellum/opt_gc_axon_collab/opt_gc_axon_collab.html

The Live Paper entitled "Parameter tuning differentiates granule cell subtypes enriching the repertoire of retransmission properties at the cerebellum input stage" shows that GrCs generate diverse response patterns to current injection and synaptic activation, ranging from adaptation to acceleration of firing. Adaptation was predicted by parameter optimisation, while acceleration requires the involvement of additional mechanisms. This implied that different electro responsive

[12] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/martinello_et_al_2019/martinello_et_al_2019.html

patterns correspond to specific synaptic properties reflecting different neurotransmitter release probability (see Figure 6).

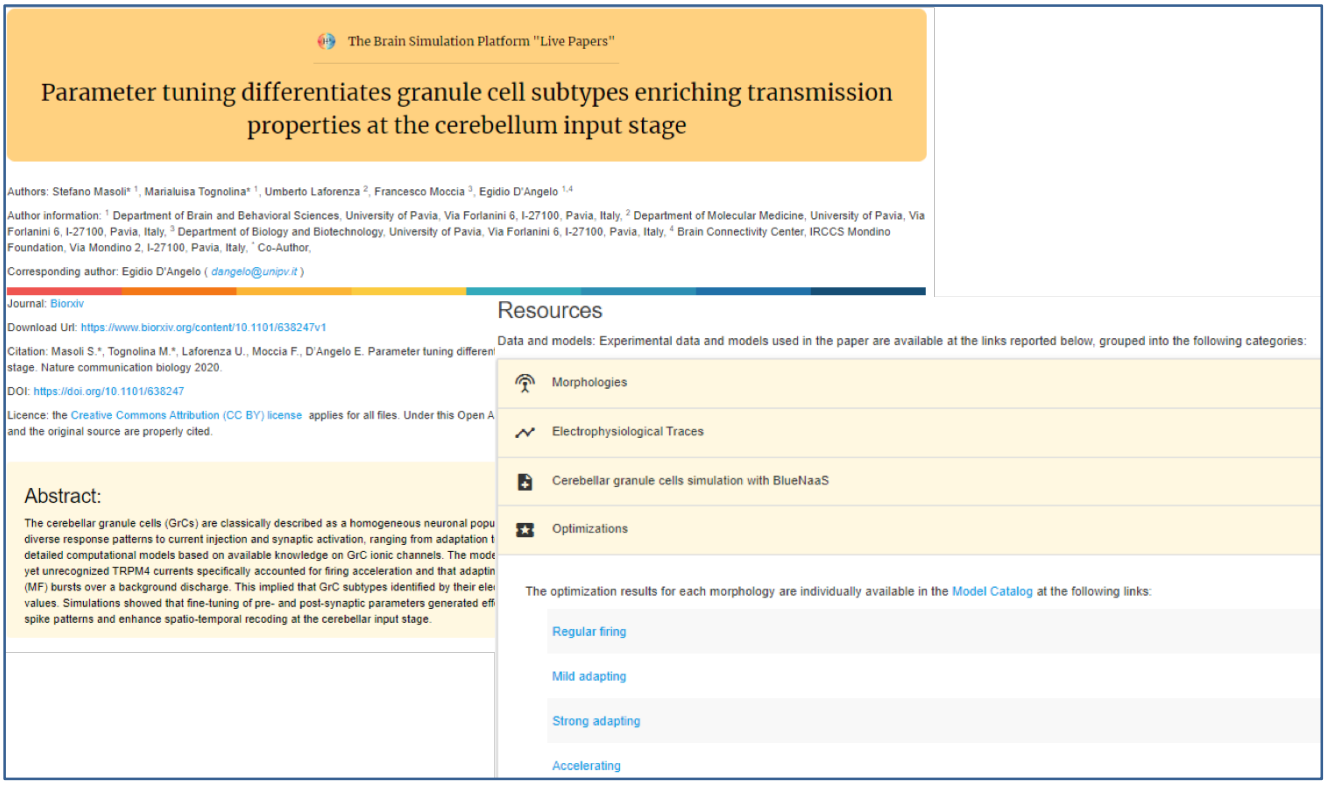

Figure 6: Screenshot of the Live Paper[13] on different granule cells subtypes models.

4.1.5 Output 4: Casali et al., 2019.

Table 14: KR6.2 Output 4 links.

Component	Link to	URL
C3129	Model Repository	https://kg.ebrains.eu/search/?facet_type[0]=Contributor&q=scaffold#Model/a8d9c6c945bff12a37678009a04b4a16
	Technical Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html

A scaffold model of the cerebellum has been developed in order to place neurons flexibly in space, connect them synaptically, and endow neurons and synapses with biologically-grounded mechanisms. Thus, the scaffold provided an effective workflow accounting for the complex architecture of the cerebellar network (see Figure 7).

[13] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/masoli_et_al_2020/masoli_et_al_2020.html

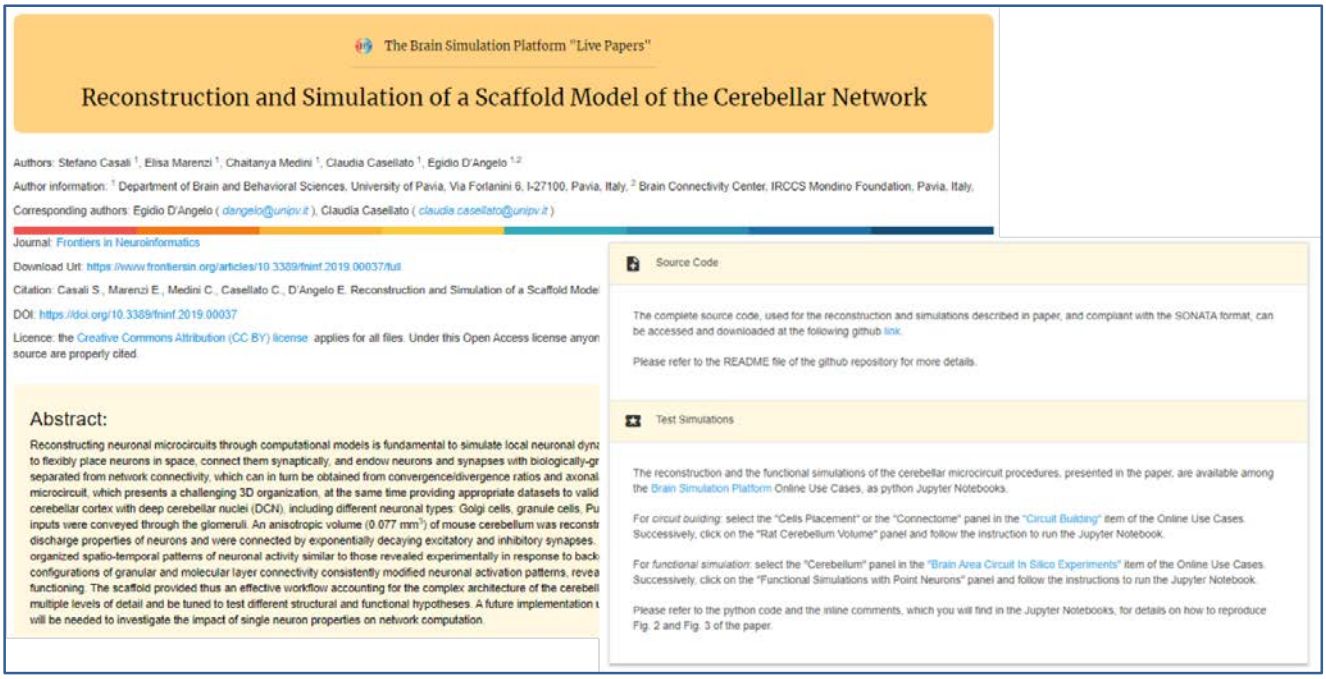

Figure 7: Screenshot of the Live Paper[14] on the cerebellar scaffold model.

4.1.6 Output 5: Geminiani et al., 2020

Table 15: KR6.2 Output 5 links.

Component	Link to	URL
C3128	Model Repository	https://kg.ebrains.eu/search/?facet_type=undefined&facet_type[0]=Model#Model/96af294049bbb92150836cd29a09d525
	Technical Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/geminiani_et_al_2019/geminiani_et_al_2019.html
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/geminiani_et_al_2019/geminiani_et_al_2019.html

The Live Paper Geminiani *et al.*, 2019 (see Fig. 8) describes simulations of the olivocerebellar scaffold, where single neurons are modelled as E-GLIF point neurons, network topology is reconstructed based on geometrical constraints and input/output signals are associated with sensorimotor signals. The results support the importance of embedding spiking neural networks with realistic neuronal dynamics and appropriate connectivity and anticipates the scale-up of the scaffold model and the embedding of plasticity rules required to investigate cerebellar learning functioning at multiple scales.

[14] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html

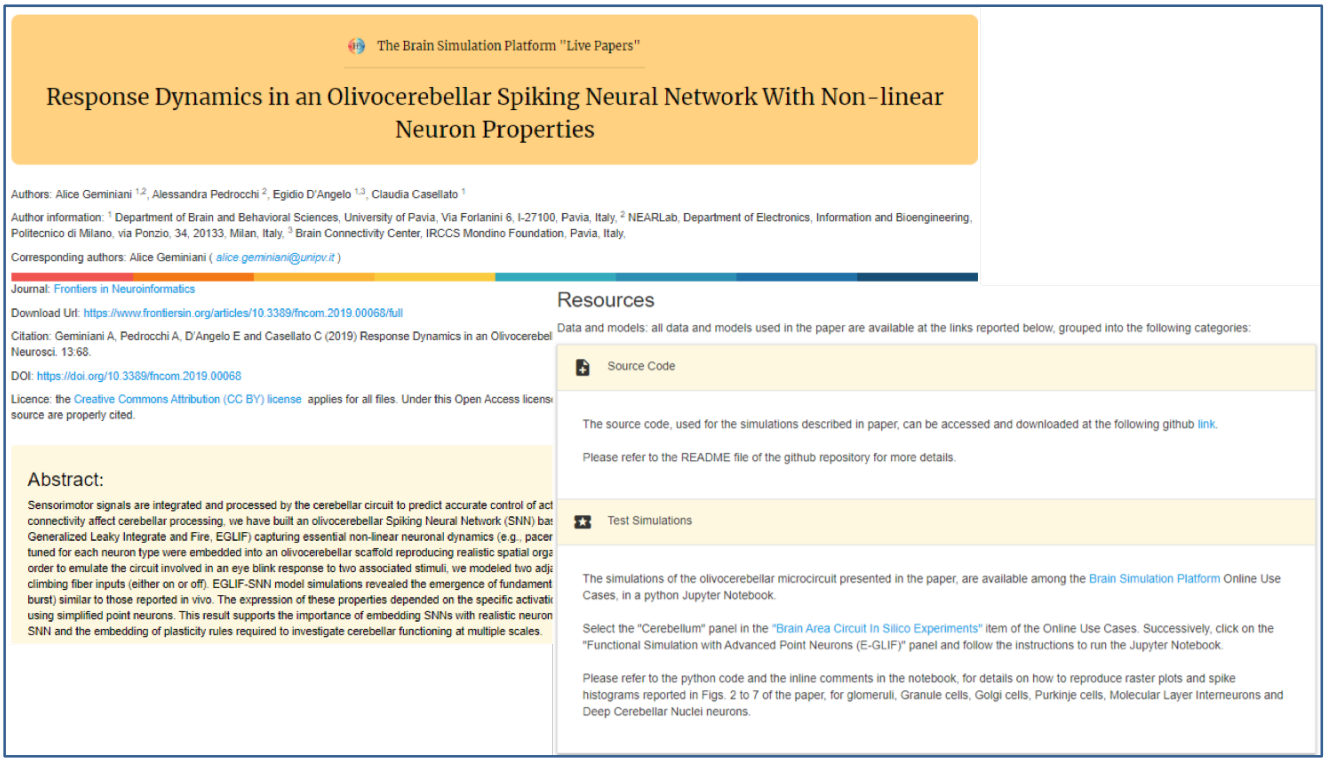

Figure 8: Screenshot of the Live Paper[15] on the olivocerebellar scaffold.

4.1.7 Output 6: Hjorth et al., 2020.

Table 16: KR6.2 Output 6 links.

Component	Link to	URL
C3134	Data, Model and Software Repositories	https://github.com/Hjorthmedh/Snudda https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.2.4/striatum-synapses-ephys-2020Q1.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.2.4/striatum-interneurons-model-2020Q1.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.2.4/striatum-interneurons-optim-2019Q3.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.2.4/striatum-interneurons-ephys-2019Q3.zip https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/Grillner_SGA2_T6.2.4/striatum-interneurons-morph-2019Q3.zip
	Technical Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/hjorth_et_al_2020/hjorth_et_al_2020.html
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/hjorth_et_al_2020/hjorth_et_al_2020.html

The basal ganglia play an important role in decision making and selection of action primarily based on input from cortex, thalamus and the dopamine system. Their main input structure, the striatum, is central to this process. This Live Paper (see Figure 9) presents, for the first time, a nearly full-scale model of the mouse striatum, using available data on synaptic connectivity, cellular morphology and electrophysiological properties to create a microcircuit mimicking the real network. A striatal volume is populated with reconstructed neuronal morphologies with appropriate cell densities, and neurons connected following rules based on appositions between neurites as possible synapses and constraints due to available connectivity data. Moreover, we simulate a subset of the

[15] https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/geminiani_et_al_2019/geminiani_et_al_2019.html

striatum involving 10,000 neurons, with inputs from the cortex, thalamus and the dopamine system, as a proof of principle. Simulation at this biological scale should serve as an invaluable tool for understanding how this complex structure works.

Figure 9: Screenshot of the Live Paper[16] on the model of the mouse striatum.

4.1.8 Output 7: Sáray et al., 2020 (in prep), Romani et al., 2020 (in prep)

Table 17: KR6.2 Output 7 links.

