Python in Neuroscience Pages 1–13

Integrating neuroinformatics tools in TheVirtualBrain

M. Marmaduke Woodman [1,*], Laurent Pezard [1], Lia Domide [3], Stuart Knock [1], Paula Sanz Leon [1], Jochen Mersmann [2], Anthony R. McIntosh [4] and Viktor Jirsa [1*]

[1] Institut de Neurosciences des Systèmes, Aix-Marseille Université, 27, Bd. Jean Moulin, 13005, Marseille, France.
[3] Codemart, 13, Petofi Sandor, 400610, Cluj-Napoca, Romania.
[2] CodeBox GmbH, Hugo Eckener Str. 7, 70184 Stuttgart, Germany.
[4] Rotman Research Institute at Baycrest, Toronto, M6A 2E1, Ontario, Canada

ABSTRACT

TheVirtualBrain (TVB) is a neuroinformatics Python package representing the convergence of clinical, systems, theoretical neuroscience in the integration, analysis, visualization and modeling of neural dynamics of the human brain as well as the imaging modalities through which these dynamics are measured. TVB is composed of a flexible simulator for both neural dynamics and modalities such as electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI), common analysis techniques such as wavelet decomposition and multiscale sample entropy, interactive visualizers for replaying cortical timeseries on the 3D surface or editing large-scale connectivity matrices, all accessible via an web browser user interface. A datatype system modeling neuorscientific data ties together these pieces with persistent data storage, based on a combination of SQL & HDF5. These datatypes combine with adapters allowing TVB to integrate other algorithms or computational systems, such as MATLAB, for which support is already provided. TVB provides infrastructure for multiple projects and multiple users, possibly participating under multiple roles. For example, a clinician might import patient data to first identify, based on electrophysiological dynamics, several potential lesion point on the patient's connectome, as obtained from diffusion spectrum imaging (DSI). These lesion points are picked up by a modeler, working on the same project, and tested for viability through whole brain simulation, based on the patient's connectome, and subsequent analysis of dynamical features. This workflow is one of several multi-user use cases for which TVB conceived. TVB also drives research forward: the simulator itself represents the culmination of several recent yet ad-hoc simulations in the modeling literature on human resting state. The availability of the numerical methods, set of neural mass models and forward solutions allows for the construction of a wide range of brain-scale simulation scenarios. TVB is therefore a platform for various tools and disparate expertises, supporting the analysis and modeling of structural and function data from the human brain. We will briefly outline the history and motivation for TVB, describing the framework and simulator, giving usage examples in the web UI and Python scripting.

Keywords: large-scale brain network, simulation, web platform, Python, virtual brain, connectivity, connectome, neural mass, time delays

*to whom correspondence should be addressed: marmaduke.woodman@univ-amu.fr, viktor.jirsa@univ-amu.fr

1 INTRODUCTION

The neurosciences, and more generally, brain and behavioral sciences, imply extensive interactions among disciplines to advance our appreciation for the relation between brain and behavior. [1] The inherent challenge, however, lies in bringing together the distributed competences of many individuals or even institutions and exchanging across interdisciplinary borders using common techniques. This situation is excerbated by the technical sophistication of modern data analysis and brain simulation, which often impedes their adoption in the communtiy.

These challenges call for two kinds of solutions. First, there is a need for comprehensive, modern computational libraries written in a widely used and available programming languages, such as MNE-Python (Gramfort et al., 2013), a Python package for treating M/EEG data via time-frequency analyses and inverse solutions and the Brain Connectivity Toolbox (Rubinov and Sporns, 2010a) for analyzing the graph theoretic properties of structural and functional connectivity. Second, there is a need for the implementation of collaborative infrastructure for sharing not only data, but expertise; CARMEN (Austin et al., 2011) and G-Node (Herz et al., 2008) are two such examples of developing platforms for collaborative work and data sharing, in the domains of cellular and systems neurophysiology. Ideally, solutions will be easily extended by its own users, as is often the case in open source and scientific projects, due to the rapid evolution of use cases and requirements.

TheVirtualBrain (TVB), with a scope falling outside of existing projects, provides new tools to fire the collaboration between experimentalists by exposing both a comprehensive simulator for brain dynamics and an integrative framework for the management, analysis simulation of structural and functional data in an accessible, web-based interface. The choice of Python was made based on the wide use of Python as the high-level language in scientific programming, the unparalleled libraries and tools available, and strong software engineering culture. Two alternatives were considered, Java and MATLAB, where the former was rejected for a relative lack of use in the community and the latter rejected for its architectural constraints and license. This choice was confirmed by the publication of the first issue of Python in Neuroscience and has made it possible for the entirety of TVB from the numerical algorithms to the web server to be written in Python.

[1] The Human Brain Project one such example.

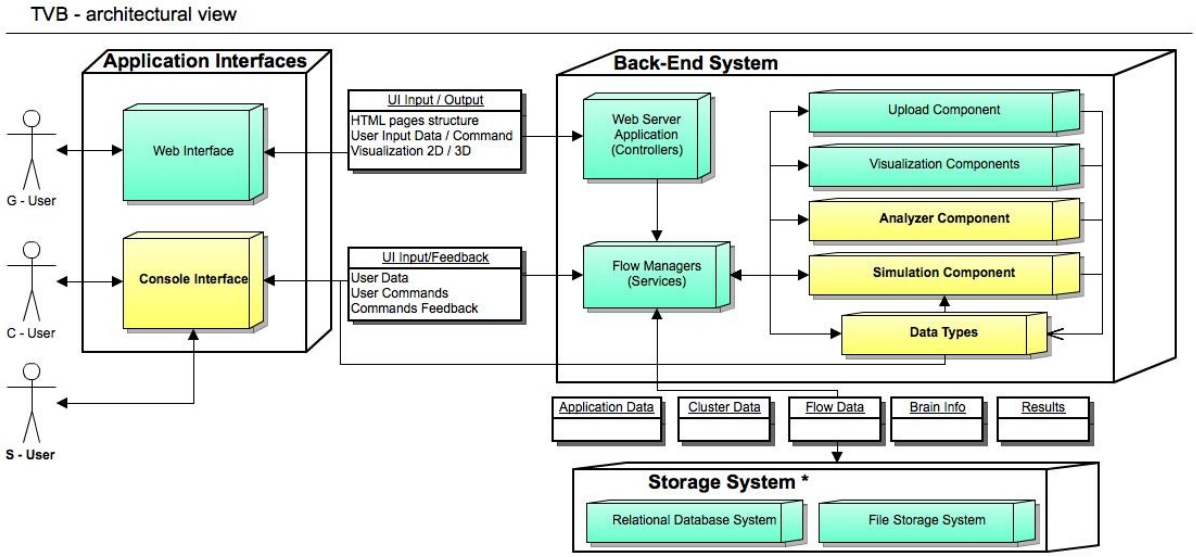


Figure 1: TVB architecture: Yellow blocks are part of the scientific library of TVB, while the green blocks are part of TVB Framework. TVB provides two independent interfaces, depending on the interaction type desired the end-user (web or console). TVB Storage layer is compulsory for the web interface, but it can be switched on/off for the console interface. The terms *G-User*, *C-User* and *S-User* refer to users of the graphical, console & database and scripting components. Here, console interface is conceptual and refers only to existing Python command lines, IPython included.

1.0.1 The framework The TVB framework was developed to allow easy integration of any computational tools along with a system for describing typical types of data. Additionally, two main constraints for the framework were to provide a web interface to allow remote collaboration and the exchange of data (or simulation results) between users, especially for users not comfortable programming. The web interface and database backend are built on combination of the CherryPy and SQLAlchemy packages. [2] The overall structure of TVB is depicted in Figure 1.

1.0.2 The simulator A significant part of TVB is simulating large-scale brain networks. While several existing simulators could have been adapted, we have estimated that TVB style simulations are far enough outside the design of other simulators to make a new development necessary. We discuss these reasons in the following.

