All Models of Brain Circuits developed during SGA2 (D4.2.1 – SGA2)

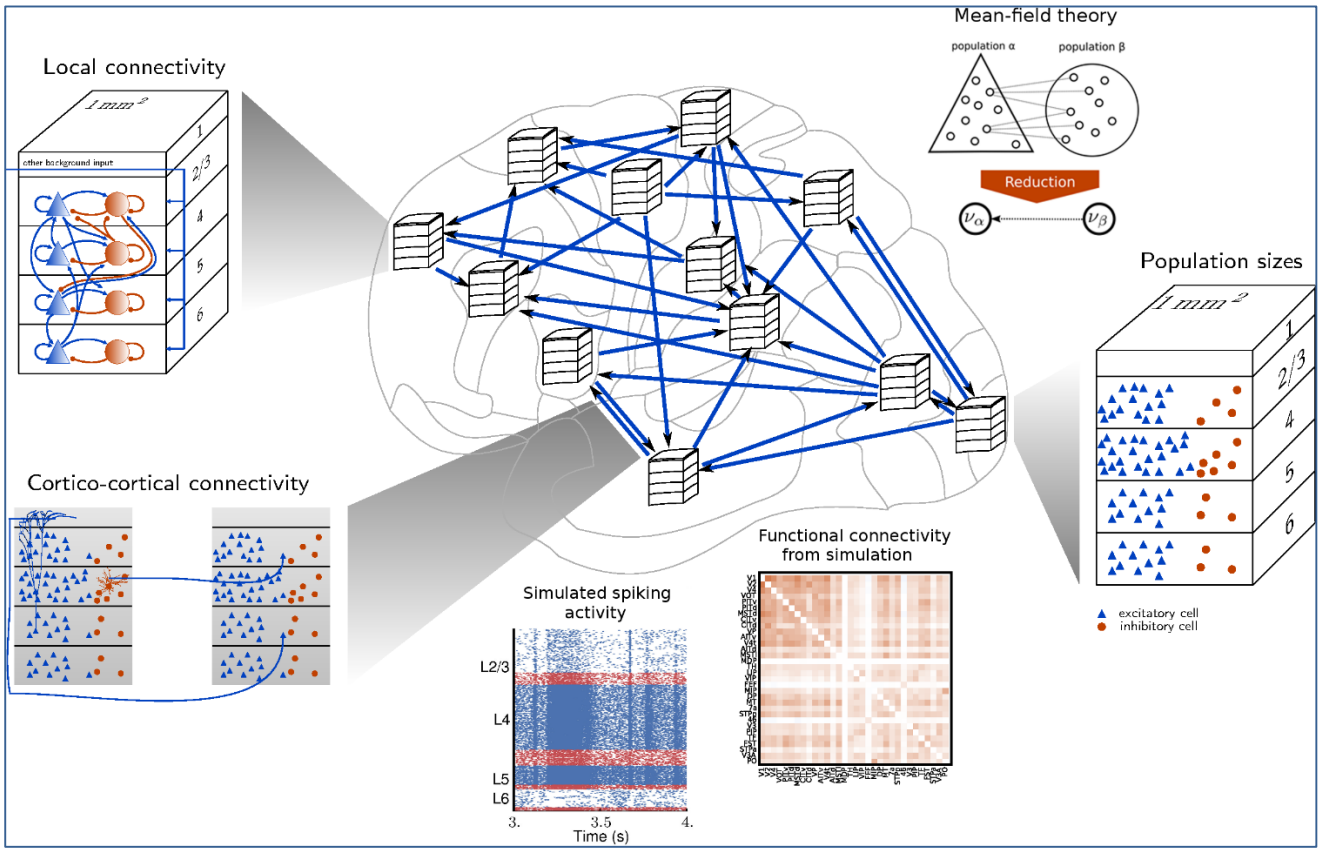

Figure 1: Multi-area model of macaque visual cortex.

A spiking model of all vision-related areas in one hemisphere of the cerebral cortex of the macaque monkey was developed (centre diagram), consisting of layered microcircuits with specific population sizes (right) and local connectivity (top left), which are interconnected in a layer-specific fashion (bottom left). With the help of mean-field theory (top right), both microscopic and macroscopic resting-state activity (bottom) are predicted. See Sec. 5 for details.

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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 report describes the progress made on the various models developed in WP4.2 (and T4.5.1) in SGA2 together with related outputs and publications.
Keywords:	Models, Simulation, Circuit
Target Users/Readers:	Scientific Community, Platform users

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History of Changes made to this Deliverable (post Submission)

Date	Change Requested / Change Made / Other Action
22 May 2020	Deliverable submitted to EC
30 Jul 2020	Deliverable approved by EC
01 Oct 2020	Minor editorial change by PCO
01 Oct 2020	Revised version resubmitted to EC by PCO via SyGMa

1. Overview

The theoretical and computational models developed in SP4 occupy a central position in the HBP. On the one hand, they are derived from experimental data produced in the HBP. On the other hand, models are implemented in the HBP Platforms, where they serve as "first users". These models also constitute the building blocks of work that will be continued in SGA3, such as bridging scales, network models, models of plasticity, models of cognitive processes and whole-brain models.

More specifically, SP4 develops methods, tools, and models for understanding the dynamics of brain circuits via mathematical analysis and neural network simulations. The simulations in this Subproject use concepts like cortical layers and areas, and simplified neuron and glial models that enable systematic mathematical insights. Methods are developed for deriving population equations for networks of individual neurons and for computing average population activities and correlations based on these equations. Tools developed here include software for predicting mesoscopic and macroscopic brain signals (for instance local field potentials and electroencephalographic signals), for analysing the electrical activity of neurons and circuits in both experimental and simulated data, and for validating network models by comparisons with experimental data. The models developed in this Subproject focus on the mammalian cerebral cortex and serve as building blocks for larger brain models, as well as starting points for developing refined and functional brain models.

WP4.2 “Simplified Spiking Models of Different Brain Areas” provides network models that can serve as prototypes or building blocks for large-scale brain simulations, and that aid the co-design of simulation technology for high-performance and neuromorphic computing by elucidating the requirements on these systems.

One important product of this work is a neuronal network model of all vision-related areas in one hemisphere of the cerebral cortex of the macaque monkey, implemented using the simulation software NEST. The model is the first to simultaneously account for the microscopic spiking activity of individual neurons and the macroscopic correlations in the activity of different areas in the resting state. It supports the hypothesis that cortical circuits are poised just below an instability, at a point where the dynamics features a rich repertoire of timescales. The corresponding publications have already received a substantial number of citations, and the model code is being taken up by various groups inside and outside the HBP. The conceptual and software framework underlying the model will help to create a functional cortical model as part of the visuomotor architectures to be developed in SGA3. Furthermore, the model will be ported to the SpiNNaker neuromorphic hardware and support the co-design of SpiNNaker and NEST. Finally, the model runs on supercomputing facilities and is thereby an essential use case for the simulation technology of NEST as it prepares for the next generation of supercomputers.

