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TECHNISCHE UNIVERSITÄT MÜNCHEN
INSTITUT FÜR INFORMATIK

Closed-Loop Neuroscience - A Vision

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TUM-I2088

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September 2020

Within only a few decades, computer technology has evolved from an emerging science to a key driving factor in virtually all areas of research and engineering. The digitization and virtualization of procedures, methods and systems enables efficiency gains beyond the limitations of the physical world. So far, neuroscience has been largely excluded from this development due to a lack of appropriate tools and techniques. Today, neurorobotics opens up a new perspective for the virtualization of neuroscience. The following report draws from this potential to outline the path towards *closed-loop neuroscience*, a fully virtualized workflow for the augmentation and acceleration of brain research.

1 Simulation Neuroscience

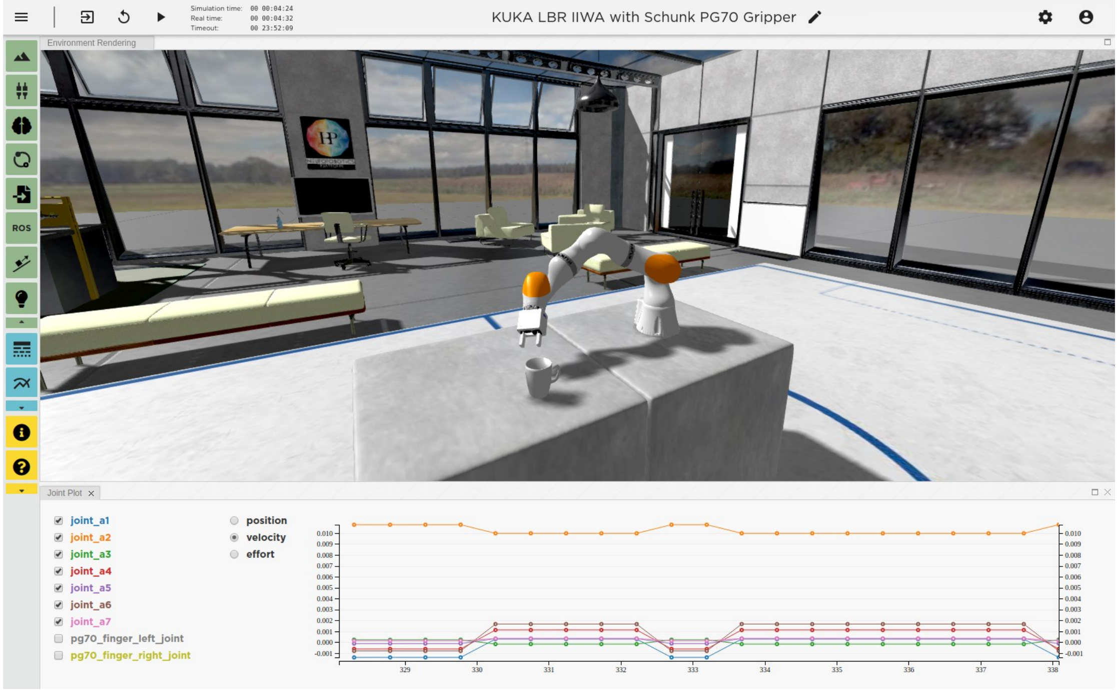
Progress in science has always been closely linked to innovations in technology. This is especially true for neuroscience, where the study of neural tissue would not have been possible at all without the development of appropriate imaging and measurement techniques. While the brain determines everything we perceive, everything we think and everything we do in every moment of our lives, its intricate structure with billions of interconnected cells does not reveal any direct insight into its inner workings. Since the first systematic study of single neurons with microscopy and tissue staining at the end of the 19th century [1], the tool set for brain research has expanded into a rich arsenal of methods ranging from single neuron recordings to state-of-the-art magnetic resonance imaging. Whereas early neuroscience was held back by a lack of measurement devices, today the abundance of neuroscientific data has become one of the main challenges in brain research. Every data set is not only highly specific to the technology by which it was acquired but also to the underlying experimental protocol. This means that even though massive amounts of data have been accumulated throughout the past decades, our knowledge about the brain has not grown at the same pace.

