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Research Resource

Computational neuroscience and neuroinformatics: Recent progress and resources

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The human brain and its temporal behavior correlated with development, structure, and function is a complex natural system even for its own kind. Coding and automation are necessary for modeling, analyzing and understanding the 86.1 ± 8.1 billion neurons, an almost equal number of non-neuronal glial cells, and the neuronal networks of the human brain comprising about 100 trillion connections. 'Computational neuroscience' which is heavily dependent on biology, physics, mathematics and computation addresses such problems while the archival, retrieval and merging of the huge amount of generated data in the form of clinical records, scientific literature, and specialized databases are carried out by 'neuroinformatics' approaches. Neuroinformatics is thus an interface between computer science and experimental neuroscience. This article provides an introduction to computational neuroscience and neuroinformatics fields along with their state-of-the-art tools, software, and resources. Furthermore, it describes a few innovative applications of these fields in predicting and detecting brain network organization, complex brain disorder diagnosis, large-scale 3D simulation of the brain, brain–computer, and brain-to-brain interfaces. It provides an integrated overview of the fields in a non-technical way, appropriate for broad general readership. Moreover, the article is an updated unified resource of the existing knowledge and sources for researchers stepping into these fields.

Keywords. Brain–computer–music interface (BCMI); Brainnet; brain-to-brain interface (B2B); BrainX^3; Connectome

1. Introduction

The modern neuroscience discipline academically began with the 'Neurosciences Research Program (NRP)' in 1962 (Adelman 2010) at MIT. The neurological disorders of human brain constitute 13% of the global disease set. It is a lot more than the cardiovascular diseases which amount to 5% of the global disease set. Different types of cancers constitute 10% of the global disease set (Kiernan 2015). Present day neuroscience researchers are a combination of physiologists, theoretical and experimental physicists, mathematicians, computer scientists, engineers, molecular biologists, doctors, clinicians, bioinformaticians, psychologists, and philosophers among others. Such a diverse mix of researchers gives a glimpse of the rich vividness of this field (figure 1).

The nervous system computes and processes information (Piccinini and Shagrir 2014) very fast. A precise and powerful mathematical theory with different functions and relations among different positions of a brain is needed for computing the activities of the nervous system. However, the detailed procedures and activities of nervous systems, as well as their underlying reasons cannot be reflected by mathematical theories alone. We need hypothetical physical systems for computing them (Copeland and Shagrir 2017; Piccinini 2011). Computation of neuronal signal is neither digital nor analog; rather it is a different kind of computation (Piccinini and Bahar 2013). There are several levels of organization in the nervous system, which can be decomposed into a number of subsystems, like cortex and brainstem (Craver 2007; Bechtel 2008). The subsystems can also be decomposed into smaller systems. These objectives have led to the formation of a distinct branch of neuroscience known as 'computational neuroscience'. Eric L Schwartz first introduced the term in 1985. The first part of the review focuses on the role of computational neuroscience in research of brain network organization along with the description of the state-of-the-art tools, software, and databases.

Computational neuroscience research generates highly complex data in large volumes. Their proper storage, accurate knowledge extraction, and quick dispersion are a big challenge. Hence, a computer-based collation, management, and analysis of neurobiological data is a required step

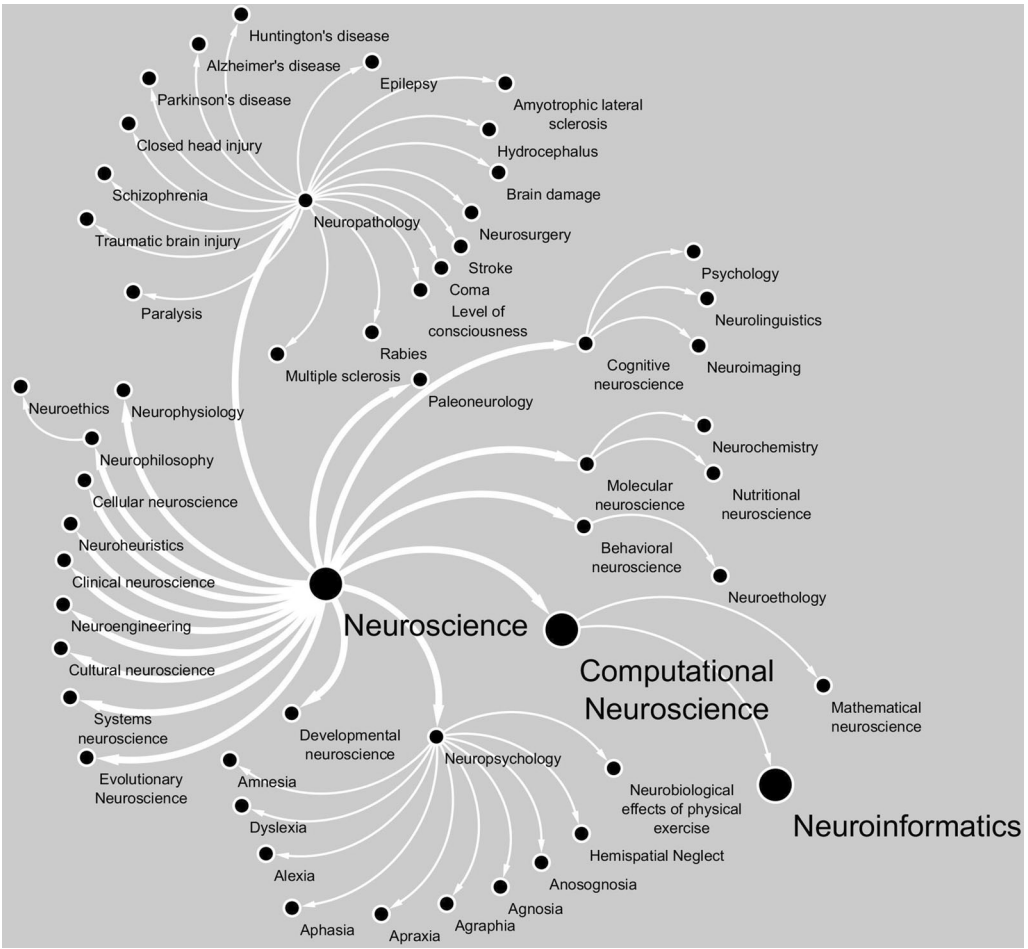

Figure 1. A few branches of Neuroscience with a focus on Computational Neuroscience and Neuroinformatics.

towards understanding several areas of neuroscience that gave rise to a new branch namely, 'neuroinformatics' (Young and Scannell 2000). Neuroinformatics research includes the development of neuroscience data storage infrastructure, advanced tools for data extraction and dispersion, and approaches for analyzing such data which may facilitate major advancements in understanding the structural and functional aspects of the human brain (Beltrame *et al.* 2000). The second part of the review describes scopes and challenges of neuroinformatics research along with a few existing languages, data sources, tools and software, simulation platforms, a few innovative applications.

2. Computational neuroscience

By an old definition (1993), 'The expression Computational Neuroscience reflects the possibilities of generating theories of brain function in terms of the information-processing properties of structures that make up nervous systems (Schwartz 1993).' A more recent brief definition (2010) is 'computational neuroscience is the theoretical study of the brain used to uncover the principles and mechanisms that guide the development, organization, information-processing and mental abilities of the nervous system (Trappenberg 2009).' In the present day scenario, computational neuroscience can also be defined as the study of brain circuits/networks to explore how the brain processes various activities according to specific information and properties of structural and functional activities with the help of computational power.

