

The coming decade of digital brain research

A vision for neuroscience at the intersection of technology and computing

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Preamble

Brain research has in recent years indisputably entered a new epoch, driven by substantial methodological advances and digitally enabled data integration and modelling at multiple scales – from molecules to the whole brain. Major advances are emerging at the intersection of neuroscience with technology and computing. This new science of the brain combines high-quality basic research, data integration across multiple scales, a new culture of multidisciplinary large-scale collaboration and translation into applications. A systematic approach, as pioneered in Europe's Human Brain Project (HBP), will be essential for meeting the pressing medical and technological challenges of the coming decade. The aims of this paper are to

- develop a concept for the **coming decade of digital brain research**
- discuss it with the research community at large, in order to identify points of convergence and common goals
- provide a scientific framework for current and future development of EBRAINS, a research infrastructure resulting from the HBP's work
- inform and engage stakeholders, funding organizations and research institutions regarding future digital brain research
- identify and address the transformational potential of comprehensive brain models for artificial intelligence, including machine learning and deep learning
- outline a collaborative approach that integrates reflection, dialogues and societal engagement on ethical and societal opportunities and challenges as part of future neuroscience research

While we do not claim that there is a 'one-size-fits-all' approach to addressing these aspects, we are convinced that discussions around the theme of digital brain research will help drive progress in the broader field of neuroscience.

1. Introduction

Research in the last two decades has yielded impressive progress in our understanding of the human brain. In confronting brain complexity, researchers have studied the brain at different levels of organization, from the processes at the level of single molecules, synapses, cells, and local circuits to the level of the brain as a whole organ with areas, nuclei and their networks, involved in a variety of brain functions but also dysfunction. Neurological disorders are the second leading cause of death after heart disease with 276 million DALYS⁸⁹ (Disability-Adjusted Life-Years; Global Burden of Disease 2019) (Feigin et al., 2019). In 2010, the total cost of brain disorders in Europe came to €798 billion (Olesen et al., 2012). To address such a challenge, we need to better understand the fundamentals of how the brain works. Hereby, we are inevitably confronted with the complexity of the organ and its sheer size but also with legitimate ethical and methodical limitations that do not allow all of the necessary datasets to be acquired directly from human material. This poses challenges for both empirical research and digital approaches to data analysis, artificial intelligence (AI), data-driven models and simulation.

Combinations of different methods, such as structural and functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) or electroencephalography (EEG) have successfully been applied to identify biological correlates of vision, motor control and executive function. However, how precisely structure is translated into brain activity and function remains unknown. In addition to connections, we also need to understand the "semantics" of how the various brain regions converse with each other (Douglas & Martin, 2007). According to (Buzsáki, 2019), global and local oscillations constitute the 'syntax' for communication within the brain.

For many brain diseases, mechanisms of genetic control have been elucidated, with concrete relevance for diagnostics and therapy. Further, molecular and cellular mechanisms of a number of signal transduction pathways have been deciphered. Nevertheless, we are still lacking important insights into

⁸⁹ <https://www.thelancet.com/gbd/about>

brain organisation, the relationship between brain structure, function, dynamics and behaviour, brain reorganisation during learning and sleep, as well as the conditions leading to brain disease and the requisites for maintenance of mental health. Moreover, the actual networks that produce cognition remain poorly understood. Speculation regarding the building of machines to simulate consciousness means that 'the hard problem' of neuroscience and the potential of using AI to decipher its organization are already part of neuroscience discourse (see e.g., (Dehaene et al., 2017; Graziano, 2019)).

While the multiscale architecture of the brain accounts for its resilience, adaptive capacity and computational power, this property also significantly contributes to the inter-individual variability found at all levels of brain organisation. The degree of variability itself varies depending on the level, brain region and other factors. Understanding the consequences of variability will ultimately lead to improved diagnostics and personalised therapies and will facilitate elucidation of the mechanisms of cognitive functions.

Innovative neuroimaging, advances in microelectronics and optical methods have contributed in recent years to an understanding of brain function at ever-higher spatial and temporal resolution and the study of brain activity and function over ever-longer periods of time; further, they have allowed scientists to better capture the dynamics of molecular, synaptic and structural changes. At the same time, large cohorts of thousands of subjects have been described with extensive data sets, but at lower resolution; these have facilitated the identification of factors determining brain health and aging such as lifestyle and genetic makeup, as well as their interplay. Such empirical research has resulted in significant volumes of highly structured data.

So, what questions can already be answered based on the current data and where is additional work needed? Sydney Brenner stated during his 2002 Nobel lecture, 'Nature's Gift to Science' (Brenner, 2003): 'We are drowning in a sea of data and starving for knowledge. The biological sciences have exploded, largely through our unprecedented power to accumulate descriptive facts ... We need to turn data into knowledge, and we need a framework to do it'. This view has also been challenged. For example, the research aims and methods used in individual laboratories are generally very diverse and often cannot be directly compared with each other. Moreover, critical data, with high-quality, rigorous quality control and provenance tracking (e.g., functional imaging data with simultaneously high spatial and temporal resolution and broad coverage including omics data), are clearly missing.

Therefore, it has become clear that defining and achieving ambitious scientific goals will require close collaboration between laboratories with expertise in different areas of neuroscience and complimentary technical expertise, for example, specialists in image analysis, neuroanatomy, data analysis, computation, physiology, biomedicine, modelling, theory and computing. Several (neuro)ethical issues and questions regarding societal needs and value are being raised in this context. Recognition of this fact is leading to closer interaction between neuroscientists and researchers from humanities. Taken together, these developments are giving rise to more collaborative ways of research and are also serving to enhance multidisciplinary collaboration, which has consequences for the underlying methods and tools, as well as for how collaborations are organised and valued.

Such close collaboration across different domains of brain research is a defining feature of big international projects like the HBP⁹⁰. The HBP is a European Flagship project in the field of Future and Emerging Technologies. Started in 2013, it was one of the first large-scale research projects worldwide and played a pioneering role in transforming digital brain research into a discipline that is more collaborative, reproducible and ethically and socially responsible (Amunts et al., 2022).

The HBP has developed foundations for scientific workflows that enable a FAIR (findable, accessible, interoperable and reusable (Wilkinson et al., 2016)) comparison among multi-scale, multi-species experimental data and theoretical and data-driven models (Eriksson et al., 2022; Schirner et al., 2022). To give a few examples, research in the project has led to new insights into the mechanisms of learning (Bellec et al., 2020; Cramer et al., 2020; Manninen et al., 2020; Göltz et al., 2021; Jordan et al., 2021;

⁹⁰ <https://www.humanbrainproject.eu/en/>

Masoli et al., 2021; Stöckl & Maass, 2021; Deperrois et al., 2022; van den Bosch et al., 2022), visuo-motor control (Abadía et al., 2021; Pearson et al., 2021), vision (van Vugt et al., 2018; Chen et al., 2020; Svanera et al., 2021), consciousness (Demertzi et al., 2019; Lee et al., 2022), sleep (Le Van Quyen et al., 2016; Rosanova et al., 2018; Capone et al., 2019), spatial navigation (Bicanski & Burgess, 2018; Stoianov et al., 2018; Northoff et al., 2020; van Beest et al., 2021), predictive coding and perception (Oude Lohuis et al., 2022) as well as language (Dehaene et al., 2015) and has resulted in new theoretical concepts and analysis methods. A special issue of the journal *Neuron*⁹¹ was devoted to cognitive architectures in 2015. The aim was to bundle together key research for understanding and modelling human brain function, with many of the featured publications resulting from collaboration in the ramp-up phase of the HBP (Dehaene et al., 2015).

The HBP has also empowered the neuroscience community to take advantage of the most recent developments in computing, simulation and artificial intelligence (AI). Experimental data, computational models and tools, instruments and dedicated hardware such as neuromorphic systems have been created in the project and made available with the intention of significantly speeding up developments in brain medicine and research as well as providing a model for low-energy consumption for the semiconductor industry ("Big data needs a hardware revolution," 2018). The consortium has developed and is operating EBRAINS as a collaborative research platform with the aim of bringing brain research to the next level through digital tools and computation and of further developing applications in medicine and neuro-inspired technologies. EBRAINS is now part of the European Strategy Forum on Research Infrastructures Roadmap (ESFRI). ESFRI aims to support a coherent and strategy-led approach to policy-making on research infrastructures in Europe, and to facilitate multilateral initiatives leading to the better use and development of research infrastructures, at the EU and international levels. EBRAINS is being developed as a sustainable research infrastructure – by scientists for scientists.

To address ethical and societal questions, the HBP is incorporating principles and practices of Responsible Research and Innovation (RRI) into the EBRAINS infrastructure through a multi-pronged approach aimed both at the governance and research levels. The goal is to anticipate, reflect on and undertake network-wide action on these and future neuroethical, philosophical and societal and legal challenges (Stahl et al., 2021). Elements include neuroethical reflection and research, proactive governance structures including foresight and public outreach and dialogue activities, data governance, diversity and equal opportunities research and support for proactively addressing issues on dual-use research of concern, misuse and commercialisation of EBRAINS research and its outcomes.