The complexity of the task to simulate the human brain is also reflected in evaluating the outcome of such simulations with respect to biological reality. Such evaluations, also termed validations, must not only deal with the large heterogeneity present in the types of experiments and measurements that experimental data are based on, but also need to cover and bridge the different scales of observation, reaching from the activity of single nerve cells to that of whole brains. To date, such validation processes in simulation neurosciences are becoming increasingly important as models become increasingly sophisticated and biologically realistic. We were able to advance the field by suggesting a thorough formalisation and standardisation of the validation process, accompanied by corresponding software libraries and an in-depth example of statistical validation of simulations performed on neuromorphic hardware systems. In a joint effort, these concepts were put to use to a large collaborative, concerted validation scenario involving multiple measurement modalities and simulations together with SP3 and SP5.

2. Introduction

In this Deliverable, we report the progress made for models of brain circuits developed in SP4 (WP4.2) and how they connect to the Key Results of SP4. Furthermore, Outputs generated in the scope of T4.5.1 contributing to KR4.5 with defining validation processes for simulations of brain activity, with a focus on data collected on the level of simulated spiking neuronal networks are also described in this Deliverable.

In SGA2, WP4.2 extended the work on a multi-layered model covering 4mm x 4mm cortical surface, which is documented in an ArXiv preprint (Senk *et al*., 2018a; P1511). An accompanying theoretical study on cortical wave propagation was recently published (Senk *et al. (2020)* P2095 – *in validation process- SGA3 publication*). In addition, computational models of calcium-mediated astrocytic functions and astrocyte-neuron interactions were published (Manninen *et al*. 2018, 2019; (P1491, P793)). Schmidt *et al*. (2018) (P1457) report on a supercomputational multi-area model of macaque cortex where each area is represented by a microcircuit. Finally, van Albada *et al*. (2018) (P1338) report on the successful transfer of the microcircuit building block to the SpiNNaker system.

Working towards KR4.5, T4.5.1 was involved with the conceptual and practical aspects of defining validation processes for simulations of brain activity, with a focus on data collected on the level of simulated spiking neuronal networks. To this extent, a formal validation process and corresponding terminology was established for network simulations, specifically against massively parallel activity data from experiments. Here, the statistical properties of observed network dynamics have been quantified and quantitatively compared between a model and matching datasets. The work involved a characterisation and adaptation of the validation process to the domain of network simulations, the development of a corresponding Python software library to administer such validation tests, and two concrete validation scenarios demonstrating its use, involving computer simulation, neuromorphic hardware, and massively parallel data. The results have been published in two companion articles (Trensch *et al.*, 2018 (P1627) and Gutzen *et al*., 2018 (P1628)) and have been further developed since. In particular, together with SP3 and SP5, these insights enabled the continuous evolution of the HBP use case centred on analysis and validation pipelines to characterise data recorded on multiple scales of observation and simulations of slow wave activity. Here, a complex modular pipeline of analysis steps ensures that the statistical spatial properties, such as wave velocities, of heterogeneous datasets and simulations are validated in a rigorous and unified manner.

3. Key Result KR4.5 Validation of spiking network model against experimental data

3.1 Outputs

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to those models

- Output 1: Mesocircuit model (C2418)
- Output 2: Tool for Validation on the Level of Network Activity (C1680)
- Output 3: Publications on conceptual implementation of model validation in simulation neuroscience (C1863)
- Output 4: Analysis and validation pipelines for SP3 use cases (C2053)

3.1.1.2 How Outputs relate to each other and the models (link to the Key Results)

The mesocircuit model (Output 1) covers the same cortical surface area as the Utah array for multi-electrode recordings. Spike data obtained from simulating this network model lends itself to a direct comparison with electrophysiologically recorded data. As part of the validation framework developed in SP6, in Output 2 *NetworkUnit* was developed as a library to perform validation testing of network models against experimental recordings of brain activity, with a focus on evaluating spiking activity data based on its statistical properties. In SP4, we investigated and formalised the underpinnings of such types of validation testing. These considerations, as well as a first description of the library in relation to realistic validation scenarios, are combined in the publications of Output 3. Finally, these Outputs were used in the design of a sophisticated validation pipeline providing a modular workflow able to compare and validate experimental and simulated data across multiple measurement modalities in the context of science conducted in SP3 (Output 4).

3.1.2 Mesocircuit model

Table 1: Mesocircuit model Links

Component	Link to	URL
C2418	Model Repository	https://wiki.ebrains.eu/bin/view/Collabs/mesocircuit/
	Technical Documentation	https://arxiv.org/abs/1805.10235
	User Documentation	https://arxiv.org/abs/1805.10235

The mesocircuit model is a cortical network model that covers with 4x4 mm² the same surface area as the Utah multi-electrode array with 10x10 electrodes. The model integrates anatomical and electrophysiological data and accounts for both spiking activity and local field potentials. The simulated model data lends itself for direct comparison with experimental data obtained in electrophysiological measurements. To date, not enough detailed structural data is available to fully constrain the network parameters. We ran parameter scans within biologically plausible bounds to assess the resulting network activity and found network states that differ qualitatively. A detailed analysis of model parameters and resulting dynamics is published in Senk *et al*. (2018a) (P1511).

The mesocircuit model is a lateral extension of the microcircuit model by Potjans & Diesmann (2014) including distance-dependent connection probabilities and delays. An accompanying theoretical

study investigates the relationship of distance-dependent connections and spatiotemporal patterns in the activity that can also be observed in corresponding experiments *This study has recently been published in Physical Review Research.* (P2095 – *in validation process*).

To visually explore spatiotemporal activity data as emerging in the 2D layers of the mesocircuit model, we implemented the interactive tool VIOLA (VIsualization Of Layer Activity). This joint work with WP7.3 is published in Senk *et al*. (2018b) (P1548).

3.1.3 Tool for validation on the level of network activity

Table 2: Tool for Validation on the Level of Network Activity Links

Component	Link to	URL
C1680	Software Repository	https://github.com/INM-6/NetworkUnit
	Technical Documentation	https://hbp-validation-client.readthedocs.io
	User Documentation	https://collab.humanbrainproject.eu/#/collab/8123/nav/61654

In order to assess the validity of a model used for brain simulation, its features must be validated against experimental findings on multiple levels in a rigorous and reproducible fashion in order to support a fair and meaningful comparison between models. For brain simulations on the scale of neuronal networks and beyond, a key aspect to assess the model's validity is to reproduce the features of population activity dynamics observed in recordings of brain dynamics, e.g. in electrophysiological experiments. The Python library NetworkUnit, forming a central part of the back end libraries for validation testing (C1680), represents a tool to formalise the validation process on the level of statistical features of spiking network activity. It is based on the SciUnit framework which makes it compatible in style with complementary validation libraries (i.e. NeuroUnit to validate single neuron models) and supports an easy integration into the HBP validation framework. A first release 0.1.0 of the library was published (https://github.com/INM-6/NetworkUnit) featuring 10 different tests in addition to various scores. Moreover, it implements both standard validation of models against experimental data, in addition to substantiation scenarios where models are compared against other models and/or simulation engines. The library, built on the functionality of the Elephant analysis toolbox (C348) and the generic Neo data model (C361), therefore represents the technical basis for validation tests for spiking neural network models. The library is continuously developed, currently at version 0.1.1, released Aug 30, 2019.