The human brain is composed of 86.1 $\pm$ 8.1 billion neurons (Azevedo *et al.* 2009) and almost an equal number of non-neuronal glial cells; the neurons being interconnected by about a 100 trillion inhibitory and excitatory synapses as well as above-threshold and sub-threshold synapses, which in turn constitute large neuronal networks (Goldental *et al.* 2014). The main motivation of computational neuroscience since the last four decades has been to explore the process of representation and manipulation of information in the brain using electrical and chemical signals. Different activities, i.e., to hear, to see, to remember and to learn among others

are controlled by various regions of the brain. There are different kinds of realistic and simplified models for simulating neuronal systems and large brain networks with the advancement of computational power (Sejnowski *et al.* 1988).

Realistic models try to incorporate different available cellular parameters, and as a result, they become computationally expensive and complex to understand. Such an example is the Hartline-Ratliff model of the lateral inhibition and interaction in Limulus eye (Hartline and Ratcliff 1974) at the network level. But even the most successful realistic brain models often fail to predict the tissue functions. The concept of receptive field introduced first by Sherrington (Sherrington 1906) as a basic functional unit of neurons and later by Hartline (Hartline 1938) led to the classical receptive field models developed in cat and primate visual systems. These, in turn, led to the explanation of a few psychophysics based experimental results, while at the same time also failing in some (Gregory 1981, 2009). Thus it is necessary to develop simple models that can capture important principles. Though these models fail to predict the complete functional and structural features of brain circuits due to incomplete information on different parameters, they can shape future research directions with the help of experimental data and programs (Sejnowski *et al.* 1988).

3. Computational neuroscience and brain network organization

The scope of computation in neuroscience is enormous. One of the research areas coming under this scope is 'brain network organization', both structural and functional (Zhou *et al.* 2006; Bassett and Bullmore 2009; Achard and Bullmore 2007; Bullmore and Sporns 2012; Goñi *et al.* 2014). Significant progress can be found in the field of studying microscopic brain dynamics (i.e., at the level of single-neuron, single-synapse, and single-molecule) over the last 50 years. However, many research issues are yet to be addressed regarding the understanding of macroscopic/mesoscopic brain dynamics, often recorded by EEG (electroencephalography), ERPs (event related potentials), MEG (MAGNETOENCEPHALOGRAPHY), and LFPs (local field potentials) among other methods. Coherent dynamic phenomena of local brain networks (thousands of neurons) as well as the entire brain regions (millions of neurons) can be understood from electrical recordings of brain activity. There are close ties between blood flow signals measured with fMRI (functional magnetic resonance imaging) and local field potentials recorded in the cortex. Any form of synchrony, stationary/traveling, oscillatory activity can be associated with the coherent brain dynamics. It is an open problem to understand how the brain dynamics at different spatial scales are functionally interrelated. Moreover, it is quite challenging to establish a connection between the dynamics of single neurons monitored by intracellular recordings and the local or distant brain regions observed using EEG, ERPs, MEG, LFPs, and fMRI among other techniques. For the very reason, we have mentioned briefly about microscopic brain dynamics and mostly concentrated on the study of macroscopic/mesoscopic brain dynamics in the following discussion.

3.1 *Microscopic brain dynamics: Single neurons and synapses*

It is very difficult to form an anatomical connection matrix of human brain (connectome) at the level of single neuron because of its larger magnitude. For example, cortex alone contains 10^{10} neurons and 10^{13} connections approximately (Murre and Sturdy 1995; Braitenberg and Schuz 1991; Sporns *et al.* 2005). Alterations of single synapses do not reflect traceable macroscopic effects. Moreover, individual neurons and connections undergo rapid plastic changes (Mountcastle 1998). The huge number and high variability of individual neurons and synapses restrict us to include the microscopic studies as basic elements of brain network organization in this section.

3.2 *Macroscopic/mesoscopic brain dynamics: Networks among brain regions as well as elementary processing units*

It is a hard task to delineate brain areas and neuronal populations. There is no unique rule for parcellation of human brain regions. A previous investigation (Van Essen *et al.* 1998) has shown that neurons are arranged in the order of 100 or more number of anatomically distinct regions and areas in the human cerebral cortex. Different criteria for parcellation may be needed for different parts of the human brain (e.g., cerebellum, brain stem, cortex or thalamus). Thus, brain network organization among anatomically distinct brain regions and interregional pathways are most feasible to form a human neuronal matrix. However, the corticothalamic matrix at the macro scale does not provide functional informative subdivisions or segregated subcircuits within each brain region. Thus, macroscopic brain network organization is often insufficient to understand human brain's functional dynamics and information processing capacities. Hence, mesoscopic brain network organization, i.e., the characterization of connection patterns among elementary processing units is crucial. Here, we have covered a

few studies that analyze brain network organization at macro/meso scale.

Just as real-world complex systems may mathematically be modeled as graphs, in the same way, both structural (e.g. anatomical) as well as functional properties of a brain may be revealed. Identification of relations for a structural network is quite challenging. Several methods for imaging and recording from various regions of the brain have been developed for such challenges (Sporns and Kötter 2004; Bressler and Menon 2010; Sompolinsky 2014). We can predict types of possible interactions among different areas of a brain by finding out the pattern of structural network connectivity. For example, small world structure of cortical networks suggests that there are many short-range functional interactions but a few long-range interactions (Bassett *et al.* 2006).

Brain functional networks reflect coordination between segregation and integration, which is established by various factors, i.e., structural nodes, path length, divergence and convergence among others (Rubinov and Sporns 2010). They are often scale-free, and have small world properties along with short path length and high clustering coefficient. There is a compromised balance between network efficiency and wiring cost (Achard and Bullmore 2007). It is a challenge to predict the functional network connectivity of a brain from its corresponding structural connectivity. Often these predictions are based on analytical measurements and network communications (Goñi *et al.* 2014), but work has already been done with cat (Zhou *et al.* 2006) and monkey brain (Achard *et al*. 2006). Such kinds of studies help in analyzing the underlying anatomical connectivity of different portions of a brain. A normal brain functional network has been correlated with age (Chen *et al*. 2013), sex (Chen *et al.* 2013), memory (Burianova *et al*. 2010), education and intelligence (Bassett *et al*. 2011; Langer *et al.* 2012; Muller and Meyer 2014), occupation, environment and stress (de Quervain *et al.* 2000) among other factors by a stream of individual investigations. Often, more complexity arises from the fact that two hemispheres of a brain are different in terms of anatomical and functional behaviors (Chen *et al*. 2013; Muller and Meyer 2014).

Brain networks have a tendency to maximize functional motifs as well as minimize structural motifs (Sporns and Kötter 2004). By definition, a functional network is a set of interactions among brain regions to perform specific functions (Bressler and Menon 2010). The topology and connectivity matrix of large-scale functional networks changes through a person's lifespan according to maturity and learning process (Bressler and Tognoli 2006). Different components of large-scale brain functional networks execute different activities with the help of other components (Miller and Cohen 2001). For example, coordination between prefrontal and posterior parietal control areas allows activities among motor and sensory areas that help in perceptuomotor processing (Corbetta and Shulman 2002; Armstrong *et al*. 2006; Ruff *et al.* 2006; Bressler *et al.* 2008). It explains how different parts of the brain communicate with each other due to various perceptions. There is no proper definition available for brain functional nodes (Bressler and Menon 2010). However, now-a-days, brain functional nodes can be identified by elevated metabolism in PET (Positron Emission Tomography), blood perfusion in fMRI, synchronized oscillatory activity in LFP recordings (Bressler and Menon 2010) and also by fNIRS (Functional Near Infrared Spectroscopy).