Looking to the next decade, we here identify gaps in our knowledge of the brain based on what has been achieved and articulate research goals for the future. We are convinced that efforts towards achieving these goals will benefit from progress in digital brain research as well as recent developments at the interface of technology and computing; these aims will also profit from the integration of neuroscience with neuroethics and multidisciplinary collaboration that engages with ethical and societal questions of need, acceptability and desirability.

2. Neuroscience: state of the art

To understand where we are in neuroscience research, it is critical to consider where we have come from and also to look to the future. Modern neuroscience was born in the last two decades of the 19th century, when the brain basically went from being regarded as an unstructured mass to being recognized as an intricate network of neurons specialized for different areas of the nervous system (DeFelipe, 2009; Mazzarello, 2010; Shepherd, 2015). New concepts on the segregation of the brain into areas, which are relevant for a certain function, gave rise to microstructural brain maps at the beginning of the 20th century (e.g., (Brodmann, 1909; Vogt & Vogt, 1919). An understanding of structure led to elucidation of

⁹¹ <https://www.cell.com/neuron/issue?pii=S0896-6273%2814%29X0043-7>

function, and the full-brain electroencephalograms of the 1930s paved the way for intracellular electrophysiological recordings in the 1950s and to a basic understanding of the physiology of neurons and synapses. In addition, the discovery of the concept of chemical neurotransmission and the subsequent pharmacological revolution in the 1950s had great implications for neurology and psychiatry (Carlsson et al., 1957) as well as for our basic understanding of how distributed computing networks like our brain can adapt flexibly to our changing world (Dayan, 2012). Explorations of the physiology of the sensory (mainly visual) and motor systems in the 1960s and 1970s, and parallel advances in their anatomy, provided valuable insights, giving rise to an updated view of the brain that we nevertheless now understand was somewhat naïve and simplistic (Shepherd MD, 2009). The 1980s saw great advances in our understanding of neuronal membrane biophysics and the functioning of receptors and ion channels, while in the 1990s the advent of full-brain imaging techniques kickstarted a period of intense progress. Novel techniques, including molecular biology, genetics, pharmacology, psychophysics, neuroimaging and computational neuroscience, in combination with electronics and computing, have progressively enriched brain studies (Finger, 1994).

The beginning of the 21st century saw the development of new tools to control brain circuits such as optogenetics, which, through activation or silencing, for the first time allowed investigation of the role of specific neuronal types (Südhof, 2017; Deubner et al., 2019; Häusser, 2021; Emiliani et al., 2022). Novel high-resolution imaging techniques, such as two-photon calcium imaging employed in animal experiments, have vastly improved our understanding of cellular and subcellular physiology (Yang & Yuste, 2017; Toi et al., 2022). In parallel with two-photon imaging, wide-field calcium imaging emerged as a powerful tool in systems neuroscience, allowing recording from multiple brain regions simultaneously with a sufficient spatio-temporal resolution to resolve behaviourally relevant information (Cardin et al., 2020; Ren & Komiyama, 2021b). Recent development of single-cell transcriptomics together with electrophysiological characterization and morphological reconstructions have enabled researchers to obtain a solid basis of knowledge concerning the neuronal types in the mammalian brain (Fuzik et al., 2016; Gouwens et al., 2020).

Researchers have proposed that global properties of stimuli could be encoded by neuronal synchronization (Brama et al., 2015). For example the 'binding by synchrony' (Gray et al., 1989) theory held that features, like the color and motion of visual objects, are consolidated into coherent perceptions when the neurons encoding these features fire at the same time, with millisecond precision. Later studies demonstrated that binding by synchrony does not occur (Lamme & Spekreijse, 1998; Thiele & Stoner, 2003; Roelfsema et al., 2004), but that features of objects are bound into coherent entities by object-based attention which, at a neuronal level, increases neuronal firing rates (Roelfsema et al., 1998; Poort et al., 2012). Morphological and high-density recording tools for complete millisecond characterization of the circuits in animals carrying out specific tasks may be within reach in a few years for hippocampocortical networks (Klausberger & Somogyi, 2008; Lisman et al., 2017), motor cortex (Li et al., 2015), the barrel cortex (Staiger & Petersen, 2021), the basalo-cortical network (Gombkoto et al., 2021)) and for some hypothalamic networks that organize sexual behaviors (Karigo et al., 2021).

At the same time, our theoretical and conceptual understanding of particular brain functions has also become richer and more complex. Links between anatomy and function can be investigated at various scales, including at micro-, mesoscale, and macroscopic levels (Zaborszky, 2021). Microscale morphological features include myelo-, cyto-, receptor architecture, cell density, synapses, single neuron spike pattern, axonal and dendritic arborization pattern, spine density and gene expression, while physiological features range from ion channel biophysics to synaptic potentials or neuronal spike patterns. Studies have revealed area-specific synaptic organization, receptor-architecture and arborization patterns that show an unsuspected complexity of connections, though it is often unclear how these features contribute to specific processing differences within and between cortical layers and areal differences (Amunts et al., 2020; Haueis, 2021; Rockland, 2022).

At the macroscale, researchers, using MRI, describe the brain in terms of interconnected cortical areas, such as the macroscale connectional pattern that underlies hierarchical processing in the visual system (Felleman & Van Essen, 1991). At this scale, the brain exhibits spontaneous and systematic patterns of

slow, low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal measured in part in resting state functional connectivity studies (Raichle et al., 2001). However, the precise relationships between BOLD imaging and details of electrophysiological patterns are yet to be determined. Architectural types are hypothesized to determine hierarchical processing (Barbas, 2015; Vezoli et al., 2021). The connectivity of transmodal areas allows them to integrate multiple unimodal sensory representations into categorical and rule-based areas (Mesulam, 1998; Pandya et al., 2015). Progress has been made in attempting to bridge from this connectivity between areas to the neuronal complexity of components within areas. Specifically, the functional imaging BOLD signal used in many human studies correlates best to local energy consumption (Viswanathan & Freeman, 2007), likely reflecting dendritic activity and interneurons precisely mapped onto layer-spanning neurons and cortical layers. Such local microcircuit and dendritic activities serve important cognitive functions when comparing internal models and top-down expectations with bottom-up information flow. These local computations might crucially contribute to the cellular mechanisms of conscious processing (Aru et al., 2020) and be missed in other electrical recording techniques measuring neuronal outputs. The understanding of layer-specific computation will be an important computational breakthrough that can be achieved by combining recording techniques sensitive to local microcircuit activity and dendritic activity (Larkum et al., 2018).

The mesoscale has been defined at the level of microcircuits, where researchers describe the brain in terms of different cell types and their intrinsic connectivity and emergent dynamics. However, the relevant units remain a matter of debate. While in the 1970s, cortical columns of various sizes (minicolumns, hypercolumns, etc.) were thought to be functional modules (Szentágothai, 1978; Jones, 1983; Mountcastle, 1997; Rockland, 2010), continued discussions propose a combination of basic circuitry types, including feedforward excitatory, recurrent feedback excitatory, feed-forward inhibitory, recurrent feedback inhibitory and inhibitory-inhibitory types (Nadasdy et al., 2006). These circuits may have been shaped through evolutionary pressure. Thus, it is important to understand the logic of evolving and maturing cortical circuits in order to identify specific circuits across species; this will tell us to what extent discrete anatomical features carry similar or dissimilar functions. An understanding of mesoscale circuits is important for properly linking micro- and macroscale descriptions of brain organization, in order to properly infer macroscale behavior from microscale features (Hauois, 2021). To this aim, wide-field fluorescence imaging can bridge the gap between neural activity at micro and macro spatial scales and provide understanding regarding how local circuits relate to larger neural networks (Cardin et al., 2020; Ren & Komiyama, 2021a). The limitations of single techniques can be mitigated by combining different recording modalities (Allegra Mascaro et al., 2015); fine examples are provided by recent studies using wide-field calcium imaging with other imaging methods, such as two-photon calcium imaging and fMRI (Barson et al., 2020; Lake et al., 2020).

The emergence of this increasing complexity went hand in hand with the rise of computational conceptualization of mental phenomena and the success of artificial neural networks. David Marr (Marr, 1982) recognized that, in addition to the level of neural implementation, there are two further levels of organization: the algorithmic and the computational level. The need to involve computational neuroscience has grown in parallel with computational capabilities, which have expanded in the 21st century to the point where computational neuroscience has become an essential companion of both experimental and clinical studies. Apart from the modelling of concrete processes or computations, we can now consider more ambitious, larger and integrative models. These models will inevitably shed light on the brain's cognitive architecture and contribute to the development of more general artificial intelligence. Brain theories integrate the computational models within conceptual frameworks and formulate principles of their functioning grounded in information theoretical frameworks such as Free Energy Principle (Friston et al., 2006) or dynamical systems theory such as Structured Flows on Manifolds (Jirsa & Sheheitli, 2022)). In addition to modelling biological information processing, computational approaches enable large and complex data sets to be analysed efficiently, supported by artificial neural networks, theory, modelling and simulation, allowing the linking of brain structure and function. Simulation at cellular-molecular-level and/or system models can facilitate the testing of specific hypotheses or prediction of properties of brain structures and dynamics, while integrating

findings from different researchers and obtained with various techniques. The integration of all experimental findings (models, texts, images, and analysis artefacts) into a unified knowledge framework is still necessary. This, in turn, is critical for translating findings from neuroscience into digital medicine, for proposing new strategies of intervention and for empowering neuro-inspired technologies that take advantage of a growing body of insights into perception, plasticity, learning and memory.