Existing neural network simulators typically focus either on abstract rate neurons, modelling e.g. neurocognitive processes, or full multicompartmental neurons treating complex spatial geometries, e.g. NEURON (Hines and Carnevale, 2001), modelling e.g. the interaction of channel distributions in dendrites. More recently, due to interest in the computational properties of spiking neurons and their relevance to experimental observations, simulators designed for spiking or oscillating neurons have become prominent, including Brian (Goodman and Brette, 2009), which we initially considered for our simulations. In TVB the network is defined with neural mass or field models (Deco et al., 2008; Coombes, 2010) rather than cellular models. The spatial extent of the modeled dynamics is macroscopic and scales reasonably to the entire cortex, using empirical measurements of corticocortical connectivity. Several technical issues are unique to this scale, such as efficient handling of dense N^2 inter-regional delays and integration of neural field-like models and connectivity on triangular meshes in 3D. Additionally, comparison with experimental data requires forward solutions that transform physiological signals to the commonly used imaging modalities such as EEG, MEG and fMRI need to be employed. For these reasons, TVB required a new simulator, built around the paradigm of whole-brain scale simulation.

[2] The full list of dependencies can be found in the project's documentation.

1.1 Obtaining and contributing to TVB

The easiest way to get started with TVB is to download a distribution from `http://www.thevirtualbrain.org`, which is available for Windows, Mac OS X and Linux. This distribution includes all of pieces, from the simulator to the web interface, and has no requirements other than a modern web browser supporting WebGL, SVG and HTML5.

Alternatively, because TVB is licensed under the GPL, the sources may be readily obtained from the public Git repositories hosted on Github (Dabbish et al., 2012), at `https://github.com/the-virtual-brain`. In order to use the simulator, only the standard scientific Python packages are required (NumPy & SciPy). The framework and web interface depend on a few more packages.

We provide an API doc, built from the docs strings using Sphinx. User's, Contributor's and Developer's manuals are also provided with TVB distributions in PDF format. The source files (in .rst) are available through the Github repository `https://github.com/the-virtual-brain/docs`. In addition, IPython notebooks(Pérez and Granger, 2007) for interactive tutorials are provided. These are based on the demonstration scripts provided

with the scientific library, and include a more detailed description of what the scientific goal is (if applicable), the components and stages of a simulation as well as a brief description in the case of reproducing previous work. Users interacting with *TheVirtualBrain* GUI may also benefit from these tutorials (`links:https://github.com/the-virtual-brain/scientific_library/wiki/Tutorials`) when displayed as snippets with IPython nbviewer.

Additionally, the user interface provides an online help overlay, that pulls information from the User's manual.

2 ARCHITECTURE

TVB is logically and technically divided into a scientific library and a framework package, where the scientific library includes datatypes, basic analyses and the simulator, while the framework handles execution infrastructure, the web-based user interface and data storage. The scientific library can function as an independent Python module, but the framework depends the scientific library for datatype definitions and algorithms.

2.1 Basic Concepts

The TVB framework is oriented around data and the operations that introduce, generate, transform and visualize the data. The relevant interface classes derive from the metaclasses in Python's abstract base class library, and provide a foundation for defining any type of data from a tuple to a set of EEG channel labels to a simulation, each of which is defined by a class implemented the datatype interface and possessing one or more datatypes as attributes. An operation is any algorithm that has been *adapted* to the framework in a class implementing the abstract adapter interface, and range from the simulator to data importers to visualizers. The goal of these twin, generic abstractions is to provide a solid basis on which to implement a storage back-end, workflow management and a number of features to support collaborative work.

Importantly, the framework supports both the use of the web-based graphical interface and the console interface for advanced user and developers. Where the console user does not wish to rely on the database persistence, this storage layer can be disabled. Specifically, TVB uses the notion of *profile* to identify in what context the application is currently running, and thus what components are expected to be loaded. For example, when the scientific library is used alone, a specific profile (*library profile*) class gets linked as current profile, which, in this case, disables data storage and the web interface. Other profiles available in TVB are: *command profile*, *deployment profile* (with web interface), and *test profiles*.

2.2 Datatypes and storage

2.2.1 TVB Traits Because an explicit goal of TVB was to provide a user interface to each of the entities and algorithms contained within, it is necessary at some point to provide metadata on how to built that interface. A traits system was developed, similar to that of IPython or EPD, allowing for attributes on a TVB class to be written out with its full metadata. An extensive set of building blocks are already implements from numeric types and arrays to lists, tuples, string, and dictionaries.

When methods of such a class with annotated attributes are invoked, they may use the traited attributes directly, accessing either a default value or one given during the instantiation of the object. Additionally, this allows the web-based user interface to introspect a class for all of its attributes and their descriptions, to provide help and choose the proper display form. The explicit typing also allows such classes to be nearly automatically mapped to storage tables, providing persistence, when the storage layer is enabled. Lastly, because such metadata is used to build the docstring of a class, the console user also may obtain extensive descriptions of class, attributes, methods and arguments in the usual way. Table **??** lists the various parts of a traited attribute and how they are used.

2.2.2 Datatypes In scientific Python code, it is conventional to provide arguments of an algorithm as a "bare" array or collection there of, and sanity checks of arguments proceed on the basis of array geometry, for example. In TVB, we consider a *DataType* to be a full, formal description of an entity involved in an algorithm that would be part of TVB.

In TVB, datatypes represent the common language, to be used between different application parts: like uploaders, analyzers, simulator and visualizers. Some of the algorithms are producing these DataTypes, while others are reading them as input. In order to decouple the definition and several usages of such entities, DataTypes are declared outside the algorithms and shared between them. For example an instance of datatype TimeSeriesRegion is created by the Simulator, and it can be accepted as input for several visualizers or analyzed by PCA and Cross Coherence algorithms.

Technically, TVB datatypes are annotated Python classes, which contain one or more fields and associated descriptive information, as well as methods for operating on the data they contain. The definition of a datatype is achieved using TVB's traiting system, mentioned in previous section.

For example, the `Connectivity` DataType, which may elsewhere be represented by a simple N by N NumPy array, is written as a class in which one of the attributes, `weights`, is a explicitly typed `FloatArray`, and the declaration of this type is complemented by explicit label, default values, and documentation strings. See Code 1.

```
class ConnectivityData(MappedType):

  region_labels = arrays.StringArray(
        label="Region labels",
        doc="""Labels for the regions ...""")

  weights = arrays.FloatArray(
        label="Connection strengths",
        doc="""... strength of connections ...""")

  tract_lengths = arrays.FloatArray(
        label="Tract lengths",
        doc="""... length of myelinated fibre tracts.""")

   speed = arrays.FloatArray(
        label="Conduction speed",
        default=numpy.array([3.0]),
        file_storage=core.FILE_STORAGE_NONE,
         doc="""... matrix of conduction speeds ...""")

  centres = arrays.PositionArray(
        label="Region centres",
        doc="""... locations for the region centers""")
```

Code 1: The COnnectivityData listing

Table 1. TVB currently available Traited Attributes

Traited Attribute	Description
default	Default value for current attribute. Will be set on any new instance if not specified otherwise in the constructor.
console_default	Define how a default value can be computed for current attribute, when console interface is enabled.
range	Specify the set of accepted values for current attribute. Mark that this attribute is usable for parameter space exploration.
label	Short text to be displayed in UI, in front of current attribute.
doc	Longer description for current attribute. To be displayed in UI as help-text.
required	Mark current attribute as required for when building a new instance of the parent class.
locked	When present and *True*, current attribute will be displayed as read-only in the web interface.
options	Used for attributes of type *Enumerate*, specifying the accepted options as a list of strings.
filters_ui	SQL filters on other attributes, to be applied in UI.
select_multiple	When *True*, current attribute will be displayed as a select with multiple options in UI (default is single-select)
order	Optional number identifying the index at which current attribute will be displayed in UI. When negative, the attribute is not displayed at all. Ascending order for indices is considered when displaying.
use_storage	When *False*, current attribute is not stored in database or file storage.
file_storage	Valid values for this attribute are: *None* , *HDF5*, or *expandable_HDF5*, When *None*, current attribute is not stored in the file-storage at all. When *HDF5*, we use regular H5 file storage. When *expandable_HDF5* value is set, a H5 stored in chunks is used.

2.3 Adapters

The framework expects algorithms to be adapted by providing a class which inherits from the base adapter, `ABCAdapter`, implementing the adapter interface:

```
class AdapterExample(ABCAdapter):

  @abstractmethod
  def get_input_tree(self):
        pass

  def configure(self, **kwargs):
        pass

  @abstractmethod
  def launch(self):
        pass
```

Code 2: The ABCAdapter listing

where `get_input_tree` builds a dictionary of input arguments required for the algorithm and for presenting menus and fields in the user interface, `configure` allows the adapter to intialize itself and its algorithm based on arbitrary arguments and `launch` invokes the algorithm. Additional methods include `get_output`, `get_required_memory_size`, `get_required_disk_size`, and `get_execution_time_approximation`.