A normal brain functional network also alters with respect to body disorders and diseases, *i.e.*, type 2 diabetes (Reijmer *et al.* 2013), Alzheimer's disease (Tijms *et al.* 2014), attention-deficit hyperactivity disorder (ADHD) (Lee *et al.* 2011), autism (Lee *et al.* 2011), Parkinson's disease (Feigin *et al.* 2007) and bipolar disorder (Leow *et al.* 2013) among others. Type 2 diabetic patients process information slowly due to the alteration or disruption in the white matter region (Reijmer *et al.* 2013). Alzheimer's patients with more severe cognitive impairment have increased topology randomness in gray matter (Tijms *et al.* 2014). Bipolar patients have been characterized by impaired inter-hemispheric but relatively preserved intra-hemispheric integration. Moreover, low white matter integrity at the corpus callosum has been found in bipolar disorder patients (Leow *et al.* 2013).

It has also been found that lesions of many brain disorders including Alzheimer's disease and schizophrenia are remarkably more plausible to be located in hub nodes of their respective brain networks (Crossley *et al.* 2014). Moreover, some previous investigations have studied various stages of different neurological disorders including autism, Alzheimer's and epilepsy using graph theory (Bartolomei *et al.* 2013; Peters *et al.* 2013; Seo *et al.* 2013). Different stages of these disorders have been compared with each other and with reference normal graphs obtained from the healthy volunteers. The comparisons highlighted that the increase of local clustering index and average path length as the severity of the disease increases. There are different kind of models to determine the abnormalities in brain circuits during different psychiatric and neurological diseases, like epilepsy, Parkinson's disease, autism, schizophrenia and disorders of consciousness (Schiff *et al.* 2014; Ching and Brown 2014; McCarthy *et al.* 2012). They consider different factors for analysis, like altered gains of neurons and synapses, abnormal oscillations, excitation-inhibition imbalance, pattern change of large-scale brain dynamics and resting state networks (Moussa *et al.* 2012). These kinds of relation provide the conceptual framework for the graph-theoretic analysis of large scale brain network (Smith *et al.* 2013; Bullmore and Sporns 2009; Battaglia *et al.* 2012).

Analysis of resting-state fMRI functional connectivity by graph theoretic studies (Astolfi, de Vico Fallani *et al.* 2007;

Dosenbach *et al.* 2007) of large-scale human brain networks often highlights small-world network properties (Bullmore and Sporns 2009; Supekar *et al.* 2009). The topology of sub-networks can be described using different graph theoretic matrices (Müller-Linow *et al.* 2008). The analysis of resting and specific task related connectivity patterns (Smith *et al.* 2009) indicated that functional networks inherit small systemic change during cognition. As discussed earlier there are different models to identify the altered patterns of functional networks during various psychiatric and neurological disorders (Bhattacharya 2001; Murias *et al.* 2007; Seeley *et al.* 2009; Uhlhaas and Singer 2007; Timmermann *et al.* 2003; Stam *et al.* 2007; Ford and Mathalon 2008). However, a lot has to be done in order to explore the hierarchy of human brain networks. Thus, the field of brain network analysis explores different aspects of brain functions and aims at finding new fundamental insights during normal and abnormal cognitive states.

3.3 *Existing tools, software and databases*

Different tools and software are available to analyze computational neuroscience data and neuroimages. They are maintained by The Source for NeuroInformatics Tools and Resources (NITRC)[1]. A few of them are discussed here. These tools and resources are freely available. Mostly, the kind of data used, other specific requirements and their sources are discussed here.

- FSL[2]: It is a library of tools for analyzing the EEG, MRI and fMRI data (freely available).
- SPM[3]: It deals with EEG, fMRI, MEG, PET and SPECT brain imaging data sequences, and their analyses (freely available).
- BrainVoyagerQX[4]: It can handle MRI, EEG and MEG data. This software incorporates statistical, numerical and image processing tools. It requires HASP license (freely available).
- Turbo BrainVoyager[5]: It is online real-time processing software to handle fMRI data. It requires HASP license (freely available).
- MRIcron[6]: It is an image viewing toolbox to deal with MRI data. It also supports some in-built statistical functions (freely available).
- itk-SNAP[7]: This is a 3D medical image segmentation software. It handles MRI and CT scan data (freely available).
- EEGLAB[8]: It is an open source environment for electrophysiological signal processing. It has interactive MATLAB toolbox for visualization, artifact removal and analysis of EEG, MEG and ECoG (ElectroCorticoGraphy) data (freely available).
- Chronux[77]: The current release can be implemented as a MATLAB library. It preprocesses, explores, and analyses neural data, *i.e.*, point process and continuous data (freely available).
- FreeSurfer[9]: It reconstructs the brain surface from MRI data, and overlays fMRI data on the reconstructed surface (freely available).
- BrainNet Viewer[10]: It is a visualization tool and constructs structural and functional networks from filtered or processed data (freely available).
- eConnectome[11]: It is a MATLAB package for imaging brain functional connectivity. It deals with EEG, MEG and ECoG data (freely available).
- MNE[12]: It has pre-processing tools and data conditioning utilities. It is a Linux based software. It deals with MEG and EEG data (freely available).
- CONN[13]: It is a MATLAB toolbox for computation, display and fMRI data analysis (freely available).
- BSMac[14]: It is a MATLAB based statistical and graphical visualization toolbox for fMRI data (freely available).
- Bioelectromagnetism MATLAB Toolbox[15]: It helps in visualization and measurement of Event Related Potential (ERP). It accepts EEG and MRI data (freely available).
- The Virtual Brain[76]: It simulates brain behavior by manipulating brain connectivity and some associated network parameters (freely available).

Table 1 lists a few computational neuroscience databases. It lists different types of data (image/network; EEG/MRI/fMRI; normal/diseased; real/simulated), the source of data, access type (freely available/paid), a brief description of the data source and sample properties of each listed database.

[1] *https://www.nitrc.org/*
[2] *http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/*
[3] *http://www.fil.ion.ucl.ac.uk/spm/*
[4] *http://www.brainvoyager.com/products/brainvoyagerqx.html*
[5] *http://www.brainvoyager.com/products/turbobrainvoyager.html*
[6] *http://neuro.debian.net/pkgs/mricron.html*
[7] *http://www.itksnap.org/pmwiki/pmwiki.php*
[8] *http://sccn.ucsd.edu/eeglab/*
[77] *http://chronux.org/*
[9] *http://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall*
[10] *https://www.nitrc.org/projects/bnv/*
[11] *http://econnectome.umn.edu/*
[12] *http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/MNE_register/*
[13] *https://www.nitrc.org/projects/conn/*
[14] *http://web1.sph.emory.edu/bios/CBIS/software.html*
[15] *http://eeg.sourceforge.net/*
[76] *http://www.thevirtualbrain.org/tvb/zwei/brainsimulator-software*

