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Review

The quest for multiscale brain modeling

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Addressing the multiscale organization of the brain, which is fundamental to the dynamic repertoire of the organ, remains challenging. In principle, it should be possible to model neurons and synapses in detail and then connect them into large neuronal assemblies to explain the relationship between microscopic phenomena, large-scale brain functions, and behavior. It is more difficult to infer neuronal functions from ensemble measurements such as those currently obtained with brain activity recordings. In this article we consider theories and strategies for combining bottom-up models, generated from principles of neuronal biophysics, with top-down models based on ensemble representations of network activity and on functional principles. These integrative approaches are hoped to provide effective multiscale simulations in virtual brains and neurorobots, and pave the way to future applications in medicine and information technologies.

Highlights

Multiscale brain modeling, along with the availability of computational technologies and biomedical data, is growing rapidly, generating an intricate set of strategies, tools, and applications.

Data-driven models use biological details at multiple scales to simulate brain activity, while task-driven models usually anticipate the functions needed to simulate behavior. Data-driven models, in turn, can proceed either bottom–up (starting from neuronal and synaptic mechanisms) or top–down (taking the moves from connectomics and brain signal recordings).

We show here how the different modeling strategies can be integrated to generate hybrid simulators allowing to fill gaps in knowledge though principled rules, to uncover hidden parameter values, to generate testable hypotheses guiding future research, and to open new perspectives for artificial intelligence toward personalized medicine and brain digital twins.

The multiscale nature of brain organization

Traditionally, knowledge about the organization of brain activity derives from experimental observations addressing a set of relatively intuitive questions – when is a circuit activated during a given behavior? Which of the circuit's features code for that behavior? What is the role of the circuit in the larger system, and how does it instantiate its computations by means of neurons and synapses? These questions imply understanding the relationship between brain structure, function, and dynamics [1], thus opening a complex scenario that involves a combination of experimental, theoretical, and conceptual approaches designed to address the multiscale organization of the brain. Computational models and simulations have matured over the years, along with the emergence of large-scale international projects, with the aim to set computational brain modeling [2–8], mapping, connectivity [9–14], and atlasing [15–21] on a principled basis and to foster technological applications [22]. However, there is so far no consensus regarding the extent to which it is necessary to accumulate and understand every single detail in a full brain simulation, nor whether there is a predefined modeling strategy. The answers will probably depend on the goals of each specific line of interrogation. Subsequently, apparently opposite approaches [such as **bottom-up and top-down modeling strategies** (see Glossary), discussed later in the text] may coexist and lead to conceptual integration – a form of understanding that provides intuition and consolidation of knowledge [23].

Relevant brain scales span the molecular organization of DNA and proteins up to cells, circuits, large-scale networks, and human social interactions because they all interface with brain structure. For example, activity-dependent gene expression regulates synaptic plasticity and circuit computation through to learning, memory and behavior [24,25]. In the current paper we focus on the part of the scale from molecular/cellular phenomena to large-scale brain dynamics, and explore how computational models can be used to explain the structure–function–dynamics relationship [1–4]. Experimentally, at the microscale, single-cell phenomena are analyzed using high-resolution techniques that can reveal, for example, intracellular membrane potential and ion concentration changes [26]. Beyond the fundamental importance of ion channels and receptors, growing evidence points to a crucial role for dendritic integration – a nonlinear

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process that endows neurons with high-dimensional computational capabilities [27–29]. At the mesoscale, recordings from multiple neurons or neuronal fields provide essential information about the distribution of activity inside local microcircuits [5,30]. The variety of neuronal subtypes and synaptic properties [31–33], together with intricate region-specific connectivity [34–37], govern local computations. At the macroscale, brain phenomena are analyzed using ensemble recording techniques (including magnetic resonance imaging, MRI; electroencephalography, EEG; magnetoencephalography, MEG; and positron emission tomography, PET). These macroscale analyses inform about the activity of large groups of neurons [8,14]. In particular, the blood oxygen level-dependent (BOLD) contrast mechanism at the basis of fMRI signals primarily reflects the input and intracortical processing of a given area rather than its spiking output [38]. The species-specific organization of functional areas and the connectome are the dominant factors here [12,13]. The fMRI voxel of a 3T MRI scanner is typically around $2 \times 2 \times 3\ mm^3$. Because the isocortex contains ~10^5 neurons/mm^3 and ~10^9 synapses/mm^3 [39], an fMRI voxel reflects the activity of about one million neurons and ten billion synapses. Thus, fMRI recordings concern large numbers of elements, and are thus remote from single neurons; however, by addressing the entire brain volume, they can inform about the large-scale architecture of brain activity [3].