3.1.4 Publications on conceptual implementation of model validation in simulation neuroscience

The concepts of model validation (assessing the validity of models based on experimental data) and model substantiation (assessing the equivalence of models and simulators) have not received as much attention in neuroscience as in other computationally strong sciences. In an initial step we lay the foundations to transfer concepts of validation testing to the domain of neural network simulations. The results of our work were published in a series of two papers (Trensch *et al*., 2018 (P1627) and Gutzen *et al*., 2018 (P1628)) and include (i) a comprehensive transfer of validation concepts to the domain, including a suggested terminology in line with existing literature and a discussion on differences to validation in other disciplines; (ii) a complete worked example of a substantiation scenario to compare models running on the NEST simulator against implementations on the SpiNNaker neuromorphic hardware, and (iii) an overview of the implementation of the validation process using NetworkUnit (part of C1680) (Figure 2). Building on these results, and initial work on extending this work to experimental data (see Gutzen *et al*., 2018 - P1628), further investigations will include, e.g., formalizing of the process of relating specific records of experimental data to the correct counterparts in the simulation.

Theoretical work published in Dahmen *et al*. (2019) (P1995) investigated the intrinsic distribution of covariance statistics in balanced network states. These results are in the process of being validated

by experimental data, and will provide a further conceptual aspect in validating activity dynamics based on mathematical understanding.

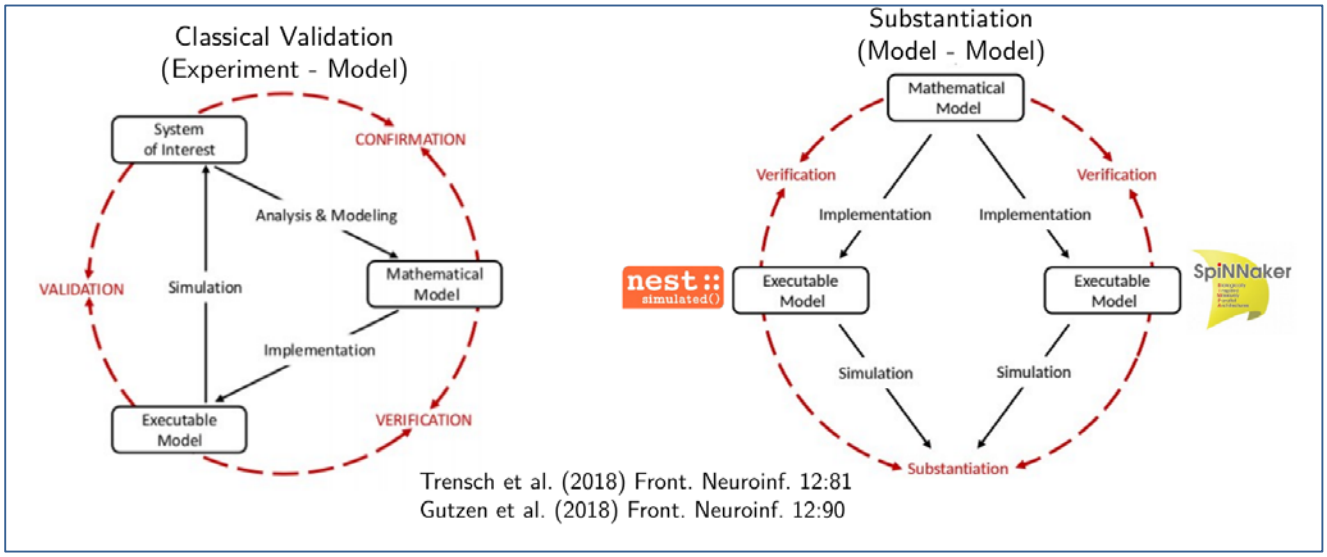

Figure 2: Formalisation of the validation process.

Formalisation of validation (left) and substantiation (right) workflows adapted to the field of computational neuroscience as developed in Output 3. The NetworkUnit library (Output 2) implements validation testing using the statistics of population activity dynamics in this framework.

3.1.5 Analysis and validation pipelines for SP3 use cases

Table 3: Analysis and validation pipelines for SP3 use cases Links

Component	Link to	URL
C2053	Repository	https://wiki.ebrains.eu/bin/view/Collabs/slow-wave-analysis-pipeline/
	Technical Documentation	NA
	User Documentation	https://wiki.ebrains.eu/bin/view/Collabs/slow-wave-analysis-pipeline/

In order to exploit the full potential of the formalised approach to validation on the level of network activity, a full, complex pipeline to compare activity data from multiple levels of observation against network activity was developed in collaboration with SP3 and SP5. The pipeline validates statistical properties of spatial patterns of activity propagation, i.e. wave-like dynamics, seen in such diverse data as spiking activity, calcium imaging, ECoG measurements or network simulations. By formalising the pipeline and reusing analysis steps in multiple ways, validation can be performed in a vastly rigorous and diversified manner. A first version of the workflow is made available and will be continuously improved during the upcoming funding phase.

3.2 Validation and Impact

3.2.1 Actual and Potential Use of Output(s)

A generic version of the mesocircuit model has been published in Senk *et al*. (2018a) (P1511). The model is currently further refined to better match experimental data.

The mesocircuit model can be validated against experimental data (T4.5.1) as it covers the same surface area as the 4x4 mm² Utah array and accounts for spiking activity and local field potentials.

We expect that the model will be used by a larger number of researchers as a building block for more complex models and a testbed for mean-field and field-theoretical approaches.

The mesocircuit model is an essential milestone on the long-term roadmap towards a multi-area model with spatial resolution in the individual areas. Furthermore, the connectivity could be adapted to a specific brain area, e.g. motor cortex, to facilitate the comparison with experimental data.

