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2. TVBase: Utilizing Computational Semantics to Map Biomedical Knowledge onto the Brain

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INTRODUCTION/MOTIVATION

Biomedical knowledge about the brain is increasing daily, alongside a rapidly growing number of scientific publications. While a holistic understanding of this plethora of information by mere reading becomes impossible, recent developments in information science and computational linguistics aim to make this knowledge programmatically accessible by adding a semantic understanding of publications via literature mining and entity recognition algorithms. However, these linguistic methods have not been sufficiently integrated into current brain imaging data standards, hindering researchers from harnessing the full potential of computational semantics in neuroscience.

METHODS

Therefore, we developed the text-mining-based semantic meta-analysis platform The Virtual Brain Adapter of Semantics (TVBase) that projects biomedical knowledge preserved in over 36 million scientific articles onto a 3D standard brain in MNI space. The literature-mining platform SCAIView [1] was used to extract ontologically defined biomedical entities, and their associations with brain anatomy, from abstracts and full texts of the PubMed database. By querying each concept, its association strength with each anatomical term, defined in the Uberon-ontology [2], was calculated using information entropy measures. To project the data onto a standard brain, we created a unique transformation matrix that links over 800 unique anatomical terms to the voxel coordinates of a parcellated brain. Our new methodology creates semantic brain maps that depict which areas of the brain a particular biomedical concept is associated with in the scientific literature and quantifies the relevance of this association by measures of information entropy.

In this study, a first external validation of semantic TVBase maps show their concordance with empirical brain maps derived from the neuromaps database [3]. Maps created from various imaging modalities were investigated, from magnetoencephalography (MEG) data to positron emission tomography imaging of tracers for neurotransmitter receptors. Statistical robustness was quantified using spatially and functionally constrained permutation testing.

RESULTS AND DISCUSSION

Using the proposed methodology, we mapped over 100,000 biomedical concepts unambiguously defined in state-of-the-art ontologies and nomenclatures from the Medical Subject Headings (MeSH) [4], Gene Ontology (GO) [5] and the Hugo Gene Nomenclature (HGNC) [6]. Validation with conceptually equivalent empirical maps shows substantial overlap with semantically extracted brain regions, mainly for MEG power distributions and dopamine, glutamate, and serotonin receptor maps, as well as for maps of cerebral blood flow and glucose metabolism. This unlocks the potential for using TVBase as proxy for empirical data and further for the integration of biological knowledge into brain network models by introducing mechanistically plausible spatial heterogeneity.

In summary, TVBase extracts region-specific information about biomedical concepts from the literature to support translational multi-scale approaches to computational neuroscience. It allows for hypothesis-free neuroimaging pattern interpretation, hypothesis generation, and applications in personalised medicine. TVBase is available as a python package or as an application programming interface (API) connected to a centralized database.

Keywords: Literature research, biomedical knowledge, computational semantics, meta-research, brain mapping, software framework, python, The Virtual Brain

ACKNOWLEDGEMENTS

Computation of underlying data has been performed on the HPC for Research cluster of the Berlin Institute of Health. PR acknowledges support by EU H2020 Virtual Brain Cloud 826421, Human Brain Project SGA2 785907; Human Brain Project SGA3 945539, ERC Consolidator 683049; German Research Foundation SFB 1436 (project ID 425899996); SFB 1315 (project ID 327654276); SFB 936 (project ID 178316478; SFB-TRR 295 (project ID 424778381); SPP Computational Connectomics RI 2073/6-1, RI 2073/10-2, RI 2073/9-1; PHRASE Horizon EIC grant 101058240; Berlin Institute of Health & Foundation Charité, Johanna Quandt Excellence Initiative; ERAPerMed Pattern-Cog.

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34. The Virtual Brain Ontology – Towards a Semantic Web for Brain Simulation

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INTRODUCTION/MOTIVATION

In the field of computational neuroscience, brain simulations with the neuroinformatics platform The Virtual Brain (TVB; www.thevirtualbrain.org) have proven to be a powerful tool both for deepening our understanding of neuronal mechanisms [1], as well as improving our capability to diagnose [2] and treat patients [3]. The employed mathematical models allow for the computation of patient-specific, individualized brain models, aiming for clinical hypothesis testing in silico [4]. The mathematical framework incorporates various local dynamic models of neural behavior, each characterized by numerous parameters governing their dynamics. But while this complexity allows for a wide range of applications, the systematic comparison between results from different models remains challenging. One potential solution is offered by highly structured knowledge representations as available in knowledge bases and ontologies, going back to Tim Berner-Lee's vision of a semantic web [5]. We therefore suggest a novel ontology incorporating both the mathematical and the biological framework of TVB and aiming to serve as a central knowledge hub for brain modelling and simulation with TVB.