Clearly, these scales are difficult to integrate, raising immediate issues. Of note, sub-millisecond spike timing is crucial for neural coding of sensory and motor patterns [40–43] and a single spike in a neuron may suffice to divert the ensemble network oscillation from its trajectory [44,45]. Moreover, short-term synaptic plasticity and the non-linear amplification properties of the dendrites can modify the network output [46,47]. A fundamental issue in understanding brain processing is therefore to correlate large-scale measurements with the activity of many microscopic sources. This non-trivial problem can be addressed using **multiscale brain modeling**.

Multiscale brain modeling

The quest for multiscale brain modeling follows attempts to understand the brain that have passed through philosophical, experimental, and theoretical phases [6], leading in recent years to a structured modeling framework that makes use of neuronal microcircuit models and virtual brains, and extends into the fields of robotic controllers and **neuromorphic hardware** [3,4,22,48–50]. This evolution reflects advances in experimental techniques, which are providing high-resolution data at multiple brain scales, and the increasing power of computing devices that allows massive simulations. Together, these elements increasingly facilitate the integration of complex datasets and tracing the causal chain of interactions over multiple scales. This effort has required the development of new informatic tools such as modeling workflows and digital brain atlases that allow piecing together the multiple levels of brain organization [22].

Facing the multiscale problem requires a well-defined strategy based on what are called **direct and inverse models** because they crucially determine the way in which brain models are generated. Basically, a direct model predicts the effects from knowledge of the causes, whereas an inverse model casts light on the causes given the effects [51] (Figure 1 and Box 1). More formally, if one knows the model $F(p)$ as well as its parameters p, one can directly predict the observable signals $d_{obs} = F(p)$. Inversely, one can determine p based on d_{obs}: $p = F^{-1}\ d_{obs}$. In brain terms, one needs to correlate the many neuronal activities that generate ensemble network properties with the **ensemble signals** measured through recording techniques such as MRI, EEG, MEG, and PET. The direct problem is often referred to as bottom-up modeling strategy (because it climbs the complexity scale from elementary causes to ensemble functions), whereas the inverse problem relates to a top-down modeling strategy (because it tries to infer the hidden causes of the ensemble observations). As discussed later, modeling can go either way, bottom-up or top-down, and the two strategies can intersect depending on the availability of

Glossary

Bottom-up and top-down modeling strategies: the bottom-up strategy for brain modeling climbs the complexity scale from elementary causes to ensemble functions, thus addressing a direct problem, whereas the top-down strategy attempts to infer the hidden causes of the ensemble observations, thus addressing an inverse problem.
Brain digital twin: a model designed to represent an object or process that is constrained by data from its physical counterpart and provides simulation data to guide choices and anticipate their consequences. Brain digital twins are envisaged as a way to personalize medical interventions, for example in neurorehabilitation and neurosurgery, through multiscale brain modeling.
Closed-loop controller: a system in which the controlled action depends on feedback from the process in the form of the value of the process variable. Typically, in a robot, feedback comes from sensors through an interaction with an object. The brain shows a closed-loop control architecture (e.g., in sensorimotor control loops).
Data-driven and task-driven models: these categories consider whether models generate emerging functions based on available biological data or, conversely, are designed to target those functions that need to be simulated.
Direct and inverse models: direct models predict the effects knowing the causes, whereas inverse models cast light on the causes given the effects.
Ensemble signals: in the context of brain activity measurements, ensemble signals include spatiotemporal recordings of electrical and metabolic correlates of brain activity obtained for instance using magnetic resonance imaging (MRI), electroencephalography (EEG), magnetencephalography (MEG), and positron emission tomography (PET).
Inference and model inversion: model inversion is the inference of parameters from empirical data by use of a generative model (e.g., a virtual brain model). Model inversion is the instantiation of the inverse problem. Inference is the process of advancing from initial hypotheses and data to conclusions by quantifying the compatibility of model and data, thereby providing an objective basis for the validity of the decision.

data and the specific problem under investigation. Given a reliable model of neural activity, a direct model can be realized at some level of complexity; however, in practice, understanding the brain often takes the inverse approach – by first recording observable system-level data (e.g., MRI, EEG, EMG, PET) and then inferring the microscopic hidden causes that generate them [52]. Although this is the most common way in which brain analysis proceeds (e.g., when clinical data are available), the challenge is the non-invertibility of the problem. Inverse problems can be linear or nonlinear depending on the nature of $F(p)$. Typically, brain mechanisms are nonlinear, and are thus inherently more difficult to represent and to solve than linear mechanisms. Numerical methods and strategies specific for the different cases are of great utility.