The NetworkUnit library (Output 1, part of C1680) has seen its second release after having been validated through an extensive validation/substantiation scenario outlined and fully published in Trensch *et al*., 2018 (P1627) and Gutzen *et al*., 2018 (P1628) (Output 2). The library is currently being further co-designed, in particular, in the context of validating spatial dynamics of UP/DOWN state transitions in experiment and simulation within the HBP (Output 3), and with respect to development of the 4x4mm spatially organised model of a single area (C2418). The library will become integrated into the developing Validation Framework services of the HBP (e.g. C722). The published results of C1863 directly relate to the NetworkUnit library by providing conceptual and practical blueprints for formalizing model validation and substantiation into a rigorous process. The library and its functionality is continuously validated through the establishment of the validation pipelines of Output 3.

The NetworkUnit library is ready for use in validation scenarios. For the future, we expect additional tests, improved documentation, inclusion of standard result data types, and a more sophisticated formalisation of experimental data based on metadata. The library is a standard component of HBP's validation framework to enable statistical comparisons of network activity in four areas: to validate models against recordings of activity data from the brain, compare different models, substantiate one model implementation against another (e.g. on a different simulation engine), and contrast dynamics features of different experimental datasets. The library also plays a major role in defining a set of standard data types for results of the analysis of activity data, as initially developed in the HBP Voucher Program and as will be continued in the work program of the upcoming funding phase. This will allow to further formalize the connection between the types of results obtained from a validation test.

3.2.2 Publications

Output 1

- Senk J, Hagen E, van Albada S, Diesmann M (2018a) Reconciliation of weak pairwise spike-train correlations and highly coherent local field potentials across space. ArXiv: 1805.10235. (P1511)

  Significance: The 4x4 mm² layered cortical network model assumes a realistic density of neurons and local synapses and accounts for both spiking activity and local field potentials.

- Senk J, Carde C, Hagen E, Kuhlen T, Diesmann M, Weyers B (2018b) VIOLA - A multi-purpose and web-based visualization tool for neuronal-network simulation output. Frontiers in Neuroinformatics 12:75. (P1548)

  Significance: The study develops concepts for the visual exploration of spatiotemporal activity patterns in simulated spike data and introduces the interactive web-based tool VIOLA (VIsualization Of Layer Activity) as a reference implementation.

Output 3

- Dahmen D, Grün S, Diesmann M, Helias M. (2019) Second type of criticality in the brain uncovers rich multiple-neuron dynamics. PNAS 116 (26) 13051-13060. DOI: 10.1073/pnas.1818972116. (preprint; arxiv:1711:10930). (P1995)
- **Gutzen R, von Papen M, Trensch G, Quaglio P, Grün S, Denker M (2018). Reproducible Neural Network Simulations: Statistical Methods for Model Validation on the Level of Network Activity Data. Frontiers in Neuroinformatics 12, 90. (P1628)**
- Trensch G, Gutzen R, Blundell I, Denker M, Morrison A (2018). Rigorous Neural Network Simulations: A Model Substantiation Methodology for Increasing the Correctness of Simulation Results in the Absence of Experimental Validation Data. Frontiers in Neuroinformatics 12, 81. (P1627)

Significance: Dahmen *et al*. (2019) combines methods from statistical physics with data analysis of massively parallel single-neuron activities to validate a new type of critical and balanced random network models with high computational performance. The companion papers Trensch *et al*. (2018) and Gutzen *et al*. (2018) present concepts, formal frameworks, concreate implementations, and examples that advance our understanding of model validation for network activity models in computational neuroscience.

4. Key Result KR4.6 Parameter space confinement of mesocircuit model for the reproduction of experimental data

KR4.6 is reported under KR4.5 because KR4.6 alone is too specific for a SP4-wide Key Result.

5. Key Result KR4.7 Release of multi-area model of macaque visual cortex, improved using new connectivity and activity data.

5.1 Outputs

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

- Output 1: Multi-area multi-layer spiking cortical models (C730, C944)

5.1.1.2 How Outputs relate to each other and the Key Result

The Output "multi-area multi-layer spiking cortical models" contains as one component the multi-area model of macaque visual cortex which is the Key Result of this work. It has benefitted from developments in NEST for supercomputers, from the corresponding user support, and from the HBP-external CoCoMac database on connectivity data for the macaque brain.

5.1.2 Multi-area multi-layer spiking cortical models

Table 4: Multi-area multi-layer spiking cortical models Links

Component	Link to	URL
C730	Model Repository	https://inm-6.github.io/multi-area-model/
	Technical Documentation	https://inm-6.github.io/multi-area-model/
	User Documentation	https://inm-6.github.io/multi-area-model/
C944	Model Repository	http://www.opensourcebrain.org/projects/potjansdiesmann2014
	Technical Documentation	http://www.opensourcebrain.org/projects/potjansdiesmann2014
	User Documentation	http://www.opensourcebrain.org/projects/potjansdiesmann2014

During the first year of SGA2, JUELICH finished and published the work on a multi-area layered spiking model of all vision-related areas in one hemisphere of macaque cortex (Schmidt *et al*., 2018 (P1457); component C730: Multi-area model of cortical network at neuronal resolution). The model

represents each area by a 1 mm^2 microcircuit with the full density of neurons and synapses, using leaky integrate-and-fire neurons. It reproduces microscopic spiking activity in V1, and fMRI functional connectivity between areas in the resting state, predicated on the system being poised at the edge of stability (Figure 3).

Further, JUELICH with UMAN completed a comparison of the cortical microcircuit model of Potjans and Diesmann (2014) between NEST and SpiNNaker (van Albada *et al.*, 2018 (P1338); component C944: Full-density model of cortical microcircuit). The work demonstrated that SpiNNaker is able to accurately simulate models of this type despite its fixed-point arithmetic, and lays the groundwork for porting even larger models to SpiNNaker. Another JUELICH publication (Maksimov *et al.*, 2018 (P1345) quantitatively and qualitatively characterises excitatory-inhibitory balance, membrane potential and neural input stability, and local excitability of cortical networks, enabling computational neuroscientists to constrain their models accordingly.