Current state-of-the-art technologies to study processes across the entire spatio-temporal spectrum, from molecules to the whole brain and from milliseconds to lifespan, are typically tailored to a specific species, genus, family, order, class or phylum. Methods developed at different levels of the phylogenetic tree (e.g., invertebrates) are only slowly being adapted for usage at other levels in this tree (e.g., rodents, and primates). An annotated atlas of all cells and cell types has just been released for *Drosophila* (Li et al., 2020). Collaboration with the *Drosophila* research community, in the form of studies that probe how genetic specification of circuit changes result in functional changes at the macrolevel, would be highly welcome (Handler et al., 2019). This information may be important for understanding how macrolevel state transitions may relate to individual differences in connectivity strengths (Taylor et al., 2022). Other examples are the exquisite reversible perturbation tools to dissect the functioning of micro- and macro-circuits (e.g., optogenetics, chemogenetics, pathway-selective perturbations), which were first developed in algae and further refined in invertebrates. These tools have gone on to revolutionize rodent research (Kim et al., 2017) but have only recently begun to be integrated in primate studies (Han et al., 2009; Gerits et al., 2012; Klink et al., 2021). Other species like zebrafish are being selectively employed to understand genetic or ontogenetic mechanisms that cannot be properly tested in mammals. Targeted perturbations can also be introduced by CRISPR/Cas9 into induced pluripotent stem cell models of neurons or brain organoids.

Increasingly, neuroscientists not only study invertebrates, rodents and nonhuman primates, but also birds at the systems level, to understand deeper principles of vocalisation learning and cognition. Birds are being studied because, while their brains are vastly different to those of mammals, some of their cognitive abilities seem to be quite similar. Such comparisons can yield basic insights into the links between brain structure and function and offer the unprecedented chance of gaining deep conceptual insights into fundamental brain functions. These studies could potentially identify a core of identical neural mechanisms in the brains of birds and mammals that constitute hard-to-replace components of advanced cognition (Stacho et al., 2020). Large-scale comparative research, where no species should be considered 'superior' to the other, is key to understanding the neuronal mechanisms underlying normal and pathological human brain functioning. However, it is also important to keep in mind that there are fundamental structural and behavioral aspects that are unique to humans as well as to any other species. For example, the number and complexity of pyramidal cells and interneurons, as well as glial cells is among the most important differences that exist between human and other species (Berg et al., 2021; Fang et al., 2022). Thus, the functional significance of the human-specific structure should be dealt with by employing a range of specific strategies. Methods have now been developed that allow us to examine human brain organization and function at a level of detail similar to that we can obtain with animal models (Eyal et al., 2018; Montero-Crespo et al., 2020). By promoting comparative interdisciplinary studies involving the direct study of the human brain and those of other species, the HBP has made the challenge of better understanding the human brain a more surmountable one.

This overview of modern neuroscience illustrates several important points: 1) Advances in neuroscience are not only the result of conceptual advances but are tightly linked to new methods and technologies. 2) New techniques allow a better understanding of the brain, but at the same time open the door to a new level of complexity and open up new questions. 3) There is an increasing need for integration of knowledge and collaboration across different domains, scales and models of neuroscience research.

3. Instrumentation

Research progress has always been tightly linked to the development of methods and instrumentation, and many new tools are facilitating profound insights into the brain's structure and function; further, researchers also have at their disposal new capabilities and considerable computational power to analyse data and simulate brain function. For the first time in the history of neuroscience, we have a dedicated research infrastructure, EBRAINS⁹², which gathers data, tools, methods, and theories, which were previously fragmented and distributed between different labs, into a joint, digital, open, interoperable platform. This provides the technological basis and tools for a new approach to international, collaborative neuroscience and represents a large-scale interface for collaborative projects, e.g., organized in the International Brain Initiative (IBI)⁹³. The NIH BRAIN Initiative is an important partner in this consortium, and is providing a broad range of innovative technologies, tools, methods and resources emerging from BRAIN-funded research (Litvina et al., 2019). Along the same lines, the European EBRA consortium developed a Shared European Research Agenda to increase the impact of brain research, advance basic, translational, and clinical brain research, improve the lives of persons with brain disorders, enable brain innovation and address societal and economic challenges in Europe and globally⁹⁴.

EBRAINS operates according to FAIR data principles and encompasses services for the sharing of neuroscience data and models, the multi-level atlas of the human, rodent and non-human primate brains, simulation, brain-inspired technologies, medical data analytics as well as dedicated tools for collaboration. In addition, EBRAINS incorporates innovative neuromorphic computing and allows for the execution of experiments in virtual robots. Fenix⁹⁵, an infrastructure coordinated by experts from leading European centres for high-performance computing, greatly facilitates research with high computing and storage demands. Through Fenix, neuroscientists can also collaborate with other research communities to jointly develop new software and solutions in the broader domains of data- and computationally-intensive research.

The EBRAINS research infrastructure attracts a broad community of users, ranging from experienced application/service developers and senior neuroscientists to young researchers and students. The infrastructure also interacts with numerous stakeholders, including funders, industry and patient organizations. Collaborative work and co-creation among stakeholders and users will be an essential part of the EBRAINS community and will guide the development and use of EBRAINS services to the benefit of society. The inherent diversity of the community is reflected in the heterogeneity of the EBRAINS research infrastructure services. The platform puts significant emphasis on the ease of use of its tools, and the interface complexity is balanced with user needs. This facilitates collaborative work, by linkage of combination of tools to form computational workflows that seek solutions to diverse problems (e.g., (Fothergill et al., 2019; Eriksson et al., 2022; Wagner et al., 2022)). In that sense, EBRAINS is changing the research paradigm scientists use to study the brain, both for large-scale neuroscience and for individual projects.

Computational workflows should be characterised by accessibility, shareability, automation, reproducibility, interoperability, portability and openness. In this context, of particular importance is the use of the Knowledge Graph⁹⁶, which includes a multi-modal information representation as well as the following 'independence' features of EBRAINS workflows:

- Independence of tools and services from the workflows in which they are used. The inputs of tools and services are parameterised so that they may produce different outputs depending on other tools and services with which they are (re-)used in diverse workflows.

⁹² EBRAINS: <https://ebrains.eu/>

⁹³ International Brain Initiative: <https://www.internationalbraininitiative.org/>

⁹⁴ <https://www.ebra.eu/sebra/>

⁹⁵ Fenix: <https://fenix-ri.eu/>

⁹⁶ <https://search.kg.ebrains.eu/>

- Independence of workflows from the underlying infrastructure in which they are executed: the Common Workflow Language (CWL)⁹⁷ is being adopted for describing workflows in a common, standard fashion, offering transparent execution in infrastructures with different requirements, dependencies and configurations.
- Independence of workflows from the underlying workflow management system. Several such systems are compatible with CWL for executing workflow steps, monitoring their execution, handling failures, automatically fetching logs and outputs and other relevant actions.

4. What is missing?

Deeper insights into brain function and dysfunction are not only now possible but are also urgently needed. Neurological and neuropsychiatric diseases create a significant burden for those directly affected, carers, relatives and society. Achieving progress in these areas is additionally motivated by philosophical questions of knowing and understanding our own nature, consciousness and cognition. These different perspectives have to come together for a better understanding the basis of brain health and the border between brain life and death. Ethical, philosophical, legal and regulatory, cultural and political challenges, which are intertwined, will need to be addressed concomitantly.

Progress in brain medicine is tightly linked to advances in basic research, where some fundamental questions still remain open. To name but a few examples, the formation of memories and the basis of conscious perception, crossing the threshold of awareness, the interplay of electrical and molecular-biochemical mechanisms of signal transduction at synapses, the role of glial cells in signal transduction and metabolism, the role of different brain states in the life-long reorganization of the synaptic structure or the mechanism of how cell assemblies generate a concrete cognitive function are all important processes that remain to be characterized. Moreover, the specific, dynamic consequences of variations in brain organisation, including cyto-, myelo-, chemoarchitecture and interregional connectivity, are not yet well understood, but likely ultimately influence the local ratio of excitatory to inhibitory cell activity, resulting in a variable balance across different brain regions (Deco et al., 2018; Demirtaş et al., 2019; Kringelbach et al., 2020; Jancke et al., 2022).