Non-invertibility depends on the fact that, in a complex system such as the brain, there are numerous element combinations and configurations that can explain the observables, a fact called **neurodegeneracy** [53]. Although neurodegeneracy is commonly regarded as a nuisance from the perspective of model inversion, it is fundamental to the redundancy of the brain and its resilience against injury and disease [23,54,55].

Data-driven models for different brain scales

Because multiscale brain modeling heavily depends on biological data, these are inherently **data-driven models** [3,4,56] and need to account for the corresponding data type and granularity (e.g., [57,58]). The data can be used either for model construction or validation. For neuron and microcircuit models, relevant data are often taken from immunohistochemical, patch-clamp, calcium and voltage sensitive-dye imaging, as well as multi-electrode array recordings *in vitro* and *in vivo* in various experimental animal models (with rodents being the most prevalently used species in many of these methodologies). For **virtual brain models**, MRI, EEG, EMG, and other non-invasive ensemble measurements in humans dominate. In **task-driven models**, system-level data and neuropsychological observations play a major role (see following text). The challenge of multiscale modeling is therefore that of mixing scales – bringing microscopic features into mesoscopic and macroscopic models and combining them with task-driven models (Figure 2).

The microscale models are based on neurons and synapses. Current knowledge of cellular biophysics allows accurate modeling of single neuron and synaptic functions, which are parameterized against biological and electrophysiological measurements [59,60] (Figure 3). The models start from the definition of molecular and membrane properties of neurons [61–63] and have a limited set of free parameters (the maximum ionic conductances) that can be determined through automatic optimization [64]. These models can then be used to generate accurate microcircuit reconstructions that maintain the fine grain of single-neuron representations and reproduce local network dynamics of, for example, isocortex, cerebellum, basal ganglia, and hippocampus [65–68]. In principle, modeling may continue in this way to build mesoscale and large-scale circuits and the whole brain fully bottom-up. However, these models overgrow rapidly [69] and need to be simplified into spiking neural networks (SNNs) composed of point neurons [70,71] to allow manageable simulations on supercomputers [6]. Various methods are available that allow multicompartment models to be compressed into single point neuron models while maintaining salient aspects of spike timing and dendritic computation [72–75]. SNNs composed of point neurons [76–78] have been used to simulate large-scale networks [70,71] and extend to **closed-loop controllers** [79,80] and neuromorphic computers [81]. SNNs can be further compressed by formalizing a transfer function that summarizes the statistical properties of the input–output relationship into mean-field (MF) models [82–84] that can be effective representations of the mesoscopic level.

Macroscale models are typically virtual brain models [48,52,85–87] which derive from anatomo-functional reconstructions supported by whole-brain recordings (e.g., MRI, EEG, EMG, PET) and

Multiscale brain models: integrated representations at different scales that account for the corresponding data type.
Neurodegeneracy: a property of complex systems, such as the brain, in which multiple element combinations and system configurations can explain a specific set of ensemble signals.
Neuromorphic hardware: an artificial computational system containing electronic circuits that mimic the neurobiological architecture of the brain. A neuromorphic computer/chip typically uses artificial neurons and synapses (physically made from silicon) to perform computation.
Virtual brain model: a digital reconstruction made of nodes (functional areas) and edges (tracts) placed in a virtual space that is capable of simulating ensemble signals derived from whole-brain recordings (e.g., MRI, EEG, EMG, PET). Nodes and edges form the connectome and are remapped onto an atlas. The nodes usually represent condensed versions of neuronal activity (e.g., neural mass or mean-field models). The spatiotemporal brain dynamics generated by virtual brain models can be correlated to those recorded experimentally to extract parameter values through an inferential process of model inversion.