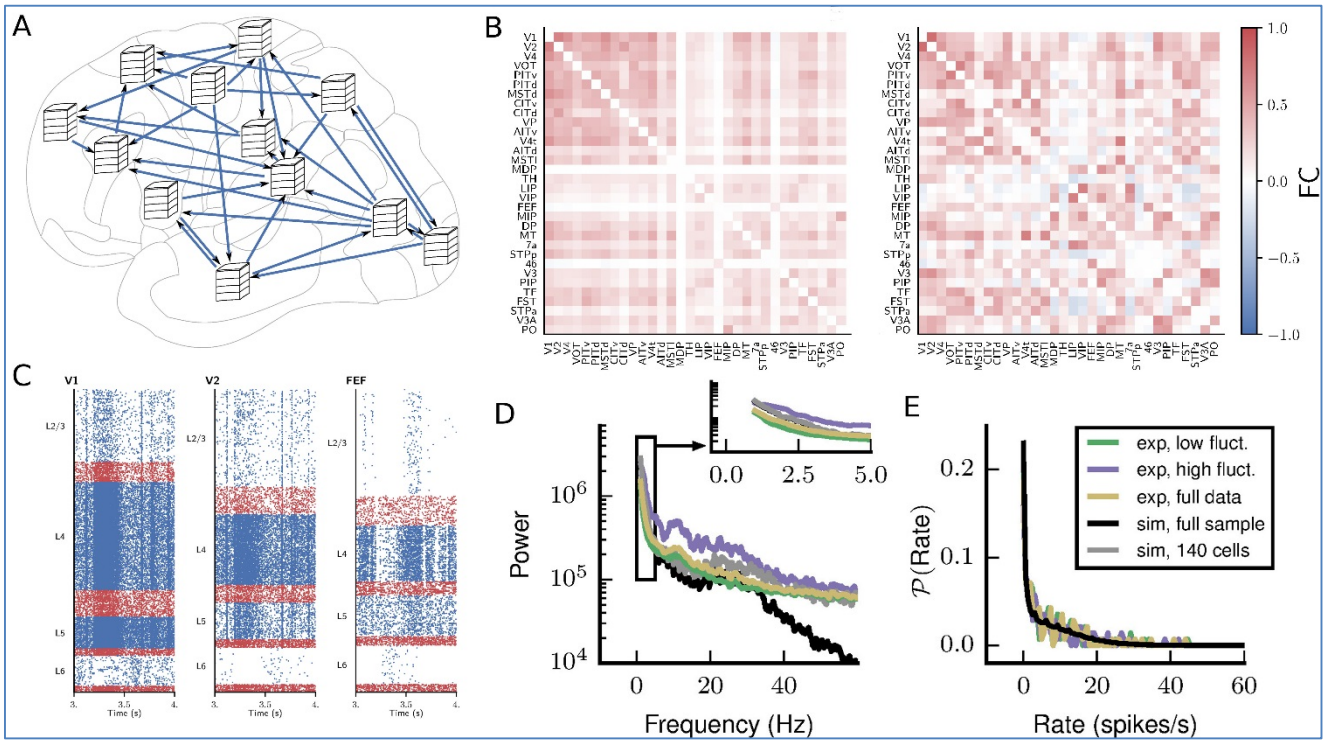

Figure 3: Overview of the multi-area model of macaque vision-related cortex.

A) Schematic illustration of the model, which consists of 32 interlinked layered microcircuits. B) Simulated (left) and resting-state fMRI (right) functional connectivity between areas. C) Example raster plots of spiking activity for three of the 32 areas. Blue, spikes of excitatory neurons; red, spikes of inhibitory neurons. D) Spectra of experimental and simulated V1 spiking activity. E) Distribution of spike rates across single neurons in V1. Green and purple curves, statistics of experimental spiking data in phases with a low resp. high level of fluctuations in the population activity. Yellow curves, statistics for low- and high-fluctuation phases combined. Black curves, statistics for the simulated spiking activity of V1. Gray curves, statistics for 140 neurons randomly sampled from V1 in the model.

In the second year of SGA2, JUELICH has contributed to a publication of the cortical microcircuit model via Open Source Brain (Gleeson *et al.*, 2019 (P2011)).

In further work, JUELICH has started to extend and refine the microcircuit and multi-area models in various directions. In the microcircuit, the role of separate somatostatin (SOM), parvalbumin (PV), and vasoactive intestinal peptide-expressing (VIP) interneuron populations and their specific connectivity and short-term plasticity is being investigated. In the context of CDP4, the multi-area model is being extended with motor-related cortical areas, which will enable visuomotor interactions to be investigated. The cortico-cortical connectivity is taken from axonal tracing data from the CoCoMac database and complemented with predictive connectomics. A motor cortex microcircuit model taking into account its specific architecture and connectivity is under development. Furthermore, JUELICH is incorporating the dual counterstream architecture of feedforward and feedback connections between cortical areas (Markov *et al.*, 2013) in the multi-area model. In collaboration with TUGRAZ, JUELICH has started to bring together anatomical constraints with

functional performance of cortical microcircuits using the learning-to-learn framework (Bellec *et al.*, 2018). JUELICH has also started collaborating with KU Leuven on modeling covert visual spatial attention and relating the model activity to V6/V6A recordings in macaque.

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

The multi-area model of macaque vision-related cortex serves as a platform for further model developments: refinements, extensions with further brain areas, application of the methods to build models of the cortex of other species, and incorporation of functional properties to yield models that can solve behavioural tasks. Current efforts in this direction include modelling of human cortex in Priority Programme "Computational Connectomics" of the German Research Foundation, extension with motor areas in the context of HBP CDP4, and combination of the learning-to-learn framework (MAASS, SP9) with anatomical constraints of the cortical microcircuit. The multi-area model further serves as a key use case for HPC and as a key planned use case for SpiNNaker. The microcircuit model serves as a use case for the BrainScaleS hardware.

An executable formal model description of the multi-area model of all vision-related areas of macaque cortex (Schmidt *et al.*, 2018 (P1457)) was made available on GitHub (https://inm-6.github.io/multi-area-model/), enabling others to build on the code. So far, it is watched by 13 users, starred by 26 users, and forked by 19 users. The total number of users outside JUELICH INM-6 interacting with the repository so far is 34. This includes people both inside and outside the HBP.

A tutorial video was published on YouTube (https://www.youtube.com/watch?v=YsH3BcyZBcU), available also in the HBP Education channel (https://www.youtube.com/watch?v=NGAqe78vmHY) and at https://www.youtube.com/watch?v=g8eOqKzVkcA and has already received >1,200 views. The videos have so far received 44 upvotes and no downvotes.

The publication on the multi-area model (Schmidt *et al.*, 2018 (P1457); Schmidt *et al.* Brain Struct Func 2018; Schmidt *et al.* ArXiv 2015) have been cited 61 times to date. The NEST-SpiNNaker comparison of the microcircuit model (van Albada *et al.*, 2018 (P1338)) has been cited 41 times to date. The publication was already viewed 23,861 times and ranks in the top 2% of papers viewed in the journal.

5.2.2 Publications

There are three key publications corresponding to this Output:

- Schmidt M, Bakker R, Shen K, Bezgin G, Diesmann M, van Albada SJ. A multi-scale layer-resolved spiking network model of resting-state dynamics in macaque visual cortical areas (2018) *PLOS CB* 14:e1006359. (P1457)

  Significance: The first spiking neural network model that incorporates a large number of areas with the full density of neurons and synapses and simultaneously accounts for microscopic and macroscopic features of resting-state activity in primate cortex.

- van Albada SJ, Rowley AG, Senk J, Hopkins M, Schmidt M, Stokes AB, Lester DR, Diesmann M, Furber SB (2018). Performance comparison of the digital neuromorphic hardware SpiNNaker and the neural network simulation software NEST for a full-scale cortical microcircuit model. Front Neurosci, 12, 291. (P1338)

  Significance: Shows that SpiNNaker can accurately simulate a full-scale cortical microcircuit, opening the road toward simulations of even much larger circuits in real time.