Several categories of adapters have been defined in TVB:

- *creators* which are internal algorithms for producing datatype instances. Each creator has one or multiple pages in the web interface, in which the user configures input parameters and chooses from the available options for computing a particular datatype.
- *uploaders*: allow the upload into TVB framework of external data, such as *gifti* files of plain *csv* files.
- *simulator* is an adapter for the simulator, adjusting it to fit the workflow mechanisms inside the framework .
- *analyzers* which offer the interface to libraries containing algorithms for the analysis of the data (wavelets, FastICA, BCT, etc).
- *visualizers*, derived from the *ABCDisplayer* base class, prepare a datatype for display. Each visualizer (Python adapter class) requires a complementary set of JS and HTML files.
- *portlets* provide a chain of analyzers leading to a visualizer.
- *exporters* prepare a datatype for export & download.

Note that the adapters and datatypes are intended to provide full power and flexibility of the framework; when the simulator is invoked from the web-based UI, it is done so through a `SimulatorAdapter` which, despite being relatively complex, is built with *traits* all the way down.

It is reasonable to ask what such a scheme offers over the more conventional approach of Python, where presumably it would have been sufficient that each adapter consist of a class with an `__init__` and `__call__` method, in the case of a function type. We note that because in the case of TVB, the context in which an object is used is more varied, e.g. not simply initialized but loaded through SqlAlchemy's ORM, and that the adapter is required to perform more tasks than just initialization and invocation, e.g. provide expected shape of result, estimate occupied memory and do not start if insufficient resources are found on current machine, it was advantageous to create a distinct set of interfaces built on top of the abstract base class framework provided by Python's standard library.

An adapter for FastICA An example of an adapter applying the FastICA algorithm to each of the state variables in a simulation time series is given in Code 3.

```
class ICAAdapter(ABCAsynchronous):

    _ui_name = "Independent Component Analysis"
    _ui_description = "ICA for a TimeSeries input DataType."
    _ui_subsection = "ica"


    def get_input_tree(self):
        algorithm = fastICA()
        algorithm.trait.bound = self.INTERFACE_ATTRIBUTES_ONLY
        tree = algorithm.interface[self.INTERFACE_ATTRIBUTES]
        filt = FilterChain(fields=
                [FilterChain.datatype + '._nr_dimensions'],
                operations=["=="], values=[4])
        for node in tree:
```

```
            if node['name'] == 'time_series':
                node['conditions'] = filt
        return tree


    def get_output(self):
        return [IndependentComponents]

    def configure(self, time_series, n_components=None):
        self.input_shape = time_series.read_data_shape()
        log_debug_array(LOG, time_series, "time_series")

        self.algorithm = fastICA()
        self.algorithm.n_components = \
                n_components or self.input_shape[2]

    def get_required_memory_size(self, **kwargs):
        used_shape = (self.input_shape[0], 1,
                self.input_shape[2], self.input_shape[3])
        input_size = numpy.prod(used_shape) * 8.0
        output_size = self.algorithm.\
                              result_size(used_shape)
        return input_size + output_size

    def launch(self, time_series, n_components=None):
        ica_result = IndependentComponents(
            source=time_series,
            n_components=int(self.algorithm.n_components),
            storage_path=self.storage_path)

        # 4-D simulation time series
        node_slice = [slice(self.input_shape[0]),
                None, slice(self.input_shape[2]),
                slice(self.input_shape[3])]

        ts = TimeSeries(use_storage=False)
        for var in range(self.input_shape[1]):
            node_slice[1] = slice(var, var + 1)
            ts.data = time_series.read_data_slice(
                    tuple(node_slice))
            self.algorithm.time_series = ts
            partial_ica = self.algorithm.evaluate()
            ica_result.write_data_slice(partial_ica)
        ica_result.close_file()
        return ica_result
```

Code 3: ICA adapter for FastICA library

Interfacing with MATLAB One of the well-known libraries for characterizing anatomical and functional connectivity is the *Brain Connectivity Toolbox* (Rubinov and Sporns, 2010b). Because it is written in MATLAB, with maintainers who prefer MATLAB, we chose not to port routines of the library to Python but instead build a MATLAB adapter which runs arbitrary MATLAB code.

This generic Matlab adapter works by generating at runtime a script with MATLAB code, wrapping the script call in Python with a try-except clause, loading and saving the workspace before and after the call, generating a workspace `.mat` file, invoking the MATLAB or Octave executable, and loading the resulting workspace file.

Despite invocation of MATLAB being a relatively slow operation, this works without problems in a single user situation, and where Octave is available, it is quite fast. In the case that many operations are necessary, they can be batched into the same run.

3 SIMULATOR

The simulator in TVB resembles popular neural network simulators in many fundamental ways, both mathematically and in terms of informatics structures, however we have found it necessary to introduce auxiliary concepts particularly useful in the modeling of large scale brain networks. In the following, we will highlight some of the interesting principles and capabilities of TVB's simulator and give rough characterization of the execution time and memory required in typical simulations.

3.1 Node dynamics

In TVB, nodes are not considered to be abstract neurons nor necessarily small groups thereof, but rather large populations of neurons. Concretely, the main assumption of the neural mass modeling approach in TVB is that large pools of neurons on the millimeter scale are strongly approximated by population level equations describing the major statistical modes of neural dynamics (Freeman, 1975). Often, averaging techniques are employed, though techniques retaining several modes have been developed (Stefanescu and Jirsa, 2008, 2011). Such an approach is certainly not new; one of the early examples of this approach consist of the well known Wilson-Cowan equations (Wilson and Cowan, 1973). Nevertheless, there are important differences in the the assumptions and goals from modeling of individual neurons, where the goal may be to reproduce correct spike timing or predict the effect of a specific neurotransmitter. A second difference lies in coupling: chemical coupling is often assumed to be pulsatile, or discrete, between neurons, whereas for mesoscopic models it is considered continuous. Typically the goal of neural mass modeling is to study the dynamics that emerge from the interaction of two or more neural masses and the network conditions required for stability of a particular spatiotemporal pattern. In the following, we shall briefly discuss some of the models available in TVB.

As we have noted, many neural mass models have been developed. One of the more prominent examples in the systems neuroscience literature is the Jansen-Rit model of rhythms and evoked responses arising from coupled cortical column (Zetterberg et al., 1978; Jansen and Rit, 1995; David et al., 2004; Spiegler et al., 2010). Advantages of the Jansen-Rit model stem from the connection made between empirical studies of neural tissue and the model's parameters, making it easier in certain cases to make concrete predictions about the relation between a dynamical regime and its neurobiological mechanism. However, because the form of the model used often employs at least six dimensions, it is not always clear how it should be analyzed or visualized. Lastly, the model requires frequent computation of exponentials, requiring considerable computational time.

For these reasons, it is often desirable to have a simpler mathematical model, which can reproduce the same qualitative phenomena as other models, implemented with fewer and simpler equations. Such is the motivation for the generic two-dimensional oscillator model provided by TVB (Strogatz, 2001; Guckenheimer and Holmes, 1983). This model can produce oscillations which are damped, spike-like or sinusoidal in nature. While these alone are not interesting, they permit the study of network phenomena, such as synchronization of rhythms or propagation of evoked potentials, while requiring less time to simulate.

However, the modeler's goals may not lead to either the Jansen-Rit or generic 2D oscillator, so several other mass models are provided by TVB: the previously mentioned Wilson-Cowan description of functional dynamics of neural tissue (Wilson and Cowan, 1972), the Kuramoto model describing synchronization (Kuramoto, 1975; Cabral et al., 2011), two and three dimensional mode-level models describing populations with excitability distributions (Stefanescu and Jirsa, 2011, 2008), a reduction of Wong and Wang's

(2006) model as presented by Deco et al. (2013) and a lumped version of Liley's model (Liley et al., 1999; Steyn-Ross et al., 1999) are among the available models in TVB.