Component	Link to	URL
C3133	Model Repository	https://kg.ebrains.eu/search/instances/Model/2d5ecf4a-2962-4a04-a42d-4a680664bea0 https://kg.ebrains.eu/search/instances/Model/92cec93d952a201a53b84eb31fa3b842
	Technical Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/migliore_et_al_2018/migliore_et_al_2018.html https://appukuttan-shailesh.github.io/hbp-bsp-live-papers-dev/2020/saray_et_al_2020/saray_et_al_2020.html https://appukuttan-shailesh.github.io/hbp-bsp-live-papers-dev/2020/romani_et_al_2020/romani_et_al_2020.html
	User Documentation	https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/migliore_et_al_2018/migliore_et_al_2018.html (Live Paper) https://appukuttan-shailesh.github.io/hbp-bsp-live-papers-dev/2020/saray_et_al_2020/saray_et_al_2020.html

[16] https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/hjorth_et_al_2020/hjorth_et_al_2020.html

		https://appukuttan-shailesh.github.io/hbp-bsp-live-papers-dev/2020/romani_et_al_2020/romani_et_al_2020.html

Models of hippocampal neurons and networks were developed and validated in a data-driven manner using systematic, general workflows. The first Live Paper, Migliore *et al.*, 2018, was the first of its kind and described how morphologically and biophysically detailed models of a variety of different hippocampal cell types were built. Now, two additional Live Papers for the hippocampus are accessible as drafts. The preliminary Live Paper Sáray *et al.*, 2020 (see Figure 10) for an in-review publication that presents a validation suite for hippocampal neuron validation. The preliminary Live Paper Romani *et al.*, 2020 (see Figure 11) describes the full reconstruction of a hippocampus CA1 region of a rat, with morphologically and biophysically detailed neurons. The manuscript is in the process of finalisation and general release of the Live Paper will happen after peer review. In the meantime, microcircuits from this model are already featured in multiple use cases of the Brain Simulation Platform and are part of the new massive open online course "*in Silico* Experimentation", currently being finalised. Our MOOC courses can be found at: https://collab.humanbrainproject.eu/#/collab/1655/nav/67025.

Figure 10: Screenshot of the Live paper on the validation suite for hippocampal neurons.

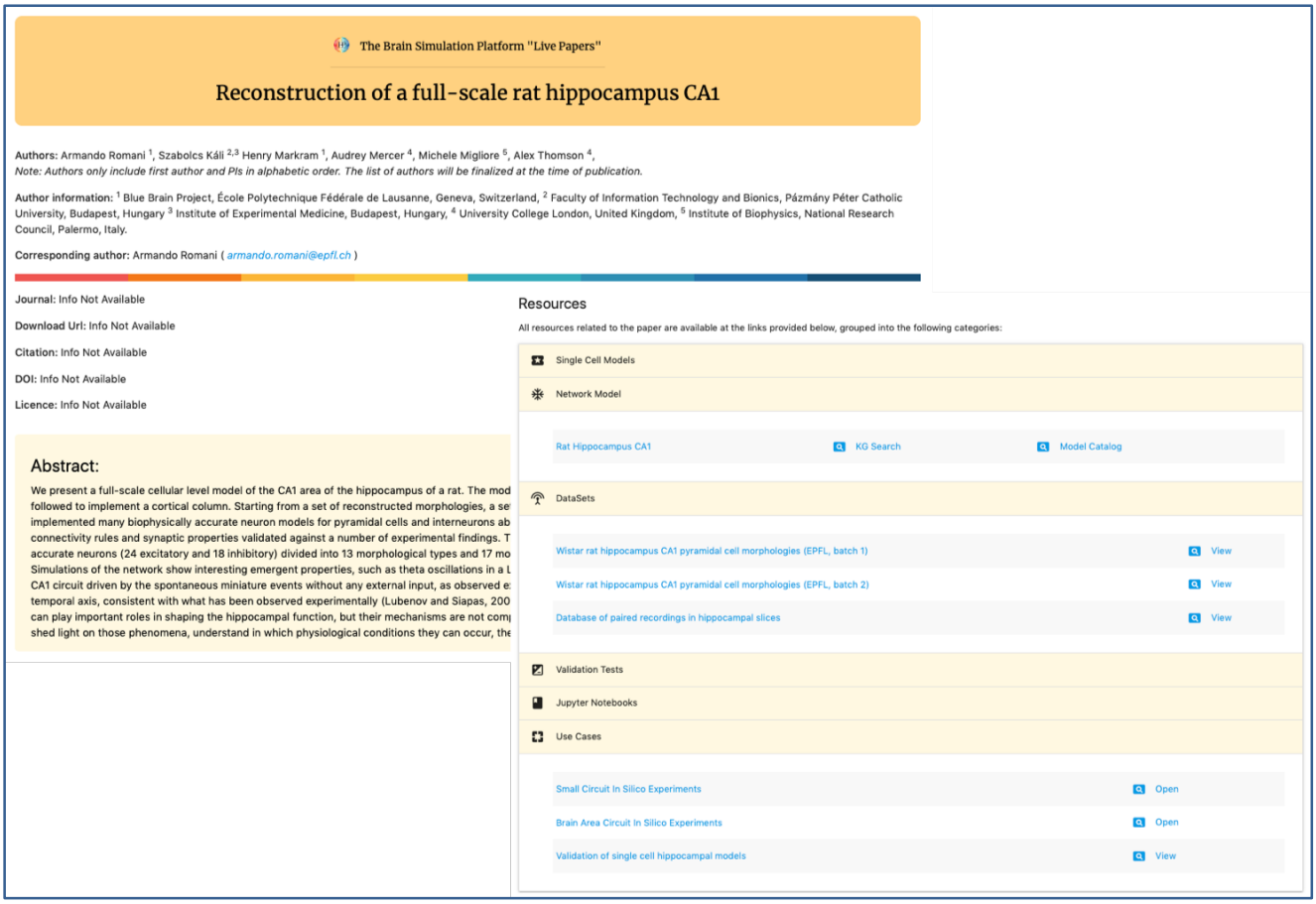

Figure 11: Screenshot of the Live paper on the reconstruction of the rat hippocampus CA1.

4.2 Validation and Impact

4.2.1 Actual and Potential Use of Output(s)

All the Outputs are publicly available on the Brain Simulation Platform contributing to engage the community.

- Output 1 - Live Paper, Amsalem *et al.*, 2020.
  - Oren Amsalem's paper just appeared in Nature Communication - thus validating the results via peer review (P2295). The method has also been deployed as an online use case of the Brain Simulation Platform: [https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/amsalem_et_al_2020/amsalem_et_al_2020.html]
- Output 2 - Live Paper, Martinello *et al.*, 2019.
  - The publication has potential applications in the context of Hippocampus full-scale model. It exploits the role of Kv7 ionic channel in mossy fibre boutons and its possible influence on synaptic plasticity at the network level. The Output has been validated.
- Output 3, Output 4 and Output 5
  - The cerebellum microcircuit models are at high maturity level and have been showcased on the Neurorobotics Platform (Showcase - Cerebellum in the NRP)
  - Developers providing the scientific case and testbench in order to find effective solutions for code implementation and simulations and to refine the informatics pipelines and HPC connections. In this way, the WP6.2 models are strongly contributing to implement and refine the BSP and NRP and to develop the entire HBP research infrastructure. The models of WP6.2 has incorporated data taken from SP1 and its output has been validated using

data taken generated in SP1 (codesign of SP1 and SP6 tasks), in CDP2 for the development of closed-loop controllers, in SP10 for the incorporation in robotic controllers (use case on NRP, https://collab.humanbrainproject.eu/#/collab/79149/nav/535740); in SP9 for the incorporation in neuromorphic hardware (Voucher #49, D6.2.1 – SGA2), in SP7 for the translation in Arbor (ongoing collaboration mentioned at Athens summit), with CDP1 for the generation of a full-scale cerebellum based on Allen Brain Atlas data (Voucher #47, https://www.humanbrainproject.eu/en/about/project-structure/partnering-projects/spinncer/), and for the refinement of HPC pipelines (PRACE projects 2018184373 with CINECA, Jülich, CSCS, https://prace-ri.eu/pr-prace-project-access-call14/). Scientists outside HBP are using the cerebellum models in POLIMI for robotic implementations (Partnering Project CEREBNEST), at ERASMUS-MC for cerebellar behavioural modelling (leading to a proposal submitted in the SGA3 Open Call program), in DIGITALBRAIN for developing cerebellar GPUs, in ALLEN BRAIN INSTITUTE for cerebellar connectivity, as well as in other universities for various scientific applications including UCL (UK), CNRS (France), Ecole Normale Supérieure (France), University of San Antonio (USA), Numerical Brain (Japan), AMRITA University India). The work with AMRITA, Allen Institute, and UCL have been awarded three new Vouchers projects for SGA3. These models are fully in the exploitation phase. The increasing number of collaborations and users, which engage at least 10 amongst the most relevant communities involved in cerebellar modelling, is providing very positive feedback. The model has also been deployed as an online use case of the Brain Simulation Platform for *in silico* experimentation: https://collab.humanbrainproject.eu/#/collab/1655/nav/66856.

  - The work in the last phases of SGA2 reveal a remarkable exploitation potential: To extend the scaffolding process developed for the cerebellum to the hippocampus and basal ganglia (preliminary steps are ongoing).
  - To fully integrate the cerebellum model into TVB simulations. This work will leverage on several activities that are being planned for the forthcoming work plan.

    To fully integrate the cerebellum model into robotic and neuromorphic simulations. Preliminary steps are ongoing are leveraging on the SGA2 Vouchers #47 ((https://www.humanbrainproject.eu/en/about/project-structure/partnering-projects/spinncer/) and #49 (https://www.humanbrainproject.eu/en/about/project-structure/partnering-projects/cerebnest/).

    To fully integrate the 4 sub circuits in a modular virtual brain of the mouse.

- Output 6 - Hjorth *et al*., 2020.
  - The publication has potential applications in the context of basal ganglia full-scale models; the paper is currently under review. The cell placement and connectome methods have furthermore been deployed as an online use cases of the Brain Simulation Platform: https://collab.humanbrainproject.eu/#/collab/1655/nav/66853
- Output 7 – Sáray *et al*., 2020 (in prep.), Romani *et al*., 2020 (in prep.).

  Anatomically and biophysically detailed models of various hippocampal cell types, a CA1 microcircuit, and the full-scale CA1 circuit, were constructed using a systematic, data-driven pipeline. A validation suite for various physiological properties of hippocampal neurons was implemented and applied during model development. The models and validations are accessible through online use cases in the Brain Simulation Platform, and will facilitate the development and validation of hippocampal models:
  - https://collab.humanbrainproject.eu/#/collab/1655/nav/66854 (online use case - single cells)
  - https://collab.humanbrainproject.eu/#/collab/1655/nav/66855 (online use case - paired recordings)
  - https://collab.humanbrainproject.eu/#/collab/1655/nav/66856 (online use case - *in silico* experiments on circuit)

- https://collab.humanbrainproject.eu/#/collab/1655/nav/66858 (online use case - validation)

4.2.2 Publications

- Output 1 - Live Paper, Amsalem *et al*., 2020. (C3135): P2295 *Amsalem et al., 2020*. An efficient analytical reduction of detailed nonlinear neuron models. Nature Communications.
  - Significance: Neuron_Reduce is a new computational tool that provides the scientific community with a straightforward capability to simplify complex neuron models of any cell type and still faithfully preserve its input-output properties while significantly reducing simulation run-time.
- Output 2 - Live Paper, Martinello *et al*., 2019. (C3133): P2110 Martinello *et al., 2019.* The subthreshold-active K(V)7 current regulates neurotransmission by limiting spike-induced Ca(2+) influx in hippocampal mossy fibre synaptic terminals. Communications Biology.
  - Significance: there are potential applications in the context of Hippocampus full-scale model. It exploits the role of Kv7 ionic channel in mossy fibre boutons and its possible influence on synaptic plasticity at the network level.
- Output 3 - Live Paper, Masoli *et al*., 2020. (C3129): P1878 (*in press* – SGA3 publication) Masoli *et al., 2020.* Parameter tuning differentiates granule cell subtypes enriching the repertoire of retransmission properties at the cerebellum input stage. Communications Biology.
  - Significance: This paper addresses the issue of cell-to-cell variability using advanced models and experimental validation. It will be used to address physiological and pathological issues in large-scale microcircuit models.
- Output 4 - Casali *et al*., 2019. (C3129): P1877 Casali et al., 2019. Reconstruction and Simulation of a Scaffold Model of the Cerebellar Network. Frontiers in Neuroinformatics.
  - Significance: This paper presents the first scaffold model pf the cerebellar microcircuit along with the informatic workflow and physiological testing. The work has potential applications for constructing cerebellar full-scale models. The scaffold principle and workflow can be extended to other brain circuits.
- Output 5 - Geminiani *et al*., 2020. (C3128): P2023 Geminiani *et al., 2020.* Response Dynamics in an Olivocerebellar Spiking Neural Network With Non-linear Neuron Properties. Frontiers in Computational Neuroscience.
  - Significance: This paper addresses for the first time the comparison between a model with simple integrate and fire neurons and its counterpart using embedding dynamic neuronal representations based on EGLIF. The paper shown that critical aspects of network computation are overlooked when simplified neurons are used.
- Output 6 - Hjorth *et al*., 2020. (C3134): P2489 (*in press* – SGA3 publication) Hjorth *et al., 2020.* The microcircuits of striatum *in silico*. Proceedings of the National Academy of Sciences of the United States of America.
  - Significance: The paper presents a full-scale cellular level model of the mouse striatum. It includes the main types of the projection neurons and interneurons, as well as intrastriatal and afferent synaptic inputs optimized against existing data. This model platform will be used to generate new hypotheses on striatal function or network dynamic phenomena.