Both the cost and the effort involved in data acquisition [2] make the collection of even more data sets until the complete brain is covered – a highly ill-defined target – not appear a viable strategy for future neuroscience. From this perspective, the synergistic integration of existing data into a coherent view to make knowledge available while at the same time identifying gaps has become a new frontier of research in neuroscience. The creation of *brain atlases* that enable this data integration is one of the main objectives of the European Human Brain Project (HBP) [3]. These atlases serve as reference models for the semantic spatial localization of neuroscientific data in the brain. In addition to the data curation expertise and the neuroinformatics tools required for this service, the HBP also provides the underlying compute infrastructure. Brain atlases make data sets better accessible and more transparent, but, of course, they cannot improve data quality and coverage. Since filling gaps through the extensive acquisition of additional data sets is no viable option, the HBP has adopted the paradigm of *simulation neuroscience* [4]. Rather than trying to reach full data coverage, this method combines data-driven statistical modeling with algorithmic approaches to generate digital reconstructions of neural tissue [5]. The resulting models can than be simulated to retrieve virtual data sets that can then be compared to the experimental ground truth. These *large-scale brain simulations* enable a new methodology for closing gaps in the data *in silico*. At the same time, the they serve as computer-executable descriptions of the brain that not only conserve knowledge but also enable predictions beyond existing experiments.

Simulation neuroscience enables completely new forms of experiments that would be impossible in the physical world: electrodes can be placed at arbitrary locations in arbitrary numbers, lesions can be studied with high precision at any spatial extent, neural parameters can be changed as desired etc. The underlying models are refined and extended as new ground truth data becomes available to make predictions more accurate and the simulation an even more powerful tool. What has so far been missing, however, is a realistic way for generating and interpreting input and output stimuli of the simulated brain. In living creatures, these signals are mediated by body that interfaces the brain with its environment through sensors and actuators. So far, this aspect has been almost completely neglected in large-scale brain simulations and computational neuroscience in general. As a result, while the neural activity simulated in response to an input might be realistic, the input signal itself is typically not.

2 Virtual Embodiment through Neurorobotics

Embedding a simulated brain in a body is essential to study neural activity under biologically accurate conditions. Only then it is possible to establish a *closed loop* of *perception – cognition – action* like in a living creature where the output of the brain affects its sensory input and vice versa. The important role of the body in cognitive processing has come to be widely recognized today and is typically summarized with the term *embodiment* [6]. Technically, endowing a brain with a body means connecting it to a robot with sensors and actuators, which has lead to the emergence of *neurorobotics* as an independent field of research at the intersection of robotics, neuroscience and artificial intelligence. In the past decades, research in this direction has progressed only slowly due to the high effort involved in setting up neurorobotics experiments. The preparation of the robot alone already requires not only the development and maintenance of expensive hardware but also the programming of drivers, software interfaces and libraries. Additional effort goes into the connection to the brain simulation and the actual conduction of the experiment.



Simulation time: 00 00:04:24
Real time: 00 00:04:32
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KUKA LBR IIWA with Schunk PG70 Gripper

☑ joint_a1
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☐ pg70_finger_left_joint
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○ position
● velocity
○ effort

Figure 1: Web frontend of the HBP Neurorobotics Platform (NRP). The screenshot depicts the platform's experiment designer, an interactive development environment for designing, running and visualizing neurorobotics simulations directly from the web browser.

Increasingly affordable compute power and storage and innovations in computing technology such as cloud platforms have opened up a completely new perspective for neurorobotics. The *Neurorobotics Platform* (NRP) developed in the HBP draws from these advances to provide a cloud-based simulation environment for virtual neurorobotics that covers the complete workflow from robot and environment design to the interfacing with a brain simulation and the final execution of the fully virtualized experiment [7, 8]. The system is accessible without any installation through a standard web browser. This implies that the actual simulation can run in a high performance computing center while users interact with it from their local devices. Figure 1 depicts a screenshot of the system's user interface. A key feature of the NRP is its support for rendering highly realistic visualizations of the simulated world. Besides allowing for more intuitive user interaction, the simulation of the robot and its environment at high fidelity is essential for making vision and other sensory input modalities as realistic as possible.