Again, should any of these be insufficient, a new model can be implemented with minimal effort by subclassing a base `Model` class and providing a `dfun` method to compute the right hand sides of the differential equations. Please refer to the `tvb.simulator.models` module of the main scientific library or the `contrib` folder for examples. In the `contrib` folder, models from the work of Larter et al. (1999); Breakspear et al. (2003); Morris and Lecar (1981); Hindmarsh and Rose (1984); Brunel and Wang (2001) have been implemented.

3.2 Network structure

The network of neural masses in TVB simulations directly follows from a pair of geometrical constraints on cortical dynamics. The first is the large-scale white matter fibers that form a non-local and heterogeneous (translation variant) connectivity, either measured by anatomical tracing (CoCoMac, Kötter (2004)) or diffusion-weighted imaging (Hagmann et al., 2008; Honey et al., 2009; Bastiani et al., 2012). The second is that of horizontal projections along the surface, which are often modeled with a translation invariant connectivity kernel, approximating a neural field; though as with other parameters in the simulator, spatial inhomogeneity is supported as well.

3.2.1 Large-scale connectivity The large-scale region level connectivity at the scale of centimeters, resembles more a traditional neural network than a neural field, in that, neural space is discrete, each node corresponding to a neuroanatomical region of interest, such as V1, etc. It is at this level that inter-regional time delays play a large role, whereas the time delays due to lateral, local projections are subsumed under the dynamics of the node.

It is often seen in the literature that the inter-node coupling functions *are* part of the node model itself. In TVB, we have instead chosen to factor such models into the intrinsic neural mass dynamics, where each neural mass's equations specify how connectivity contributes to the node dynamics, and the coupling function, which specifies how the activity from each region is mapped through the connectivity matrix. Common coupling functions are provided such as the linear, difference and periodic functions often used in the literature.

3.2.2 Local connectivity The local connectivity of the cortex at the scale of millimeters provides a continuous 2D surface along horizontal projections connect cortical columns. Such a structure has previously been modeled by neural fields (Amari, 1977; Jirsa and Haken, 1997; Liley et al., 1999). In TVB, a cortical mesh, as obtained from structural MRI data and simplified, provides a spatial discretization on which neural masses are placed and connected with a local connectivity kernel, itself only a function of the geodesic distance between the two masses. This is considered to provide a reasonable approximation of a neural field, the appropriateness of which depends on the properties of the mesh and the imaging modalities that sample the activity simulated on the mesh (Spiegler and Jirsa, 2013). In fact, the implementation of the local connectivity kernel is such that is can be re-purposed as a discrete Laplace-Beltrami operator, allowing for the implementation of true neural field models that use a second-order spatial derivative as their explicit spatial term.

TVB currently provides several connectivity kernels, of which a Gaussian is one commonly used. Once a cortical surface mesh and connectivity kernel and its parameters are chosen, the geodesic distance (i.e. the distance along the cortical surface) is evaluated between all neural masses (Mitchell et al., 1987), and a cutoff is chosen past which the kernel falls to 0. This results in a sparse matrix that is used during integration to implement the approximate neural field.

3.3 Integration of stochastic delay differential equations

In order to obtain numerical approximations of the network model described above, TVB provides both deterministic and stochastic Euler and Heun integrators, following recent literature on numerical solutions to stochastic differential equations (Klöden and Platen, 1995; Mannella, 2002; Mannella and Palleschi, 1989).

While the literature on numerical treatment of delayed or stochastic systems exists, it is less well known how to treat the presence of both. For the moment, the methods implemented by TVB treat stochastic integration separately from delays. This separation coincides with a modeling assumption that in TVB the dynamical phenomena to be studied are largely determined by the interaction of the network structure and neural mass dynamics, and that stochastic fluctuations do not fundamentally reorganize the solutions of the system (Ghosh et al., 2008; Deco et al., 2009, 2011, 2012).

Due to such a separation, the implementation of delays in the regional coupling is performed outside the integration step, by indexing a circular buffer containing the recent simulation history, and providing a matrix of delayed state data to the network of neural masses. While the number of pairwise connections rises with n_{region}^2, where n_{region} is the number of regions in the large-scale connectivity, a single buffer is used, with a shape $(horizon, n_{cvar}, n_{region})$ where $horizon = max(delay) + 1$, and n_{cvar} is the number of coupling variables. Such a scheme helps lower the memory requirements of integrating the delay equations.

3.4 Forward solutions

A primary goal of TVB is not only to model neural activity itself but just as importantly the imaging modalities common in human neurosciences, using so-called forward solutions, which allow for the projection of neural activity into sensor space. To account parsimoniously for other ways in which simulated data might be saved, such as simple temporal averaging, we refer to each of these simply as *Monitors*, which take as input neural activity and output a particular projection thereof. In most cases, this takes the discrete-time form of

$$\hat{y}[j,t] = \sum_{i=1,\tau=1}^{N_W,N_k} W[j,i]K[\tau]y[i,t-\tau]$$

where $y[i,t]$ is the amplitude of the i^{th} neural mass at time t, $K[\tau]$ is a temporal kernel, and $W[j,i]$ is a spatial kernel, usually projecting the state variable of interest of the i^{th} neural mass to the j^{th} sensor.

Where necessary for computational reasons, monitors employ more than one internal buffer. The fMRI monitor is one example: given a typical sampling frequency of simulation may be upward of 64 kHz, and the haemodynamic response function may last several seconds, using only a single buffer could require many gigabytes of memory for the fMRI monitor alone. Given that the time-scale of simulation and fMRI differ by several orders of magnitude, the subsequent averaging and downsampling is justified.

In the cases of the EEG and MEG monitors, K implements a simple temporal average, and W consists of a so-called lead-field matrix as typically derived from a combination of structural imaging data of the patient, which provides the locations and orientations of the neural sources, and the locations and orientations of the EEG electrodes and MEG gradiometers and magnetometers. As the development and implementation of such lead-fields is well developed elsewhere (Sarvas, 1987; Hamalainen and Sarvas, 1989; Jirsa et al., 2002; Nolte, 2003; Gramfort et al., 2010), TVB provides access to the well-known OpenMEEG package, however, the user is free to provide their own.

3.5 Performance

A primary goal of the simulator is to be available as a pure Python package, and secondarily, to be fast enough. We have not found it useful to develop theoretical estimates of the time and space complexity of the algorithms, given that much of the heavy lifting is already done in native code by NumPy and other standard libraries. Instead, in the following, we profile a set of eight characteristic simulations on both memory use, specifically the heap size as measured by Valgrind's `massif` tool (Nethercote and Seward, 2007), and function timing as measured by the `cProfile` module of the standard library.

Measurements were performed on an HP Z420 workstation, with a single Xeon E5-1650 six-core CPU running at 3.20 GHz, L1-3 cache sizes 384 KB, 1536 KB and 12 MB respectively, with main memory 4 x 4 GB DDR3 at 1600 Mhz, running Debian 7.0, with Linux kernel version 3.2.0-4-amd64. The 64-bit Anaconda Python distribution was used with additional Accelerate package which provides acceleration of common routines based on the Intel Math Kernel Library. A Git checkout of the trunk branch of TVB was used with SHA `6c644ab3b5`.

Eight different simulations were performed corresponding to the combinations of either the generic 2D oscillator or Jansen-Rit model, region-only or use of cortical surface, and two conduction speeds, $v_c = 2.0$ and $v_c = 20.0$ (m/s). In each case, a temporal average monitors at 512 Hz is used, and the results are discarded. The region-only simulation was run for one second while the surface simulation was run for 100 ms.

mw: [Table of profiling results to go here. Profiling has been done, table will be added soon. Nothing surprising here.]

4 USER INTERACTION

4.1 Graphical Interface Interaction

A graphical web interface was chosen as a solution to give users quick interaction with *TheVirtualBrain* . The web interface is easy to access (locally or remotely) through a web browser, it can be used by different types of users, including those without programming knowledge, and it offers great support while learning about *TheVirtualBrain* concepts and workflow expectations. In our architecture diagrams, the actor accessing *TheVirtualBrain* through the web interface is called a *G-User*.

The http is served using *Cherrypy* `http://www.cherrypy.org/` which is a minimalist, object- oriented web framework, in combination with *Genshi* templating system, to support the separation of layers as guided by the *Model View Controller (MVC)* pattern.

4.1.1 Projects, Accounts, Operations & Data TVB uses entities like: Account, Project, Operation, DataType and Workflow, for modeling G-User actions and artifacts.