Further, the need for interaction with the brain (both 'reading' and stimulation/manipulation) originally driven by clinical requirements, has opened novel and expanding fields such as the assessment of awareness in disorders of consciousness (e.g., unresponsive wakefulness syndrome, locked-in syndromes), brain-machine interfaces, cognitive enhancement, sensory restoration, and sense-expanding technologies, which have relevance beyond the medical sector. There is also a need for brain recordings of high temporal and spatial resolution and activity control that are at the same time minimally or non-invasive. These technological advances require interdisciplinary work from neuroscience and areas such as micro- and nanoelectronics, optics, light-controlled drugs, nanorobotics, new materials (e.g., graphene), etc. It is to be anticipated that advances in security, biocompatibility, reactive changes in the brain (e.g., gliosis, cell death), signal-to-noise ratio, problems related to invasiveness (surgical, infections) and closed-loop control of brain function will be made soon; these advances will bring with them consequences in terms of legal and ethical issues.

While progress in these fields has been impressive, a comprehensive understanding of underlying processes requires an integration of each system (e.g., visual, sensorimotor) with the rest of the brain, with the body and with the environment. Furthermore, it requires integration of molecular, subcellular, cellular and systems levels, to reach a 'multiscale' understanding that incorporates the emergent properties of all these complex relationships. All these levels act differently in different brain states, and they can also malfunction, resulting in a large variety of neurological and neuropsychiatric diseases. In order to understand the process holistically, one needs to understand all the individual steps, which is today in many cases difficult or impossible. It is necessary to approach the individual steps at the

⁹⁷ <https://www.commonwl.org/>

relevant level of abstraction and to develop a theory, and, in addition, to have access to the relevant data at the different levels of brain organisation through a multi-level atlas.

The newest computational models are now able to integrate microscopic features, such as those of specific ion channels, synaptic receptors and neuromodulators, and evaluate their impact at the level of cellular subpopulations. Recently, this approach was even extended to the whole brain level, by studying the effect of molecular targets of anaesthetics such as propofol, and their impact at the level of large-scale activity. For example, changing K^+ conductance, or the kinetics of inhibitory (GABA-A) synaptic receptors, can induce a switch of brain activity to synchronized slow-waves, similar to the effect of anaesthetics⁹⁸. This is an example of an area where computational models can make a real contribution, through identifying mechanisms by which microscopic changes can be causally linked to macroscopic behaviour. It also illustrates that simulation can bridge multiple modalities and scales, a prerequisite for addressing multi-level brain organisation and function.

Models are also tools to investigate how physiological mechanisms can be perverted in pathological conditions, e.g., where microscopic changes or modifications at the protein level can lead to aberrant behaviour or clinical symptoms (Mäki-Marttunen et al., 2019). Among the best understood cases are epilepsy disorders, where several microscopic targets have been identified, leading to abnormally high excitability. This may result in seizures at the behavioural level, which can be focal or generalised. In the case of seizures and their spatial profiles, concrete measurements can be precisely obtained by electrical recordings, and then used to generate and test realistic parameters in computational models that can then become particularly precise for these disorders. However, the brain signals of many other pathologies such as schizophrenia are not well understood, and computational models also have a potentially important role to play here – not only in identifying mechanisms but also in predicting potentially informative macroscopic and/or behavioral features.

This type of interplay between experimental measurements and modelling predictions is very powerful and has led to impressive advances in understanding network-level phenomena such as oscillations, waves, etc. (Breakspear, 2017; Tort-Colet et al., 2021; Marder et al., 2022). The extension of such an approach to the level of the whole brain, however, is more challenging because of the high level of complexity involved, as well as the still-insufficient temporal and spatial resolution of non-invasive human imaging and recording techniques. Linking these models with imaging requires a deep biophysical understanding of the different signals involved. This is particularly relevant when computational models are used to quantitatively predict imaging data (e.g., patient data), and to build precise loops between computational models and clinical data, which should ultimately lead to a better understanding of neurological diseases.

Box 1: Technological, methodical and computational challenges

Brain research poses enormous technological and computational challenges for brain interfacing, analysis and mechanistic understanding, data interpretation and modelling of brain processing. To cite but some examples:

- The complexity of data (multi-level brain organization, hierarchies, parallel information processing, redundancy, electrochemical processing, etc.). A key aspect of this complexity is the relationship between different scales that speaks to the level of granularity (and accompanying data) that is most apt for elucidating these relationships. One approach from physics is the notion of 'renormalization'; namely, the conservation of laws from one scale to the next (e.g., sparse coupling, hierarchical dynamics, computational principles, etc.). In addition, measurements at all relevant scales are required to obtain information on how low-level states combine to generate states at higher level, and to account for neurodegeneracy, i.e., the propensity for different system configurations to support the same or similar functions.

⁹⁸work in progress in showcase 3 of the HBP: <https://www.humanbrainproject.eu/en/follow-hbp/news/2022/06/20/how-ebrains-used-investigate-disorders-consciousness/>

- Many behaviours and some mechanisms are unique to humans, but a large proportion of data is not directly accessible and remains unknown (e.g., reactions at the cellular level cannot be measured in the living human brain). Comparative approaches as well as modelling and simulation are strategies to overcome this problem.
- The specific spatial and temporal resolution of data sets, given the multiscale nature of brain spatial and temporal activity. Scale integration is challenging (from micro- and nanometre scales, through meso- to macroscale) as is the need to capture brain dynamics. This requires representation of different scales in a common framework according to the topography of the findings, i.e., in multi-level and multi-scale atlas and models that accounts for the temporal domain.
- The large size of 'subsystems' (e.g., large molecules such as neurotransmitter receptors with many atoms and complex, dynamic structures, large networks, whole-brain perspective as compared to regions of interest, large cohorts).
- The wide spectrum of response patterns, dynamics, plasticity and behaviour of the system, not only in physiological but also in pathological conditions.
- The changing nature of the system, which manifests plasticity at different spatial scales (from dendritic spines to large networks; processes such as spike adaptation, LTP (long-term potentiation), LTD (long-term depression)) or neurodegeneration after lesions.
- The accuracy and reliability of predictions and analyses, applicable to individual subjects, which is particularly critical for translating applications into brain medicine.
- The lack of a comprehensive brain theory, or a selection of competing theories.
- The lack of integrability and documentation of extensive brain collections using modern experimental approaches, including those over 100 years old in Europe and worldwide, to make better use of historical brain preparations and data. These number in the many tens and hundreds of thousands of specimens and, for the most part, are not yet digitized and/or available via web-based tools. Some of them include rare species or brains obtained under conditions that cannot be reproduced any more (e.g., untreated patients with brain disorders). Making this digitally accessible for researchers worldwide would be of significant benefit to evolutionary, comparative and also clinical research; however, this aspiration is linked to significant challenges in data exchange and storage.

5. Ethical and societal questions as drivers of responsible digital brain research

Digital brain research should be driven by scientific curiosity and a desire to promote society's best interests; further, it should reflect societal priorities, including a better understanding of the brain, the development of better diagnostic tools and more effective treatment of brain diseases. In this section, we briefly suggest how we can ensure that societal concerns are addressed and reflected in the research and its outcomes and describe approaches for guaranteeing that research and innovation processes are carried out responsibly. Future research programmes must integrate anticipatory practices, neuroethical reflection, multi-stakeholder and citizen engagement and support ongoing compliance with current legislation, regulation and good research practice. This includes careful consideration of the role of gender and diversity in data generation and governance of research, attention to potential dual-use research of concern or misuse of neuroscientific findings as well as reflection on the ethical sustainability of the research, its impact on human rights and its long-term societal and political implications.

Additional social and legal issues to be considered in relation to digital brain research include those raised by data protection and General Data Protection Regulation-compliant data governance, social desirability, acceptability, and sustainability of digital brain models and issues raised by the possibility of advanced artificial cognition, brain-inspired computing and neurorobotics research, among others. In one example, the intersection of neuroscience and technology is likely to lead to new approaches to AI. Digital brain research must ensure adequate representation of diversity in data (sex/gender, age, ethnicity/race etc.) on brain health and brain architecture as well as in the involved scientists,

practitioners, and stakeholders; this diversity will help ensure that the discipline remains vigilant to the much-discussed issues linked to the reproduction of biases in AI and can ensure that it proactively engages with new concerns that may arise from novel approaches, technologies and applications.

The framework of Responsible Research and Innovation (RRI) defines a multidisciplinary approach to tackling the ethical, philosophical, societal, and regulatory challenges that accompany the vision of future digital brain research. Furthermore, RRI-inspired research and practices can be useful in building a future where responsible digital brain research is proactive in its recognition of existing and emerging societal and ethical challenges.

Digital brain models are a key concept and model for future brain research. They raise significant philosophical questions (e.g., what are the limits of access of brain-machine interfaces to other brains?) (Evers & Sigman, 2013) and ethical and social issues (e.g., are there potentially problematic applications of the technology? Who is involved in the analysis and decisions on potential applications? How would we like to use such models in society?) (Evers & Salles, 2021). Conceptual clarity is a prerequisite for informed debates on the ethical issues raised by digital brain research. Approaching such questions through the framework of RRI includes reflection on the meaning and adequacy of the concepts involved, engagement and dialogue between different disciplines in neuroscience research, including philosophers, ethicists, and social scientists with societal stakeholders like policymakers, interest organisations and the public.