- Gleeson, P., …., van Albada, S.J. ... & Silver, R.A. (2019). Open Source Brain: a collaborative resource for visualizing, analyzing, simulating, and developing standardized models of neurons and circuits. Neuron, 103(3), 395-411. (P2011)

Significance: Provides a new resource for standardized models of neurons and neural circuits, supporting reuse and reproducibility in computational neuroscience.

6. Key Result KR4.8 Release of draft implementation of generic network model with glial contribution

6.1 Outputs

6.1.1 Overview of Outputs

6.1.1.1 List of Outputs contributing to this KR

- Output 1: Neuronal-glial network model (C2359)
- Output 2: Order reduction for network models (C2358)

6.1.1.2 How Outputs relate to each other and the Key Result

Output 1 and 2 are independent outputs. In Output 2, we used a generic neuronal network model (without the glial component which was developed during SGA2) to develop model order reduction methodology. The developed methods in Output 2 can be applied in the future for the model developed Output 1.

6.1.2 Neuronal-glial network model

Table 5: Neuronal-glial network model Links

Component	Link to	URL
C2359	Model Repository	https://collab.humanbrainproject.eu/#/collab/19/nav/369318?state=model.11dfe94d-b46a-4bb2-8700-020680754e53
	Technical Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/369318?state=model.11dfe94d-b46a-4bb2-8700-020680754e53
	User Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/369318?state=model.11dfe94d-b46a-4bb2-8700-020680754e53

During the first year of SGA2, TTY-Saatio developed the first draft version of the generic network model with astroglial influence. The work was presented in the Organization for Computational Neuroscience meeting (Acimovic *et al*. 2019 (P2390); C2359). The neuronal component of the model is described according to a well-established theoretical formalism, the leaky integrate-and-fire with adaptation neuron model. The astroglial component of the model is based on a well-known Li-Rinzel type of calcium model and a prominent astroglial mechanism, the so-called slow-inward current (SIC), described using several mathematical equations. The astroglial component is selected based on the work done during the first year of SGA2 (Manninen *et al*. 2018 (P1491), Manninen *et al*. 2019 (P793)). Neuron-to-neuron interactions within a network are modelled to represent cortical inhibitory-excitatory circuits. The astrocyte-neuron interactions are constrained using unpublished data on astrocyte locations and morphologies, kindly provided by HBP SP1 (DeFelipe group). The model explains how the astrocyte component, operating on a slower time-scale compared to the neuronal component, supports and modulates activity regimes spontaneously arising in cortical networks *in vitro* (Figure 4). The model is validated against experimental data (presented in Teppola *et al*. 2019 (P2068); available in:

https://github.com/HTeppola/Front_Cell_Neurosci_Network_Burst_Analysis) using optimisation algorithms stemming from the development work within the HBP (SP6). In a summary, we developed a novel neuronal-glia network model and used tools developed in the HBP.

During the second year of SGA2, as a joint work between TTY-Saatio and JUELICH we implemented a novel astroglial component as an integral part of NEST simulator (the component is currently open source, public, with an example of usage available, and will be included in a NEST release. This work provides a contribution to infrastructure development in the HBP. The NEST-implementation of the above-described neuron-glia network model was compared against our first-year initial simulations of the model with Matlab simulator. The work demonstrated that using the astroglial component we are able to simulate the spontaneous network activity more accurately compared to spiking network implementation with neuronal elements only. In summary, we have developed a novel theory model for neuron-glia networks, implemented it in NEST, contributed to infrastructure development by providing a new glia-component to NEST, used data from HBP SP1 to develop the model and from our own studies to validate the model, and used computational tools from HBP SP6.

In addition to model and infrastructure development, we tested the suitability of mathematical model order reduction techniques (MOR; Lehtimäki *et al*. 2019 (P2392), 2020 (P2389); C2358; available in: https://github.com/Mikkolehtimaki/neuro-mor) for simplification of network components and analysis of network dynamics. With MOR techniques we achieved substantial reduction in simulation times. We conclude that such techniques may be useful in future development of simulators and will help in the development of large-scale brain area specific neuron-glia network models. We used the MOR methods developed in section 6.1.3 for analysis of network model.

We have started expanding the work on modelling neuron-glia interactions in clinical directions, including modelling human network dynamics in neurodevelopmental diseases (Mäki-Marttunen *et al*. 2019 (P2005)). This work is done in collaboration with scientists from the HBP and external ones.

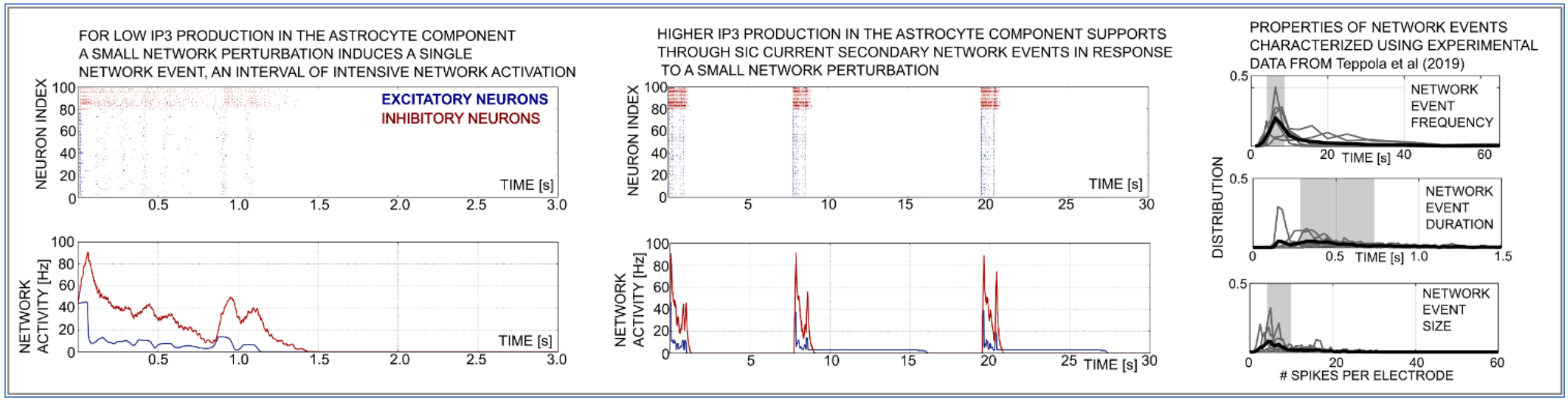

Figure 4: Simulation of astrocyte component together with spiking network model.