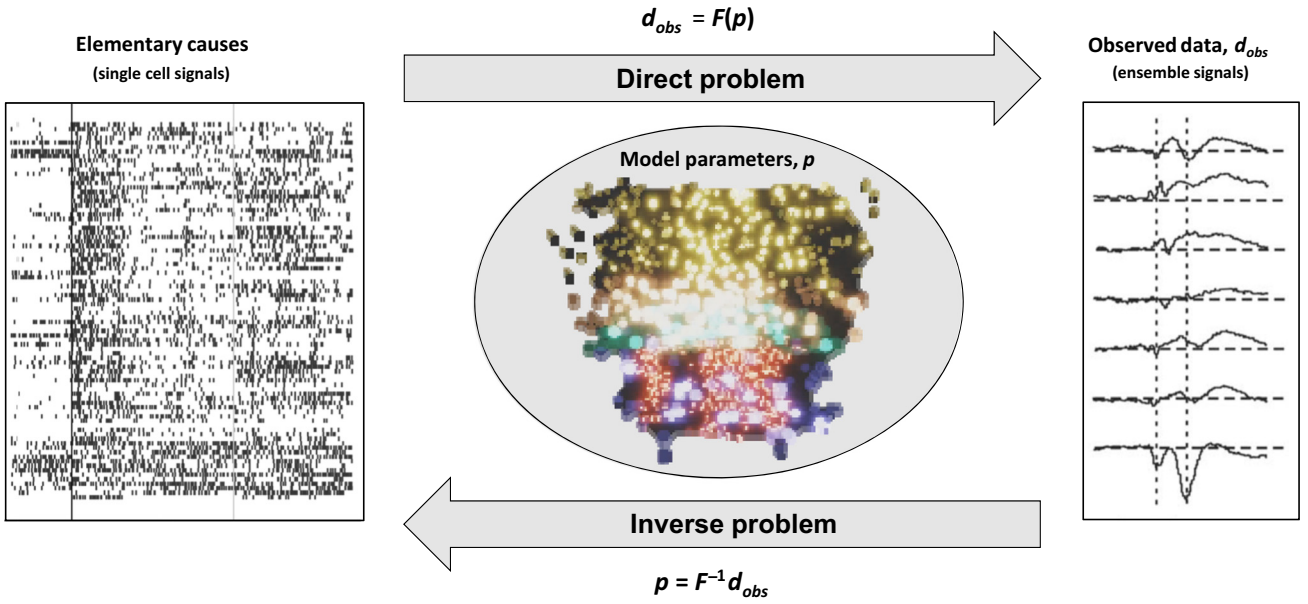

Figure 1. Direct and inverse brain models. Brain modeling can be conceived, as in the most common case of physical systems, in two ways: reconstructing ensemble signals given the elementary causes (direct model) that generate them or, conversely, deconvolving ensemble signals into their elementary causes (inverse model). The elementary causes are a multitude of neuronal activities, whereas the ensemble signals are collective measurements often called observables. The figure shows that neuronal microcircuits are indeed the models that can interconvert elementary causes into ensemble signals in either sense, direct or inverse. Solving the direct problem is a constructive process, whereas solving the inverse problems requires specific mathematical procedures of model inversion that, in most cases, yields statistical parameters of the underlying neuronal population rather than a one-by-one prediction of single neuron activities. In this example, which is taken from the cerebellar cortical circuit, the traces on the right are local field potentials (LFPs) [96], the raster plot on the left shows spikes in multiple individual neurons (microendoscopic calcium imaging *in vivo*, kindly provided by Egidio D'Angelo and colleagues), and the model in the center is a detailed reconstruction of the cerebellar cortical microcircuit [66]. Abbreviations: d_{obs}, *observable signals; F, model; p, parameters of the model.*

by atlases that allow the model to be placed in a virtual brain space (Figure 4). Different from microscale models, which are made of neurons and synapses, virtual brain models are made of nodes (functional areas) and edges (tracts) that reproduce the connectome. The nodes contain simplified models of neuronal activity (e.g., neural masses, NMs) [84,86]. NMs represent several