In addition to offering practical advantages such as lower costs and simple setup, virtual neurorobotics experiments most importantly provide the most advanced tool set for research on embodied systems available:

- Experimental results become easily reproducible since full descriptions of setups and protocols can be directly shared online through the NRP.
- The speed of virtual experiments can be adjusted as desired, which enables the study of complex brain models that cannot be simulated in real time.

- Unlike setups with physical robots, virtual neurorobotics experiments are capable of fully replicating the dynamics of the biological tissue such as muscles without any physical constraints imposed by materials, sensors or motors.
- Virtual experiments can be launched at arbitrary numbers without any limitations except for those imposed by the amount of compute power and storage available.

The last point is of particular importance and bears disruptive potential for neuroscience. By launching a multitude of experiments with varying parameters, hypotheses can be checked in a fraction of the time required for preparing and conducting physical experiments. This makes neurorobotics and its realization through the NRP a key factor for fulfilling the full potential of simulation neuroscience.

3 Towards Closed-Loop Neuroscience

With the NRP, it is for the first time possible to create virtual neuroscientific experiments that capture all relevant biological systems and processes at a high level of detail – from the individual neurons in the brain to the morphology of the body in which it is embedded. Data gathered in these experiment can therefore be directly compared to those from physical experiments without any extrapolation or intermediate approximation. It cannot be stressed enough that this a huge qualitative and quantitative step beyond simulation neuroscience, which is only concerned with the modeling and simulation of neural circuitry without principled consideration of the cognitive relevance of the activity patterns that arise from it. The latter is only possible when the brain simulation is put into the closed perception – cognition – action loop of a neurorobotic system. We will consequently refer to the new paradigm outlined in this report as *closed-loop neuroscience*[1].

The essence of the closed-loop neuroscience paradigm is captured in Figure 2 at the example of an experiment on motor control after stroke that was fully virtualized in the NRP. It is based on an actuated platform for forelimb retraction tasks with mice, the NRP model of which is shown in the upper middle inset [11]. Details on experimental procedures and results have been published by Allegra Mascaro et al. [12]. As can be seen in the figure, the simulation of the mouse body is based on a highly detailed musculoskeletal model that is connected to the brain simulation. The virtualized *in silico* experiment implements the same experimental protocol as its physical counterpart. This makes it possible to assess the quality of the simulation by the fidelity at which it reproduces data from the physical experiment. Differences between the data directly inform the refinement of models and the adjustment of parameters. Unknown and not observable variables can thereby be algorithmically reconstructed. Notably, this is exactly in line with the methodology in simulation neuroscience. The refined virtual experiment will not only comply better to the physical ground truth but also yield more confident predictions for future studies. As soon as real-world data becomes available, models can be further adjusted. In fact, closed-loop neuroscience therefore actually closes two loops at the same time:

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[1] *Closed-loop neuroscience* has already been mentioned earlier in the context of traditional experimental neuroscience [9, 10]. In this report, we use the term to exclusively denote virtual brain research based on neurorobotics and simulation neuroscience.