Table 1. A few databases for computational neuroscience research

Resource name	Resource description	Sample properties	Access
Brain-image-related resources			
Allen Brain Atlas[16]	Multimodal atlas of the human brain, integrates anatomical and genetic in-formation (Lein *et al.* 2007; Hawrylycz *et al.* 2012)	Healthy volunteer	Free
Brain Maps[17]	High-resolution scanned images of brain sections of various species (da Fontoura Costa and Bollt 2006; Mikula *et al.* 2007)	Healthy human volunteers, primates, and non-primates	Free
OASIS[18]	Cross-sectional/longitudinal images (Marcus *et al.* 2007; Marcus *et al.* 2010)	Healthy volunteers and Alzheimer's disease patients	Free
Brain Development (Imperial College)[19]	Images of 600 patients (adults and neonates) (Robinson *et al.* 2010; Kuklisova-Murgasova *et al.* 2011)	Fetuses, healthy and prematurely born neonates	Free
Whole Brain Atlas[20]	Images of various parts of the brain (Sutton 1999)	Healthy and various diseased patients	Free
StarPlus fMRI data[21]	Data, software, and documentation of the StarPlus fMRI dataset (Birn *et al.* 2002)	Healthy volunteers	Free
COBRE Database[22]	fMRI and phenotypic data of 72 patients and 75 healthy volunteers (Hanlon *et al.* 2011)	Healthy volunteers and schizophrenia patients	Registration required
IBSR Database[23]	MRI data and Eco scans of adults, child, normal volunteers and tumor patients (Wang *et al.* 2013; Mason *et al.* 1997)	Healthy and diseased individuals	Free
The ADHD-200 Sample[24]	Resting state fMRI scans along with phenotypic information of Attention Deficit Hyperactivity Disorder (ADHD) patients (Brown *et al.* 2012)	ADHD patients and developing individuals	Registration required
Descriptive resources			
Brain Architecture Management System[25]	Part-wise human brain description and rat connectomics study data (Bota *et al.* 2003; MacKenzie-Graham *et al.* 2003)	Healthy rat, mouse and human	Free
Bipolar Disorder Neuroimaging Database[26]	Raw and interpreted MRI data (Kempton *et al.* 2008)	Human bipolar disorder patients	Free
Biomarker-related resources			
ADNI[27]	Biomarker samples of Alzheimer's disease patients and healthy volunteers (Mueller *et al.* 2005)	Healthy volunteers and Alzheimer's disease patients	Written request required
Simulated resources			
Brain Web[28]	Simulated MRI data (Cocosco *et al.* 1997)	Healthy human brain	Free

[16] *http://human.brain-map.org/*

[17] *http://brainmaps.org/index.php?p=about*

[18] *http://www.oasis-brains.org/app/template/Tools.vm;jsessionid=F64E1937A76C41CAAB06BCB516EA4A1C*

[19] *http://brain-development.org/*

[20] *http://www.med.harvard.edu/aanlib/home.html*

[21] *http://www.cs.cmu.edu/afs/cs.cmu.edu/project/theo-81/www/*

[22] http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html

[23] *https://www.nitrc.org/frs/?group_id=48*

[24] http://fcon_1000.projects.nitrc.org/indi/adhd200/

[25] *http://map.loni.usc.edu/data/brain-architecture-management-system-bams/*

[26] *https://sites.google.com/site/bipolardatabase/*

[27] *http://www.adni-info.org*

[28] *http://brainweb.bic.mni.mcgill.ca/brainweb/*

Table 1. continued

Resource name	Resource description	Sample properties	Access
EEG-related resources			
SCCN EEG/ERP Database[29]	EEG database supporting text, EEG, and MATLAB file format (Delorme *et al.* 2002)	Normal and experimental human psychological data	Registration required
PhysioNet[30]	EEG recordings of 22 individuals with intractable seizure (Shoeb 2009)	Pediatric subjects with intractable seizure	Free
Berlin Brain-Computer Interface Database[31]	EEG recordings of healthy and psychological patients (Sajda *et al.* 2003)	Normal and experimental human psychological data	Free
The Bern-Barcelona EEG Database[32]	EEG signals of 5 individuals and source code for data analysis (Andrzejak *et al.* 2012)	Focal and non-focal EEG signals	Free
Multiple resources			
SchizConnect[33]	Virtual database for Schizophrenia neuroimaging (Gollub *et al.* 2013)	Schizophrenia patients and healthy individuals	Registration required
Brainsignals.de[34]	List of publicly available brain signals data	EEG, MEG, MRI, fMRI and ECoG databases	Free (registration required)
LONI Image Data[35]	Data of medical imaging projects	healthy and diseased individuals	Application required
COINS[36]	Offers tools to securely collect, store and share data and manage different studies (Turner *et al.* 2011)	Clinical data	Registration required

In order to maintain the huge resources, generated and used in computational neuroscience, a distinct sub-branch, called 'neuroinformatics' has emerged. The following two sections cover an introduction; languages, data, tools and software, simulation platforms used by the neuroinformatics community; a few new approaches; and resources.

4. Neuroinformatics

The field of neuroinformatics is an extended and elaborated application of tools and databases applied to broader, heterogeneous types of neuroscience data, which come in a wide range of spatial scales (Morse 2008). For example, a human brain must be represented at multiple levels and resolutions by properties of its neuronal and non-neuronal cells for detailed

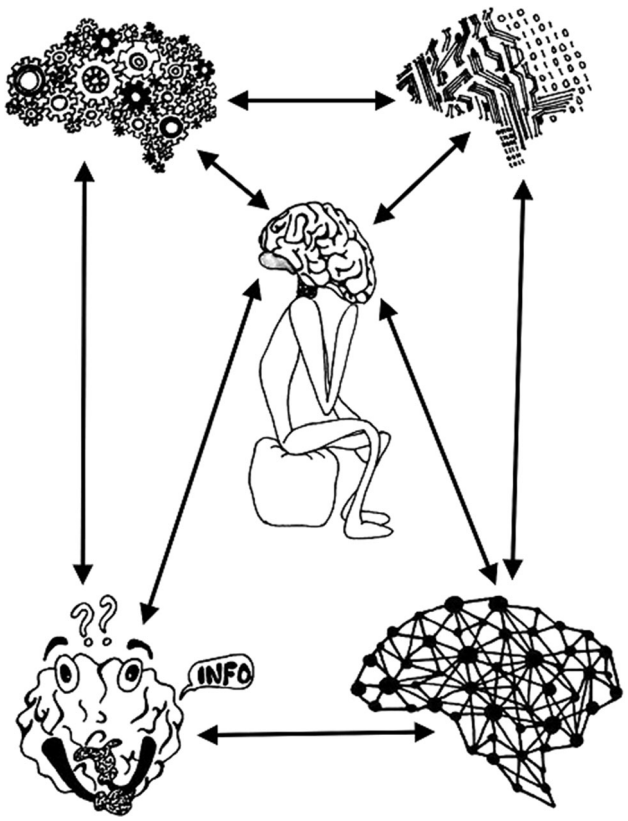

Figure 2. Pondering of the human brain to understand its own mechanisms has led to the discipline neuroscience and its sub-disciplines), *i.e.*, computational neuroscience, and neuroinformatics among others.