6. Brain models as enablers of future brain research

The accelerated development of information and communication technologies in the past two decades has not only supported the development of simulation and machine learning technologies, but has also made data and models interoperable within a common ecosystem leading to novel types of brain models. Directly tapping into the results stemming from basic research on the brain, brain simulation is expected to play a key role in elucidating essential aspects of brain processes (by demonstrating the capacity to reproduce them *in silico*) such as decision-making, sensorimotor integration, memory formation, etc. While mindful of some of the ethical and philosophical issues they raise, one may also envision the potential use of such models and simulations to address specific questions in brain research. From there, it is easy to envision how generic brain models can be customised to capture some of the distinct features of a given patient's brain. For example, an individual's structural and functional brain imaging data may constrain a generic digital brain model and render it subject-specific, thus enabling its use as a personalised analysis template or *in silico* simulation platform. A concrete instance of such an approach is the *Virtual Epileptic Patient*, wherein neuroimaging data inform *in silico* simulations of an epileptic patient's brain to support diagnostic and therapeutic interventions, clinical decision-making and prediction of consequences (Jirsa et al., 2017). Multilevel atlas data represent another data source that can inform personalized brain models in instances where data cannot be directly obtained from that subject (Amunts et al., 2022 eNeuro).

Such personalised 'Virtual Brains' can be seen as a stepping-stone towards something even more theoretically and technically, and possibly ethically challenging, but also better adapted to the ever-changing nature of brain activity across all time scales. We see the logical culmination of personalised brain simulation in a model that is continuously informed and updated by real-world data, a type of model referred to as a 'digital twin'.

The concept of the 'digital twin' in this context needs to be carefully defined to avoid obscuring the limitations of the approach and to avoid creating unrealistic expectations of exact fidelity or even counterproductive hype (Evers & Salles, 2021). Historically, the concept of the digital twin originated in the realm of industry and manufacturing (Grieves & Vickers, 2017; Grieves, 2019), and comprises three components: the physical object, its virtual counterpart and the data flow back and forth between the two. Empirical data measured for the physical object are passed to the model, and information and

processes from the model are passed to the physical object. Today, the term 'digital twin' is widely used beyond its origins in the industrial domain and is now applied in many areas of research, including in biological and medical fields, although the concepts behind this term may differ.

In manufacturing, the digital twin is more than a general simulation model. It is the specific instance of the general model for an individual object fed with empirical data from that specific object, e.g., an airplane engine in the industrial domain (Tao et al., 2019).

One reading of a digital twin speaks to the dialectic between machine learning and generative modelling in AI. Generative models underwrite interpretability and explainability. Furthermore, they enable the move from 'big data' to 'smart data' (or more precisely selecting and integrating data features to maximise expected information gain). A generative model is a probabilistic specification of the mapping from (latent) causes to (measurable) consequences. In this sense, a digital twin can be taken as a formal specification of a model that is apt for generating the responses of a cell, subject, or cohort in question. Crucially, getting the generative model right affords an interpretable and mechanistic account of empirical data. Coincidentally, it casts the distinction between bottom-up and top-down modelling in terms of model fitting (i.e., inversion) and model selection (i.e., hypothesis), respectively.

In constructing a 'digital twin' of a living organ, one is confronted by important challenges over and above those encountered when constructing the digital twin of an inanimate object. The brain is by far the most complex and multi-faceted organ. The question arises, to what extent can the digital twin concept be applied to neuroscience and the brain? The term digital twin, if applied 1:1 to the brain, could trigger major misunderstandings. Here, we want to contribute to the discussion by clearly defining the term in the specific context of brain science. We distinguish purpose-driven digital twins from the abstract idea of a full digital replica (or duplicate/copy) of the brain, the latter being the complete representation of all aspects of the brain at all levels (see Box 1). A full replica of the brain is neither achievable nor does it seem of clear practical use. When we speak of digital twins in what follows, we mean purpose-driven digital models generated for specific questions, unless explicitly indicated otherwise. The digital twin as discussed here should be understood as a virtual model designed to adequately represent an object or process that is constrained by data from its physical counterpart and that provides simulation data to guide choices and anticipate their consequences. The digital twin is thus a copy in the practical sense, usually associated with a model of a function or process, and its power lies in its usefulness in dealing with relevant problems faced by its physical counterpart at an appropriate level of abstraction. The aim is thus not to resemble the biological brain in as much detail and on as many levels as possible but rather to selectively reduce the amount of information to the data that has proven predictive for a specific (research) question – keeping the model as simple as possible but as complex as necessary.

Even for a specialized model that aims to understand specific aspects of brain structure and dynamics or predict the progression of disease in a specific patient, one still needs a comprehensive source of data to draw from in order to generate sufficiently information-rich, complex Virtual Brain models. Such curated data systems have been created, for example in the form of the Human Brain Project's high-resolution multi-level human brain atlas on EBRAINS. These serve as an interface for integration of structural and functional data modalities. With each model, it must be demonstrated whether more data makes the model more powerful or not, i.e., do the added data enable more accurate, testable predictions? This also serves as an ongoing loop for testing whether the data selection is suitable for the question at hand, i.e., whether it reflects the major determining factors (Box 2: Categories of digital brain models).

Box 2: Categories of digital brain models

- Brain models

Brain models are digital representations of the brain. The term is used in different contexts; common examples include digital atlases, artificial neural networks, anatomical models, network models, cognitive and behavioural models and mathematical and data-driven models.

- **Personalised brain models**

Personalised brain models are special types of models that are personalised by integrating specific data of one individual into a more general model (e.g., as enabled by the Virtual Epileptic Patient).

- **Digital twins**

Next-generation personalised brain models that continuously evolve by being informed with real-world data. They are designed in a purpose-driven way, integrating data relevant for a specific research question.

- **Full replica**

The idea of a complete digital representation of all aspects of a brain at all levels (hypothetical concept).

An important distinction between the digital twin and other personalized Virtual Brain models is that the digital twin constantly receives new information from the real world to immediately adjust to its environment. In a neuroscience context, a 'digital twin' of a brain in the above sense holds much promise as an approach for continuously adapting interventions in functional neurorehabilitation or for tailoring neurotechnology-based interventions. Applications making use of a high-fidelity digital twin of a human brain updated in quasi-real time will require technical developments (e.g., ecological immersion of that twin brain in simulated environments, high-bandwidth, stable brain-machine interfaces, very high computational power) that do (partly) not exist yet; as such, they remain a long-term objective for a rather distant future. This is not to say, however, that digital twins cannot already be applied in neuroscience and medicine today, provided they adequately address the intrinsic limitations of current brain models, of available personalization processes and those faced by current technologies in updating them at the required frequency. The twin thus defines the current horizon of our digital neuroscience roadmap and must be appropriately taken into account as a driver for future developments, e.g., in the EBRAINS architecture and neurotechnology and other platforms in the field.

While the use of digital twins of the brain in concrete applications may still seem some way off, the era of digital brain research has, without question, already started, both in real world settings and research alike. Digital brain research is an umbrella concept under which data, models, theory, methods and computational technology are integrated for all research and development efforts undertaken in the framework of the HBP. Its value rests upon a successful demonstration of internal and external validity (features of experimental results) as well as ecological and construct validity (features of interpretative claims). It enables researchers to address some of the major challenges that have hindered progress in neuroscience for decades. These challenges include our understanding of intra- and inter-subject variability, non-identifiability of mechanisms and multiscale complexity. EBRAINS provides the infrastructure and user interfaces to allow interoperation of the required components of data, models and methods; in doing so, it *de facto* establishes the operational basis for the concept of the digital brain to take centre stage in neuroscience research (Amunts et al., 2022).

We propose that there are three areas where digital brain models of all kinds (see Box 1) could be fruitfully applied in the short-to-medium term: (1) basic brain research, (2) applications in medicine, and (3) brain-derived technologies.

(1) Basic brain research

Digital brain models and their simulation should not replace basic research and knowledge accumulation but can be rather thought of as a useful 'engineering' tool that functions currently as an in-progress predictive model with a dual purpose: (1) putting current knowledge to the test, and (2) anticipating the effect of interventions on a single individual, desired effects, etc. The latter can be appealing as the number of interventional methods is expanding (deep brain stimulation (DBS), transcranial magnetic stimulation, transcranial direct current stimulation, transcranial focused ultrasound stimulation, drugs, optogenetics, photopharmacology). Although there are already various studies where computational brain models make predictions, drive the design of and explain effects observed in interventional

research (Frank et al., 2004; Frank et al., 2007), these methods are currently often applied 'semi-empirically' with the available information about electrode location; circuit connectivity, function, and electrical models; genetic promoters of neuronal types; expression patterns of neuroreceptors and their signalling pathway models, etc. The digital twin may allow rational decision-making regarding these parameters, the testing of outcomes, followed by re-evaluation of the model and so forth.