5. Key Result KR6.3

In order to deliver modelling and simulation capabilities for detailed modelling of neurons and brain circuits into the HBP platforms, SP6 builds on best-in-class community software and contributes to its extension and maturation. At the same time, a major SP6 contribution is to provide a tightly

integrated ecosystem of workflows, allowing end-to-end modelling at scale. Necessary functionality not found in community software is being co-developed with the science drivers. These tools and standards are made available through the Brain Simulation Platform and benefit the computational neuroscience community in multiple ways. This key result covers the fundamental scales from molecular and subcellular (addressing biochemical processes), through single cell and brain tissue (addressing biophysical processes and structures), to whole brain network (addressing functional questions).

5.1 Outputs

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

Table 18: List of Outputs contributing to KR6.3.

Output	Name	Component ID
1	Molecular-Level Modelling & Simulation Tools	C1633
2	Subcellular-Level Modelling & Simulation Tools	C1632, C3106
3	Single Cell Modelling & Simulation Tools	C1668, C1669, C3137
4	Brain Tissue Modelling & Simulation Tools	C1714, C1715, C1670, C3132
5	Whole Brain Modelling & Simulation Tools	C209, C349, C1667

5.1.1.2 How Outputs relate to each other and the Key Result

Depending on the scientific study, the different Outputs can be used independently, as they represent consolidated, novel functionality for modelling and simulation at specific scales. For example, Output 3 (single cell modelling and simulation tools) can be used to study human neurons as done in other parts of SP6. However, the Outputs can also build on each other for other scientific investigations. For example, Output 1 (molecular modelling and simulation tools) can computationally predict parameters that can be used for plasticity studies supported by Output 2 (subcellular modelling and simulation tools), or models of neurons from Output 3 can be used in brain tissue models generated using Output 4 (brain tissue modelling and simulation tools) or simplified for whole brain modelling studies (Output 5).

At the same time, the Outputs directly support KR6.3 targeting the advancement of computational tools. KR6.3 enables KR6.4, which is the delivery of this functionality in an online platform. The relationship with the scientific KR6.1 and KR6.2 is reciprocal. On the one hand, the Outputs of KR6.3 are guided by the scientific questions of KR6.1 and KR6.2. On the other hand, the Outputs of KR6.3 enable the Outputs of KR6.1 and KR6.2.

5.1.2 Output 1: Molecular Level Modelling & Simulation Tools

Table 19: KR6.3 Output 1 links.

Component	Link to	URL
C1633	Software Repository	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html https://mcm.h-its.org/sda/doc/doc_sda7/doc.html
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html https://mcm.h-its.org/sda/doc/doc_sda7/doc.html ArDock: https://ardock.ibcp.fr

		Central Nervous System: https://mmb.irbbarcelona.org/webdev/slim/CNS/public/ MoDEL: http://mmb.irbbarcelona.org/MoDEL/ MoDEL_CNS: http://mmb.irbbarcelona.org/MoDEL-CNS/#/ SDA: https://mcm.h-its.org/sda/doc/doc_sda7/index.html webSDA: https://mcm.h-its.org/webSDA
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html https://mcm.h-its.org/sda/doc/doc_sda7/doc.html ArDock: https://ardock.ibcp.fr Central Nervous System: https://mmb.irbbarcelona.org/webdev/slim/CNS/public/ MoDEL: http://mmb.irbbarcelona.org/MoDEL/ MoDEL_CNS: http://mmb.irbbarcelona.org/MoDEL-CNS/#/ SDA: https://mcm.h-its.org/sda/doc/doc_sda7/index.html webSDA: https://mcm.h-its.org/webSDA

SP6 has advanced molecular-level modelling and simulation capabilities by (see Figure 12):

1) ArDock - is a structural bioinformatics web server for the prediction and the visualisation of potential interaction regions at protein surfaces. ArDock ranks the surface residues of a protein according to their tendency to form interfaces in a set of predefined docking experiments between the query protein and a set of arbitrary protein probes. The server was released in 2018 (P1372 [17]).
2) CNS - a database of bioactive conformers of ligands binding to neuronal proteins (CNS) and a database of MD trajectories for relevant signal transduction proteins (MoDEL_CNS) are integrated as an API in the Brain Simulation Platform.
3) SDA - software for Simulation of Diffusional Association of Macromolecules enabling the computation of protein-protein association rates. A new release, 7.2.4, with updated documentation and Python auxiliary scripts, was made in 2020. SDA was applied to compute kinetic parameters for modelling a neuronal signalling cascade (P2205).
4) multiPIPSA - software for comparison of the electrostatic properties of proteins. A new release with a new Python wrapper and updated documentation was made. MultiPIPSA was used to compare isoforms of the enzyme, adenylate cyclase, a key component of neuronal signalling cascades (P785[18]).

[17] Reille S. *et al.,* (2018) Identification and visualization of protein binding regions with the ArDock server. Nucleic Acids Research. https://doi.org/10.1093/nar/gky472

[18] Tong R., Wade R.C. & Bruce N.J. (2016) Comparative electrostatic analysis of adenylyl cyclase for isoform dependent regulation properties. Proteins: Structure, Function, and Bioinformatics. https://doi.org/10.1002/prot.25167

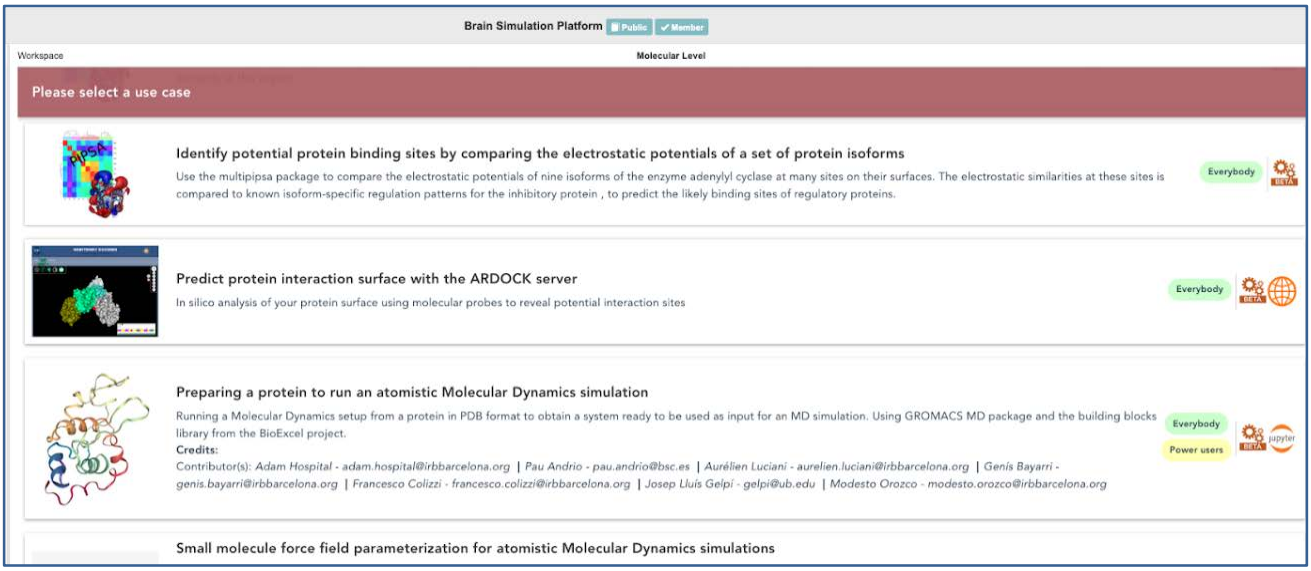

Figure 12: Screenshot of the molecular level tools[19] integrated as use cases in the BSP.

5.1.3 Output 2: Molecular Level Modelling & Simulation Tools

Table 20: KR6.3 Output 2 links.

Component	Link to	URL
C1632	Software Repository	https://subcellular.humanbrainproject.eu/model/meta?publicModel=CaM_Ca_spatial
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/subcellular_level/subcellular_app/subcellular_app.html
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/subcellular_level/subcellular_app/subcellular_app.html
C3106	Software Repository	https://github.com/CNS-OIST/STEPS
	Technical Documentation	https://github.com/CNS-OIST/STEPS
	User Documentation	https://github.com/CNS-OIST/STEPS/blob/master/README.md

SP6 has advanced subcellular-level modelling and simulation capabilities by:

1) Developing a unique web-based environment (C1632) for creation and simulation of reaction-diffusion models integrated with a molecular repository, complementing other public databases with quantitative data on proteins in subcellular compartments (see Figure 13). The environment allows also to import, combine and simulate existing models expressed with BNGL and SBML languages. It supports two types of models: rule-based models convenient and computationally efficient for modelling big protein signalling complexes and chemical reaction network models with the STEPS simulator.
2) Extending the community simulator STEPS (C3106): The STEPS simulator has been extended to improve the achievable parallelism. This allows for larger simulations to be run across computing platforms with multiple CPUs, demonstrating strong and weak scaling. The latest release version 3.5.0 as of 29 January 2020, is available as open source.

[19] https://collab.humanbrainproject.eu/#/collab/1655/nav/362934

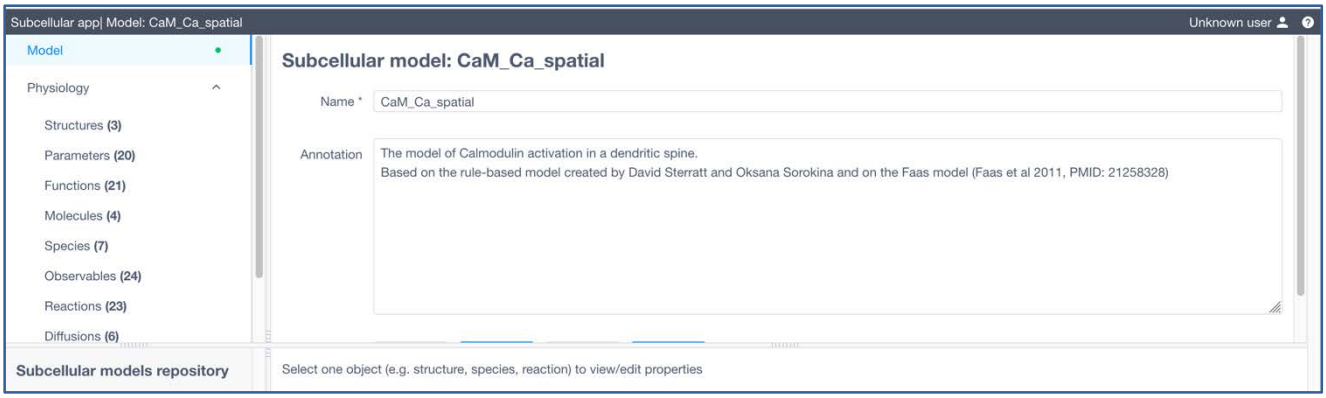

Figure 13: Screenshot of the subcellular app[20] in the BSP.

5.1.4 Output 3: Single Cell Modelling & Simulation Tools

Table 21: KR6.3 Output 3 links.

Component	Link to	URL
C1668	Software Repository	https://kg.ebrains.eu/search/instances/Software/fa4751e5-dcca-4c7b-afbc-9e4c948d35ed https://github.com/BlueBrain/NeuroR https://github.com/BlueBrain/morphio
	Technical Documentation	https://kg.ebrains.eu/search/instances/Software/fa4751e5-dcca-4c7b-afbc-9e4c948d35ed https://github.com/BlueBrain/NeuroR https://github.com/BlueBrain/morphio
	User Documentation	https://kg.ebrains.eu/search/instances/Software/fa4751e5-dcca-4c7b-afbc-9e4c948d35ed https://github.com/BlueBrain/NeuroR
C1669	Software Repository	https://github.com/bluebrain/bluepyopt https://github.com/BlueBrain/eFEL https://github.com/BlueBrain/BluePyMM https://github.com/BlueBrain/BluePyEfe
	Technical Documentation	http://bluepyopt.readthedocs.io/en/latest/
	User Documentation	https://www.frontiersin.org/articles/10.3389/fninf.2016.00017/full
C3137	Software Repository	https://github.com/orena1/neuron_reduce
	Technical Documentation	https://github.com/orena1/neuron_reduce
	User Documentation	https://www.nature.com/articles/s41467-019-13932-6

SP6 has advanced single cell modelling and simulation capabilities by (see Figure 14):

1) Developing an Advanced Morphology Processing Toolkit, NeuroM, and Morphology Repair tools (C1668). The former allows the analysis, visualisation and checking of neuron morphologies from various sources as a key ingestion step for any neuronal modelling process. The latest release version 1.4.19 as of 19/02/2020 is available as open source. The latter is a newly open sourced software that allows the computationally repairing of reconstructed morphologies from artefacts and missing branches. Those applications are built on top of a morphology reader/writer library (MorphIO) which also has been open sourced.
2) Developing a unique, world-leading set of software tools for the generation of electrical models of morphologically detailed neurons of arbitrary brain regions and species. The developed tools

[20] https://subcellular.humanbrainproject.eu/model/meta

comprise eFEL and BluePyEFE for the automated extraction of electrical features from electrophysiological experiments, BluePyOpt as the central tool for parameter optimisation, and BluePyMM a tool to test large numbers of neuronal models. All tools have been made available as open source (BluePyEFE newly so).

3) Developing a new, unique analytical approach for reducing the complexity of neuron models while retaining their key input/output functions and their computational capabilities (C3137). The approach has been published (P2295) and is available as open source. A use case for applying this simplification to networks is available in the Brain Simulation Platform.