[29] *http://sccn.ucsd.edu/~arno/fam2data/publicly_available_EEG_data.html*

[30] *http://www.physionet.org/pn6/chbmit/*

[31] *http://www.bbci.de/activities/*

[32] *http://ntsa.upf.edu/downloads/andrzejak-rg-schindler-k-rummel-c-2012-nonrandomness-nonlinear-dependence-and*

[33] *http://www.schizconnect.org/*

[34] *http://brainsignals.de/*

[35] *https://ida.loni.usc.edu/services/Menu/IdaData.jsp?project=*

[36] *http://coins.mrn.org/*

modeling and simulation. Neuronal properties include morphology, subcellular and molecular architecture, and physiology of $\sim 10^{11}$ neurons. Properties of an equal number of non-neuronal cells (astrocytes, oligodendrocytes, and microglia among others) must also be considered. Moreover, the behavior of $\sim 10^{14}$–10^{15} synapses must be included in an ideal holistic brain model. Each synapse is a complex molecular machine at the sub-micron level. In addition to that neuronal modulation, the activity of glia and synaptic activity by peptides, neurotransmitters, hormones and other molecules should be accounted for in such a model. Further complexities arise in terms of the temporal (structural and functional) variations in individual brains (environmental conditions, health, maturity and developmental stage), individualistic variations (gender and experience) and species variations (homology) (Frackowiak and Markram 2015). The size and complexity of data make it difficult to believe that a single mind or a single supercomputer or even a single country's neuroscientists can shoulder a problem of such size without the help of neuroinformatics.

Neuroinformatics is thus becoming an integral part of neuroscience and clinical research for conducting scientific inquiry and practicing medicine (Morse 2008). Figure 2 schematically depicts the interdependence of this field with that of the neuroscience and computational neuroscience. Dedicated databases and tools of this field are required for understanding the normal as well as disordered nervous system states and clinical applications (Morse 2008). Neuroinformatics facilitates the maintenance of neuroscience databases. The field is associated with the development of analytical tools and computational models for the data sharing, knowledge integration, and analysis of big data of neuroscience (Bjaalie and Grillner 2007). It acts as a unifying framework for neuroscience towards new discoveries in human brain organization (Frackowiak and Markram 2015).

According to the International Neuroinformatics Coordinating Facility[37] (INCF), the challenge in neuroscience is that data is generated in individual laboratories and get collected in huge volume all over the world. Neither the state-of-the-art tools/infrastructure, standard, culture, nor a community to actually bring these pieces together is still available. Neuroinformatics is about data organization, annotation, integration into atlases and models, and simulations of such knowledge in order to better understand the human brain and nervous system.

Millions of people around the globe suffer from brain diseases and disorders. New investments in neuroscience are scarce as it is too risky, complex, and highly expensive. When it comes to scientific data, data tend to be very precise. Implementing a universal standard for such precise multi-scale data is a major problem. A super data infrastructure is very much needed to address this kind of multiscale data. Brain disorders are complicated and heterogeneous. Attempting to understand a brain disorder with all its variables [genetics, imaging, clinical profiles (proteins and other blood variables)] is difficult and time-consuming. Then the prediction of next course or what happens to patients over time is the demand of the present decade. Neuroinformatics is a whole endeavor in response to such a demand which supports neuroscientists in bringing together, sharing and integrating their data to accelerate humankind's understanding of the brain.

5. Advances in neuroinformatics

In this section, the languages, data, tools, software, and simulation platforms used by the neuroinformatics community are discussed along with a few new approaches to the field.

5.1 *Languages for data storage and exchange*

Generally, BrainML (Gardner *et al.* 2002, 2003), NeuroML (Gleeson *et al.* 2010), and PyNN (Davison 2015) are used for exchanging neuroscience data. Here we briefly discuss them. Moreover, PyNN being a simulator-independent language allows model comparison among multiple simulators.

BrainML provides a standard XML metaformat for neuroscience data exchange. Description formats for different biological objects (animal model/cortex/neuron) are available (Le Novère 2006) in it. BrainML is being built on the BrainMetaL metalanguage. It uses hierarchical trees of controlled-vocabulary descriptors linked to specific attributes (lexicons) (Gardner *et al.* 2002, 2003).

NeuroML[38] focuses on developing an XML based language for the neuronal system models. The project provides a common data format for defining neuronal cells and network models. It is a simulator-independent neuronal model description language. It can define data-driven models of neurons as well as their networks with high degrees of biological details. This language allows the description of the complex branching structures of dendritic trees and axonal projections, and their biophysical properties. It allows the description of chemical synapses with short-term synaptic plasticity, electrical synapses, voltage and calcium gated ion channels, and both large and small scale network structure (Gleeson *et al.* 2010).

PyNN[39] is a simulator-independent language to build models of neuronal networks. PyNN API facilitates modeling at the level of a neuron population as well as layers, columns and the connections among them. It has a standard model library of neurons, synapses, and synaptic plasticity. A code written with PyNN API using Python can be run on any PyNN supported simulator, *i.e.*, NEURON (Carnevale and Hines 2006), NEST (Plesser *et al.* 2015), PCSIM (Pecevski *et al.*

[37] *http://www.incf.org/*

[38] *https://neuroml.org/*

[39] *http://neuralensemble.org/PyNN/*

2009), and Brian (Goodman and Brette 2009) among others. PyNN imparts validity to modeling studies by checking results of multiple simulators (Davison *et al.* 2008; Davison 2015).

5.2 *Data*

Here we discuss a few of the data sources used by the neuroinformaticians. Brede Database (Nielsen 2014) lists 186 published neuroimaging articles and 586 experiments. Human Connectome Project (Van Essen *et al.* 2012) aims at identifying group differences across the lifespan by comparing imaging data in 6 age groups (4–6, 8–9, 14–15, 25–35, 45–55, 65–75 years). Brainnetome (Jiang 2013) deals with identification, characterization, network manifestation and genetic basis of brain networks.

Brede[40] lists data from functional neuroimaging related research articles with Talairach coordinates. The database has a program package written in MATLAB, called as Brede Toolbox. It structures data from each article into one or multiple experiments which are supported by simple ontologies for brain regions, journals, persons and topics (Nielsen 2014).

Human Connectome Project[41] (HCP) characterizes brain connectivity, function, and variability in normal human beings. It aims to build a network map among the functional and anatomical connectivity of normal and disordered brains. It has multiple imaging modalities (diffusion-weighted MRI, resting-state fMRI, task-based fMRI, T1- and T2- weighted MRI for structural and myelin mapping and combined MEG and EEG). It is acquiring and sharing pilot multimodal imaging data collected across different age range of human lifespan[42] (in 6 age groups, i.e., 4–6, 8–9, 14–15, 25–35, 45–55, 65–75 years) for identifying group differences across the lifespan and compare data across scanner platforms (Van Essen *et al.* 2012).

Brainnetome[43] investigates human brain hierarchy from genetics and neuronal circuits point-of-view. It aims at identification, study of dynamics and characteristics, network manifestation of functions and malfunctions, analysis of genetic basis, simulation and modeling of brain networks (Jiang 2013).

5.3 *Tools and software*

There exist a lot of tools and software for neuroinformatics research. A few of them (Gleeson *et al.* 2007; Glaser and Glaser 1990; Aguiar *et al.* 2013; Stalling *et al.* 2005; Ermentrout 2002) are discussed here.

neuroConstruct[44] is used in developing realistic 3D neuronal networks. It facilitates models to incorporate dendritic morphologies and realistic cell membrane conductances. It has been developed in Java. Its script files can be used in many neuronal simulation platforms. It uses the latest NeuroML (Gleeson *et al.* 2010) specifications (ChannelML, MorphML and NetworkML). neuroConstruct can create, visualize, and analyze multi-compartmental neuronal networks in 3D space. It allows modeling brain function by building, visualizing, and analyzing network models in 3D space using a user-friendly GUI (Gleeson *et al.* 2007).