In order to be successful, underlying models must be biologically realistic, i.e., anatomically adequate and functionally comprehensive. This requires the integration of highly heterogeneous data across scales, including *in vivo* and *ex vivo*, in the same spatial reference framework. In an alternative, complementary approach, Cell Atlas Network (BICAN) will extend to the whole human brain the approach used in the US Cell Census Network (BICCN), undertaking in-depth characterization of (small-scale) components of the mammalian brain, e.g., the most detailed and comprehensive multi-modal model of the primary motor cortex including single-cell transcriptomes and proteomes, chromatin accessibility, DNA methylomes, spatially resolved single-cell transcriptomes, morphological and electrophysiological properties and cellular resolution input-output mapping (Callaway et al., 2021).

Based on this concept, brain simulation plays a key role in elucidating brain complexity by allowing the testing of hypotheses about the brain's multi-level organization and its functions that control the surrounding body. Clearly, following this line of research, it will become more and more important to interconnect simulations executed at different spatial levels (e.g., the EBRAINS simulation engines Gromacs at the molecular level, ARBOR and NEURON at the cellular level, NEST at the systems level, The Virtual Brain at the whole-brain level, and the neurorobotics platform at the level of the embodied organism and its environment (see *Brain-derived technologies*)).

Unlike with the real living brain, the embedded simulated brain can be sampled at any point in space and time. It will be possible to look at all the processes in such a brain (provided those processes are modelled in the simulation, based on real-world data and/or on physics/chemistry) and perform this observation with simulated measurement devices, e.g., multi-array electrodes, fMRI scanners. Then, in principle, all kinds of functional hypotheses can be tested in a full-body and closed-loop environment; further, it will also be possible to build dynamic anatomical atlases, e.g., atlases that allow for the observation of the changes and processes in a brain section under a specific stimulus – in real simulation time.

The multiscale complexity of the living brain, the limited accessibility for measurements and our incomplete understanding of brain processes makes the realisation of the digital twin approach difficult to say the least. The BigBrain as an anatomical model of a brain may serve as the scaffold for the integration of twin data in a strict sense (Amunts et al., 2013), data from other sources such as dynamic cellular data and those from experimental population studies as well as synthetic data simulated by models and different brains. Such an approach also determines the limitations and ranges of validity of the digital twin strategy, which is crucial for the responsible use of and subsequent trust in the technology. Nevertheless, such data-driven models may represent the closest digital representation of a living human brain that is achievable at any given point in time.

(2) Brain medicine

From such digital twins, personalised twins can be derived with the aim of improving diagnostics and therapy for patients in a new and powerful way and therefore supporting strategies towards brain health such as that recently published by the European Academy of Neurology (Bassetti, 2022). Analogous to cardiac digital twins (Gillette et al., 2021), i.e., digital replicas of patient hearts derived from clinical data that match all available clinical observations, human electrophysiological replicas have great potential for informing clinical decision-making and also for facilitating the cost-effective, safe and ethical testing of novel device therapies. Digital twins in medicine address a defined spatial scale, with a defined granularity, consider a defined time interval and serve a dedicated purpose. An application of the digital twin approach for Alzheimer's disease has been proposed just recently (Stefanovski et al., 2021), and while careful consideration of data privacy, security and safety aspects will be required, personalised twins might also offer a uniquely powerful strategy for treating such conditions.

The Virtual BigBrain enables construction of individual connectomes based on neuroimaging and EEG data of a subject and anatomical data from the BigBrain model (Jirsa et al., 2017). The ongoing *EPINOV* clinical trial employing the TVB represents a major step forward in this regard; scientists have developed individual models of the brains of patients undergoing epilepsy surgery to guide and predict the best seizure outcome (Proix et al., 2017). Here again, the strategy is to combine population data with data from an individual brain to develop a Virtual Brain model, a twin, that is realistic enough to allow simulation of the intervention prior to surgery. Patients with super-refractory seizures, i.e., seizures which persist over periods of anaesthesia, often require prolonged intensive care and are at a very high risk of permanent neurological damage and death. For such patients, a digital twin might be used to examine a vast array of models, with ongoing feedback from EEG, responses to drugs and blood ion and gas concentrations, all readily available in intensive care environments.

As one example, DBS, and neurosurgery in general, would massively benefit from personalised twins, which could help in planning the procedure in such a way as to ensure maximum protection and preservation of healthy tissue. In particular, it could inform surgeons of the need to re-compute the model based on the brain signals detected by sensors during surgery. This would require running simulations nearly on-the-fly, e.g., before or during surgery, which means stringent requirements for high-availability service and security. This information could be fed to augmented reality glasses or an operating microscope, to provide the surgeon with online predictions of surgical damage. Certainly, this is not yet in close reach. Applications in intensive care units following stroke or traumatic brain injury would have similar requirements. Beyond invasive therapeutic interventions, a digital twin would be a powerful tool for predicting the consequences of brain lesions and pathophysiology, which is sometimes described in terms of computational neuropsychology, namely, characterising lesion-deficit relationships *in silico*, using synthetic lesions (Parr et al., 2018). This could revolutionise our capacity to personalise neurorehabilitation, while integrating complex information generated by virtual reality and robot-based therapies together with fine measurements of patients' responses and progress.

Other applications could employ simulations to test a 'clinical' simulated population that could be far larger than a real one, therefore providing data amplification by creating cohorts of 'digital patients'. This could be particularly interesting for evaluating rare diseases, for studying the influence of gender or for predicting disease progression (Maestú et al., 2021). Moreover, the more diverse (and heterogeneous) the sources of data used for training, the greater the performance of the model on other datasets, resulting in good generalizability. This is one of the most interesting features provided by federated systems, which facilitate increasing the diversity of data sources (e.g., (Dayan et al., 2021)).

Recently, the AlphaFold system developed by DeepMind (Jumper et al., 2021), an application of deep learning methods, has enabled prediction of protein 3D structure. This could be generalized to test the drug-protein or drug-protein-system interactions at a systems level. Another perspective would evolve from testing the effect of drugs in a virtual environment to uncover the mechanisms of the drug not only at molecular but also systemic levels. Considering that quantum mechanics/molecular mechanics are computationally highly demanding, such an approach at a systems level would require highly scalable tools run on the most powerful supercomputers. For example, fine-grained models of local microcircuits with molecular or cellular resolution, like those constructed and simulated using NEURON and ARBOR, can be directly used to map the local distribution of some molecules (e.g., ion channels, receptors) and then be used to simulate the impact of drugs on this system. These low-scale models can be tuned according to a given pathological condition and then transformed into patient-specific mean field models advancing the precision of digital twins.

Finally, it would be expected that brain twins contribute to 'human body twins'. This perspective goes beyond merely adding another organ, because it would allow modelling the interactions of nervous system activity with those of other organs at the systems level.

(3) Brain-derived technologies

A fundamental challenge is to establish what level of granularity in brain modelling, what transitional computations, and what kind of simulated development is required to support the emergence of a variety of cognitive and sensorimotor functions. Models of the human brain, simulated in embodied settings, i.e., having the ability to control virtual or physical bodies interacting with realistic virtual or actual physical environments, and receiving time-dependent input streams to produce behavioural outputs, represent a uniquely attractive platform for investigating the links between brain structure, brain activity and cognitive and functional performance.

How such bottom-up assembly and the emergent behaviour of the digital twin system can be evaluated against biological data remains an ongoing challenge, because typical synthetic development environments do not match the natural environment. As argued by Ed Yong (2019). The Human Brain Project Hasn't Lived Up to Its Promise. The Atlantic⁹⁹ "large-scale simulations are useful for understanding weather and galaxies, but 'planetary systems are not about anything other than themselves. A brain is built to be about other things.' Simulating the tissue is do-able, but meaningless."

The previous paragraphs provide several examples where simulation has led to progress in in basic neuroscience and brain medicine for well-defined research questions. Additionally, the Human Brain Project from its start aimed to develop biologically accurate brain and nervous models ("Booklet | Brain-inspired intelligent robotics: The intersection of robotics and neuroscience sciences," 2016), and to use such models to develop new technologies. In other words: a simulation of certain processes occurring in the brain is embedded in a real or simulated body with all its sensors and actuators connected to the simulation. In principle, these sensors and actuators can just as well be real or simulated or a combination thereof. Likewise, this body is embedded in a real or virtual world. Once we have these elements, simulated or real, we can combine them in any sensible way.

Obviously, this approach is heavily dependent on models representing the physics of the real world, and it also requires sophisticated software that can simulate spatial environments in high fidelity and that can provide adequate physics of environments, sensors and actuators, connection to brain simulators, facilities for storing the results of simulations, graphical rendering and the orchestration of these complex software modules. All of these (co-)simulations can be run at different time scales (ideally of course in real time), in closed-loop or open-loop scenarios and with entities modelled at different granularities.