An *Account* or *User* is needed for accessing *TheVirtualBrain* through the web interface. When *TheVirtualBrain* web interface is fired for the first time, the G-User is requested to set their username and a password for the first account – which acts under an *administrator* role. After this, more users can *register* for accounts, which then need to be validated by the admin account.

A *Project* in *TheVirtualBrain* is a logical grouping entity, which can be used in several ways by the end-user; for example one could choose to create a project for each experiment in *TheVirtualBrain* , while others might create projects for each subject of a group. Each project has a single *User* (or *Account*) as owner, but a project can be shared with multiple users to allow for collaborative research.

Any execution of an Adapter results in an *Operation* in the context of a project. Multiple operations will be executed under the same project. For example we will have operations created for each execution of a simulation, each run of a Fourier analyzer, or launch of a Brain Visualizer. An operation changes status over time, from *started* into *canceled*, *finished successfully* or *finished with error*. One operation can have multiple input and output parameters and parameters can be scalars or DataTypes.

A *Workflow* in *TheVirtualBrain* is a set of operations with their artifacts, and wraps around a simulation as the leading component. A workflow can be seen as a default *tag*, placed by the system on Operations and DataTypes which are logically, sequentially, connected. Custom tags can also be added by the end-user both on DataTypes and Operations, for tracking entities inside a Project.

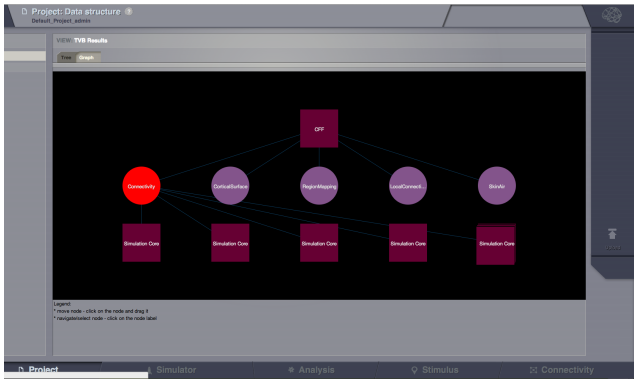
4.1.2 Simulator Interface The *Simulator* page is a presented as a configurable multicolumn interface that combines *TheVirtualBrain* simulation, analysis and visualization functionalities (Fig.3 A).

On the left column, a history of all simulations is kept and can be accessed at any time. Each simulation can be renamed or deleted.

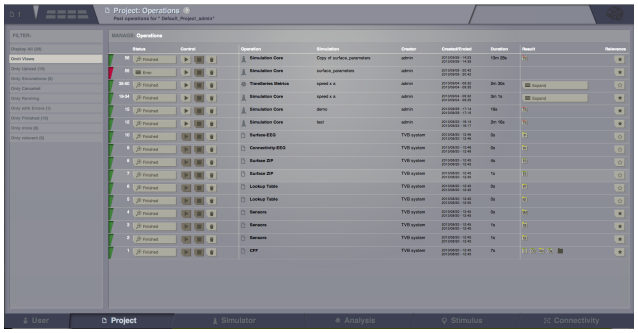
The middle column of the *Simulator* area is where users configure their large-scale brain network model. On the top of this column there is a blank field to name each particular configuration and a button to launch simulations. Via this column, users have access to all the configurable components that might be used in a simulation, namely:

- long range connectivity (i.e., the connectome or connectivity matrix);
- long range coupling function (to scale the weights in the connectivity matrix);
- conduction speed;
- cortical surface;
  - local connectivity kernel;
  - local connectivity strength (can be configured to be different for each vertex);
  - region mapping (correspondences between vertices of the surface and anatomical regions in the connectome);
- stimulus
- local dynamics model (i.e. neural mass model)
  - state variable range;

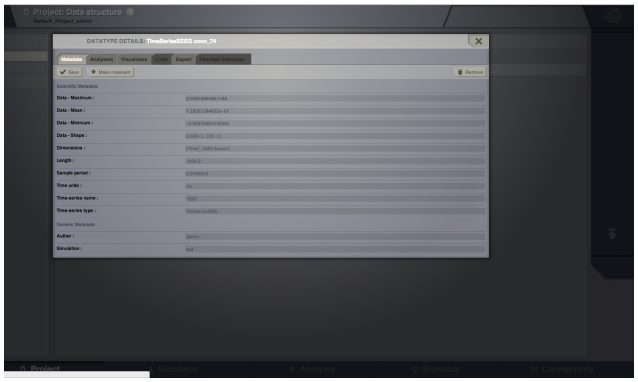
(A)



(B)

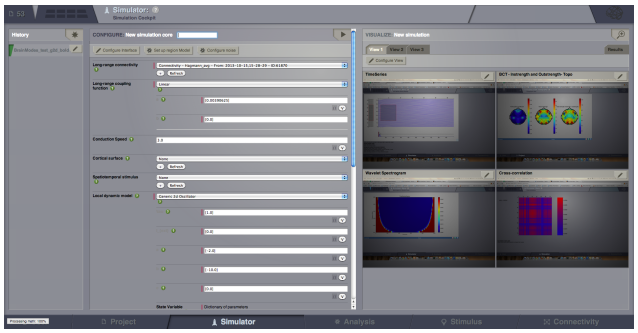


(C)

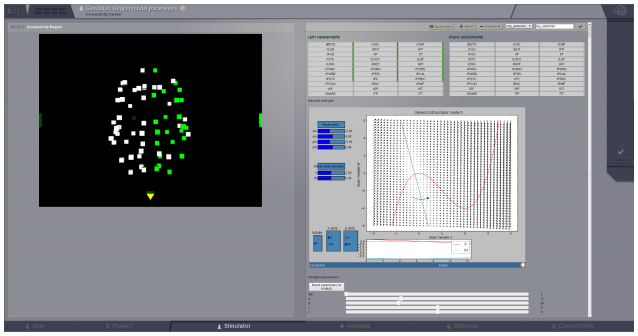


(D)

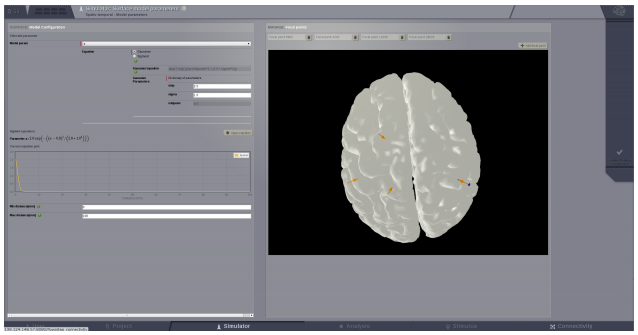
Figure 2: *TheVirtualBrain* Data Organization (A) View all Projects (B) 2D graph display of Operations with their input and output DataTypes (C) View all Operations in current project with their status, duration, results, etc (D) DataType details and further available operations for it. This menu becomes available after clicking a DataType result from several places in *TheVirtualBrain*



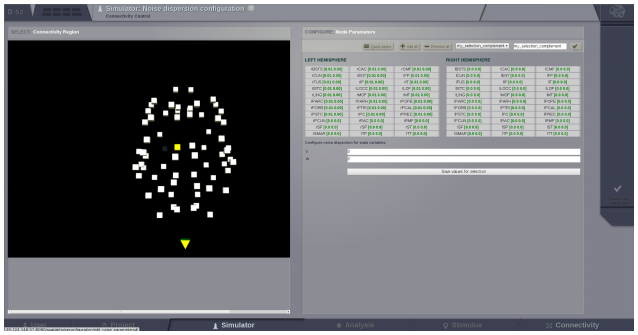
(A)



(B)



(C)



(D)

Figure 3: *TheVirtualBrain* Simulator Area: (A) View of the main interface. Left, the history column keeps the information about the simulations and their status; middle, the simulation core column is where simulations are configured (e.g., change model, parameters, simulation length); and right, the visualization column, gives the possibility to configure visualizers to display the resulting time series or visualizers that will add an analysis step before displaying the results. (B) Region-based simulation configuration area. The parameters of the local model can be set independently for each node, that is, the dynamics of each node may be different. (C) Surface-based simulation configuration area. In a similar fashion, the model parameters are *spatialized* by defining them as a function of a certain kernel (e.g., Gaussian kernel). (D) Noise configuration area.