Neurolucida[45] is used for creating and analyzing neuron reconstructions from microscope images. It can map and analyze the distribution of cells in a region of interest along with quantification of axons, dendrites, nodes, spines and synapses. It can quantify volume, proximity of one object to another, and distance between the object and an anatomical boundary (Glaser and Glaser 1990).

Py3DN[46] analyzes 3D data collected with Neurolucida (Glaser and Glaser 1990) with its in-house tools. It facilitates mathematical representation of neuronal topology, visualization, and analysis of the neurons. It is a Python-based application and uses the open-source Blender program to create 3D representations of raw and processed data. A user can import Neurolucida reconstruction data, access it using intuitive data structures and Python, do morphometric analysis, and construct 3D graphical representations of the results with Py3DN (Aguiar *et al.* 2013).

Amira[47] is a multifaceted 3D software platform for visualization, manipulation of microscopy, computed tomography, MRI and other imaging modality data. It focuses on visualization and analysis of volumetric data generated in medicine, biology and microscopy. Amira is designed with the goals of ease of use, flexibility, interactivity, extensibility, scripting interface, multi-platform support, and state-of-the-art algorithms (Stalling *et al.* 2005).

X Windows Phase Plane plus Auto (XPP-AUT)[48] solves difference, differential, delay, functional and stochastic equations along with boundary value problems. It has the code for the popular bifurcation program, called as AUTO[49]. It was originally developed for complete numerical analysis of the dependence of solutions on parameters. However, later it has been applied in computational and theoretical neuroscience (Ermentrout 2002). The open source program has the capabilities for handling up to 590 differential equations (Brette *et al.* 2007; Ermentrout 2012).

[40] *http://www.imm.dtu.dk/~faan/ps/Nielsen2003Brede_abstract/Nielsen2003Brede_abstract.html*

[41] *http://www.humanconnectomeproject.org/*

[42] *http://lifespan.humanconnectome.org/*

[43] *http://www.brainnetome.org/en/brainnetomeproject.html*

[44] *http://www.neuroconstruct.org/*

[45] *http://www.mbfbioscience.com/neurolucida*

[46] *http://py3dn.sourceforge.net/*

[47] *http://www.fei.com/software/amira-3d-for-life-sciences/*

[48] *http://www.math.pitt.edu/~bard/xpp/xpp.html*

[49] *http://indy.cs.concordia.ca/auto/*

5.4 *Simulation platforms*

Simulation platforms in general are needed for building neuronal computational models. They provide tools to build numerically sound and computationally efficient models. These platforms help users to solve biological issues rather than get gimmicked by the related computational difficulties. Often, these platforms are used for education in neurobiology. Some are designed with a focus on dynamics, size, and structure of large networks of neurons. A few others deal with heterogeneous network simulations with different model neurons and their synapses as components.

NEURON[50] is a free open source simulation environment. It is well-suited to problems of complex experimental data (anatomical and biophysical properties). It has a user-friendly interface and a library of biophysical mechanisms that can be extended by a user (Carnevale and Hines 2006). It facilitates efficient network modeling and offers a user scope of customizable initialization and simulation flow control (Brette *et al.* 2007).

GEneral NEural SImulation System (GENESIS)[51] and its version for parallel and networked computers (PGENESIS) are the first macro scale modeling systems in computational neuroscinece. GENESIS can simulate biological neuronal systems at different levels, *i.e.*, a single neuron, large neuronal network, subcellular components and biochemical reactions, and system-level models (Bower and Beeman 1998). GENESIS version 3 (development version) will enable import and export of model descriptions in a common simulator-independent XML format.

NEural Simulation Tool (NEST)[52] can model networks of spiking neurons of varying size (Plesser *et al.* 2015). It can model laminar cortical networks, the auditory or visual cortex of mammals and models of learning and plasticity among others (Gewaltig and Diesmann 2007; Brette *et al.* 2007). NEST can be used with SLI (NEST's native simulation language interpreter), PyNEST (Eppler *et al.* 2008) and PyNN (Davison 2015).

PyNEST[53] is a user interface to NEST. It combines the simulation kernel of NEST with Python. PyNEST facilitates easy set up for simulations than SLI (Eppler *et al.* 2008; Plesser *et al.* 2015).

CSIM: A neural Circuit SIMulator[54] simulates heterogeneous networks with neurons and synapses as components. It can simulate up to a few thousand neurons with 1,000,000 synapses. A parallel (distributed) version of CSIM is also available for researchers (Pecevski *et al.* 2009).

Parallel Circuit SIMulator (PCSIM)[55] is the successor of CSIM. It simulates networks containing up to millions of neurons with billions of synapses. It allows distributed (via MPI) and multithreaded simulation of large neuronal networks (Pecevski *et al.* 2009).

NeoCortical Simulator (NCS)[56] is a parallel (MPI-based) spiking neuronal network simulator capable of large discrete-time simulations (million neurons with billion synapses). The simulator is well versed with cell membrane voltage dynamics and customizable ion channels of neuron models. It supports multi-compartment cells (Drewes *et al.* 2009). Currently, a web-based application, known as 'Neocortical Builder (NCB)', is also available (Berlinski *et al.* 2014). NCB is used for creating simulation input, building brain models, and output parameters with NCS. It provides a graphical interface for streamlining the brain simulations. It also provides real-time applications for neurobotics along with the integrate-and-fire neurons and conductance-based synapses.

Multiscale Object-Oriented Simulation Environment (MOOSE)[57] simulates neuronal systems at multiple levels (Ray *et al.* 2008). It operates at many levels of detail, *i.e.*, stochastic chemical computations, a single neuron, spiking neuron network and multi-compartment single-neuron models (Dudani *et al.* 2013). It supports many model formats including SBML[58], NeuroML (Gleeson *et al.* 2010), HDF5[59], GENESIS Kinetikit[60] and Neuroscience Simulation Data Format (NSDF) for writing data.

Parallel Stochastic Ion Channel Simulator (PSICS)[61] computes the behavior of neurons with ion channel position and stochasticity. It uses population statistics for electrically compact homogeneous channel populations. Input models to PSICS can be created with any XML-aware text editor (Cannon *et al.* 2010). Specification of channel distributions and the positioning of stimuli and recorders are achieved with ICING[62].