METHODS

We have developed The Virtual Brain Ontology (TVB-O): the first knowledge representation that formalizes the mathematical framework at the core of TVB by annotating it in a hierarchically structured manner. Additionally, we have integrated the Gene Ontology (GO, [6]), a biological knowledge graph, into TVB-O. This was achieved using a semi-automatic approach reducing the 1,117,589 biological processes from GO to 215 biochemical pathways and electrophysiological processes that have a potential surrogate in brain modelling. These 215 processes were clustered by their function and linked to the relevant large-scale brain network model (BNM) components of TVB, i.e., model parameters and variables. As an additional function for interoperability, we have implemented full compatibility with the standardized XML-based language Low Entropy Model Specification language (LEMS, [7]) for defining BNMs succinctly.

RESULTS AND DISCUSSION

TVB-O is a central knowledge resource for brain modelling that provides standardization and information for over 370 parameters across 8 biological and 9 phenomenological models. The rich annotation of multimodal information in TVB-O ranges from synonyms, definitions, explanations and further resources over default values to biological surrogates of BNM components. This link between modelling parameters and biological processes is achieved by the annotation of 215 biological processes from GO. The relationship between entities is described by 43 newly defined properties, e.g., "is_coefficient_of".

As an example, we identified the process "positive regulation of neuronal action potential" from GO as electrophysiologically relevant and assigned it to the cluster "Excitation". One of the model parameters annotated to the cluster "Excitation" was the amplitude of the excitatory postsynaptic potential "A_JR" from the Jansen-Rit model [8].

TVB-O is providing its information in a mathematically rigorous machine- and human-readable way. It therefore allows for new inferences of relationships between biological entities and BNM components, based on formal logics and computational semantics. It is also capable of the automated generation of executable code for brain simulations with TVB using LEMS. Furthermore, a key feature of TVB-O is to provide suggestions for candidate mechanisms based on a protein, process or pathology of interest.

TVB-O is providing a novel integrated knowledge resource with a growing number of annotated neural models for the general neuroscientific community, from scientists to clinicians, that paves the way for a better understanding of the neuronal mechanisms involved in specific pathologies and aims to improve standardization and reproducibility in computational neuroscience.

Keywords: brain modelling, biological pathways, ontology, The Virtual Brain, semantic web, knowledge graphs, gene ontology

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Computation of underlying data has been performed on the HPC for Research cluster of the Berlin Institute of Health. PR acknowledges support by EU H2020 Virtual Brain Cloud 826421, Human Brain Project SGA2 785907; Human Brain Project SGA3 945539, ERC Consolidator 683049; German Research Foundation SFB 1436 (project ID 425899996); SFB 1315 (project ID 327654276); SFB 936 (project ID 178316478; SFB-TRR 295 (project ID 424778381); SPP Computational Connectomics RI 2073/6-1, RI 2073/10-2, RI 2073/9-1; PHRASE Horizon EIC grant 101058240; Berlin Institute of Health & Foundation Charité, Johanna Quandt Excellence Initiative; ERAPerMed Pattern-Cog.

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83. Simulating ^{18}FDG-PET based on a neurogliovascular ATP model in The Virtual Brain

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INTRODUCTION/MOTIVATION

While positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) is an established imaging technique in clinical oncology, it is of emerging relevance in neurology in the field of neurodegenerative diseases. Recent approaches aim to use it as a functional measure of brain activity and connectivity , analogous to electroencephalography (EEG) or functional magnetic resonance imaging (fMRI). From a computational viewpoint, large-scale brain simulation with The Virtual Brain (TVB, www.thevirtualbrain.org) can reproduce such measures through biophysically grounded forward models, linking neuronal activity to EEG and fMRI signals. However, this link is not yet fully understood for FDG-PET. Besides the neuronal energy consumption, it further involves vascular and glial mechanisms. In this work, we propose a mechanistic forward model relating glucose metabolism and hence FDG-PET signals to the underlying electrophysiological activity in a large-scale brain simulation.

METHODS

We employ a bottom-up approach, encompassing the impact of neuronal firing on adenosine triphosphate (ATP) levels and energy metabolism. Therefore, we make use of an existing neurogliovascular model of ATP metabolism [1]. Derived from this, we propose a forward model that takes the simulated raw neuronal activity as an input and outputs a virtual FDG-PET signal, allowing for the calculation of a virtual static PET image and virtual PET-derived functional connectivity (FC). Model optimization and validation are performed based on a data set of simultaneous resting state fMRI and functional FDG-PET [2].