A software environment that was designed to perform all these steps, run simulations based on diverse sets of data from biological experiments as well as input from real world robots, and integrate machine learning on top of those simulations is the neurorobotics platform of the HBP¹⁰⁰. While this platform was originally conceived of for the purpose of designing neurorobots, i.e., robots that are controlled by biologically inspired models of the brain, over time it has evolved into a software environment that can be used to connect and integrate all types of entities ranging from simulated mouse bodies by way of sophisticated sensor models to various neuron and brain simulators. Today, the neurorobotics platform can be considered to be both an environment for robot design, and at the same time, an execution platform for neuroscientific experiments. It is therefore a powerful vehicle for *virtualizing neuroscience*, up to the point where system-level *in vivo* experiments can be replaced with *in silico* experiments that run completely inside this platform.

In addition, the neurorobotics platform allows for training the 'brain' (AI-based controller) of embodied robots with real neuroscientific data, even before they are built. It is also conceivable that a simulated copy of the real environment in which they will be used serves as the reference basis for the training, so

⁹⁹ <https://www.theatlantic.com/science/archive/2019/07/ten-years-human-brain-project-simulation-markram-ted-talk/594493/>

¹⁰⁰ <https://www.neurorobotics.net/>

that they can be pre-trained before they are shipped to the end user, who will only need to make small adaptations to (emergent) behaviour to ensure that the robot performs its tasks in a perfect manner. We suggest that such robots (or parts of them) would be very good examples of “*brain-derived technologies*.”

We will refer to approaches following this paradigm as brain-derived technologies as they are directly based and built on findings from brain research. Importantly, these findings can be implemented at different levels of organization. In neuromorphic engineering, the main components, i.e., biological neurons, are emulated by functionally equivalent electrical circuitry to construct highly energy-efficient, possibly analogue, processors and sensors. Likewise, the neural models running on these systems can be derived from specific types of neurons, microcircuits or brain regions that have been identified in biological brains. When connecting these systems to robotic embodiments (both simulated and/or physical) or to biological organisms, it becomes possible to replicate some aspects of the full closed loop of perception, cognition, and action. Modelling can thereby be extended to the complete organism and address all aspects of complex cognitive processes at the behavioural level. Brain-derived technologies are therefore not limited to approaches that mimic structural features of the brain but can also encompass cognitive models and architectures along with their underlying neural dynamics. These technologies will be important new tools for brain research and enable new innovations in computing, robotics and AI.

One field expected to benefit greatly from this approach is neurorehabilitation, where realistic models of brain-body interactions will be useful in elucidating the neural mechanisms at play. (Rowald & Amft, 2022) The combination of highly detailed brain models with models of the spinal cord and of the musculoskeletal system indeed affords special opportunities, such as allowing investigation of the relationship between neural activity and resulting motor behaviour in a detailed, quantitative manner. Personalised models could thus be integrated into decision-support systems to guide the choice and combination of rehabilitation strategies by a physician or a therapist. They may also support breakthrough developments in central nervous system (including spinal cord) stimulation technology and functional electrical stimulation, improving the efficacy of these techniques and expanding their relevance to a greater breadth of conditions. A very promising recent application reported successful epidural electrical stimulation to treat spinal cord injury (Rowald et al., 2022).

Similarly, the combination of high-fidelity models of both the human musculoskeletal and central nervous systems is also expected to support the emergence of *in silico* technologies for so-called *electroceuticals*, i.e., medical devices that provide neurostimulation for therapeutic purposes (e.g., in Parkinson’s disease, epilepsy, etc.). There is little doubt that the medical device industry would have a fundamental interest in tools guiding their product design, generating predictions regarding efficacy and overall de-risking of the whole product development process. With the brain atlases and the multiscale brain simulators created by the HBP, it thus seems timely to consider the collection and integration of new data (e.g., dielectric properties) as a prelude to the development of simulation tools and services geared towards the evaluation of electroceuticals. Simulating the effect of such electroceuticals seems to be overdue, given that DBS is already being widely used.

The HBP has supported the SpiNNaker many-core and BrainScaleS physical emulation neuromorphic computing platforms in establishing the first open neuromorphic computing services and has contributed to the further development of these technologies. Neuromorphic technologies, where both data transfer and processing are event- i.e., spike-based, provide a multitude of opportunities for edge computing, mobile robotics and neuroprosthetics. Considering current trends in automation of mobile systems and deployment of ‘always-on’ sensor arrays, in particular, neuromorphic devices are expected to deliver enhanced, low-latency capacities for perception, cognition and action, while reducing the impact of onboard operations on the system’s energy consumption (Göltz et al., 2021; Cramer et al., 2022). For example, combining spike-driven processing units with spike-generating sensors (e.g., dynamic vision sensors, dynamic audio sensors) into complete neuromorphic systems (sensors and processing units) will make it easier to perform data fusion and overcome constraints related to the heterogeneity of data sources. Advances in the neurocomputational understanding of learning by neuronal circuits, especially

through synaptic plasticity, will also provide new ways of endowing neuromorphic circuits with ever-more complex functionalities at a lower training cost (e.g., one-shot and continuous on-line learning). In particular, the restriction to local plasticity constitutes a manifest advantage over conventional von Neumann architectures.

The circuitry of *analogue neuromorphic processing systems* such as BrainScaleS emulates the ion flows in biological neurons by electrical currents. Unlike traditional microprocessors that are based on the classic von Neumann architecture, every silicon neuron is physically incorporated into the chip with dedicated components. Like in the brain, these neurons exchange information based on spikes, which allows for an extremely efficient implementation and is one of the reasons why neuromorphic systems are a promising technology for a new generation of real-time-capable and extremely energy-efficient computers. An important consequence of their direct derivation from the brain's structure is that neuromorphic processors are typically not well suited for loading external data but instead support learning online in real-time. This unique feature enables new types of learning rules that do not require large data sets but adapt dynamically as required.

Learning rules based on spike timing-dependent plasticity are a remarkable success story of brain-derived systems. They are directly rooted in experimental results and have become a cornerstone for research on learning algorithms in both theoretical neuroscience and neuromorphic engineering. Importantly, traditional machines have also benefited considerably from brain research. One of the most prominent examples are arguably convolutional neuronal networks, precursors of which have originally been derived from the architecture of the visual cortex.

Another important area where basic brain research has fostered the emergence of new technologies is that of neuromorphic sensors, particularly dynamic vision sensors and dynamic audio sensors. The former mimic the functioning of the retina and, like neuromorphic processors, encode information with spikes. The characteristics of these are completely different from their traditional counterparts. Since they only signal changes rather than capturing full image frames, they can operate extremely efficiently, give rise to new types of image processing algorithms, and ideally complement neuromorphic processors.

From a technological perspective, the human brain is also the most promising 'Rosetta Stone' for the implementation of advanced cognitive abilities in artificial systems. Modern artificial agents are characterised by limited levels of intelligence, difficulty in generalising beyond provided training sets and an often-superficial understanding of their environment. The lack of generalisability implies either the necessity for large data sets (the resource-intensive big data paradigm), continuous human supervision (remotely controlled systems) or extensive, rigid mission planners accounting for any allowable occurrence (for planetary or ocean exploration). The superficiality of perception and lack of explainability imply a lack of robustness of and trust in artificial perception systems, a known obstacle to the emergence of, e.g., effective driving automation. To mitigate against such limitations, brain-inspired multi-area model architectures must be developed in conjunction with new embodied and incremental learning algorithms, with a view to finding those that best emulate the functional mechanisms underlying human perceptual cognition. Harnessing such mechanisms and understanding the emergence of cognitive functions will be essential for creating explainable, reliable and eventually more general AI.

The functional architecture of the brain with its different regions is the basis for many types of cognitive architectures that have been defined for technical systems. This is especially true for robotics, where brain-derived approaches are studied extensively. Examples include the research on phenomena related to embodiment or the development of novel perception and sensing systems such as artificial whiskers, inspired by the actual somatosensory system in rodents

Future developments in neural networks for artificial intelligence applications will see a convergence between mainstream AI and neuromorphic technologies. Multiscale brain models can make a critical contribution to the construction of advanced robotic controllers. These could embed plastic rules and

autonomously adapt through their interaction with the environment. Thus, basic brain science will be key in informing the development of these technologies. Moreover, neuromorphic computing might help reduce the substantial carbon footprint of large deep learning models (Strubell et al., 2019).

7. Conclusion

An improved understanding of brain function depends on a deeper understanding of brain organization and a better appreciation of the fundamental mechanisms – the actual biological processes, their relationships and the rules that govern them. Only then can we target prevention, therapies and mechanism-based diagnoses. Although now feasible, digital twins of the brain are still at an early stage and once developed have to undergo rigorous testing and validation before they can meaningfully address brain disorders and become the basis for disruptive new health technologies. Therefore, we need to understand the computational goals and algorithms of the systems and subsystems to be able to see the limitations and possibilities of implementation in individual cases. Further, brain twins raise ethical questions that we will need to address in an open dialogue with society. Twins can be seen as a kind of endpoint for ongoing developments of brain models and analytics.