Mvaspike[63] is involved with event-based modeling and simulation. It handles the events with an event-driven simulation algorithm which sorts the events, updates the neurons and propagates the spikes. The tool maintains a good

[50] *http://www.neuron.yale.edu/neuron/*

[51] *http://www.genesis-sim.org/GENESIS/*

[52] *http://www.nest-simulator.org/*

[53] *http://www.nest-simulator.org/introduction-to-pynest/*

[54] *http://www.lsm.tugraz.at/csim/*

[55] *http://www.lsm.tugraz.at/pcsim/*

[56] *http://www.cse.unr.edu/brain/ncs*

[57] *http://moose.ncbs.res.in/*

[58] *http://sbml.org/Main_Page [Systems Biology Markup Language (SBML) is a representation format, based on XML, for communicating and storing computational models of biological processes.]*

[59] *https://support.hdfgroup.org/HDF5/ [Hierarchical Data Format, version 5.]*

[60] *http://genesis-sim.org/ [GENESIS version 2.3 and higher contain Kinetikit. Kinetikit is an interface and utility for developing simulations of chemical kinetics.]*

[61] *http://www.psics.org/*

[62] *http://www.psics.org/icing/index.html [A stand-alone graphical tool for creating and visualizing ion channel distributions.]*

[63] *http://mvaspike.gforge.inria.fr/*

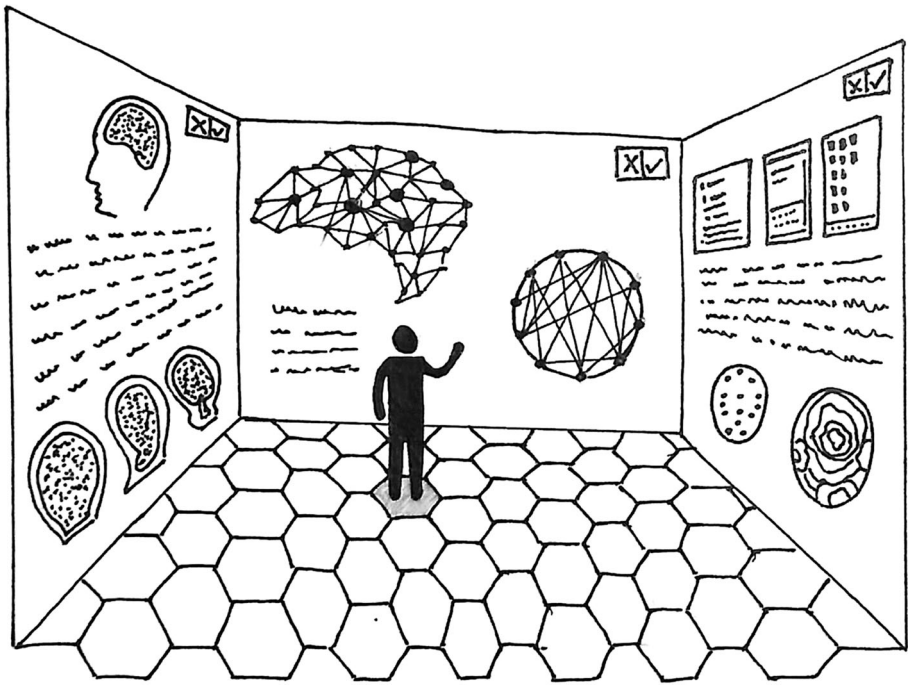

Figure 3. BrainX^3 (Arsiwalla *et al.* 2015), a 3D simulation of the human cerebral connectome.

balance between modeling freedom and simulation efficiency (Kaabi *et al.* 2011).

Brian spiking neuronal network simulator (Brian)[64] is a simulator for spiking neuronal networks. It defines neuronal models by differential equations. It is a Python-based simulator and uses vector-based computation (Goodman and Brette 2009). It is currently available in two versions, *i.e.*, Brian 1.x and Brian 2.x (Stimberg *et al.* 2014).

5.5 *A few innovative applications*

Here we discuss a few interesting and innovative neuroinformatics applications like BrainX^3 (Arsiwalla *et al.* 2015), Brain-Gene Ontology (Kasabov *et al.* 2008), Brain Cartography (Frackowiak and Markram 2015), and Brain Cartography and Connectomics (Sporns 2015). These applications use computation to explore and analyze various behaviors of human brain networks. They hold greater scope of upliftment for human health and life, albeit with a need for more improvement and fine-tuning.

BrainX^3 (Arsiwalla *et al.* 2015) is a 3D simulation of the human cerebral neuronal matrix. It uses biophysical dynamics and anatomical structure for activity reconstruction and function prediction. Interestingly, it can be used in a virtual reality chamber for real-time interactions using natural gestures (figure 3). Presently, it can process networks of up to 4000 nodes. A laptop version of BrainX^3 is under development. This technology has many future applications. One among them is the virtual brain surgery. A surgeon can access several virtual surgical procedures along with their pros and cons on models based on the patients' data via BrainX^3. However, such an application requires optimization of BrainX^3 with parallel computing.

Brain-Gene Ontology (BGO) includes data (animations, concepts, experimental publications, genetic, knowledge, facts, graphs, software simulations, theories, and visualizations among others) of mammalian brain functions, diseases, and their interrelationships. It also lists brain organization, gene regulatory networks, and simulation models (Kasabov *et al.* 2006, 2008).

Brain Cartography (Frackowiak and Markram 2015) represents the science or practice of drawing maps for the brain. It identifies brain regions and localizes them for neurosurgical uses. It provides an anatomical framework for the brain's structural and functional architecture. The future endeavors aim for inter- and intra-individual variability and representation of brain organization across different spatial and temporal scales.

Brain Cartography and Connectomics (Sporns 2015) represents a brain as a complex network of neurons and their interconnecting synapses. A connectome is simply a wiring diagram of neuronal connections in the brain. However, cartographists face many tough challenges while representing a connectome, because varieties of data at different scales of resolution have to be associated with it. They have to incorporate and arrange multilevel information (temporal, dynamic, definition, hierarchical organization, structure, function, relational, and models among others) at one go for construction of a connectome. For building a human connectome, these challenges have to be overcome. Table 2 lists a few worldwide databases in the area of neuroinformatics.

[64] *http://www.briansimulator.org*

Table 2. Some worldwide databases in the area of neuroinformatics

Resource name	Resource type	Source
INDI[65]	Neuroimaging database of resting state fMRI data	Free, registration required
Philadelphia Neurodevelopmental Cohort[66]	> 9500 Individuals (8–21 yrs) from the greater Philadelphia area	Free, available through the database of Genotypes and Phenotypes (dbGaP[67])
GSP[68]	Collection of neuroimaging, behavior, cognitive, and personality data for 1,500 human participants	Free, delivered on a single USB drive upon request (Holmes et al, 2015)
NDAR[69]	Contains 117,573 subjects by age; 80,578 individuals	Free
Enhanced Nathan Kline Institute-Rockland Sample[70]	Ongoing, > 1000 participants	Free, requires a data usage agreement
OpenfMRI[71]	Number of currently available datasets is 37 and number of subjects across all datasets is 1411	Free
PCP[72]	ABIDE[73] (539 individuals suffering from Autism Spectrum Disorder (ASD) and 573 typical controls); The ADHD-200 Sample (374 children and adolescents suffering from ADHD and 598 typically developing controls [7–21 years old]); Beijing Normal University Enhanced Sample (180 healthy college students)	Free

6. Discussion and conclusions

This review along with its compilation of research resources tries to encompass the journey of neuroscience towards technology. Neuroscientists are always up against the task of understanding the function of human brain. It is a very daunting task with billions of brain cells and approximately 100 trillion connections among them. Leave alone the overall view; some believe we are still scratching the surface of this enigma called a brain. Recently the contents of three cylindrical chunks of mouse brain tissue, each of the size of a grain of salt are analyzed by VAST[74]. VAST is a manual computer program that can automatically label neuronal structures by space-filling segmentation and annotation. It labels individual dendrites, glia, mitochondria, neurons, and blood vessels with different colors. The researchers (Kasthuri *et al.* 2015) created an inventory of 1700 annotated synapses. The data refuted 'the Peters' rule' that physical proximity is enough to predict synaptic connectivity. Thus the very basis of estimation of neuronal connectivity is shaken now. This is just one facet of neuroscience that deals with small-scale neuroscience and advanced imaging technology.