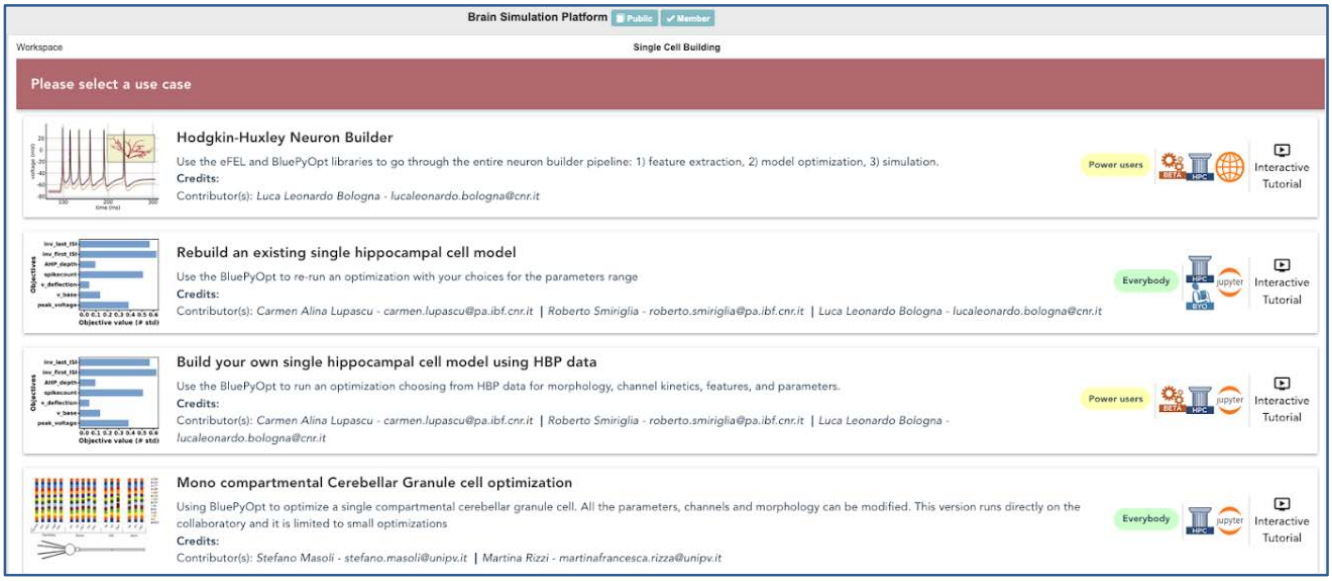

Figure 14: Screenshot of the single cell tools[21] integrated as use cases in the BSP.

5.1.5 Output 4: Brain Tissue Modelling & Simulation Tool

Table 22: KR6.3 Output 4 links.

Component	Link to	URL
C1714	Software Repository	https://github.com/BlueBrain/CoreNeuron
	Technical Documentation	https://github.com/BlueBrain/CoreNeuron
	User Documentation	https://www.frontiersin.org/articles/10.3389/fninf.2019.00063/full (P2051)
C1715	Software Repository	http://github.com/neuronsimulator/nrn
	Technical Documentation	https://github.com/neuronsimulator/nrn/blob/master/README.md
	User Documentation	https://github.com/neuronsimulator/nrn/blob/master/README.md
C1670	Software Repository	https://github.com/AllenInstitute/sonata https://github.com/BlueBrain/libsonata
	Technical Documentation	https://github.com/AllenInstitute/sonata/blob/master/docs/SONATA_DEVELOPER_GUIDE.md https://github.com/BlueBrain/libsonata
	User Documentation	https://doi.org/10.1371/journal.pcbi.1007696
C3132	Software Repository	https://github.com/bluebrain/snap https://github.com/BlueBrain/DMT https://github.com/BlueBrain/SimulationRunner/

[21] https://collab.humanbrainproject.eu/#/collab/1655/nav/66852

	Technical Documentation	https://github.com/bluebrain/snap https://github.com/BlueBrain/DMT https://github.com/BlueBrain/SimulationRunner/
	User Documentation	https://github.com/bluebrain/snap https://github.com/BlueBrain/DMT https://github.com/BlueBrain/SimulationRunner/

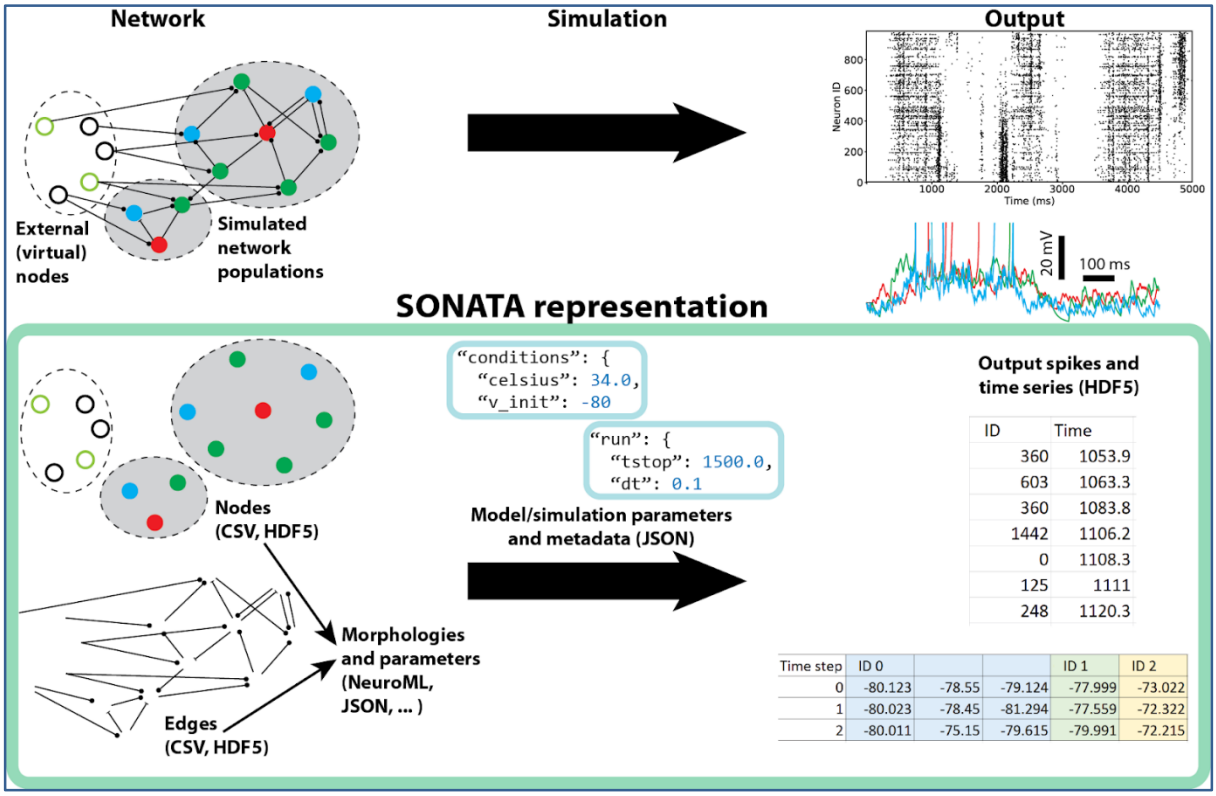

Figure 15: Overview of the SONATA data format (Figure taken from P2184[22]).

SP6 has advanced brain tissue modelling and simulation capabilities by:

1) Contributing to and adopting SONATA (C1670): definition and adoption of the new file format for model exchange of networks of point neurons and/or detailed neurons has been advanced. Support for this format in PyNN has been implemented and a convenient C++ and Python access layer has been open sourced (libsonata). The SONATA file format and its ecosystem have been published (P2184; see Figure 15).

2) Releasing a new version of the community simulator for networks of detailed neurons, NEURON 7.7.1 (C1715). It includes performance improvements for both strong scaling and weak scaling scenarios. The developments ensure the support for the various models used as part of HBP work and on the various computing clusters available.

3) Releasing a new version of the simulation engine for networks of detailed neurons at the largest scale, CoreNEURON 0.17 (C1714). This engine is a key enabler for large-scale network models of the BBP, such as the cerebellum model or the hippocampus CA1 model, and is optimised to run on diverse HPC architectures. Recent advancements include a transparent integration with the NEURON simulator and advanced code generation. The work has been published (P2051) and is available as open source.

4) New open sourcing of multiple software tools underlying the Brain Simulation Platform's *in Silico* Experimentation capability as co-developed with the neocortex modelling (C3132): a) Blue Brain SNAP – a Simulation and Neural network Analysis Productivity layer that supports neuronal network models in SONATA. This tool provides unique functionality for circuit analysis; b) Data-

[22] http://dx.doi.org/10.1371/journal.pcbi.1007696

Model-Test (DMT) - a validation suite for data-driven network models; 3) Simulation Runner - a convenience layer providing a configuration layer for network simulations in Neuron.

5.1.6 Output 5: Whole Brain Modelling and Simulation Tools

Table 23: KR6.3 Output 5 links.

Component	Link to	URL
C349	Software Repository	https://github.com/NeuralEnsemble/PyNN/
	Technical Documentation	https://neuralensemble.org/docs/PyNN/developers_guide.html
	User Documentation	https://neuralensemble.org/docs/PyNN/
C209	Software Repository	https://www.nest-simulator.org/download/#releases (version 2.20.0)
	Technical Documentation	https://www.nest-simulator.org/publications/index.php?type=article&category=nest_technology&year=.*
	User Documentation	https://www.nest-simulator.org/documentation/
C1667	Software Repository	https://www.nest-simulator.org/download/#releases (version 2.20.0)
	Technical Documentation	https://www.nest-simulator.org/publications/index.php?type=article&category=nest_technology&year=.*
	User Documentation	https://www.nest-simulator.org/documentation/

SP6 has advanced whole-brain modelling and simulation capabilities by:

1) Extending PyNN (C349): the simulator-independent language for building neuronal network models, PyNN, has been extended to support the latest versions of the NEST and Brian 2 community simulators and improve support for the SONATA file format. These features are available in the latest release 0.9.6 of March 2020, available as open source.
2) Releasing a new version of the community network simulator for point-neuron networks, NEST 2.20.0 (C209), capable of the largest scales. This new version comes with strongly improved documentation, both in technical delivery (now on readthedocs.io), consistency and quality. NEST now incorporates the infrastructure for the representation of third factor plasticity rules. As an example, the Clopath plasticity rule was released with NEST 2.18.0. In addition, a pull request against NEST has been made for the compartmentalised third factor plasticity rule by Urbanczik and Senn (C2696). The prototype implementation of a vastly improved, unified user interface and backend for connectivity generation (C2678) was integrated into the NEST master branch early in M23 and is thus available for public testing; at this time, it is planned to release this work as part of NEST 3.0 towards the end of M24. The (C1667) component provides optimised network communication for the simulation of huge sparsely connected neural networks in the NEST Simulator.

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

- Output 1 – Molecular-Level Modelling and Simulation
  - These tools have been applied to the work done and published in Task T6.1.1 and have provided the basis for Task T6.4.2. The software has also been relevant to the application work done in CDP6.
  - Made accessible through multiple online use cases in Brain Simulation Platform

https://collab.humanbrainproject.eu/#/collab/1655/nav/362934

- Foundation of several papers and accompanying Live Papers, e.g.

  https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/bruce_et_al_2019/bruce_et_al_2019.html

  https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/kokh_et_al_2019/kokh_et_al_2019.html

- These tools are also distributed and freely available outside the HBP platform and have a sizable international user community.

- Output 2 – Subcellular-Level Modelling and Simulation
  - The tools have been used for multiple research tasks in WP6.1, in particular modelling of plasticity (KR6.1 Outputs 6 and 7).
  - Made accessible through multiple online use cases in Brain Simulation Platform

    https://collab.humanbrainproject.eu/#/collab/1655/nav/362934
  - https://subcellular.humanbrainproject.eu/model/meta
  - Foundation of several papers and accompanying Live Papers, e.g.

    https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/lindroos_et_al_2018/lindroos_et_al_2018.html
  - STEPS is also distributed and freely available outside the HBP platform and has a sizable international user community.
- Output 3 – Single Cell Modelling and Simulation
  - The tools have been used for multiple research tasks in WP6.2, in particular for modelling of hippocampal, cerebellar, basal ganglia and human neurons.
  - Made accessible through multiple online use cases in Brain Simulation Platform

    https://collab.humanbrainproject.eu/#/collab/1655/nav/66851

    https://collab.humanbrainproject.eu/#/collab/1655/nav/66852

    https://collab.humanbrainproject.eu/#/collab/1655/nav/66854

    https://collab.humanbrainproject.eu/#/collab/1655/nav/66898
  - Foundation of several papers and accompanying Live Papers, e.g.

    https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/migliore_et_al_2018/migliore_et_al_2018.html

    https://humanbrainproject.github.io/hbp-bsp-live-papers/2018/eyal_et_al_2018/eyal_et_al_2018.html

    https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/masoli_et_al_2020/masoli_et_al_2020.html

    https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/amsalem_et_al_2020/amsalem_et_al_2020.html
  - MorphIO, NeuroM, eFEL, BluePyOpt, BluePyMM, BluePyEFE are also distributed and freely available outside the HBP platform and have a sizable international user community.
- Output 4 – Brain Tissue Modelling and Simulation
  - The tools have been used for multiple research tasks in WP6.2, in particular modelling of hippocampal, cerebellar, basal ganglia tissue models.
  - Made accessible through online use cases in Brain Simulation Platform

    https://collab.humanbrainproject.eu/#/collab/1655/nav/66855

https://collab.humanbrainproject.eu/#/collab/1655/nav/66856

- Foundation of several papers and accompanying Live Papers, e.g.

  https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html

  https://humanbrainproject.github.io/hbp-bsp-live-papers/2020/hjorth_et_al_2020/hjorth_et_al_2020.html

  https://appukuttan-shailesh.github.io/hbp-bsp-live-papers-dev/2020/romani_et_al_2020/romani_et_al_2020.html

- SONATA, libsonata, NEURON/CoreNEURON, Blue Brain SNAP, DMT, SimulationRunner are also distributed and freely available outside the HBP platform and have a sizable international user community.