With this goal in mind, a digital infrastructure that can host such digital brain twins, and which provides interoperability, information security, multi-level data, access to knowledge-based computing resources including high-performance computing and other relevant technologies may foster progress in understanding the rules and refining our digital brain twins to a point where they pass validation testing and become useful for clinical translation. EBRAINS is an infrastructure that is capable of hosting such developments. To make that successful, training of younger generations to work with EBRAINS and leverage the potential of new digital tools is key.

Structuring data and knowledge such that they can easily be recombined and integrated towards a plethora of digital brain twins by the research community – together with delivering the powerful technology with which complex simulations of these twins can be performed – may in itself represent a disruptive technology for generating scientific insight.

8. Scientific Goals – a Roadmap

Short term

- combination of and close mapping between bottom-up and top-down models to speed up the theoretical approach to understanding how information processing is mechanistically implemented in the vertebrate brain
- building on a whole set of complex high-resolution regional models and integrating them into cognitive architectures
- using the existing expertise of EBRAINS to create state-of-the art brain atlases for other animal models like birds
- leveraging the potential of next-generation multilevel human brain atlases for neuroimaging, modelling and clinical applications
- extending the multi-level human brain atlas with physiological and functional knowledge, e.g., providing the foundations for a curated and standardised perturbational atlas of effective connectivity, built on, for example, intracortical stimulation and simultaneous intracranial (stereo EEG) and extracranial (high-density EEG) recordings before and after lesions and for maps of cortical reactivity and connectivity (TMS-EEG), multimodal neuroimaging data sets in healthy controls and patients

- developing detailed models integrating neuronal data with those from glial cells, molecular and immunological signalling pathways as well as vasculature
- developing neurorobotics experiments that connect brain models to robotic embodiments to enable the study of closed-loop systems that can interact with the environment
- based on developments in the field of epilepsy and the ongoing EPINOV trial, developing personalised brain models for several other brain diseases using neuroimaging and physiological data of individual brains in combination with atlas data from post-mortem and *in vivo* brains
- producing more complex combined models of several brain regions (e.g., cerebellum and striatum with cortex) or of different scales (e.g., whole-brain activity with detailed cellular models) to represent biologically realistic circuits; simulating these models and comparing the results with empirical data
- approaching multiscale dynamics and deciphering how they relate to structure
- generating the most comprehensive model of the hippocampus as a key region involved in Alzheimer's and epilepsy, integrating macro-, meso- and microscopical levels, to derive therefrom a twin of a rodent's and/or non-human primate's hippocampus
- translating theoretical and data-driven models for brain medicine into neurosurgery, and creating new, high bandwidth interfaces with the brain
- taking inventory of currently discussed brain theories and corresponding strategies of aligning experimental work and theory
- incorporating tools for automated meta-analysis of the literature
- piloting, fine-tuning and co-creating the European Health Data Space strategy to make it fit-for-purpose for neuroscience research
- establishing sustainable and long-term collaborations between neuroscience, social science and the humanities, and developing systematic and sustainable approaches to societal engagement and reflection on ethics, values and needs of societal stakeholders and citizens (including patient communities).

Middle term

- creating ultra-high-resolution integrated models of the brain's cellular and axonal structure as a spatial framework of a multilevel brain atlas with resolution down to the sub-micrometre scale with imaging data incorporating proteomics, genomics, connectomics and molecular information to better understand how the different levels of brain organisation contribute to brain function, dysfunction and behaviour.
- developing such models for different phases of brain development and aging
- developing more complex combined models, across several regions and/or scales and predicting features of brain structure and function based on the simulation platform of EBRAINS
- implementing first behavioural, information and graph theory analyses, complemented by whole-brain computational approaches, based on a multiscale, causal (stimulation and recording) approach for the diagnosis and treatment of stroke, disorders of consciousness, neurodegenerative and mental diseases
- developing a set of criteria to quantify the goodness-of-fit and the predictive power of large-scale brain models; special attention should be paid to the notorious problem of overfitting small empirical data sets.
- generating whole-brain models of sleep-wake states, attention and using twins in diagnostics to monitor consciousness

- simulating complex behaviour in robots and robot simulations with rich environments, using whole-brain and organism models that are capable of learning from and interacting with the environment
- generating useful new principles for the machine learning field and reaching the 'tipping point' at which the level of understanding of brain mechanisms behind perception, memory, cognition, decision-making and motor control will significantly impact the fields of artificial intelligence, robotics and neuromorphic technology
- using general models of neuronal function to study inter-species differences
- integrating meta-analytic results with imaging, signals, and experimental artefacts
- making available existing brain collections at large scale via web-based tools
- developing and implementing a federated data space fit-for-purpose for cutting-edge AI and allowing cross-border privacy-preserving data sharing of GDPR-sensitive high-dimensional brain-related data in line with the European Health Data Space Strategy

Long term

- developing realistic, large-scale brain models of sensorimotor function, cognitive, perceptual and language function
- evaluating emerging models of learning and adaptivity in biological brains for their potential to enable fundamentally new concepts and algorithms for machine learning and artificial intelligence and novel engineering applications (e.g., new materials, artificial life, replacing and enhancing brain function).
- developing highly efficient and real-time-capable brain-derived neuromorphic control systems for robots that are capable of online learning and interacting with rich and complex environments
- constructing dynamic anatomical brain atlases based on neurorobotics experiments that enable the real-time observation of neural activity in a brain area that occurs in response to a specific stimulus applied to the body
- constructing data-driven models of development and aging, applying these models to brain medicine in children and adolescents, and providing these algorithms to industry to emulate learning, development and self-repair and for application of detailed anatomical and physiological models in brain medicine (e.g., preparation of brain surgery, diagnostics, monitoring rehabilitation) and co-developing human body twins
- applying simplified, yet reasonably realistic twins for different functional systems in brain medicine, with the option of updating them on-the-fly with information from real-life sensor data, e.g., during diagnostics, rehabilitation or in acute situations such as surgery or intensive care
- developing combined, multi-organ models that hasten the advent of *Patient Twins* by reflecting mechanisms of regulation of the nervous system with respect to the function of inner organs and the body
- integrating literature-, image- and signal-based meta-analysis with models to provide a consolidated knowledge base
- new neurotechnological interventions that specifically target malfunctioning brain circuits
- computing data-driven, trustworthy AI models to predict the risk for progression of chronic neurological diseases

Supporters

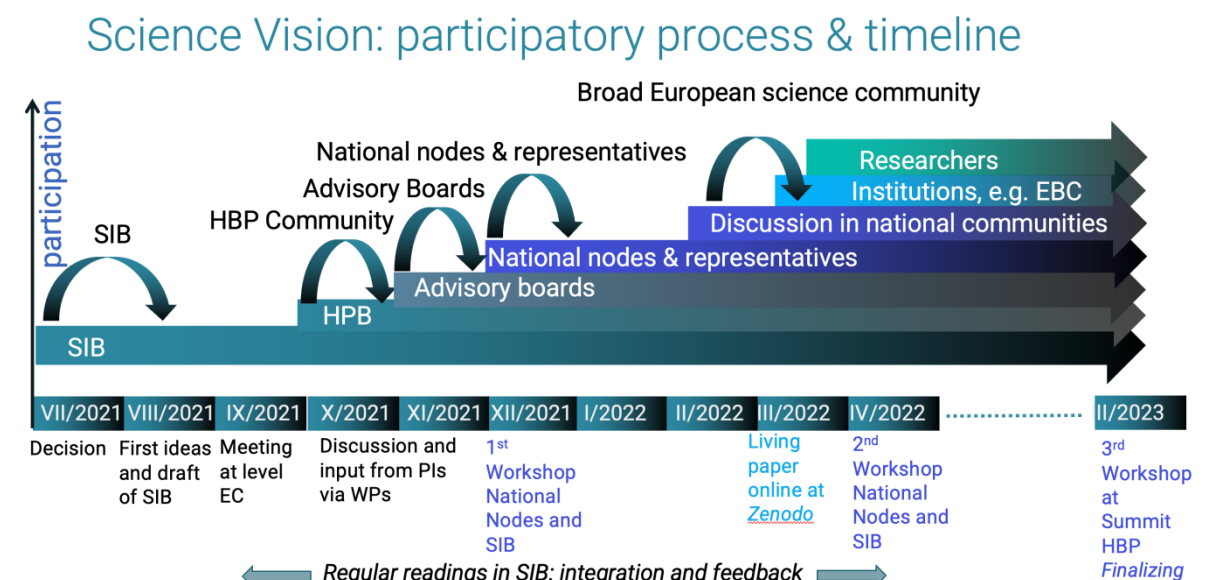
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Annex 1

White paper: Participatory process and timeline



Annex 2

Statements of support

Rafael Yuste: "As a European working in the US, I strongly support this initiative, it could help put European neuroscience in a leadership position and help European countries capitalize on the benefits of working together towards the same goal."

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