RESULTS AND DISCUSSION

Our model predicts the empirical PET data to a large extent while outperforming an existing forward model that is in use for fMRI. We observe high correlations between simulated and empirical static PET, for which the model was optimized based

on a subset of 3 subjects. Further, the same model reproduces the FDG-PET derived FC, for which the model has not been optimized. We show *in silico* fundamental differences between FDG-PET signal outputs and fMRI, including dependence on amplitude and frequency of the underlying neuronal activity for FDG- PET. Overall, our results suggest that the neurogliovascular ATP model may provide additional insights into brain function compared to other imaging modalities that do not take into account energy metabolism.

The model extends the fields covered with TVB to a larger variety of clinical applications, as PET is more frequently available than fMRI in clinical routine – for example, in the diagnostic workup of neurodegenerative diseases. Moreover, FDG-PET-derived FC promises to complement restrictions that are immanent to fMRI-based approaches, as it inherits a different degree of noise and differs in the resolution of time and space. Ultimately, the presented model is a step towards a better understanding of cerebral glucose metabolism and its relationship to brain activity.

Keywords: FDG, PET, brain simulation, glucose metabolism, The Virtual Brain

FIGURES

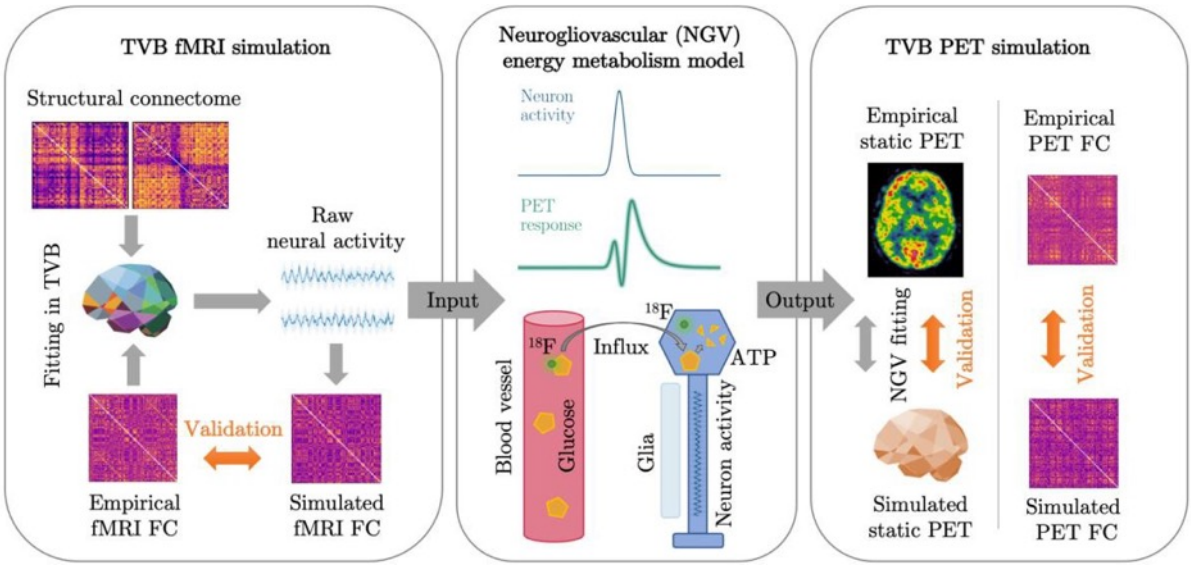

Figure 1: Simulating [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) in The Virtual Brain (TVB). Left: Structural connectomes (SC) are used as an input to TVB, in order to produce raw neural activity. By optimizing model parameters to reproduce functional connectivity (FC) derived from functional magnetic resonance imaging (fMRI), we obtain physiologically plausible raw activity. Center: The simulated neural activity acts as an input to a biophysical forward model of the neurogliovascular (NGV) energy metabolism. Spiking activity is ensued by the consumption of adenosine triphosphate (ATP) and triggers a "hunger" signal. Therefore, glucose and FDG molecules are released from blood vessels into the neuron to compensate for the consumed ATP. The FDG is trapped in the cell and gives a contribution to the FDG-PET signal. Right: This virtual FDG-PET signal is optimized to reproduce empirical static PET data of a subset of subjects. The remaining subjects are used for data validation, taking also into account FDG-PET-derived FC.

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86. Simulating deep brain stimulation using a multiscale model in The Virtual Brain

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INTRODUCTION

Deep brain stimulation (DBS) is a successful symptom-relieving neuromodulation technique established for many different neurodegenerative diseases. However, the effects of DBS on the local scale around the electrode and on the global scale of macroscopic brain regions are still insufficiently understood. Recently, we established a multiscale model for DBS that combines fine-grained spiking modeling for the surrounding areas of the electrode and coarse-grained mean-field modeling to offer a whole-brain perspective on the effects of DBS [1]. The code of this model and the data used in this previous study are publicly available on EBRAINS. We provided proof of concept for virtual DBS in a co-simulation multiscale environment with The Virtual Brain (TVB). However, bringing such a virtual DBS model to the clinic for improving and accelerating DBS programming for the individual Parkinson's disease patient warrants extensive validation. Furthermore, our previous model was not sensitive to the exact 3D location of the electrode, which is a crucial factor for the successfulness of DBS.