- Output 5 – Whole Brain Modelling and Simulation
  - PyNN is the required programming interface for the Neuromorphic Computing Platform, the default programming interface for brain models in the Neurorobotics Platform, and provides a bridge to models previously described in PyNN and models described in SONATA underlying the Brain Simulation Platform.
  - Numerous groups across science and infrastructure subprojects of the HBP use NEST, including SP1, SP3, SP4, SP9, SP10, CDP2, CDP4, CDP5 and partnering project CerebNEST. Close interaction with these user groups guides NEST development. In collaboration with SP9, we have also established NEST as the gold standard for validating neuromorphic computing systems.
  - Made accessible through multiple online use cases on the HBP Platforms.
  - PyNN and NEST are also distributed and freely available outside the HBP platform and have a sizable international user community.

All Outputs have been extended and increased maturity over their state at the end of SGA1 as per plan and Milestone MS6.3.10.

5.2.2 Publications

- Output 1 – Molecular-Level Modelling and Simulation (C1633): P2205 Bruce *et al.*, 2019. Regulation of adenylyl cyclase 5 in striatal neurons confers the ability to detect coincident neuromodulatory signals. PLOS Computational Biology.
  - This publication is a scientific validation of the multi-scale modelling and simulation approach bridging molecular simulations and Brownian dynamics simulations.
- Output 3 – Single Cell Modelling and Simulation (C3137): P2295 Amsalem *et al.*, 2020. An efficient analytical reduction of detailed nonlinear neuron models. Nature Communications.
  - This publication describes a novel analytical approach for reducing the complexity of neuron models while retaining their key input/output functions and their computational capabilities.
- Output 4 – Brain Tissue Modelling and Simulation (C1714, C1715): P2051 Kumbhar *et al.*, 2019. CoreNEURON: An Optimized Compute Engine for the NEURON Simulator. Frontiers in Neuroinformatics.
  - This publication described the optimised CoreNEURON simulation engine and its transparent integration with the NEURON Simulation environment.
- Output 5 – Whole Brain Modelling and Simulation (C1670+C349): P2184 – Dai *et al.*, 2020. The SONATA data format for efficient description of large-scale network models. PLOS Computational Biology.

- This publication, on the SONATA model and simulation results format, includes a description of tools for converting models from SONATA to/from other formats.

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

The set of online use cases, tools, and services on the Brain Simulation Platform has been significantly improved and extended also during the second year of SGA2. To date, there are 42 active use cases online on the BSP, spanning different model levels. Of these 42 use cases, 11 are related to molecular and subcellular models, 16 to single cells, nine to brain circuits and six to model validation. Overall, 704 unique users, external to the HBP, are running these use cases and have created so far 2,548 new Collabs to carry out their work. Of particular importance is the use of the BSP for educational purposes. This aspect is of paramount relevance for extending the user base. There are 2 MOOCs linked to the BSP use cases; 11,776 students have enrolled in the open online courses as of today, which represent the user base for MOOC-related BSP use cases. So far, students have created 2,048 Collabs to follow their educational plan. All the model building and simulation tools present in the BSP are unique in the field, especially for entry-level users, who can run use cases using computing resources made freely available on a variety of HPC systems through a close interaction with the FENIX infrastructure and the ICEI program. Use cases can run on any of the HPC systems where simulation engines have been installed and software stacks deployed. To date, the available HPC systems 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. The reader can check out a typical example of access through the service account by running the Hodgkin-Huxley Neuron Builder workflow at: https://collab.humanbrainproject.eu/#/collab/1655/nav/66852

6.1 Outputs

6.1.1 Overview of Outputs

6.1.1.1 List of Outputs contributing to this KR

Table 24: List of Outputs contributing to KR6.4.

Output	Name	Component ID
1	Interactive tutorials	C1614, C3112
2	Integration of the Service Account and Model Catalog registration functionalities	C1634
3	Integration of rat hippocampus CA1 circuit into Brain Area Circuit use case	C1615
4	Deployment of simulation and visualisation stack	C1636
5	Web-access to molecular level tools	C1997
6	Model Validation tools based on the Knowledge Graph	C722
7	Python libraries for structured model validation tests	C1680

6.1.1.2 How Outputs relate to each other and the Key Result

All these Outputs have been the result of our efforts to develop and maintain a set of highly integrated, web-accessible model-building and simulation tools, able to attract more users to the Platform. They are strongly interrelated and also link to many Outputs from other Key Results (from SP5, SP6, and SP7). This interrelation should be self-evident by navigating through the BSP site and executing any use case.

6.1.2 Output 1: Interactive tutorials (C1614, C3112)

Table 25: KR6.4 Output 1 links.

Component	Link to	URL
C3112	Software Repository	https://humanbrainproject.github.io/hbp-sp6-guidebook/getting_started/getting_started.html - video-tutorials
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/getting_started/getting_started.html - video-tutorials
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/getting_started/getting_started.html - video-tutorials

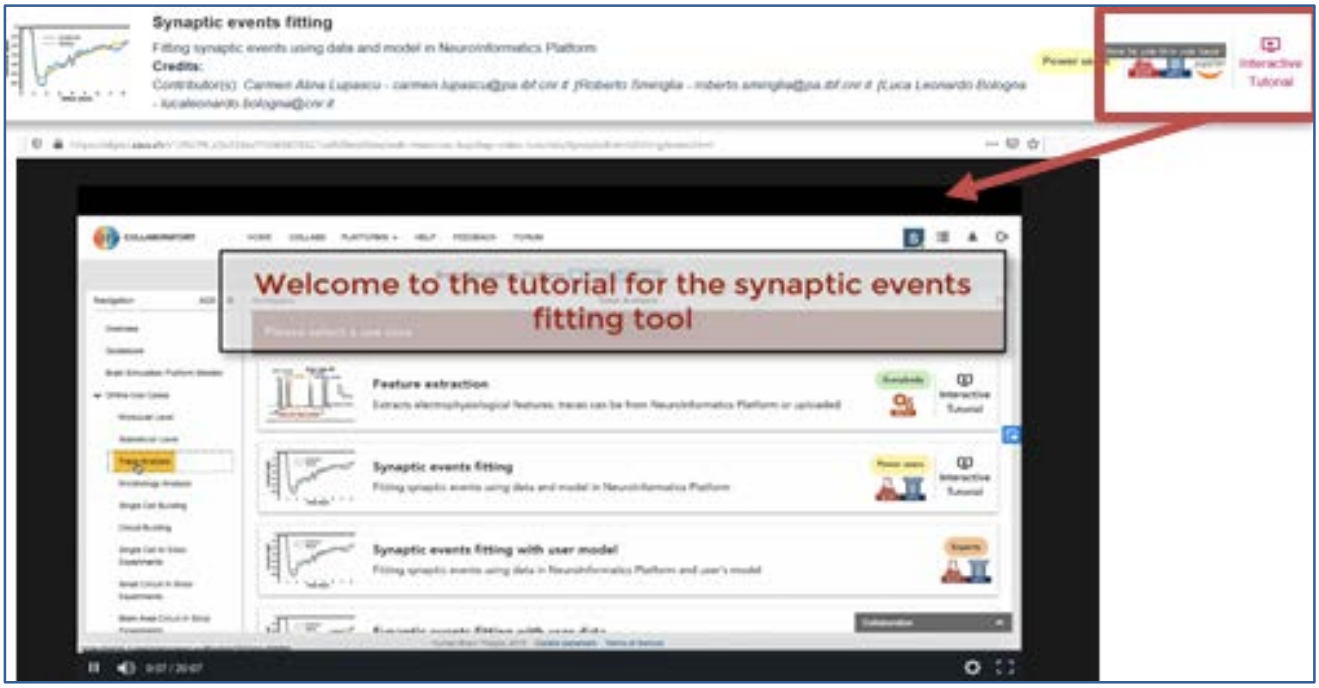

Figure 16: Screenshot from a typical interactive video tutorial[23].

Interactive video tutorials have been added to online use cases (for example, see Figure 16). They are a unique, friendly way for a user to have a first glimpse at how to exploit a use case. Each video allows the user to interactively navigate through all the steps needed to execute the use case, choosing among many possible wa ys of execution. To see how one works, look for the "Interactive tutorial" button on any use case of the Brain Simulation Platform here: https://collab.humanbrainproject.eu/#/collab/1655/nav/66850. A complete list of all the available video tutorials is provided in the dedicated section of the BSP Guidebook: https://humanbrainproject.github.io/hbp-sp6-guidebook/getting_started/getting_started.html#video-tutorials

[23] https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/web-resources-bsp/bsp-video-tutorials/SynapticEventsFitting/index.html

6.1.3 Output 2: Integration of the Service Account and Model Catalog registration functionalities (C1634)

Table 26: KR6.4 Output 2 links.

Component	Link to	URL
C1634	Software Repository	https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Hodgkin_Huxley_Neuron_Builder_CDP2_P1 https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Synaptic%20events%20fitting https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Rebuild%20an%20existing%20single%20hippocampal%20cell%20model https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Build%20your%20own%20single%20cell%20model%20using%20HBP%20data
	Technical Documentation	https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Hodgkin_Huxley_Neuron_Builder_CDP2_P1 https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Synaptic%20events%20fitting https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Rebuild%20an%20existing%20single%20hippocampal%20cell%20model https://collab.humanbrainproject.eu/#/collab/1655/nav/323540?state=software,Build%20your%20own%20single%20cell%20model%20using%20HBP%20data
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/single_cell_building/hippocampus/p1_hh_neuron_builder/p1_hh_neuron_builder.html https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/trace_analysis/syn_events_fit/syn_events_fit.html https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/single_cell_building/hippocampus/rebuild_existing/rebuild_scm.html/ https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/single_cell_building/hippocampus/build_scm_hbp/build_scm_hbp.html

Several use cases have been improved with the Service Account functionality (see Figure 17 - the Hodgkin-Huxley Neuron Builder provides this functionality). This allows the users to submit jobs to the CSCS Piz Daint HPC system, without HPC credentials being required. Also, depending on the use case, the users have now the possibility to register a model in the Model Catalog for future use, after the model optimisation process is ended.

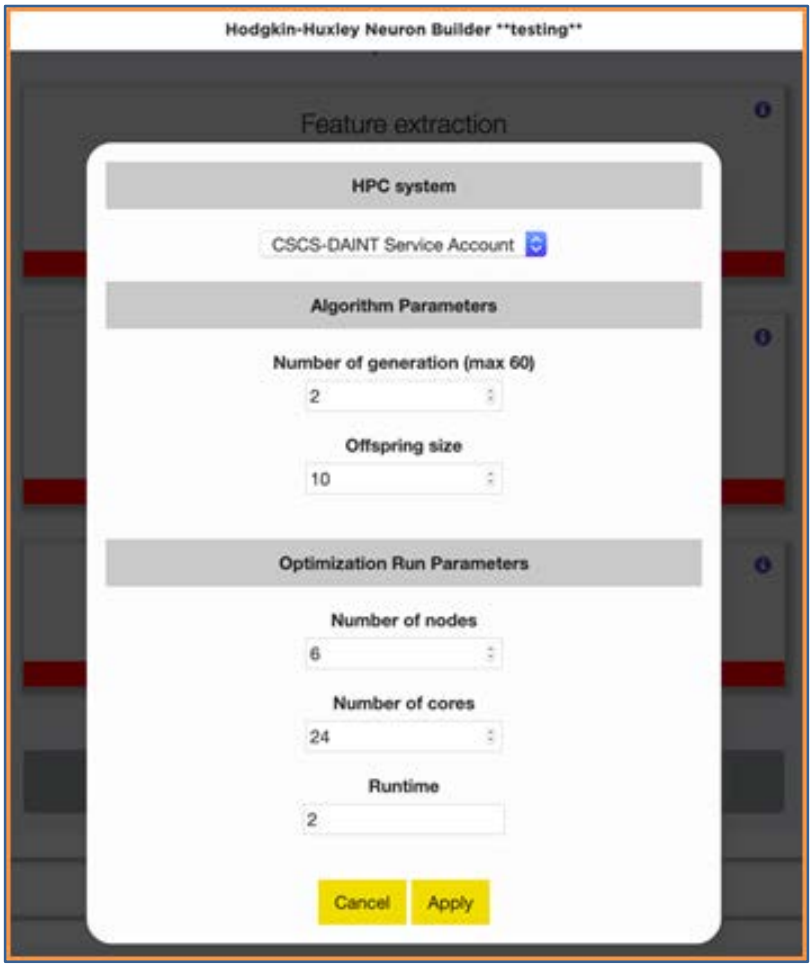

Figure 17: Screenshot from the "Hodgkin-Huxley Neuron Builder[24]" workflow.

6.1.4 Output 3: Integration of rat hippocampus CA1 circuit into Brain Area Circuit use case (C1615)

Table 27: KR6.4 Output 3 links.