- state variables to be recorded and stored;
- initial conditions (seed and type of noise used to set random initial conditions);

- integration scheme;
  - if stochastic, the seed for numpy's rand can be set as well as the type of noise (white, coloured);
  - integration time step size;
  - monitors (you can set the monitors period to downsample the raw time-series)
  - simulation length

Additional information about the components (e.g., modules, datatypes and their attributes) is available by clicking on the interrogation mark icon next to each element. This documentation is pulled from the annotations provided by the traits system and doc strings.

Specific pages are accessible for setting up the neural mass model parameters in region-based and surface-based simulations, as well as for configuring the noise amplitude in stochastic integrations (only for region-based simulations) (Figs. 3 B, C and D) The 'Set up region Model' area consist of an interactive phase-plane display. This tool shows the 2-dimensional planes of the general n-dimensional phase space of the local dynamic model. This tool is used to observe how the dynamics of the physical model change as a function of its parameters, acting as a guide to set those parameters appropriately.

For surface-based simulations the model parameters are defined as a function of distance from a central focal point (vertex of the surface). Thus, there is an extra layer of complexity by spatially varying the model parameters.

On the right column, different displays can be configured to exhibit the simulated time series or to add an analysis step and see those results (e.g., compute the correlation coefficients and visualize the resulting matrix).

It is possible to launch parallel simulations to systematically explore a set of components (e.g., a parameter of the the local dynamics model, coupling strength, conduction speed, among others. The resulting maps will be presented either in a discrete (Fig.4 A) or a continuous 2D plot.

psl: [Maybe mention that the value presented in the pse images is a float representing a certain charactersitic of a time-series collection (eg, for exploring synchronization one should use the kuramoto index parameter.)]

4.1.3 Analysis & Visualizers *TheVirtualBrain* does not aim to compete at the analysis level with other tools in Neuroscience that are highly specialized and with great history in data analysis, like FSL (Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012) , SPM (Friston et al., 1995), FieldTrip (Oostenveld et al., 2011) and Brainstorm (Tadel et al., 2011). What we offer is a minimalist set of algorithms to post-process your simulated results (or even process imported patient measured scans) inside *TheVirtualBrain* , mainly for quick validations.

Included in *TheVirtualBrain* are adapters for *Fast ICA* from the python library *sklearn*, a python implementation of *Fourier Spectral Analysis*, the, Matlab based, Brain Connectivity Toolbox *BCT* `https://sites.google.com/site/bctnet/`, as well as a range of other analyzers.

For each of the DataTypes produced in *TheVirtualBrain* , one or more visualizers are available. *TheVirtualBrain* has a number of visualizer types, each developed with the technology that provides the best support for the specific requirements of a given visualization:

1. *WebGL viewers:* are based on *HTML 5 Canvas* element and the *gl* context. These viewers offer nice 3D display, vectorial zoom support, user interaction with the scene (rotate, translate), quick response (even when thousands of vertices and edges are to be manipulated) and good resolution for exported images.
2. *SVG viewers:* offer great selection, zoom and scaling effects and extraordinary quality for exported images, while having a relatively low number of elements to display on the page. We use such viewers for manipulating and displaying TimeSeries, Covariance or Cross Coherence DataType results. These visualizers were developed expressly for these data types in TVB, and provide a richer level of interaction than Canvas based visualizers.
3. *MPLH5 viewers:* emphMatplotlib has an *HTML 5* backend that we use for viewing some of *TheVirtualBrain* 's DataTypes (like Fourier or Wavelet) `https://code.google.com/p/mplh5canvas/`
4. *Other* simpler viewers in *TheVirtualBrain* are using JIT `http://philogb.github.io/jit/` or FLOT `http://www.flotcharts.org/` - JS libraries. These are mainly 2D graph displayers for some simple *TheVirtualBrain* generated data.

4.1.4 Connectivity Tools *Connectivity* in the context of *TheVirtualBrain* is a DataType, mapping structural information about a subject (a real single individual or an average template). For editing and viewing a Connectivity, *TheVirtualBrain* has a specific page, where the *G-User* can manipulate connectivity strength and lengths starting from the granularity of an edge.

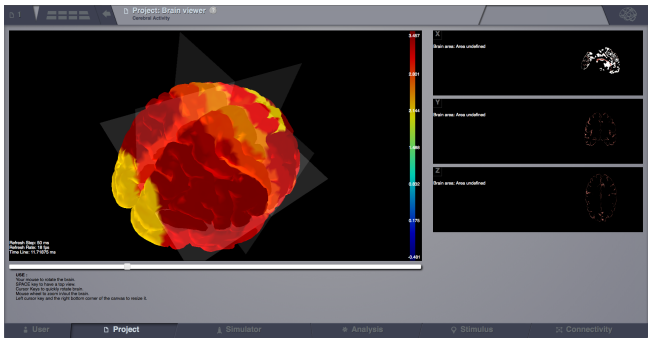
We do not store or use information about the exact anatomical path or a connection, only the region centers and connection weights and lengths.

4.1.5 Stimulus Editor In the *Stimulus* area, an interactive environment assists users to generate stimulation patterns (e.g., a modeling study about TMS) that maybe be later included in a simulation. Similarly to the mechanism employed to vary model parameters from node to node, stimulation patterns are generated independently for region-based and surface-based simulations. In the former, a unique temporal profile can be specified for each node, although the amplitude of the stimulation can be modulated individually for each node. In the latter, in addition to the temporal profile, it is possible to select several vertices on the surface to define the foci around which a spatial pattern is centered (Fig. 6). A stimulation profile in *TheVirtualBrain* is a Pattern datatype, and it can be either temporal or spatiotemporal depending the spatial support of the network.

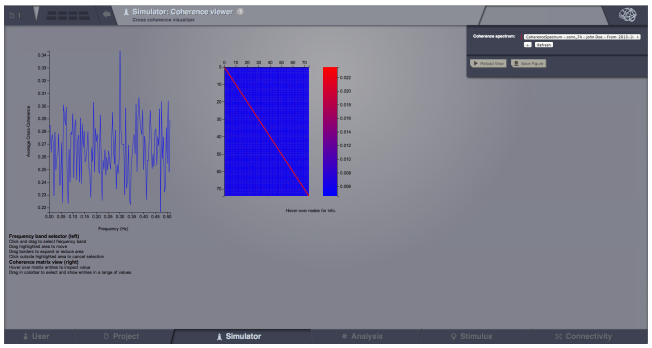
psl: [a]dded the image for the sake of completeness, but maybe remove.

4.2 Console and scripting

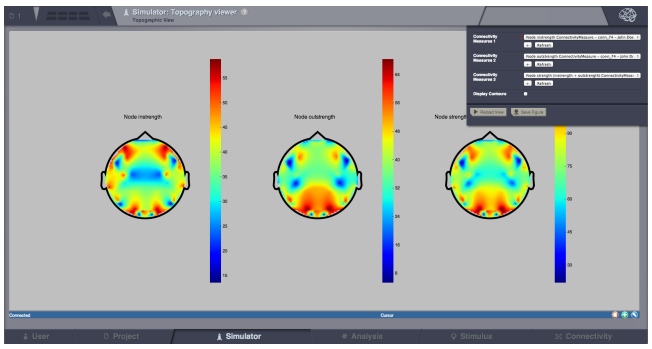
The components of TVB are of course accessible from a Python script or, more conveniently, from any of the IPython interfaces. For example, the tutorials for the simulator have been developed as



(A)



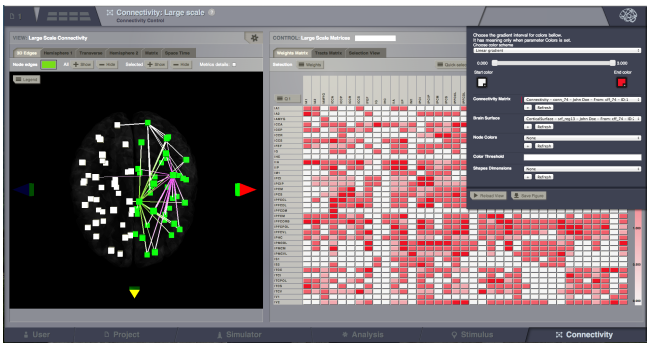
(B)