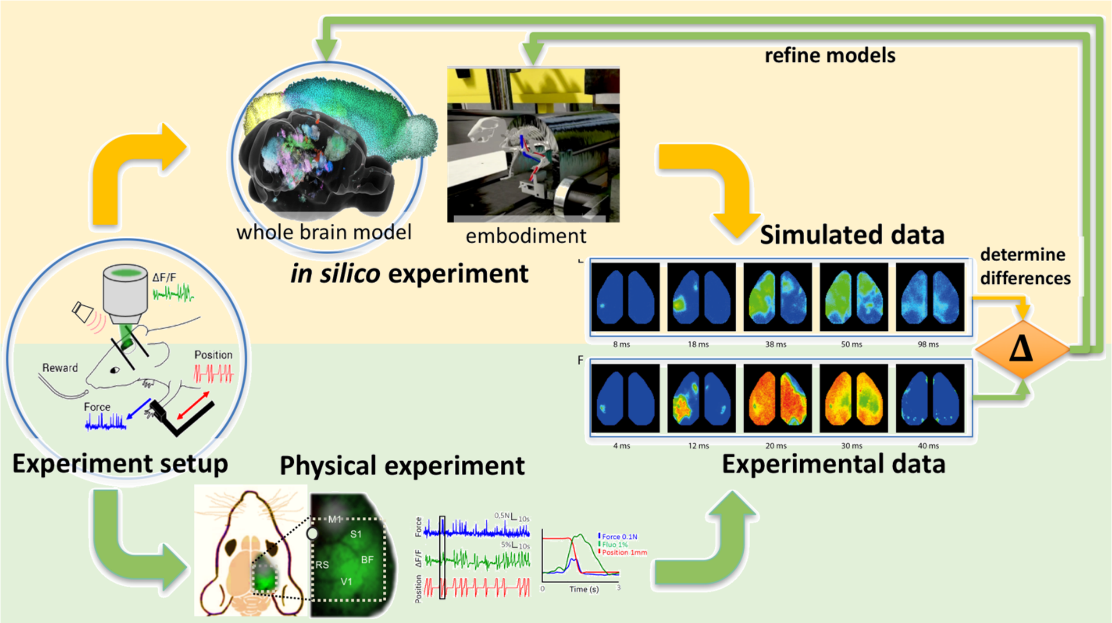

Figure 2: Iterative refinement of embodied brain models with neurorobotics in closed-loop neuroscience. An experiment is conducted both physically and *in silico* as a simulation on the NRP. The resulting data are compared with the physical ground truth to further refine the simulation and make more accurate predictions for experiments that have not been executed physically yet. Figure prepared by Marc-Oliver Gewaltig with image content from HBP and NRP collaborators.

- The *perception – cognition – action loop* between brain, body and environment
- The *iterative prediction and model refinement loop* between the virtual experiment and the physical experiment

Even though this concept of closed-loop neuroscience will be disruptive for brain research, it still integrates with existing methodology. Rather than replacing proven approaches, it augments them by making them amenable to digitization and the productivity gains enabled by computer technology.

4 An Interactive Dynamic Brain Atlas

Closed-loop neuroscience will have a lasting effect on how neuroscientific data is collected and processed. At first glance, the opportunity of extensive in silico experiments on the NRP is likely to result in even larger masses of data that need to be curated. However, since these data sets can be reproduced at any time, it is sufficient to only store a compact definition of the underlying experiment rather than the full data set. The quality of simulated data from closed-loop experiments is therefore fundamentally different from traditional neuroscientific data sets. This has substantial implications for brain atlases.