Component	Link to	URL
C1615	Model Repository	https://object.cscs.ch/v1/AUTH_c0a333ecf7c045809321ce9d9ecdfdea/rat-ca1-network-model-v7-r2019.06
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/brain_area_circuit_in_silico_experiments/hippocampus/configure_run_brainregion_preconf_model_data/configure_run_brainregion_preconf_model_data.html
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/brain_area_circuit_in_silico_experiments/hippocampus/configure_run_brainregion_preconf_model_data/configure_run_brainregion_preconf_model_data.html

[24] https://collab.humanbrainproject.eu/#/collab/1655/nav/66898

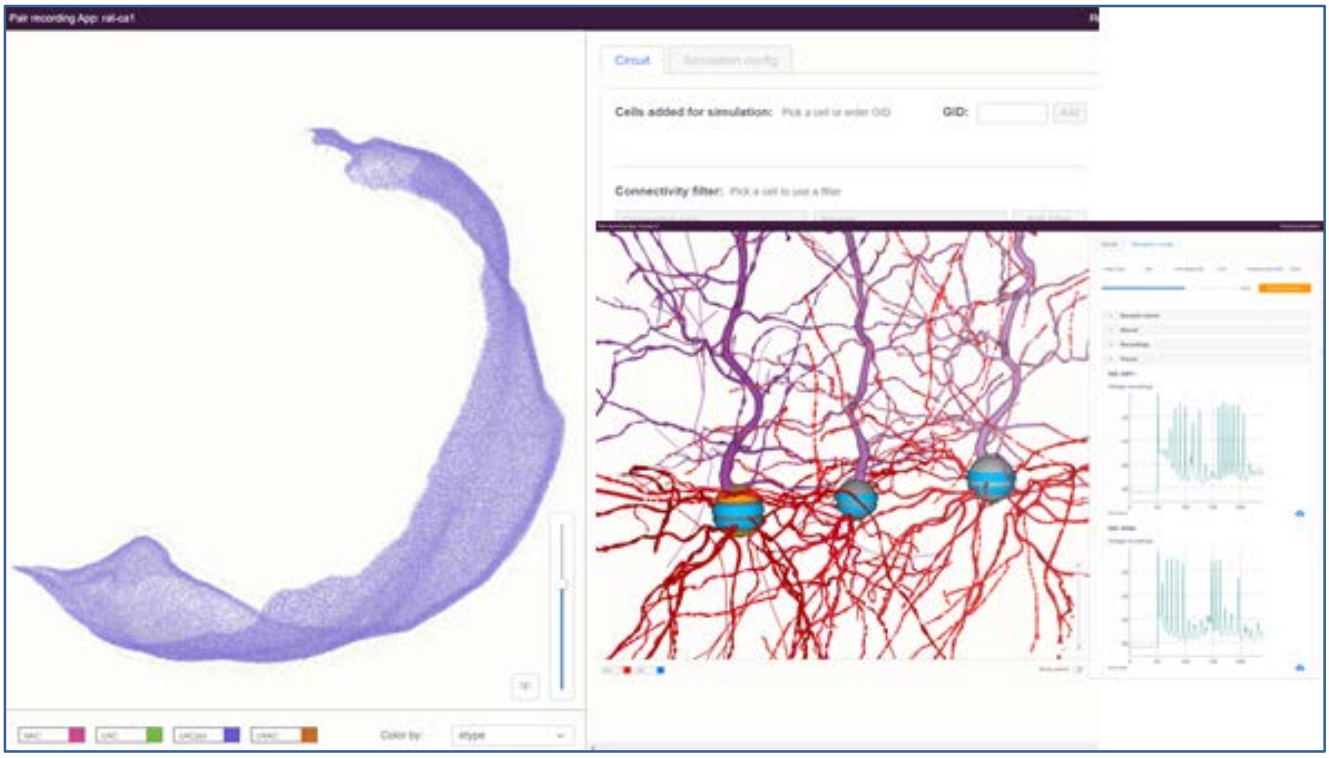

Figure 18: Screenshot from the "Brain Area Circuit in Silico Experiments[25]" use case.

The latest internal HBP release of the rat hippocampus CA1 circuit has been integrated into the Brain Area Circuit *in Silico* Experiments use case GUI; through an intuitive point and click interface, it allows a user to extract a small sub-circuit from the full model, by selecting individual neurons and their relative connections (see Figure 18). The user can then set up his own configuration of synaptic activation and stimulation and/or recording sites and launch *in silico* experiments to explore the behaviour of the circuit under different conditions. This can be seen at: https://collab.humanbrainproject.eu/#/collab/1655/nav/66856.

6.1.5 Output 4: Deployment of simulation and visualisation stack (C1636)

Table 28: KR6.4 Output 4 links.

Component	Link to	URL
C3139	Software Repository	https://github.com/BlueBrain/spack
	Technical Documentation	https://github.com/BlueBrain/spack
	User Documentation	https://github.com/BlueBrain/spack#-spack

[25] https://collab.humanbrainproject.eu/#/collab/1655/nav/66856

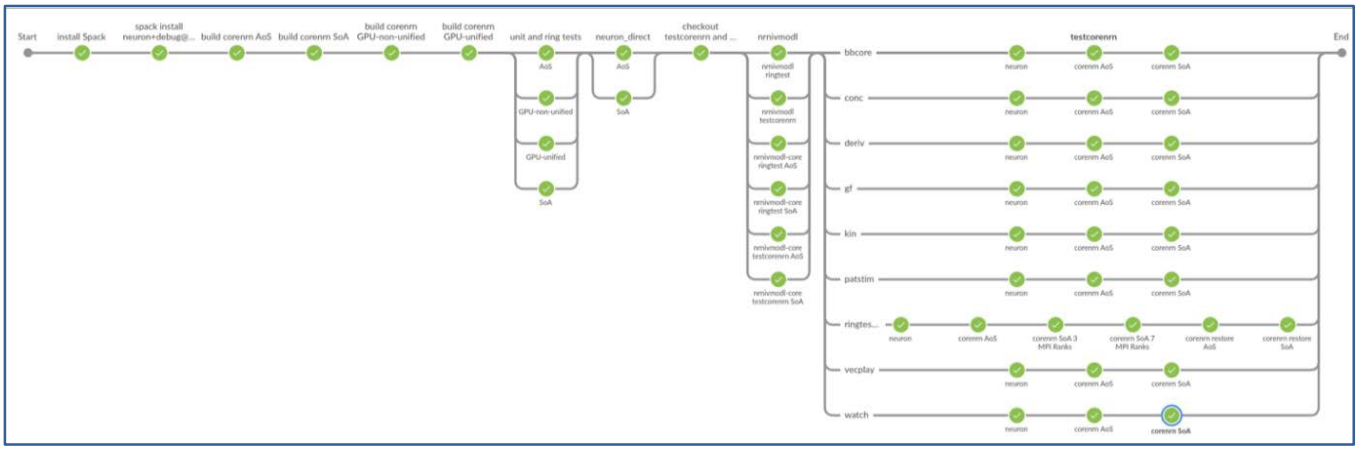

Figure 19: Visualisation of Jenkins pipeline that utilises Spack build operations.

As part of software development and deployment lifecycle, Package Management tools and Continuous Integration (CI) tools have been adopted. Spack is a multi-platform package manager that builds and installs multiple versions and configurations of software. Jenkins and Travis are two implementations of CI, used on local computing platforms or Github, respectively. These CI tools activate as code modifications are developed and committed to the git repositories, allowing automated tests to run and detect any regressions in application behaviour. Such tests inform developers to correct any problems before code is merged into the master development branches.

For the deployment of model building and simulation stacks, multiple system compilers and mpi libraries are provided by the different HPC sites and can be engaged with a variety of optimisation flags. These combinations are registered into Spack manager as "specs", with certain requirements and dependencies. The same package can be built with multiple versions and changing the dependencies. Simulation engines, such as NEURON and CoreNeuron, and modelling tools, like BluePyOpt, are continuously updated on all the supercomputer systems connected to the BSP, to follow the systematic updating/upgrading of hardware, firmware and software that occurs very frequently at the different HPC sites.

Figure 19 shows Spack deployment used in conjunction with Jenkins CI to access a dashboard to view all the available build options and stages. Here one can verify that all stages completed successfully or, in the event of failures, dive into the faulty stage to find which test has issues, so that it can be resolved with additional patches.

6.1.6 Output 5: Web-access to molecular level tools (C1997)

Table 29: KR6.4 Output 5 links.

Component	Link to	URL
C1997	Software Repository	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html
	Technical Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html
	User Documentation	https://humanbrainproject.github.io/hbp-sp6-guidebook/online_usecases/molecular_level/molecular_level.html

A set of use cases (Jupyter Notebooks for APIs for programmatic access to external web servers and databases) was developed. These tools aim to assist setup of molecular dynamics simulations, estimation of protein association rates and finding protein binding sites. They make use of several open source tools, such as ArDock, CNS_MoDeL, SDA and multiPIPSA.

During SGA2, this Task has, as planned in "beyond state of the art", developed new documented online use cases in the Brain Simulation Platform. These provide an environment that greatly facilitates the use of the software and should, with access to the HBP, increase the range of researchers who can use the associated molecular simulation tools. This work is complementary to

other efforts in the international molecular dynamics simulation field to make simulation tools more accessible.

6.1.7 Output 6: Model validation tools based on the Knowledge Graph (C722)

Table 30: KR6.4 Output 6 links.

Component	Link to	URL
C722	Software Repository	https://github.com/HumanBrainProject/hbp-validation-framework https://github.com/HumanBrainProject/hbp-validation-client/
	Technical Documentation	https://hbp-validation-client.readthedocs.io/en/master/
	User Documentation	https://collab.humanbrainproject.eu/#/collab/1655/nav/18580 https://humanbrainproject.github.io/hbp-sp6-guidebook/reference/reference_index.html#reference-documentation-for-platform-components

The Model Validation web service has been modified to store all information about models, validation tests, and validation simulations in the Knowledge Graph (KG), instead of in a custom database (the web service provides the backend for the Model Catalog and Model Validation Collaboratory apps and for the model validation Python client, used in many of the online use cases,). This sets the stage for much deeper integration of model validation with data curation, neuromorphic computing, and provenance tracking, which will take place in the next phase of the project. For example, all curated datasets available through the Knowledge Graph Search app can now potentially be used as reference data for validating models (for example, see Figure 20).

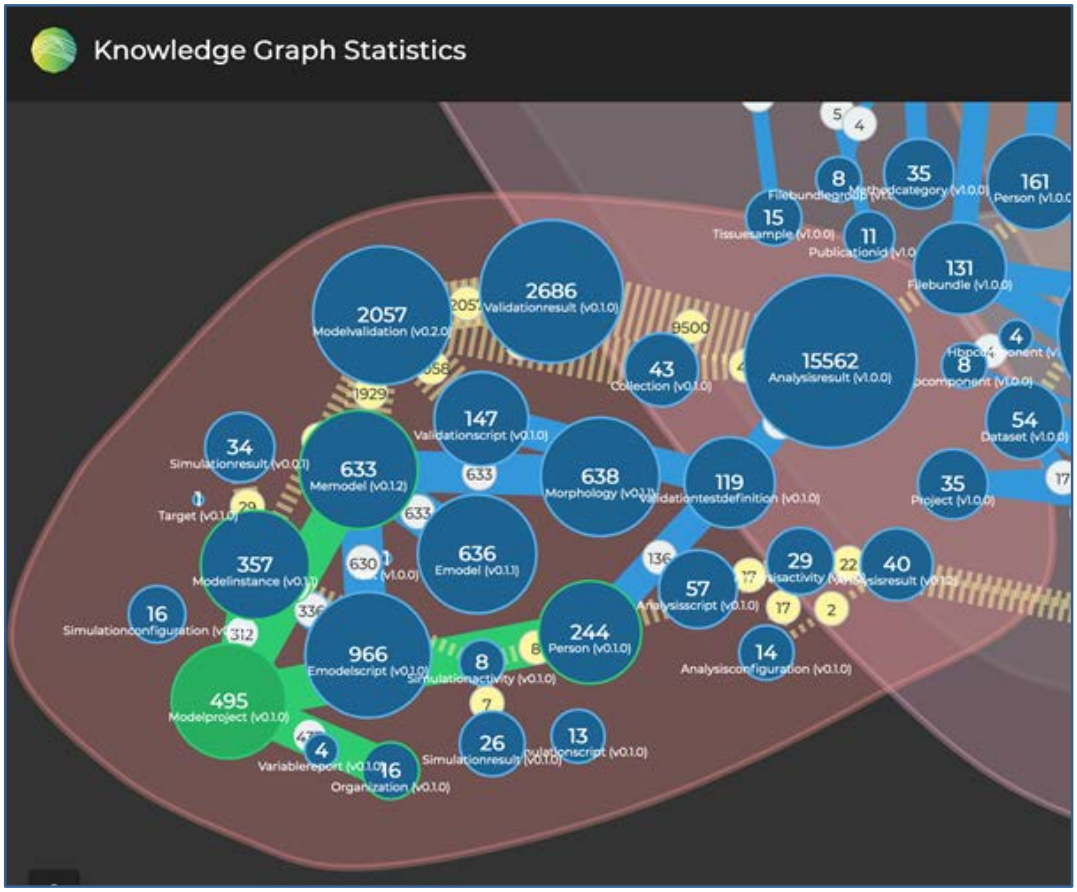

Figure 20: Screenshot of the Knowledge Graph statistics app[26].

[26] https://kg.ebrains.eu/statistics/

6.1.8 Output 7: Python libraries for structured model validation tests (C1680)

Table 31: KR6.4 Output 7 links.

Component	Link to	URL
C1680	Software Repository	https://github.com/KaliLab/hippounit https://github.com/appukuttan-shailesh/basalunit https://github.com/cerebunit https://github.com/appukuttan-shailesh/morphounit https://github.com/appukuttan-shailesh/eFELunit https://github.com/INM-6/NetworkUnit
	Technical Documentation	N.A.
	User Documentation	https://hippounit.readthedocs.io/ https://cerebtests.readthedocs.io/en/latest/ https://cerebmodels.readthedocs.io/en/latest/

Test libraries are Python modules that contain tests specific to certain biophysical scenarios (for example, see Figure 21). HippoUnit, CerebUnit and BasalUnit are validation suites catering to models of hippocampus, cerebellum and basal ganglia, respectively; MorphoUnit targets testing of neuronal reconstructions and network structures; NetworkUnit is aimed at testing of spiking networks, and eFELunit is a generic module intended for testing of eFEL features extracted from computational models.