METHODS

In this study, we compared our multiscale DBS model with empirical DBS ON and OFF resting-state fMRI BOLD data (N=2, biphasic stimulation). We also extended our previous multiscale model to allow for a high-resolution modeling around the DBS electrode by interfacing TVB with electrical field (E-field) modeling, which includes the electromagnetic properties of the surrounding tissue of the electrode and estimates the electrical field changes due to the DBS pulses. To this end, we adapted the surface-based modeling approach of An et al. [2] to include high-resolution modeling around the DBS electrode and traced the activations of the fibers towards cortical

regions. Inputting the localizations of Sensight directional DBS leads (N=9, Medtronic Percept), we simulated local field potentials and BOLD data.

RESULTS AND DISCUSSION

Virtual DBS showed increases as well as decreases in BOLD activity and correlations among sensorimotor and basal ganglia (BG) regions (Fig. 1ACD). For some single regional and selective pairwise correlations, those stimulation effects seem to be congruent with decreases or increases in empirical data (Fig. 1ACD). Further, we established a first link between the individual simulated dynamics (local field potentials based on the individual localizations of the Sensight DBS lead, N=9) and the clinical improvements of patients after DBS using principal component analysis (PCA) (Fig. 1B). Our results are still preliminary and warrant further testing and validation on larger sample sizes. With the virtual DBS model, we can observe the local and global dynamics simultaneously (Fig. 1C-E) which has the potential to identify DBS network effects and generate new hypotheses for the mechanisms of DBS. Our extended multiscale model is sensitive to different parameters of the E-field (amplitude/frequency of the stimulus, precise location) and can be used in the future to test different DBS programming and/or surgical targeting which may determine optimal clinical outcome tailored to individual symptomatic profiles.