The activity of astrocyte component controls the intensity of neuron-astrocyte interaction via slow SIC current and the overall activity of cortical spiking network. Left column: Spiking network activity in the presence of weakly active astrocyte. Middle column: Higher activity in astrocytes induce additional network events. Right column: Summary of the experimental data (Teppola *et al*., 2019 (P2068)) used to construct and validate computational model.

6.1.3 Order reduction for network models

Table 6: Order reduction for network models Links

Component	Link to	URL
C2358	Model Repository	https://github.com/Mikkolehtimaki/neuro-mor https://collab.humanbrainproject.eu/#/collab/19/nav/369318?state=model.75585067-9465-404c-8afe-89827549360e
	Technical Documentation	https://github.com/Mikkolehtimaki/neuro-mor
	User Documentation	https://github.com/Mikkolehtimaki/neuro-mor

The current trend in theoretical and computational neuroscience is to incorporate multiple physical levels of the brain into mathematical models, which often results in large networks of interconnected neurons and other brain cells, i.e. in high-dimensional dynamical systems that correspond to equally high computational demand. Mathematical Model Order Reduction (MOR) methods, adapted from control and systems theory, have not been extensively utilised in the field. We performed benchmarking of five different variants of Proper Orthogonal Decomposition (POD) and Discrete Empirical Interpolation Method (DEIM) methods. As a test case, we used a network of 50 compartmental Hodgkin-Huxley cells, based on a neuron model with dendritic and somatic compartment (Pinsky and Rinzel, 1994), resulting in a system of 500 coupled nonlinear ordinary differential equations. We showed that the reduced order model consumes a smaller amount of computational resources than the original model (Figure 5) (Lehtimäki *et al*. 2019 (P2392); C2358; https://github.com/Mikkolehtimaki/neuro-mor). The population behaviour of the reduced model starts to change with lower dimensions. We conclude that the work shows the potential benefits of the POD+DEIM method, while also giving insight into the limitations of the method and future development directions of the method.

We have started applying MOR methods to computational neuroscience model classes that have a potential to describe system level and cognitive phenomena in the brain. These model classes include so called mean field models for large populations of neurons. This work is done to prepare for the SGA3 phase. We compared state-of-the-art methods for improving the simulation time of a neuronal mean-field model and showed that a nonlinear Fokker-Planck-McKean-Vlasov model, discretised from a multi-dimensional nonlinear partial differential equation, can be accurately approximated in low-dimensional subspaces with MOR methods (Lehtimäki *et al*. 2020 (P2389)). Particularly, using POD and different variations of the DEIM methods, we were able to improve the simulation time by over three orders of magnitude while achieving low approximation error.

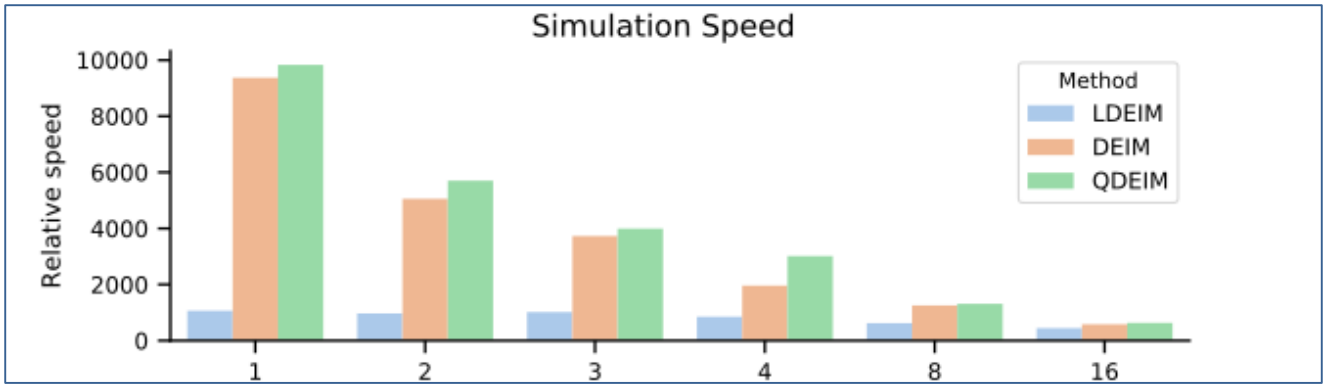

Figure 5: Simulation speed gained with nonlinear Fokker-Planck-McKean-Vlasov model

See Lehtimäki et al. 2020 (P2389)

6.2 Validation and Impact

6.2.1 Actual and Potential Use of Output(s)

The full neuron-glia network model will form a theoretical basis for development of neuron-glia interaction models for in vitro systems. It is expected to guide future development of astroglial modelling for in vivo systems as well. The astroglial component of the full model served as a use case for HBP infrastructure development, the NEST simulator and possibly also for SpiNNaker. None of these platforms/tools currently has the capacity to present the influence from glial cells. The publication on which the astroglial component is based on (Manninen *et al*. 2018 (P1491)) is viewed 3,342 times and cited 10 times. The data used to validate the neuron-glia network model (Teppola *et al*. 2019 (P2068)) is viewed 1,644 times and is publicly available (https://github.com/HTeppola/Front_Cell_Neurosci_Network_Burst_Analysis). The implementation and benchmarking of MOR methods (Lehtimäki *et al*. 2019, 2020 (P2392, P2389)) to simplify network models was made available on GitHub (https://github.com/Mikkolehtimaki/neuro-mor), enabling others to apply the methods for other application areas. The work also won two best poster prizes in international conferences: 1) Best poster award in CNS*2019 conference (Recipients: Ippa Seppälä & Mikko Lehtimäki, July 17, 2019, 2) Best poster prize in 3rd HBP Student Conference on Interdisciplinary Brain Research (Recipient: Mikko Lehtimäki).

Both Output 1 and 2 have been extensively disseminated in various events including scientific (Output 1) and technical (Output 2) conferences and workshops. Based on interest, the bioscience community outside the HBP seems very keen on applying our models. As an example, the neuron-glia network models, MOR methods and NEST implementations are being exploited in a clinically-oriented EU ERA-NET NEURON SYNSCHIZ-project for modelling the mechanisms of human brain networks in neurodevelopmental disorders since the beginning of 2020. Overall, we expect large exploitation of both Outputs, since the field of modelling glial cells is in its developmental phase.

6.2.2 Publications

Output 1:

- Manninen T., Aćimović J., Havela R., Teppola H., Linne M.-L. Challenges in reproducibility, replicability, and comparability of computational models and tools for neuronal and glial networks, cells, and subcellular structures. Frontiers in Neuroinformatics 12: 20, 2018. (P1491)

  Significance: Neural simulators do not conventionally contain glial modules. Based on this initial work a new module to describe glial components for neuronal-glial networks in NEST was developed and implemented.