Box 1. Direct and inverse problems

In a direct problem, one can compute the behavior of the system given some parameters, p, that describe it. The physical parameters are the model parameters, and the solution of the mathematical model's equation is the state of the physical system. This physical state will then influence some observables, d_{obs}, which can be accounted for by introducing the observation operator, F, that converts (maps) the state of the physical system onto what is observed, such that $d_{obs} = F(p)$. Opposite to the direct problem, in the inverse problem one aims to determine the model parameters that produce the data d_{obs}. This implies searching for the model parameters p such that (at least approximately), $d_{obs} = F(p)$. The simplest and most intuitive case is that of a linear system in which d_{obs} and p are linearly related, such that $p = F^{-1} d_{obs}$. Unfortunately, even for linear systems, solving inverse problems normally requires minimization of an objective function to identify the best or optimal model – the one that best matches the data. This can be done using functionals, which are scalar-valued mappings, using for instance Euclidean (e.g., least-square) and probabilistic (e.g., Bayesian) approaches [51]. Nonlinear inverse problems are inherently more difficult [132]. For a given observation, $d_{obs} = F(p)$ = constant defines a manifold spanned in the subspace of relevant parameters. In the simplest instance, the parameter manifold will be topologically simple, but may also comprise disconnected manifold regimes in more complex situations. Every point on the manifold corresponds to a potential realization by the multiscale system that leads to the same observed behavior. Neither improved optimization nor more data or increased sampling rate will resolve the issue of searching for the 'best' set of parameters because this problem is inherently ill-posed. There is no 'best' set of parameters, but instead a so-called neurodegenerate range of parameters that are representative of the different mechanisms that can lead to the identical behavior. The problem of neurodegeneracy is closely linked to the challenge of non-identifiability in machine learning and artificial intelligence [53]. Historically, non-identifiability has been treated particularly in the context of low-dimensional systems, and more recently with numerical methods adapted to higher dimensions such as profile likelihood approaches.