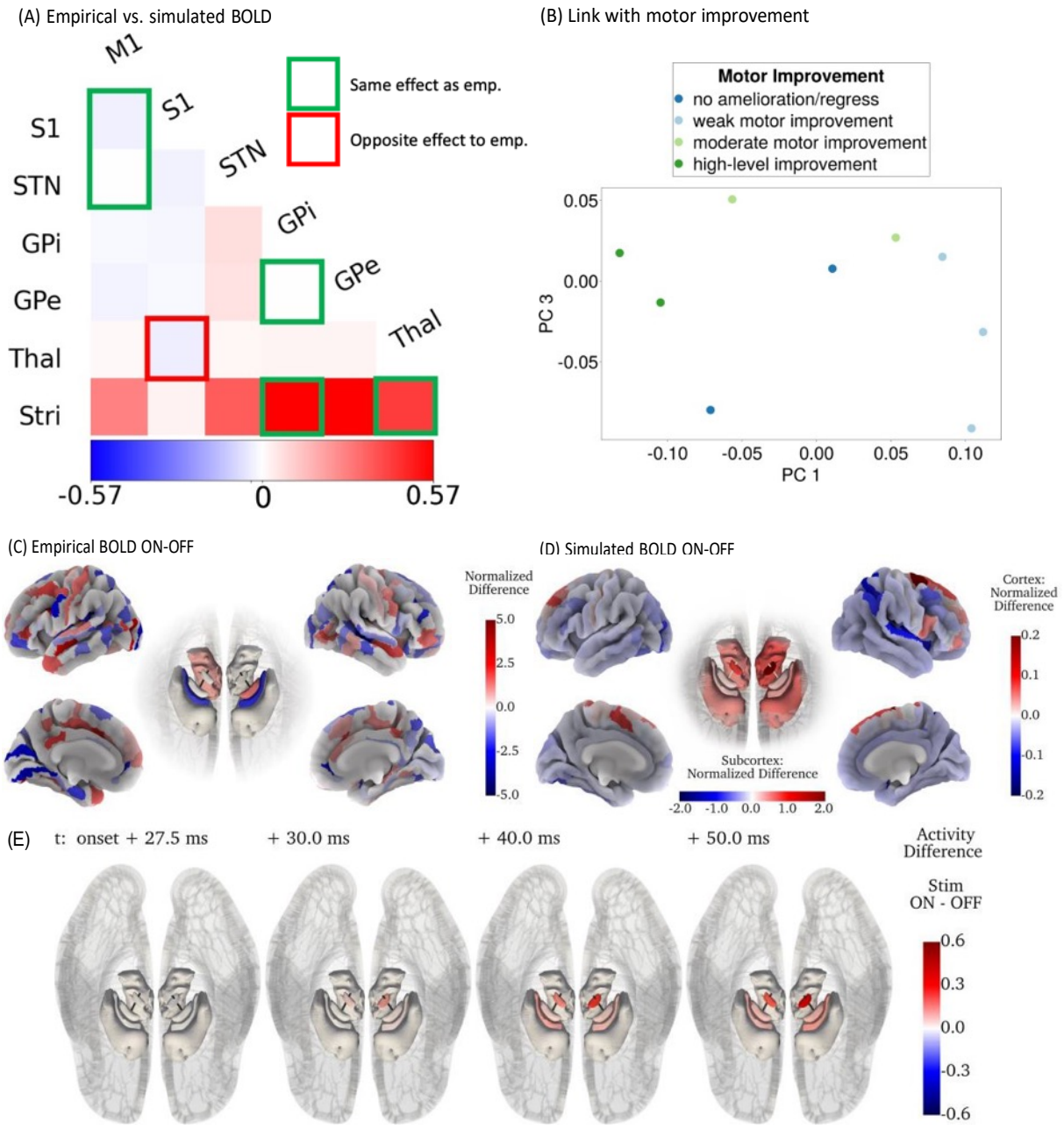

Figure 1: Comparison of simulated DBS effects with empirical BOLD data and first link of simulated dynamics with clinical symptoms. (A) Simulated data was able to capture 5 out of 6 increases/decreases of BOLD correlations under DBS ON (in the left hemisphere). (B) PCA on the simulated dynamics shows a reasonable classification of patients based on their motor improvement under DBS ON. (C) Empirical and (D) simulated BOLD activity fluctuations due to DBS. (E) Snapshots of the simulated LFP signal in the BG regions after stimulus onset.

Keywords: The Virtual Brain, multiscale modelling, electric-field modelling, deep brain stimulation

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90. TheVirtualBrain in the Neurorobotics Platform: Haken-Kelso-Bunz bimanual coordination

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INTRODUCTION

TheVirtualBrain (TVB) [1] is a computational framework for modelling and simulating whole brain dynamics at the level of large-scale networks, which allows for the integration of structural and functional neuroimaging data [2]. The Neurorobotics Platform (NRP) [3] is a set of software tools to prepare, execute and monitor simulations of virtual agents interacting in a closed loop with their environment. The latter can be implemented in game engines, such as Unity, or in simulation environments such as MuJoCo or Gazebo [4]. We present a first demonstration of an embodied virtual brain simulation that exhibits a phase transition in bimanual sensorimotor coordination following the classical Haken-Kelso-Bunz (HKB) model [5], via closed-loop co-simulation of TVB and Gazebo in the NRP.

METHODS

We embedded the bimanual coordination task dynamics into a TVB network model by (a) augmenting the network with two nodes representing the Gazebo fingers, (b) selecting a HKB like oscillatory model [6] for the dynamics of each network node and their mutual coupling, (c) setting directed connections implementing the loop Left Motor Cortex (LMC) -> Right Finger (RF) -> Left Sensory Cortex (LSC) -> Right Motor Cortex (RMC) -> Left Finger (LF) -> Right Sensory Cortex (RSC) -> LMC (Figure 1), and (d) reducing the weights of all other brain connections and removing all time delays to the TVB time step of integration (0.1 ms). At every time step of simulation, the activity of the motor cortices determines the position and velocity of the Gazebo fingers, acting as motor commands, whereas the actual position and velocity of those fingers update the state of the respective TVB RF and LF nodes (by overwriting it), which then couple to the sensory cortices, acting as proprioception, eventually directed to the motor cortices. The oscillations go through three successively increased frequency plateaus (by modifying accordingly a frequency parameter), the middle of which corresponds to the critical frequency that destabilizes the antiphase mode of coordination.

The NRP platform implements a hub-and-spokes architecture with NRP Core as the hub and distributed "engines" for constituent simulators, employing a client-server paradigm for communications. The NRP core (a) orchestrates the co-simulation of the TVB and Gazebo engines, and (b) carries out the data exchange, as well as mathematical transformations of the data via transceiver functions (in Python).