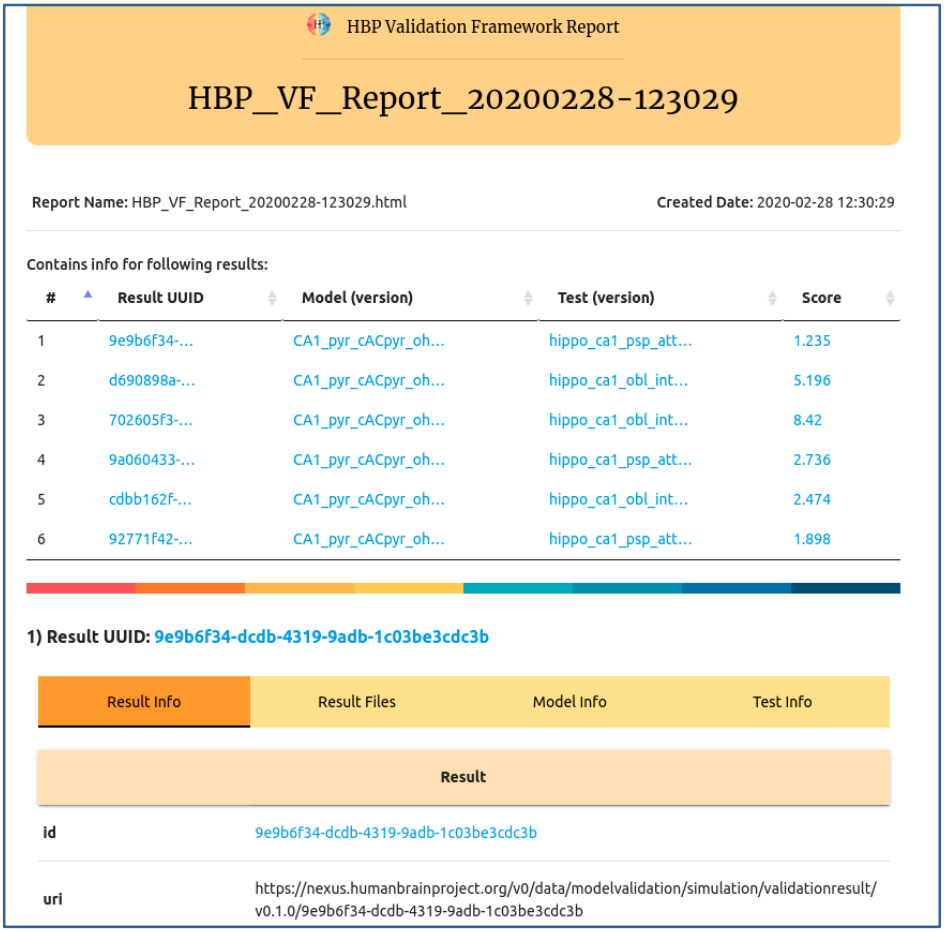

Figure 21: Auto-generated report of model validation tests[27] from the HippoUnit library.

[27] https://collab.humanbrainproject.eu/#/collab/1655/nav/98319

The latest releases of all the test modules ensure Python 3 compatibility, as well as usage of recent versions of other dependencies. Additionally, MorphoUnit has added a population level morphology test, and HippoUnit has added features to make existing tests more customisable.

6.2 Validation and Impact

6.2.1 Actual and Potential Use of Output(s)

As the direct result of activities targeting all users (beginners or expert, HBP internal or external) these Outputs have been implicitly or explicitly used for research or educational purposes. Overall, 885 users accessed the BSP and executed at least one use-case, by copying it to their own Collab for further use. Of these, 695 were external users (i.e. users who have no HBP accreditation) and 157 were HBP members not involved in the development of the BSP tools and services (the remaining 33 users were BSP staff, which includes use case developers and testers). The total number of use cases executed on the BSP by external users was 3,941, which resulted in the creation of 2,521 new Collabs. The number of BSP page views since 21 June 2017 (i.e. the release date of BSPv2), as computed by Google analytics, is approximately 166,000. This includes about 100,000 accesses by the selenium tests, which are regularly performed on the entire set of use cases. For the Live Papers, the overall number of page views to date is 2,351. All Outputs are already contributing to the future Research Infrastructure; the BSP and all of its use cases, using all these Outputs, are already accessible from the EBRAINS website (see https://ebrains.eu/services/simulation/brain-simulation).

6.2.2 Publications

No publications.

7. Conclusion and Outlook

The Outputs produced by these Key Results are aligned with the planned work, and no changes were needed; the necessary Python2->Python3 conversion of all Python code presented a risk of many use cases becoming unusable. As a mitigation measure, we gave higher priority to this issue, reducing the efforts to solve other minor issues/improvements, and the risk did not materialise. The web accessible suite of highly integrated model building and simulation tools, backed by HPC computing resources, is now a robust, reliable set of applications with a high overall TRL, that has been designed and implemented to provide continuing support to users with any level of skills in the neuroscience field, during SGA3 and beyond.

Our success is demonstrated by the growing number of users exploiting the Platform (see Figure 22). A key success factor has been the close integration and interaction among the different institutions involved in SP6, and the strong spirit of collaboration with Partners in SP5 (for integration with the KG) and SP7 (for HPC tools and resources). However, the continuous effective and successful use of the Outputs and, ultimately, the ability to maintain and increase the number of users during SGA3 and beyond will depend on the new EBRAINS Platform architecture and its compatibility with the work done in the past years.

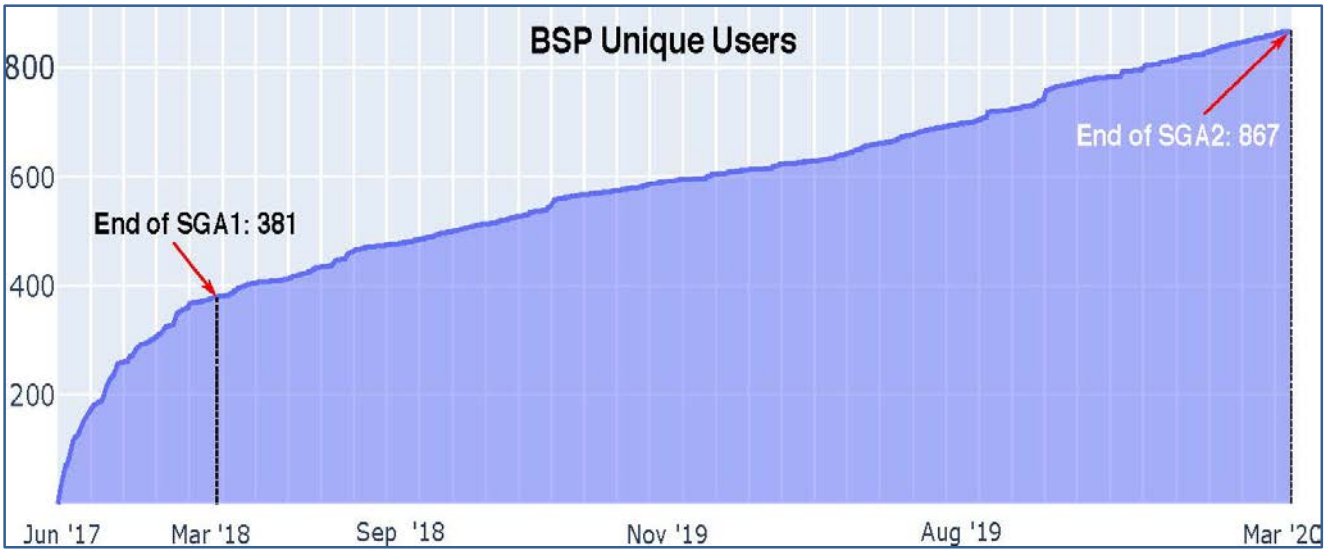

Figure 22: Number of BSP users as a function of time.

Annex A: 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, C3136) - 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
Basal ganglia	n/a	D1 MSN	Intracellular reaction network GPCR/Ca model	Exploitation	Blackwell *et al.*, 2018	Public
Basal ganglia	n/a	D1 MSN	Computational form of the model (ODEs)	Exploitation	Blackwell *et al.*, 2018	Public
General	n/a	General	Intracellular reaction network model (CamKII/PP2B)	Exploitation	Eriksson *et al.*, 2018	Public
General	n/a	General	Computational form of the model (ODEs)	Exploitation	Eriksson *et al.*, 2018	Public
Inhibition and Calcium Cascades (C1781, C1782, C1784, C3156) - https://www.humanbrainproject.eu/en/brain-simulation/inhibition-and-calcium-cascades/						
General	General	General	Dendritic spine model with inhibition (python)	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication)
General	General	General	Dendritic spine model with inhibition (NEURON)	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication)
General	General	General	Spine morphometry estimator	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication)
General	Mouse	General	Simplified Ca-dependent cascade model	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication)
General	Mouse	General	Full Ca-dependent cascade model	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication)
General	General	General	Signal detection protocol	Exploitation	Ludwig *et al.*, 2019	Public; Live Paper
Molecular Signalling Cascades (C1698, C3136) - https://www.humanbrainproject.eu/en/brain-simulation/molecular-signalling-cascades/						
General	Rat	General	Predicted association rate constants of G proteins to AC5 complexes	Exploitation	Bruce *et al.*, 2019	Public; Live Paper
General	Rat	General	MD Trajectories of AC5 G-protein complexes	Exploitation	Bruce *et al.*, 2019	Public; Live Paper
General	Rat	General	Predicted association rate constants of G proteins to AC5 complexes	Exploitation	Bruce *et al.*, 2019	Public; Live Paper
General	Rat	General	MD simulation models of AC5 G-protein complexes	Exploitation	Bruce *et al.*, 2019	Public; Live Paper
General	Rat	General	BD simulation association models of AC5 G-protein complexes	Exploitation	Bruce *et al.*, 2019	Public; Live Paper
Basal ganglia	Mouse/rat	D1R MSN	Model of AC signalling cascade	Exploitation	Bruce *et al.*, 2019	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/45d6786c-c3c7-4565-83cb-4620c10e2753
Molecular Modelling (C2893, C1661) - https://www.humanbrainproject.eu/en/brain-simulation/molecular-models/						

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
General	General	General	PLUMED scripts	Exploitation	Capelli *et al.*, 2019	Public; Model in KG: https://kg.ebrains.eu/search/instances/Model/19873bd656c4c82d25ed20da04f56df4
General	General	General	MD model of M2 with POPC membrane	Structured	Publication in progress	Public; Collaboratory storage
General	General	General	MD model of M2 with mixed membrane	Structured	Publication in progress	Public; Collaboratory storage
General	General	General	Model for analysis of protein-ligand dissociation	Exploitation	Kokh *et al.*, 2019	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/9a7140b9-bfef-49b0-8f89-3a089de5cc1c
Multiscale (SGA1 C766, C3051) - 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 model; electrophysiology and subcellular signalling	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
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	Electrophysiological and subcellular signalling model of the direct-pathway striatal projection neuron--baseline activation of D1R	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/de5f8b959f72ad18594967150f0cbcec903c803d
Striatum	n/a	Medium spiny neuron	Electrophysiological and subcellular signalling model of the direct-pathway striatal projection neuron--half activation of D1R	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/de5f8b959f72ad18594967150f0cbcec903c803d
Striatum	n/a	Medium spiny neuron	Electrophysiological and subcellular signalling model of the direct-pathway striatal projection neuron--full activation of D1R	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/de5f8b959f72ad18594967150f0cbcec903c803d

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Striatum	n/a	Medium spiny neuron	Electrophysiological and subcellular signalling model of the direct-pathway striatal projection neuron--transient activation of D1R	Exploitation	Lindroos *et al.*, 2018	Public; Live Paper: Model in KG: https://kg.ebrains.eu/search/instances/Model/de5f8b959f72ad18594967150f0cbcec903c803d
Human Neurons (SGA1 C1029, C3135) - 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
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
Basal Ganglia (SGA1 972, C3131, C3134) - https://www.humanbrainproject.eu/en/brain-simulation/basal-ganglia/						
Striatum	Mouse/rodent	Pyramidal cell	Afferent synaptic connections	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	dSPN 1, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	dSPN 2, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	dSPN 3, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Striatum	Mouse/rodent	Medium spiny neuron	dSPN 4, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	iSPN 1, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	iSPN 1, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	iSPN 2, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	iSPN 3, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Medium spiny neuron	iSPN 4, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Fast-spiking interneuron	FS 1, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Fast-spiking interneuron	FS 2, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Fast-spiking interneuron	FS 3, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Fast-spiking interneuron	FS 4, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Low threshold-spiking interneuron	LTS, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Striatum	Mouse/rodent	Cholinergic interneuron	ChIN, single cell model	Exploitation	Hjorth *et al.*, 2020	Public; Live Paper
Cerebellum (SGA1 C3023, C3130, C3129, C1647) - https://www.humanbrainproject.eu/en/brain-simulation/cerebellum/						
Cerebellum	Rat	Granule cell mono compartmental	Granule cell - Mono compartmental	Exploitation	Masoli *et al.*, 2017	Public; Model in KG: https://kg.ebrains.eu/search/instances/Model/9d4220b8dbeba24a84935c20cca23806
Cerebellum	Rat	Granule cell mono compartmental	Granule cell - Multi compartmental	Exploitation	Masoli *et al.*, 2017	Public; Model in KG: https://kg.ebrains.eu/search/instances/Model/8587bb11b16f4ad13087682d3004a292
Cerebellum	Mouse	Purkinje cell multi compartmental	Purkinje cell - Multi compartmental	Exploitation	Masoli *et al.*, 2015	Public; Model in KG: https://kg.ebrains.eu/search/instances/Model/237b8b47c6362f2761a68da37a9655c9
Cerebellum	Mouse	Golgi cell	Morphologies	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Golgi cell	Single cell model	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Stellate cell	Morphologies	Exploitation; publication pending	Publication in progress	Private