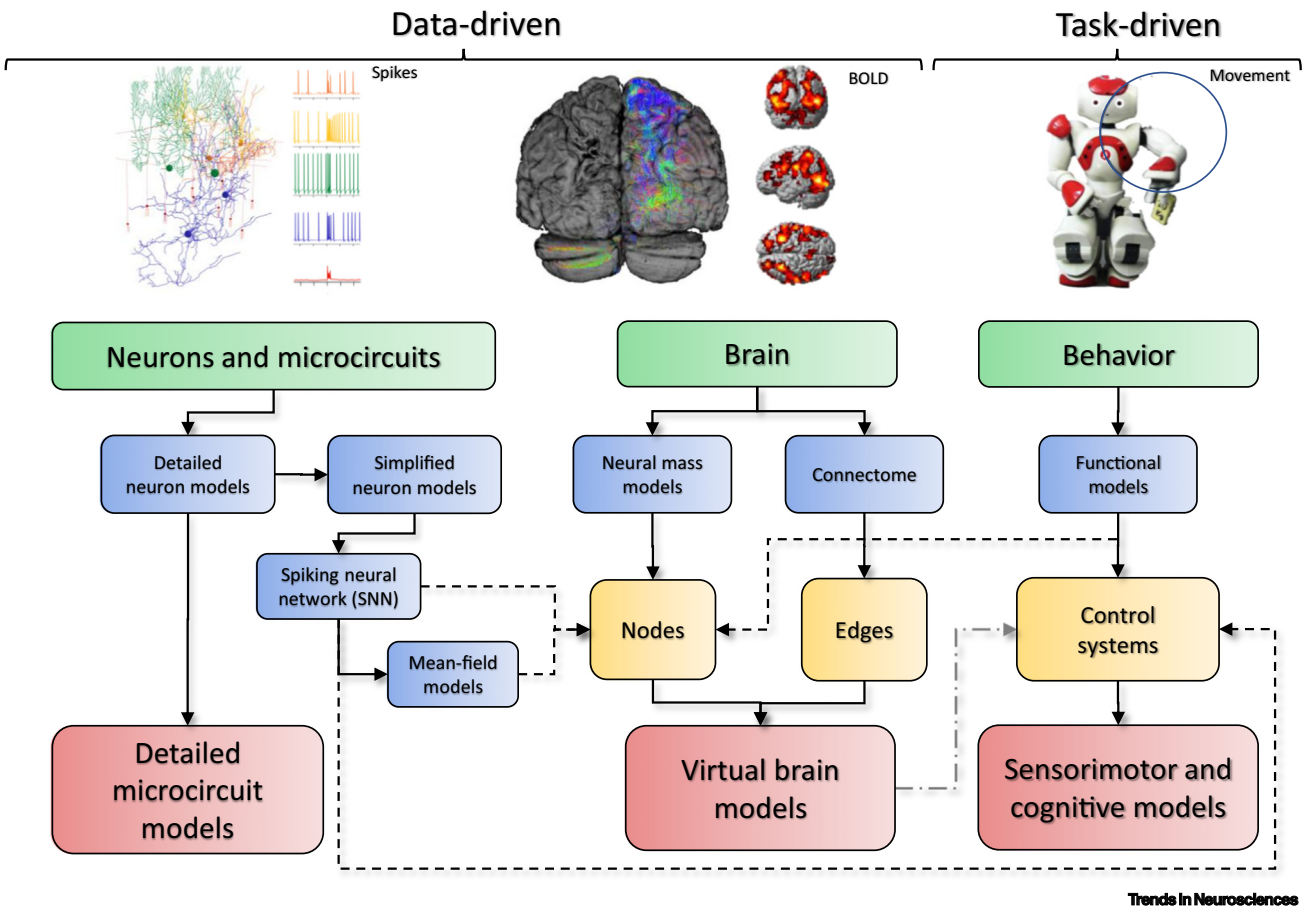

Figure 2. Integrated brain modeling workflow. The top illustrations show data types used for modeling at the scales of neurons [93], microcircuits [65], whole brains [105], and behavior [79,80]. The scheme summarizes what we propose as the main ontology of multiscale brain modeling. The left column includes models of the bottom-up flow in which multicompartmental neurons are modeled based on their elementary properties and are used to generate detailed microcircuit models. These models are then simplified to assemble spiking neural networks (SNN) made of single point neurons and transformed into mean-field (MF) models. Two top-down flows are drawn in the middle and rightmost columns, addressing the brain and behavior scales. Classically, modeling proceeds vertically and the different scales are independent. We provide examples of how bottom-up and top-down models can be integrated (broken arrows). The bottom-up models can be assembled into top-down models, thus providing the core elements for hybrid virtual brains, closed-loop controllers, and task-driven models at mixed scales. The embedding of virtual brain models into task-driven control systems has not yet been achieved. Abbreviation: BOLD, blood oxygen level-dependent.

dimensions of local circuit dynamics by absorbing the many degrees of freedom of a SNN into few collective variables (Figure 4 and Outstanding questions). Once wired through the connectome, the nodes give rise to brain dynamics that can be correlated to those recorded experimentally. Variants of this design include The Virtual Brain (TVB) [48] and dynamic causal modeling (DCM [88]) (see following text).

More detailed considerations about the specific modeling scales are discussed in the following text, but it is worth emphasizing the crucial point that single neuron properties are lost in virtual brain and task-driven models. Nonetheless, the current availability of simplified microscale models brings a turning point because SNNs of MF models can be inserted into, for example, virtual brains or closed-loop controllers (Figure 2 and following text). Such hybrid systems could integrate simulations at mixed scales, thus allowing the engagement of single neuron and microcircuit properties to be explored in large-scale brain dynamics and various behavioral contexts.