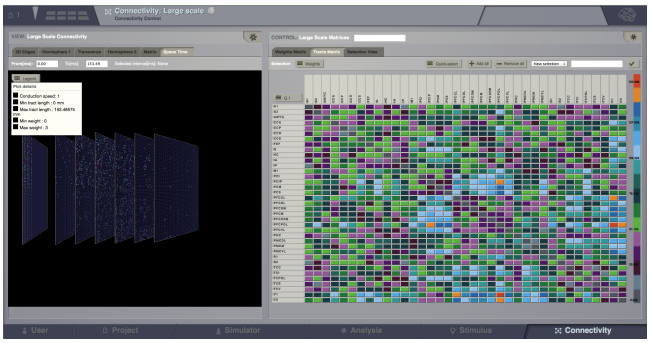
(C)

(D)

Figure 4: *TheVirtualBrain* visualizers: (A) WebGL: 3D display of region level simulated signal, mapped on a brain cortical surface (B) SVG: Cross Coherence (C) MPLH5: Topographic view with Connectivity in/out strength measures (D) FLOT: Parameter Space Exploration results grid

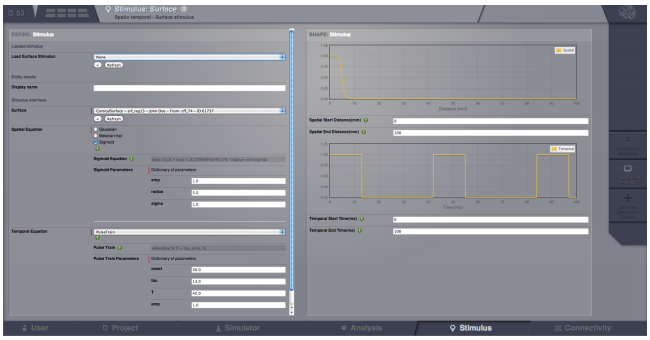


(A)



(B)

Figure 5: Connectivity Tools: (A) Left side: Displaying weighted connections between selection of nodes, with 3D manipulation. Right side: Editing weight connections, singular or bulk. (B) Left side: Show effect of connectivity delays (in milliseconds) when conduction speed is 1 mm/ms. Right side: Editing and displaying one quadrant from the matrix of connection tracts.



(A)

Figure 6: Stimulus Editor for a surface-based simulation.

IPython notebooks, due to its ability to mix text, mathematics, code and figures.

4.2.1 `hello_brain.py` To give a basic feel for scripting TVB simulations, we will walk through a simple example of a region-level simulation.

```
from tvb.simulator.lab import *
```

which is an all-in-one module making writing scripts shorter, in the style of `pylab`, as it imports everything from `pylab`, `numpy` and most of TVB's simulator modules. Next, we build a simulator object:

```
sim = simulator.Simulator(
    model        = models.Generic2dOscillator(),
    connectivity = connectivity.Connectivity(),
    coupling     = coupling.Linear(a=1e-2),
    integrator   = integrators.HeunDeterministic(),
    monitors     = (
            monitors.TemporalAverage(),
    )
)
```

where we've employed a two dimensional oscillator with default parameters, the default connectivity, a linear coupling function with a slope of $1e-2$, and deterministic Heun integrator and a monitor that temporally averages the network dynamics before providing output.

While TVB strives to keep modules independent of one another, it is typical for mathematical dependencies to arise between, for example, the mass model and the integration time step, so after configuring a simulator object, it is necessary to invoke

```
sim.configure()
```

which results in walking the tree of objects, checking and configuring the constraints among parameters recursively.

The next step is to run through the simulation, collecting output from the simulator. In this case, it is as simple as

```
ys = array([y for ((t, y),) in  sim(simulation_length=3e2)])
```

where the simulator has been called, returning a generator which performs the integration and returns, for each monitor, the current time and activity. In a case where EEG and fMRI monitors, for example, were used, we might write

```
eeg, mri = [], []
for (t_eeg, y_eeg), (t_mri, y_mri) in sim(3e2):
                if y_eeg is not None:
                eeg.append(y_eeg)
                ...
```

Because fMRI and EEG monitors have very different timescales, whenever one monitor return data and the others do not, the others contain `None`, hence the check. Building more complex logic in this loop would permit, for example, online feedback and modification of connectivity.

After the simulation loop has finished, you may wish to see the result, following the previous listing,

```
plot(ys[:, 0, :, 0], 'k', alpha=0.1)
```

Here we note that `ys` is four dimensional. The simulator has the convention of treating mass model state as a three dimensional array of state variables by nodes by statistical modes. Because `ys` is an array collected over time, the first dimension is time, and the plot here is of each node's first state variable, over time.

Many more demonstrations of the various features of the simulator can been found in scripts distributed with the sources of TVB, or browsed online at `https://github.com/the-virtual-brain/scientific_library/tree/trunk/tvb/simulator/demos`.

For more details see the Ipython notebook Tutorial: Anatomy of a Region Simulation `http://nbviewer.ipython.org/urls/raw.github.com/the-virtual-brain/scientific_library/trunk/tvb/simulator/doc/tutorials/Tutorial_Anatomy_Of_A_Region_Simulation/Tutorial_Anatomy_Of_A_Region_Simulation.ipynb`

5 FUTURE WORK

Since the recent release of the 1.0 version of TVB, it has been officially considered *feature* complete, however, in several cases, the development of features has outstripped other essential parts of software projects. Going forward, general priorities include advancing test coverage, improving documentation for users, and preparing PyPI and Debian packages. In the mean time, TVB's Google groups mailing list continues to fill any gaps.

In the simulator itself, continued optimization of C and GPU code generation will take place to increase the rate at which parameter sweeps can be performed. Additionally, an interface *from* MATLAB to TVB is being developed to allow use of the simulator through a simple set of MATLAB functions. As this infrastructure is based on an HTTP and JSON API, it will likely enable other applications to work with TVB as well.

Lastly, as TVB was originally motivated to allow a user to move from acquired data to simulated data as easily as possible, we will continue to integrate the requisite steps

1. Diffusion tensor imaging & tractography pipeline
2. Connectome project
3. Structural imaging processing via FreeSurfer (pySurfer, NiPy, etc.)
4. NeuroML project

ACKNOWLEDGMENTS

Several authors have also participated in the development of TVB. They are cited in the `AUTHORS` file in TVB distribution and deserve also our warm acknowlegments. LP whishes to thank specifically Y. Manhoun for his implication in the conception and development of the first prototype of the TVB architecture. The research reported herein was supported by the Brain Network Recovery Group through the James S. McDonnell Foundation and the FP7-ICT BrainScales. PSL and MMW received support by from the French Ministère de Recherche and the Fondation de Recherche Medicale.

REFERENCES

Amari, S. (1977). Dynamics of pattern formation in lateral-inhibition type neural fields. *Biol. Cybern.*, 22:77–87.

Austin, J., Jackson, T., Fletcher, M., Jessop, M., Liang, B., Weeks, M., Smith, L., Ingram, C., and Watson, P. (2011). Carmen: Code analysis, repository and modeling for e-neuroscience. *Procedia Computer Science*, 4:768–777.

Bastiani, M., Shah, N. J., Goebel, R., and Roebroeck, A. (2012). Human cortical connectome reconstruction from diffusion weighted mri: the effect of tractography algorithm. *Neuroimage*, 62(3):1732–1749.

Breakspear, M., Terry, J. R., and Friston, K. J. (2003). Modulation of excitatory synaptic coupling facilitates synchronization and complex dynamics in a biophysical model of neuronal dynamics. *Network*, 14(4):703–732.

Brunel, N. and Wang, X.-J. (2001). Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. *J. Comput. Neurosci.*, 11:63–85.

Cabral, J., Hugues, E., Sporns, O., and Deco, G. (2011). Role of local network oscillations in resting-state functional connectivity. *Neuroimage*, 57(1):130–139.

Coombes, S. (2010). Large-scale neural dynamics: simple and complex. *Neuroimage*, 52(3):731–739.

Dabbish, L., Stuart, C., Tsay, J., and Herbsleb, J. (2012). Social coding in github: transparency and collaboration in an open software repository. In *Proceedings of the ACM 2012 conference on Computer Supported Cooperative Work*, pages 1277–1286. ACM.

David, O., Cosmelli, D., and Friston, K. J. (2004). Evaluation of different measures of functional connectivity using a neural mass model. *Neuroimage*, 21(2):659–673.