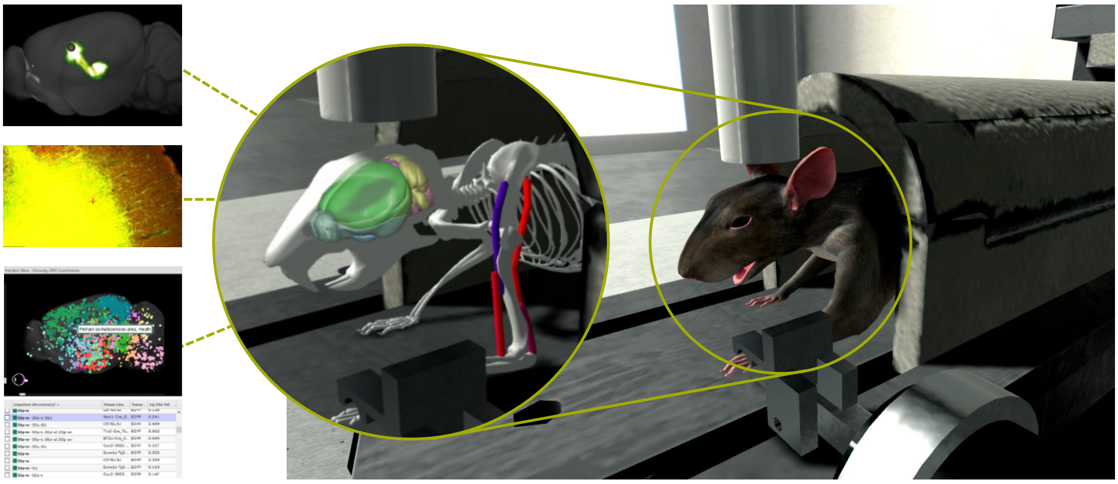

Figure 3: Conceptual draft of an interactive brain atlas embedded in the NRP. Data is directly anchored to corresponding brain regions with live-visualization during an experiment as the simulated brain interacts with the environment through its body. The 3D visualization of the mouse brain has been generated with *Brain Explorer 2* [13, 14] by the Allen Institute for Brain Science, the raw data samples on the left are taken from the *Allen Mouse Brain Connectivity Atlas*, Experiment 303617548 [15].

Even the state-of-the-art brain atlases developed in the HBP are only capable of registering static measurements at corresponding locations in the reference brain map. Virtual closed-loop experiments on the NRP, by contrast, enable full inspection of the state of the brain with measurements only being a metaphor for filtering relevant data. During an experiment, the data view can switch to any desired level of detail as long as it is covered by the underlying model. Activity patterns can be directly observed in the context of the underlying sensory input and motor output. It is even possible to actively modulate activity through direct stimulation of neurons or interaction in the simulated environment. These advanced modes of unlimited direct access to running experiments will enable a completely new type of *interactive dynamic brain atlases*.

Figure 3 sketches a concept for this new form of brain atlas. The starting point for accessing brain data is no longer a static data set but a running closed-loop experiment in the NRP. As indicated by the inset, users can directly look inside the brain and the body to access live visualizations of neural activity and the states of muscles and sensory organs. Measurements can be displayed in familiar formats e.g. by providing *virtual magnetic resoncance imaging (vMRI)* in the NRP. Experiments can be slowed down, accelerated and stopped as desired to study brain activity and the resulting behavior at the same time. As indicated in the left inset of the figure, static information from existing data sets is still accessible in parallel like in a traditional brain atlas. With the addition of behavior and interactivity, brain mapping in a sense evolves from 3D brain atlases that only contain spatially ordered static information to *4D brain atlases*.

5 Conclusion and Research Agenda

In this report, we have introduced *closed-loop neuroscience*, a new paradigm for in silico brain research. Differently from previous definitions coming from traditional experimental neuroscience, this paradigm is based on fully virtualized experiments where a biologically accurate brain simulation is connected to a comprehensive body simulation in a closed loop of perception – cognition – action. The key tool for the realization of this new type of experiment is the Neurorobotics Platform developed in the European Human Brain Project. Data generated with the NRP can be directly compared with ground truth results from physical experiments for iterative model refinement. Well-calibrated in silico experiments can generate predictions for new experimental protocols and enable full inspection of the system without any of the constraints imposed on measurements in physical setups. The description of brain activity is no longer confined to static data sets that are organized in brain atlases. In the future, in silico data could be displayed live, for example through virtual MRI directly in the NRP through an *interactive dynamic brain atlas.*

The first major steps towards this vision have already been successfully completed: The NRP has reached a high level of maturity and is freely available to the public. It incorporates a rich set of virtual body models and environments, including the full experimental setup described by Allegra Mascaro et al. [12]. With the successful implementation of this experiment, a first proof-of-concept of the proposed methodology is readily available. What is next is the addition of other relevant experimental setups, brain models and body models. It cannot be stressed enough that this process needs to be driven by the neuroscience community. Only then it can be ensured that the development of both the NRP and the experiments that it supports will deliver the features and performance required for widespread acceptance. With more and more contributions becoming available, the quality of in silico data generated in the NRP will improve at high rate and an increasing number of experiments can be conducted completely in silico, paving the way for fully *virtualized brain research* [16].

Acknowledgements
Part of this research has received funding from the European Union' s Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2) and No. 945539 (Human Brain Project SGA3).

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