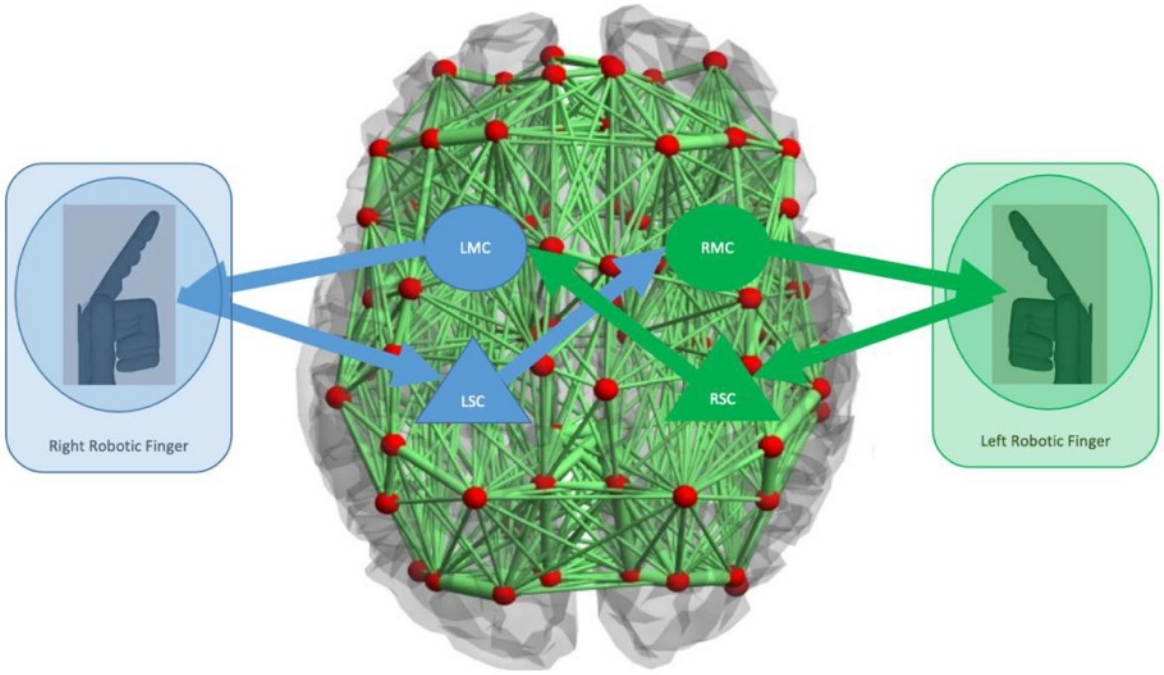

Figure 1: Model architecture. TVB network augmented with two Gazebo fingers. Task related directed connections shown as thick arrows in blue (green) for right the (left) finger.

RESULTS AND DISCUSSION

The co-simulation starts with initial conditions chosen to result to an antiphase mode of bimanual coordination. During the middle (critical) frequency plateau a phase transition takes place to the inphase coordination mode spontaneously, with the assistance of noise (Figure 2; see also [7] for an animation).

Future work can increase the biological realism of both the brain dynamics (e.g., inducing the phase transition due to interhemispheric crosstalk and respective time delays [8]), and on the side of the robotic fingers' biomechanics. Such a co-simulation framework allows researchers to perform in-silico experiments of brain and behaviour interactions for testing hypotheses or making predictions e.g., for lesions or perturbations, while integrating neuroimaging, neuromuscular and behavioural data.