Output 2:

- Lehtimäki M., Paunonen L., Linne M.-L. Projection-based order reduction of a nonlinear biophysical neuronal network model. In Proceedings of the 58th IEEE Conference on Decision and Control, Nice, France, December 11–13, 2019. (P2392)

  Significance: Mathematical model order reduction methods developed in this work can be employed to accelerate the simulation and analysis of high-dimensional nonlinear models such as models of neuronal networks. Model order reduction methods require no simplifications of the modeled system and allow every variable to be reconstructed at any time.

7. Key Result KR4.9 Release of draft multi-layered cortical network model with spatially organised connectivity

7.1 Outputs

7.1.1 Overview of Outputs

7.1.1.1 List of Outputs contributing to this KR

- Output 1: Mesocircuit model (C2418)

7.1.1.2 How Outputs relate to each other and the Key Result

NA

7.1.2 Mesocircuit model

Table 7: Mesocircuit model Links

Component	Link to	URL
C2418	Model Repository	https://wiki.ebrains.eu/bin/view/Collabs/mesocircuit/
	Technical Documentation	https://arxiv.org/abs/1805.10235
	User Documentation	https://arxiv.org/abs/1805.10235

We released the implementation of the mesocircuit model corresponding to Senk *et al*. (2018a) (P1511) internally in the HBP Collaboratory. The model accounts for spiking activity and local field potentials. A theoretical manuscript has been published together with the corresponding code (P2095 – *in validation process*).

7.2 Validation and Impact

7.2.1 Actual and Potential Use of Output(s)

The mesocircuit model can be validated against experimental data (T4.5.1) as it covers the same surface area as the 4x4 mm² Utah array and accounts for spiking activity and local field potentials.

We expect that the model will be used by a larger number of researchers as a building block for more complex models and a testbed for mean-field and field-theoretical approaches.

The microcircuit has meanwhile been used in 17 peer-reviewed publications and the respective article is cited by 71 peer-reviewed publications. We hope for a similar success for the mesocircuit model. For the publication of the executable model description we will use the latest technology as developed in T4.2.3 for the multi-area model.

The mesocircuit model is a component on the long-term roadmap of constructing multi-area models with spatial resolution in the individual areas.

7.2.2 Publications

- **Senk J, Korvasová K, Schuecker J, Hagen E, Tetzlaff T, Diesmann M, Helias M (2020) Conditions for wave trains in spiking neural networks. Phys. Rev. Research 2, 023174. (P2095 – *in validation process*)**

  Significance: The study unifies mathematical models that describe brain tissue as a continuous excitable medium with neuronal network models composed of a large number of impulse-coupled nerve cells, and demonstrates that both models can explain wave-like activity patterns by the same underlying mechanism.

- Senk J, Hagen E, van Albada S, Diesmann M (2018a) Reconciliation of weak pairwise spike-train correlations and highly coherent local field potentials across space. ArXiv: 1805.10235. (P1511)

  Significance: The 4x4 mm² layered cortical network model assumes a realistic density of neurons and local synapses and accounts for both spiking activity and local field potentials.

8. Conclusion and Outlook

T4.2.1: We published a preprint that formally describes the construction of the mesocircuit model and shows activity results (Senk *et al*. 2018a (P1511)). A neuroscientific insight is that the model reconciles the weak pairwise spike-train correlations with the highly coherent field potentials across space. The executable model description has been internally released. In addition, a manuscript about the theoretical basis of spatiotemporal activity patterns has been accepted for publication by Physical Review Research (P2095). Furthermore, we reviewed the state-of-the art of visualisation approaches and developed the tool VIOLA to visually analyse multi-dimensional dynamic data in layered networks. This study was conducted in collaboration with SP7 and a manuscript has been published in Frontiers of Neuroinformatics (Senk *et al*. 2018b (P1548)). The mesocircuit model is an essential milestone on the long-term roadmap towards a multi-area model with spatial resolution in the individual areas.

T4.2.2: We developed a new neuron-glia network model and implemented it in the HBP infrastructure, NEST simulator. Through this work we provide a systematic analysis how to extend theoretical neuroscience models to incorporate the selected mechanisms of neuron-glia interaction. The implementation of astroglial component in NEST additionally provides an important step towards developing theoretical large-scale models in order to address astroglial influences in activity regulation, information transfer, synchronization and learning in brain networks, both in vitro and in vivo. Additionally, we were able to improve the simulation time by over three orders of magnitude while achieving low approximation error when benchmarking different variants of Proper Orthogonal Decomposition (POD) and Discrete Empirical Interpolation Method (DEIM) methods for typical cns models describing populations of neurons. The work on model order reduction/simplification has potential to impact the simulator tool development in the future and forms a basis for developing mean field models of astroglial networks during SGA3.

T4.2.3: Several outcomes with a wide impact were achieved during this period. The work plan was unchanged, but instead of the planned refinement of the vision-related multi-area model, the focus has been on extending the model with motor areas, which fits better with CDP4 (visuomotor integration) and the planned SGA3 Task T3.2 on visuomotor architectures. Furthermore, in view of direct comparability of the multi-area model with macaque rather than human data, the planned collaboration with WP4.2 was focused on electrophysiological data (VANDUFFEL) rather than fMRI. The NEST-SpiNNaker comparison study has met a strong interest both scientifically and in the media. One lesson learned in this context is that press releases need to be worded very carefully to avoid sometimes overly optimistic media reporting. The study will serve as the basis for also porting the multi-area model to SpiNNaker in SGA3, and thereby enabling ever larger-scale simulations on SpiNNaker. In this work, we learned more effective communication between computational neuroscientists and neuromorphic system developers. The multi-area model has become an important benchmarking application for NEST on high-performance computing systems. To maximize

impact, the multi-area model will be brought to the Brain Simulation Platform to enable users to easily run it on the available supercomputers.

T4.5.1 provided a novel, comprehensive, formalised, and practically usable framework to perform validation testing for spiking network models of the brain, including technical implementation and conceptual work substantiated by a rich use case. The results are available as a software library and two publications. The conceptual work led to the initial development of an intricate pipeline to tackle and combine multiple science cases in the context of SP3. These pipelines are implemented in a generic, configurable, and modular manner using a workflow manager, such they can be re-used and adapted easily for other projects inside and outside the HBP. The successful use of these validation concepts demands their further development. As planned for SGA3, this involves the extension of the library to include more complex types of statistical comparisons, including also spatio-temporal aspects of the dynamics. On the conceptual side, a further formalisation of the validation process is necessary to consider the specifics of experimental data based on its metadata, and to semantically match analysis methods, validations tests and test scores based on the underlying analysis data type. The continued efforts to integrate validation testing on the level of activity data into the Validation Framework of the HBP aims to automatise as much as possible the process of testing models against readily available data, and in the long run improves the level of confidence of conclusions drawn from network models of the brain.