Deco, G., Jirsa, V., and McIntosh, A. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat. Rev. Neurosci.*, 12(1):43–56.

Deco, G., Jirsa, V., McIntosh, A., Sporns, O., and Kötter, R. (2009). Key role of coupling, delay, and noise in resting brain fluctuations. *Proc. Natl. Acad. Sci. U.S.A.*, 106(25):10302–10307.

Deco, G., Jirsa, V., Robinson, P. A., Breakspear, M., and Friston, K. (2008). The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLoS Comput. Biol.*, 4(8):e1000092.

Deco, G., Ponce-Alvarez, A., Mantini, D., Romani, G. L., Hagmann, P., and Corbetta, M. (2013). Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *J Neurosci*, 33(27):11239–11252.

Deco, G., Senden, M., and Jirsa, V. (2012). How anatomy shapes dynamics: a semi-analytical study of the brain at rest by a simple spin model. *Front. Comput. Neurosci.*, 6:68.

Freeman, W. J. (1975). *Mass Action in the Nervous System*. ACADEMIC PRESS New York San Francisco London.

Friston, K., Holmes, A., Worsley, K., Poline, J., Frith, C., and Frackowiak, R. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.*, 2:189–210.

Ghosh, A., Rho, Y., McIntosh, A., Kötter, R., and Jirsa, V. (2008). Noise during rest enables the exploration of the brain's dynamic repertoire. *PLoS Comput. Biol.*, 4(10):e1000196–e1000196.

Goodman, D. F. M. and Brette, R. (2009). The brian simulator. *Front. Neurosc.*, 3(2):192–197.

Gramfort, A., Luessi, M., Larson, E., Engemann, D., Strohmeier, D., Brodbeck, C., Parkkonen, L., and Hämäläinen, M. (2013). Mne software for processing meg and eeg data. *Neuroimage*.

Gramfort, A., Papadopoulo, T., Olivi, E., and Clerc, M. (2010). Openmeeg: opensource software for quasistatic bioelectromagnetics. *Biomed. Eng. Online*, 9:45.

Guckenheimer, J. and Holmes, P. (1983). Nonlinear oscillations, dynamical systems, and bifurcations of vector fields.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., and Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol.*, 6(7):e159.

Hamalainen, M. and Sarvas, J. (1989). Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. *IEEE Trans. Biomed. Eng.*, 36(2):165–171.

Herz, A. V., Meier, R., Nawrot, M. P., Schiegel, W., and Zito, T. (2008). G-node: an integrated tool-sharing platform to support cellular and systems neurophysiology in the age of global neuroinformatics. *Neural Networks*, 21(8):1070–1075.

Hindmarsh, J. and Rose, R. (1984). A model of neuronal bursting using three coupled first order differential equations. *Proc. R. Soc. London, Ser. B*, 221(1222):87–122.

Hines, M. L. and Carnevale, N. T. (2001). Neuron: a tool for neuroscientists. *Neuroscientist.*, 7(2):123–135.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., and Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proc. Natl. Acad. Sci. U.S.A.*, 106(6):2035–2040.

Jansen, B. and Rit, V. (1995). Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biol. Cybern.*, 73(4):357–366.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., and Smith, S. M. (2012). Fsl. *Neuroimage*, 62(2):782–790.

Jirsa, V. and Haken, H. (1997). A derivation of a macroscopic field theory of the brain from the quasi-microscopic neural dynamics. *Phys. D*, 99(4):503–526(24).

Jirsa, V., Jantzen, K., Fuchs, A., and Kelso, J. (2002). Spatiotemporal forward solution of the eeg and meg using network modeling. *IEEE Trans. Med. Imag.*, 21(5):493–504.

Klöden and Platen (1995). *Numerical solution of stochastic differential equations*. Springer.

Kuramoto, Y. (1975). *Self-entralnment of a population of coupled non-llnear oscillators*, chapter 52, page 420. Number 39 in Lectures On Physics: International Symposium on Mathematical Problems in Theoretical Physics. Springer.

Kötter, R. (2004). Online retrieval, processing, and visualization of primate connectivity data from the cocomac database. *Neuroinformatics*, 2(2):127–144.

Larter, R., Speelman, B., and Worth, R. (1999). A coupled ordinary differential equation lattice model for the simulation of epileptic seizures. *Chaos*, 9(3):795–805.

Liley, D. T., Alexander, D. M., Wright, J. J., and Aldous, M. D. (1999). Alpha rhythm emerges from large-scale networks of realistically coupled multicompartmental model cortical neurons. *Network*, 10(1):79–92.

Mannella, R. (2002). Integration of stochastic differential equations on a computer. *Internat. J. Modern Phys. C*, 13(9):1177–1194.

Mannella, R. and Palleschi, V. (1989). Fast and precise algorithm for computer simulation of stochastic differential equations. *Phys. Rev. A*, 40:3381–.

Mitchell, J. S., Mount, D. M., and Papadimitriou, C. H. (1987). The discrete geodesic problem. *SIAM Journal on Computing*, 16(4):647–668.

Morris, C. and Lecar, H. (1981). Voltage oscillations in the barnacle giant muscle fibre. *Biophys. J.*, 35(1):193–213.

Nethercote, N. and Seward, J. (2007). Valgrind: a framework for heavyweight dynamic binary instrumentation. *ACM Sigplan Notices*, 42(6):89–100.

Nolte, G. (2003). The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Phys Med Biol*, 48(22):3637–3652.

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). Fieldtrip: Open source software for advanced analysis of meg, eeg, and invasive electrophysiological data. *Comput Intell Neurosci*, 2011:156869.

Pérez, F. and Granger, B. E. (2007). IPython: a System for Interactive Scientific Computing. *Comput. Sci. Eng.*, 9(3):21–29.

Rubinov, M. and Sporns, O. (2010a). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*,

52(3):1059–1069.

Rubinov, M. and Sporns, O. (2010b). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, 52(3):1059–1069.

Sarvas, J. (1987). Basic mathematical and electromagnetic concepts of the biomagnetic inverse problems. *Phys. Med. Biol.*, 32(1):11–22.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., and Matthews, P. M. (2004). Advances in functional and structural mr image analysis and implementation as fsl. *Neuroimage*, 23 Suppl 1:S208–S219.

Spiegler, A. and Jirsa, V. (2013). Systematic approximations of neural fields through networks of neural masses in the virtual brain. *Neuroimage*, 83C:704–725.

Spiegler, A., Kiebel, S. J., Atay, F. M., and Knösche, T. R. (2010). Bifurcation analysis of neural mass models: Impact of extrinsic inputs and dendritic time constants. *Neuroimage*, 52(3):1041–1058.

Stefanescu, R. and Jirsa, V. (2008). A low dimensional description of globally coupled heterogeneous neural networks of excitatory and inhibitory. *PLoS Comput. Biol.*, 4(11):26–36.

Stefanescu, R. and Jirsa, V. (2011). Reduced representations of heterogeneous mixed neural networks with synaptic coupling. *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.*, 83(2):–.

Steyn-Ross, M. L., Steyn-Ross, D. A., Sleigh, J. W., and Liley, D. T. (1999). Theoretical electroencephalogram stationary spectrum for a white-noise-driven cortex: evidence for a general anesthetic-induced phase transition. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics*, 60(6 Pt B):7299–7311.

Strogatz, S. (2001). Nonlinear dynamics and chaos: with applications to physics, biology, chemistry and engineering.

Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., and Leahy, R. M. (2011). Brainstorm: a user-friendly application for meg/eeg analysis. *Comput. Intell. Neurosci.*, 2011:879716.

Wilson, H. and Cowan, J. (1972). Excitatory and inhibitory interactions in localized populations of model neurons. *Biophys. J.*, 12(1):1–24.

Wilson, H. and Cowan, J. (1973). A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. *Kybernetik*, 13(2):55–80.

Wong, K.-F. and Wang, X.-J. (2006). A recurrent network mechanism of time integration in perceptual decisions. *J. Neurosci.*, 26(4):1314–1328.

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., and Smith, S. M. (2009). Bayesian analysis of neuroimaging data in fsl. *Neuroimage*, 45(1 Suppl):S173–S186.

Zetterberg, L. H., Kristiansson, L., and Mossberg, K. (1978). Performance of a model for a local neuron population. *Biol Cybern*, 31(1):15–26.