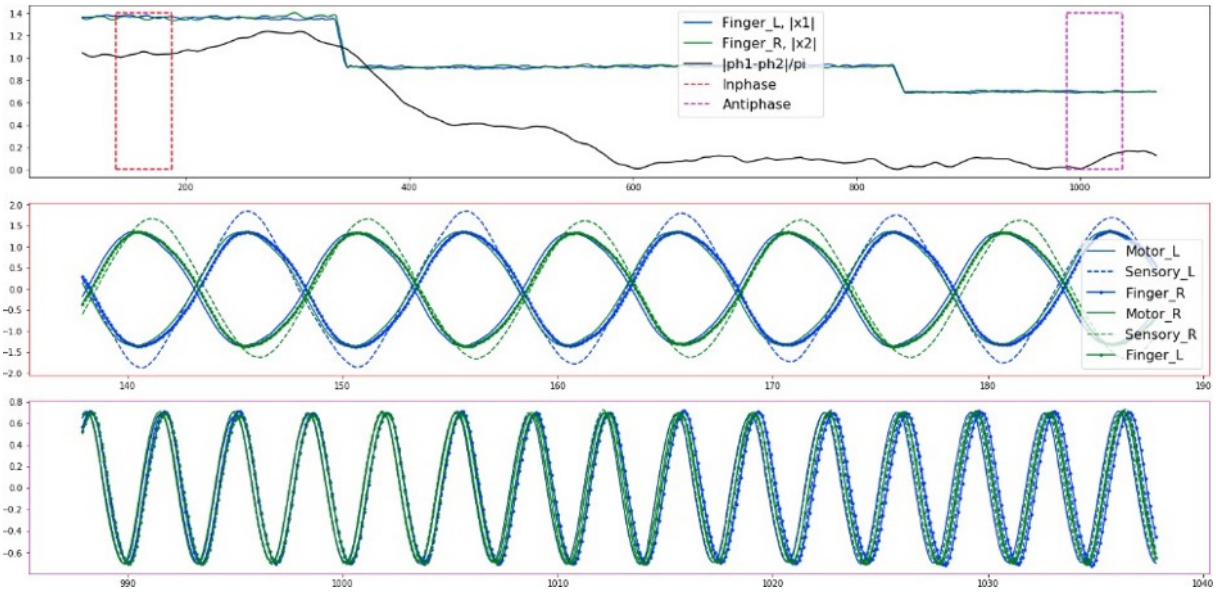

Figure 2: Model simulation. Co-simulation time series exhibiting a phase transition from an antiphase to an inphase mode. Top: Finger position amplitudes and normalized phase difference (black) for three frequency plateaus Middle (bottom): Motor and sensory cortices' activities, and finger positions (see legend for line styles) corresponding to the red (magenta) inserts of the top panel, exhibiting antiphase (inphase) synchronization, respectively. Right (left) finger circuit showed in (blue) green.

Keywords: TheVirtualBrain, Neurorobotics Platform, Gazebo, Haken-Kelso-Bunz model, bimanual coordination, phase transition, Co-Simulation, embodied brain

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100. Multiscale Co-Simulation of TheVirtualBrain with NEST, ANNachy and NetPyNE (NEURON) spiking networks

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INTRODUCTION

TheVirtualBrain (TVB) [1] is a state-of-the art computational framework for modelling and simulating whole brain dynamics at the coarse level of large-scale networks, which allows for the integration of structural (structural and diffusion MRI) and functional (BOLD/fMRI/PET, EEG/MEG/SEEG/iEEG) neuroimaging data [2]. TVB dynamics results from interactions among network nodes, either whole brain regions or local patches of neural tissue on the surface of brain's grey matter, which are modelled by neural mass population models. Spiking neural network simulators aim at modelling and simulating specific systems or circuits of the brain at a much finer scale, using neuronal models, either point (as for NEST [3] and ANNarchy [4] simulators), or multicompartmental (as for NEURON [5] and its network-building python interface, NetPyNE [6]) as their elementary modelling and computational units, generating spiking dynamics. We introduce TVB-multiscale [7], a new Python toolbox for Co-Simulation of TVB with all three of the above spiking simulators, which facilitates the implementation in a unified and user-friendly manner of so-called interfaces, i.e., data transformations and exchanges between the large-scale activity of the whole brain, as modelled in TVB, and neuronal networks extending on several brain regions.

METHODS

TVB and spiking network models are interfaced at the mesoscale of neuronal population dynamics, as the state variables of the TVB neural mass models capture the average dynamics of neuronal population activity, and statistical averages of the same activity are computed from spiking neural networks. A mapping is formed between TVB state variables and populations modelled as spiking networks, to which a label of the brain region of the TVB network, where they reside, is assigned. Interfaces are implemented in a modular architecture consisting of (a) "transformer" classes for converting average population activity (usually spiking firing rate, as well as current or voltage), to total individual neuronal activity (e.g., spike trains) and vice-versa, employing the software Elephant

[8], (b) “communicator” classes for exchanging data between simulators and transformers, and (c) “TVB proxy” nodes that represent TVB brain regions withing the spiking network. “TVB proxies” act either as stimulating devices, which mimic the transformed dynamical activity of TVB model state variables and couple to target neuronal populations (Figure 1), or as devices, which record the activity of spiking neuronal populations to update

- by overwriting - the respective TVB state variables of the brain region where they reside (Figure 2).