Another experiment compared the way monkey and human brains respond to abstract information. According to it, monkeys recognize a pattern but do not realize it and take it no further. However, humans take it on to the next level of analysis collectively. The researchers (Wang *et al.* 2015) found that inferior frontal gyrus of the cortex was intensely activated only in human brains for such kind of analysis that made them unique in processing abstract information analysis. A reader cannot refrain from self-wonder with such kind of precise discoveries. There are many other equally astounding facets of neuroscience, which remain to be solved/refuted with coming age technology. Many-a-times computational neuroscience comes to aid in these scenarios.

Computational neuroscience approaches further our understanding of brain function, and help in translating the acquired knowledge into technological applications. Be it cellular and synaptic dynamics or biophysical basis of

[65] http://fcon_1000.projects.nitrc.org/ [International Neuroimaging Data-sharing Initiative.]

[66] *https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html*

[67] *http://www.ncbi.nlm.nih.gov/gap*

[68] *https://dataverse.harvard.edu/dataverse/GSP* [Brain Genomics Superstruct Project.]

[69] *https://ndar.nih.gov/* [National Database for Autism Research.]

[70] http://fcon_1000.projects.nitrc.org/indi/enhanced/

[71] *https://openfmri.org/*

[72] *https://preprocessed-connectomes-project.github.io/* [Preprocessed Connectomes Project.]

[73] http://fcon_1000.projects.nitrc.org/indi/abide/ [Autism Brain Imaging Data Exchange.]

[74] *http://openconnecto.me/Kasthurietal2014/Code/VAST/*

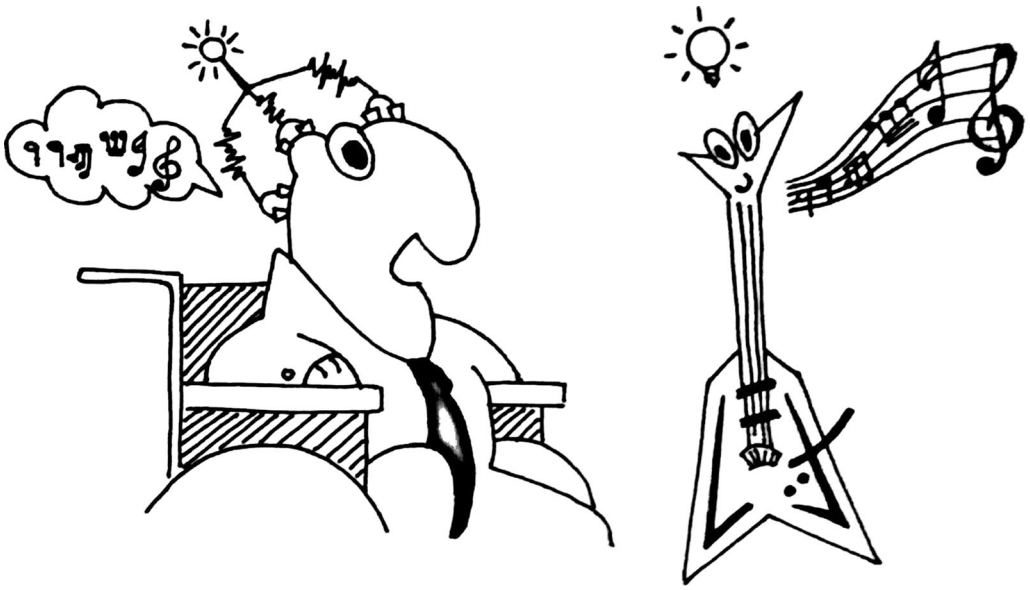

Figure 4. Brain-Computer Music Interface (BCMI) that detects brainwave signals of a disabled person and allows him to control musical systems.

Figure 5. Brainnet is an organic computing device created with multiple interconnected brains. It has emerged as an alternative to super-computation and hyper-performance.

neuronal computation or algorithms for the analysis of neuronal data, the field has provided analytical and computational skills for understanding the neuronal systems. Let us take two instances of research where computational neuroscience plays an upper hand for extraordinary developments. It gives power to a disabled musician to control a musical performance via a Brain Computer Music Interface (BCMI)[75]. A BCMI system (figure 4) detects brainwave signals of a disabled musician and allows him to control musical systems.

On a very different note of computational neuroscience related development, Brainnets, (Pais-Vieira *et al.* 2015; Ramakrishnan *et al.* 2015) have emerged as an alternative to super-computation and hyper-performance. A Brainnet is a system of multiple interconnected animal brains. It has a distributed and parallel computing architecture. Brainnets add an immense opportunity for the upliftment of human life. How good it will be if a crucial surgery can be

[75] *http://neurosciencenews.com/bcmi-paramusical-ensemble-2269/*

performed by a Brainnet of multiple eminent surgeons around the world (figure 5). Some non-invasive ethically approved first steps have already been taken in this direction. A few researchers of University of Washington, USA first reported about the direct human brain-to-brain interface. It records EEG signals of one human brain and uses transcranial magnetic stimulation (TMS) to deliver information to another human brain. Some researchers of Starlab Barcelona, Spain (Grau *et al.* 2014) have used brain-computer interfaces (BCI) and non-invasive computer-brain interfaces (CBI) to achieve B2B (computer-assisted brain-to-brain) communication between human subjects (hyperinteraction) (Rao *et al.* 2014). These are a few of the wonders made possible by computational neuroscience.

With the advent of computational neuroscience, generation and analysis of the enormous amount of data became easy. On the other hand, such kind of big data need proper handling, a common standard/protocol of data generation, storage, appropriate retrieval and requirement-specific merging for rich analysis. The field of Neuroinformatics handles such kind of requirements. A few hand-picked recent developments in the field of Neuroinformatics can help a reader to get a grasp of its power. BrainBrowser (Sherif *et al.* 2014) is a visualization library which provides on-demand visualization of remote datasets. It enables a user to visualize volumetric neuroimaging data and 3D surface in any modern web browser without any further requirements. The Brain Genomics Superstruct Project (GSP) (Holmes *et al.* 2015) enables exploration of inter-links among behavior, brain function, and genetic variation.

Functional analysis of human brain invariably leads towards creation and analysis of connectomes, a relatively new term researchers started using from 2005 (Sporns 2015). A connectome is simply a wiring diagram of neuronal connections in the brain. Generating connectomes even in part is complex, assembling them is tough, and analyzing them is yet new to the research fraternity. It is a good thing that the projects dedicated to connectomics of human brain follow open data policies which generate scope for many future discoveries. A disorder-specific human connectome holds new hope for solving the complex brain disorders. Computing techniques like probabilistic clustering can identify communities and hubs in the human connectome (Hinne *et al.* 2015). Such methods can be used to study the connectomics of brain disorders, and generate predictive models for disease spread pattern and consequences (Fornito *et al.* 2015). Function-specific connectomes, *i.e.*, 'functional connectome of speech control' has already been discovered (Fuertinger *et al.* 2015). The connectome of the human brain is getting constructed even as we are writing this review, which can revolutionize the whole human perception regarding behavior, intelligence, memory, and diseases.

Advanced experimental methods, imaging techniques and support from neuroinformatics infrastructure have illuminated many areas of neuroscience, and yet many other questions lay unanswered. This article is an introductory guide to a few of the already existing knowledge bases and research in computational neuroscience and neuroinformatics. It aims to help many of the scientific fraternity who put their nascent steps into these fields to solve these unanswered questions.

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