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Cerebellum	Mouse	Stellate cell	Electrophysiology	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Stellate cell	Ion channels	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Stellate cell	Single cell model	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Deep cerebellar nuclei	Electrophysiology	Structured	Unpublished	Private
Cerebellum	Mouse	Deep cerebellar nuclei	Single cell model	Structured	Unpublished	Private
Cerebellum	Rat	Granule cells	Granule cells regular	Exploitation	Masoli *et al.*, 2020	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/31465cac31e598aebe9abaad48acc6f7
Cerebellum	Rat	Granule cells	Granule cells mild adapting	Exploitation	Masoli *et al.*, 2020	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/4af000106729670820a52a21fd13a5f9
Cerebellum	Rat	Granule cells	Granule cells adapting	Exploitation	Masoli *et al.*, 2020	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/39fe56b528600a3b6ce0562cdc54cadf
Cerebellum	Rat	Granule cells	Granule cells accelerating	Exploitation	Masoli *et al.*, 2020	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/9d75be374c1ef7b7c912d00b455591eb
Cerebellum	Rat	Granule cells	GrC morphology	Exploitation	Masoli *et al.*, 2020	Public; Live Paper
Cerebellum	Mouse	Purkinje cells	Purkinje cells morphologies	Exploitation; publication pending	Publication in progress	Private
Cerebellum	Mouse	Basket cells	Basket cells morphologies	Incubator	Unpublished	HBP internal
Cerebellum	Rat/mouse	Granule cells	Plasticity glomerulus	Incubator	Unpublished	HBP internal
Cerebellum	Rat/mouse	Granule cells, Golgi cells, Purkinje cells, stellate cells, basket cells, Deep cerebellar nuclei cells	Cerebellum network model with point-neurons	Exploitation	Casali *et al.*, 2019	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/5c10fd2f35808140fd153ba92b4e25e6
Cerebellum	Rat/mouse	Golgi cells and other single cells	Complex electroresponsive dynamics in olivocerebellar neurons represented with extended-generalised leaky integrate and fire models	Exploitation	Geminiani *et al.*, 2019a	Public: https://github.com/AliceGem/E-GLIF

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Cerebellum	Rat/mouse	Granule cells, Golgi cells, Purkinje cells, stellate cells, basket cells, Deep cerebellar nuclei cells, DCN interneurons, Inferior Olive neurons	Olivo-cerebellum network model with advanced point-neurons	Exploitation	Geminiani *et al.*, 2019b	Public; Live Paper; Model in KG: https://kg.ebrains.eu/search/instances/Model/96af294049bbb92150836cd29a09d525 Online use case: https://collab.humanbrainproject.eu/#/collab/80131/nav/542500
Cerebellum	Rat/mouse	Granule cells, Golgi cells, Purkinje cells, stellate cells, basket cells, Deep cerebellar nuclei cells, DCN interneurons, Inferior Olive neurons	Olivo-cerebellum network model with advanced point-neurons and long-term plasticity	Structured	Publication in progress	Online use case: https://collab.humanbrainproject.eu/#/collab/80477/nav/545010
Cerebellum	Rat/mouse	Granule cells, Golgi cells, Purkinje cells, stellate cells, basket cells	Cerebellum network model with multi-compartmental single cell models	Structured	Publication in progress	Public code: https://github.com/dbbs-lab/scaffold; Online use case: https://collab.humanbrainproject.eu/#/collab/79605/nav/540654
Hippocampus (C1620, C3133) - https://www.humanbrainproject.eu/en/brain-simulation/hippocampus/						
Hippocampus CA1	Rat/mouse	Pyramidal cells, interneurons	Synaptic plasticity models	Exploitation; publication pending	Solinas *et al.*, 2019	Public; Live Paper
Hippocampus (CA1)	Rat	Pyramidal cells, interneurons	Single cell models	Exploitation	Migliore *et al.*, 2018	Public; Live Paper; Models in KG: https://kg.ebrains.eu/search/instances/Model/2d5ecf4a-2962-4a04-a42d-4a680664bea0
Hippocampus (CA1)	Rat	Pyramidal cells, interneurons	Network model	Exploitation; publication pending	Publication in progress	Live Paper (private; waiting for publication); Model in KG: https://kg.ebrains.eu/search/instances/Model/92cec93d952a201a53b84eb31fa3b842
Somatosensory Cortex (C3132) - https://www.humanbrainproject.eu/en/brain-simulation/mouse-sscx/						
Somatosensory cortex	Mouse	n/a	Mouse SSCx microcircuit network model	Structured	n/a	Online use case allowing simulations: https://bbp.epfl.ch/public/simulationapp/index.html#/circuits/sscx_hbp_sa_mouse_microcircuit

Brain Region	Species	Cell Type	Artefact Name	Life Cycle Stage	Publication	Dissemination Status
Whole Mouse Brain (C3128) - https://www.humanbrainproject.eu/en/brain-simulation/whole-mouse-brain-model/						
Cerebellum	Rat/mouse	Granule cells, Golgi cells, Purkinje cells, stellate cells, basket cells, Deep cerebellar nuclei cells, DCN interneurons, Inferior Olive neurons	Olivo-cerebellum network model with advanced point-neurons and long-term plasticity Modular architecture: cerebro-cerebellar loops	Structured	Publication in progress	Public; Scaffold codebase: https://github.com/dbbs-lab/scaffold; Plasticity module: https://github.com/dbbs-lab/extra-cereb-nest; Online use case: https://collab.humanbrainproject.eu/#/collab/79916/nav/541051

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

Model Name	Data Use in Model	Data Source	HBP Funded	Data Locations
Signalling Cascades (C3051, C3136)				
Intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No	n/a
CaMKIIs intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No	n/a
MGluR intracellular reaction network model	Dose response or time series data of substances and similar	Literature	No	n/a
Inhibition and Calcium Cascades (C1781, C1782, C1784, C3156)				
Dendritic spine model with inhibition	Spine reconstruction data and morphometry from somatosensory cortex L2/3 pyr neurons	ENS	No	Curation in progress
Signal detection protocol	Spine reconstruction data and morphometry from somatosensory cortex L2/3 pyr neurons	ENS	No	Curation in progress
Molecular Signalling Cascades (C1698, C3136)				
AC5, G protein and complex electrostatic potential grid files	Protein electrostatics	SGA1, T6.1.1; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/10a9a23a2dcf0a6d795b28ffa5504af1
MD Trajectories of AC5 - G protein complexes	Structures of AC5 - G protein complexes	SGA1, T6.1.1	Yes	n/a
Model of AC signalling cascade	Rate constants for G protein association	SGA1, T6.1.1; SGA2, T6.1.1	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/45d6786c-c3c7-4565-83cb-4620c10e2753
Molecular Modelling (C2893, C1661)				
Homology structural models	Modelled adenylyl cyclase (AC) isoform structures	SGA1, T6.1.1; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/10a9a23a2dcf0a6d795b28ffa5504af1
	AC isoform electrostatic potential grid files	SGA1, T6.1.1; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/10a9a23a2dcf0a6d795b28ffa5504af1
Model for analysis of protein-ligand dissociation	Rate constants for HSP90, ML model	SGA2, T6.1.1; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/9a7140b9-bfef-49b0-8f89-3a089de5cc1c
Multiscale (SGA1 C766, C3051)				
Single cell electrophysical model including a subcellular cascade	Validation data (dendritic); Ca transient (fluorescent)	SGA1, T6.1.4	Yes	n/a
	Validation data (somatic); Electrophysiology (FI)	SGA1, T6.1.4	Yes	n/a
	Subcellular cascade D1R/AC5/cAMP/PKA	SGA1, T6.1.2	Yes	n/a
	Conversion recipe (DataSpace)	SGA1, T6.1.4	Yes	n/a

Model Name	Data Use in Model	Data Source	HBP Funded	Data Locations
Human Neurons (SGA1 C1029, C3135)				
Passive model	Morphology	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI DOI
	Electrophysiology - passive transients	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
	Spine data	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
Active model	Electrophysiology – single cell recordings	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
	Electrophysiology pair recordings	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
	Electrophysiology extracellular stimulations	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
	Electrophysiology spike trains	RUP/SGA1, T1.2.1, T1.2.2, T2.2.6	Yes	DOI
Basal Ganglia (SGA1 972, C3131, C3134)				
Striatal projection neuron model	Morphology reconstruction – single neuron	RUP/SGA1, T6.1.6	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/9f90c14f-d12a-42e2-bfe7-8a7ad2652b44
	Morphology reconstruction – population	SGA2, T6.1.6	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/9f90c14f-d12a-42e2-bfe7-8a7ad2652b44
	Electrophysiology, single cell recordings - population	SGA2, T6.1.6	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/e0cfa3fb-22d2-48c7-bb4c-a6374bfc848b
Striatal fast-spiking interneuron model	Morphology reconstruction – population	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8bec4750-e9a1-44ac-8dc9-647c14b63fe7
	Electrophysiology, single cell recordings - population	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/02f1aec9-c709-4dd3-8929-3833569078eb
Striatal low threshold-spiking interneuron model	Morphology reconstruction – single neuron	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/f83aac60-7e9c-4933-94ce-ca4f5a90cb5a
	Electrophysiology, single cell recordings – single neuron	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/495de3d5-f9d5-4a4a-acd2-4ade0eaefb22

Model Name	Data Use in Model	Data Source	HBP Funded	Data Locations
Striatal cholinergic interneuron model	Morphology reconstruction – single neuron	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/749eab9b-3159-4eb8-a36b-85757208e3c1
	Morphology reconstruction – population	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/766d173d49c9b9b8a2bf879d58670634
	Electrophysiology, single cell recordings – single neuron	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/7d545473-405d-45f9-b0c4-05b627bf793a
	Electrophysiology, single cell recordings - population	SGA2, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/e95adf4f93d83428ae3de5847332806e
Excitatory afferent synapse model	Electrophysiology, paired recordings	SGA2, T6.1.6, T6.2.4	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/7d545473-405d-45f9-b0c4-05b627bf793a
Cerebellum (SGA1 C3023, C3130, C3129, C1647)				
Granule cell - Mono compartmental	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4, T6.2.4; Literature	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/40a8ed8caae4989506d69fd290b67a90
	Granule mono morphology	SGA1, T1.2.4, T6.2.4; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/9d4220b8dbeba24a84935c20cca23806
Purkinje cell - Multi compartmental	Purkinje cell p43 mouse morphology	RUP, T6.4.5; Literature	Yes	Knowledge Graph: https://kg.ebrains.eu/search/instances/Model/237b8b47c6362f2761a68da37a9655c9
Golgi cell, single cell model	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4, T6.2.4; Literature	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/17196b79-04db-4ea4-bb69-d20aab6f1d62
Granule cell, single cell model	Electrophysiology	RUP, T6.4.5; SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/7dc5d5d5-4323-41d6-bdfd-0b841cfe7000
Purkinje cell, single cell model	Electrophysiology	SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes	n/a

Model Name	Data Use in Model	Data Source	HBP Funded	Data Locations
Stellate cell, single cell model	Electrophysiology	SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/3ca4af33-64bd-437a-9c53-2dac19e10168
Basket cell, single cell model	Electrophysiology	SGA1, T1.2.4; SGA2, T1.2.5; Literature	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/37c082e4-02cf-407d-829a-6fbf0cffc110
Cerebellum network model with point-neurons	Cell densities	Literature	No	n/a
	Layers width	Literature	No	n/a
	Connectivity ratios (convergence and divergence)	Literature	No	n/a
	Functional simulation parameters	Literature	No	n/a
Olivo-cerebellum network model with advanced point-neurons	Cell densities	Literature	No	n/a
	Layers width	Literature	No	n/a
	Connectivity ratios (convergence and divergence)	Literature	No	n/a
	Functional simulation parameters	Literature	No	n/a
Cerebellum network model with detailed single cell models	Cell densities	Literature	No	n/a
	Layers width	Literature	No	n/a
	Connectivity ratios (convergence and divergence)	Literature	No	n/a
	Functional simulation parameters	Literature	No	n/a
Hippocampus (C1620, C3133)				
Network model	Atlas	Literature	No	n/a
	Cell densities	Literature	No	n/a
	Cell type composition	Literature	No	n/a
	Morphology reconstructions	RUP, T6.4.4; SGA1, T6.2.4; SGA2, T6.2.3	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/d69a109f-15d9-4fa7-9fd7-ed32c79edce2 (more data in curation)
	Bouton density	Literature	No	n/a
	Number of synapses per connection	Literature	No	n/a
	Paired electrophysiological recordings	SGA1, T1.2.6	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/3df3bf4c-0361-483b-8e86-8580ff44eedf
	Synaptic parameters	Literature	No	n/a

Model Name	Data Use in Model	Data Source	HBP Funded	Data Locations
Hippocampal cell models (mouse)	Morphological reconstructions – various cell types	RUP, T1.2.4; SGA1, T1.2.5; SGA2, T1.2.2	Yes	Curation in progress
	Morphological reconstructions – CA1 pyramidal cells	SGA1, T1.2.1	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/d40c0f1c7365b5b14be937c3a7860c06
	Single neuron electrophysiological recordings	RUP, T1.2.4; SGA1, T1.2.5; SGA2, T1.2.2	Yes	Curation in progress
Hippocampal network models of subregions (mouse)	Atlas	Literature	No	n/a
	Cell densities	Literature	No	n/a
	Cell type composition	Literature	No	n/a
	Synaptic bouton density	Literature	No	n/a
	Paired electrophysiological recordings	SGA1, T1.2.6	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/3df3bf4c-0361-483b-8e86-8580ff44eedf
Somatosensory Cortex (C3132)				
Mouse SSCx circuit network model	Cell densities needed for network generation (new data)	SGA1, T6.2.2	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8ad57043a61b27ddb9cfbe9d570d930a
	Layer thickness	SGA1, T6.2.2	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8ad57043a61b27ddb9cfbe9d570d930a
	Density of all neurons, used for circuit building	SGA1, T6.2.2	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8ad57043a61b27ddb9cfbe9d570d930a
	Density of interneurons, used for validations	SGA1, T6.2.2	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8ad57043a61b27ddb9cfbe9d570d930a
	Synaptic density, used for validations	SGA1, T6.2.2	Yes	DOI: https://kg.ebrains.eu/search/instances/Dataset/8ad57043a61b27ddb9cfbe9d570d930a
Whole Mouse Brain (C3128)				
Cerebro-cerebellum loop	Cell densities	Literature	No	n/a
	Layers width	Literature	No	n/a
	Connectivity ratios (convergence and divergence)	Literature	No	n/a
	Functional simulation parameters	Literature	No	n/a