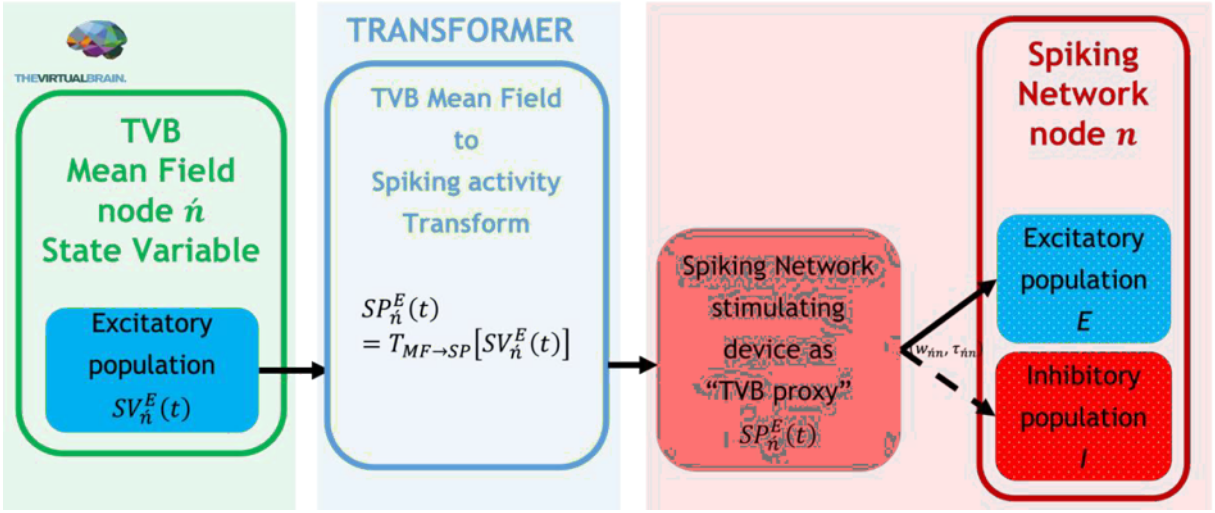

Figure 1. TVB to spiking network coupling.

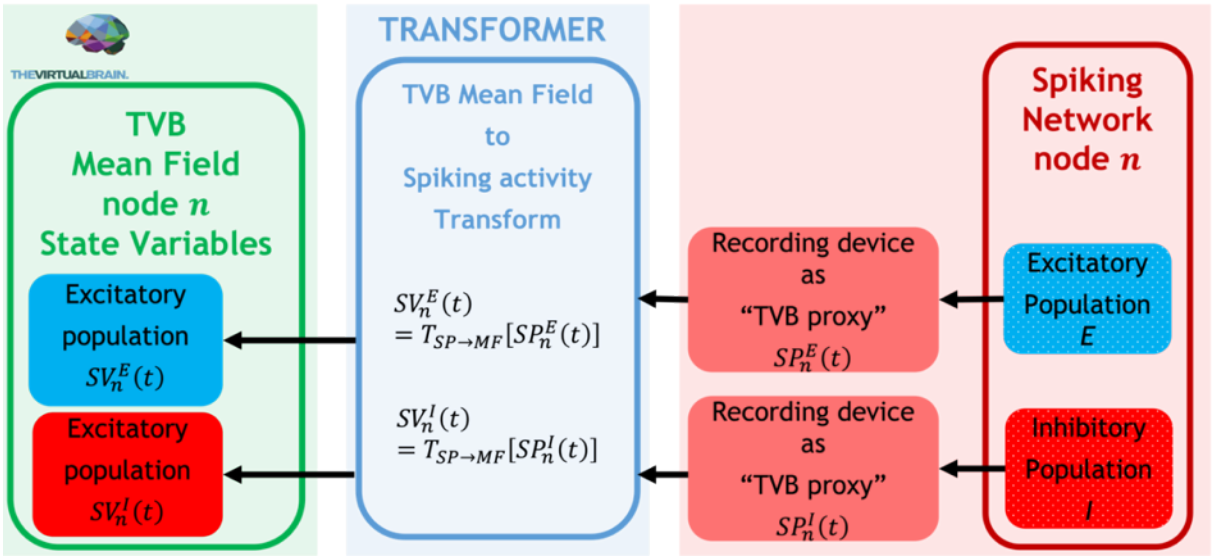

Figure 2. Spiking network to TVB update.

RESULTS AND DISCUSSION

TVB-multiscale opens the possibility for computational studies, in which a specific neural system that is the focus of the scientific inquiry is embedded into a biologically realistic spatio-temporal whole brain context and interacts

with it. TVB provides input to the spiking network differentiated in terms of dynamics (e.g., frequency content) and/or the source brain region, this input is processed by the spiking network implementing functions beyond the complexity and specificity of the TVB neural mass models, and then the output of the spiking network feeds back to the rest of TVB affecting the global brain dynamics. It has already been used to integrate TVB e.g., with an ANNarchy spiking model of basal ganglia for virtual Deep Brain Simulation modelling [9], or with a NEST spiking network model of the cerebellum in a study of sensorimotor integration of freely whisking mice [10]. Ongoing studies model thalamocortical networks using TVB with NetPyNE Co-Simulation. Such use cases further validate the implemented interfaces with neuroimaging and spiking data. Future software development will improve the computational efficiency of Co-Simulation, test (unit and integration) coverage, and documentation.

Keywords: TheVirtualBrain, NEST, ANNarchy, NetPyNE, NEURON, Co-Simulation, brain network models, spiking neural networks, Python, scientific software

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