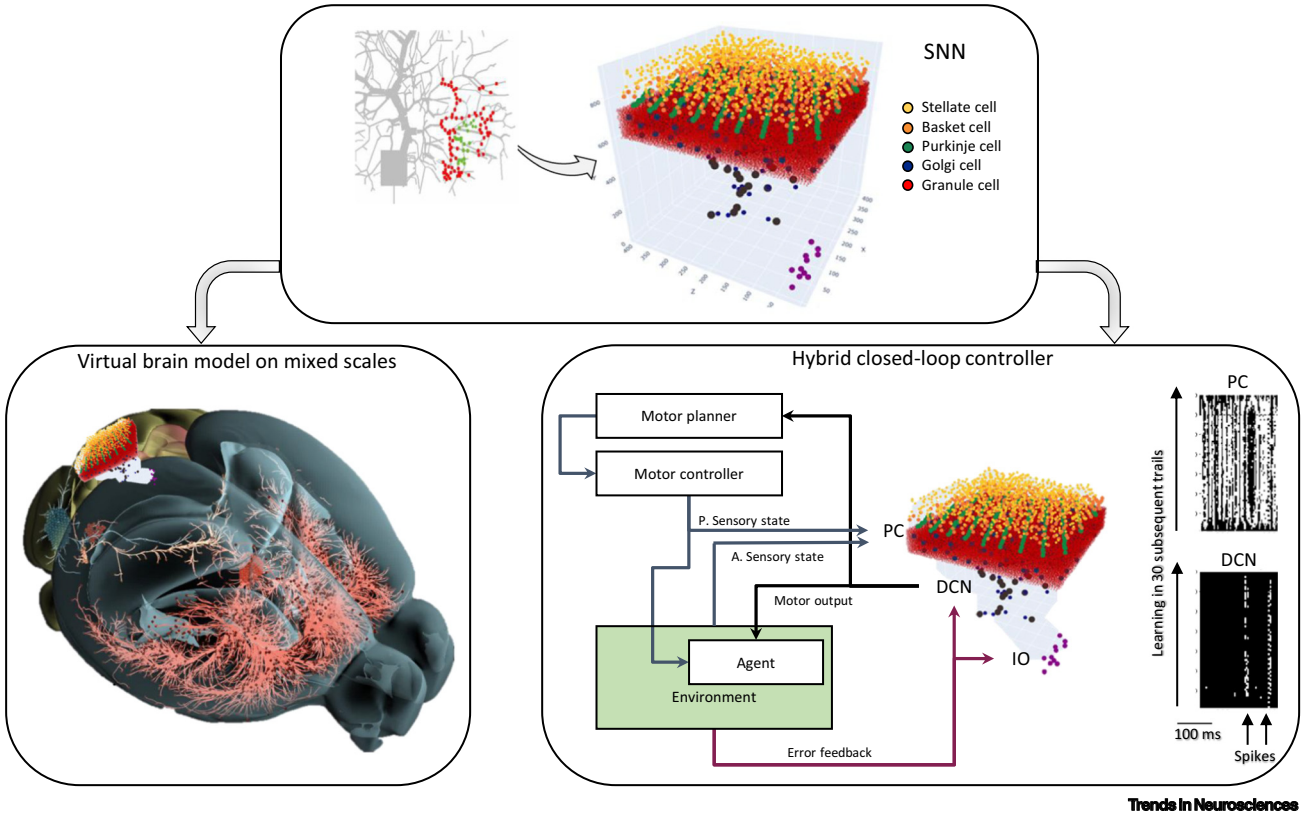

Figure 3. Bottom-up workflow: from neurons to circuits. The figure illustrates how models can propagate low-level features into high-level constructs. (Top left) A model of a cerebellar Purkinje cell shows multiple compartments and synapses on the dendrites [92]. (Top right) Models of different cerebellar neuron types (e.g., [92,94,95]) can be connected to generate a detailed neuronal microcircuit model [65,66] and transformed into a point-neuron spiking neural network (SNN) made of simplified neurons [78]. (Bottom left) The SNN can then be embedded into the connectome, for instance of a Virtual Mouse Brain Model derived from the Allen Mouse Connectome Atlas [18] (cerebello-thalamo-cerebrocortical connections drawn with Allen Brain Explorer: https://connectivity.brain-map.org/). The connectome can then be remapped in mouse brain space [112] and the SNN embedded into the cerebellar nodes generating a TVB on mixed scales. (Bottom right) The cerebellar SNN can be embedded into a closed-loop robotic controller [50,78–80,119,120] to simulate adaptation of the EBCC. A task-dependent architecture made of motor planning and command modules interacting through a robotic plant with the environment (e.g., an object) is interfaced with the SNN. The activity of neurons acquires millisecond precision during learning (in the raster plots, the vertical black strip shows spike suppression in PCs, the vertical white strips show spike activation in DCN cells) [120]. Abbreviations: DCN, deep cerebellar nuclei; EBCC, eye-blink classical conditioning; IO, inferior olive; PC, Purkinje cell; TVB, The Virtual Brain.

Neuron and microcircuit models

Neuron and microcircuit models implement a bottom-up strategy that generates network activities: $d_{obs} = F(p)$, where $F(p)$ is a biophysical model of neuronal activity (Figure 3). Biophysically detailed models are the backbone of the bottom-up flow [62,89] and are *de facto* active tissue models that reproduce the biological properties of real neurons and microcircuits from 3D morphology to ion channel gating and localization [90,91]. The voltage- and time-dependence of the gating process of membrane ion channels can generate a rich set of functional states including regular firing, bursting, oscillations, rebounds, and resonance, as exemplified by recent models of cerebellar neurons [61,92–94]. The non-linear effects caused by the gating process are extended by the presence of multiple compartments, thereby generating the local dendritic and axonal computations that integrate with synaptic transmission. The synapses are added as specialized mechanisms that activate receptor-channel models at specific locations [95]. The properties expressed by these neurons can be retrieved in local field potentials (LFPs) that represent the ensemble activity of neuronal populations [5,96]. Clearly, as far as single neuron and synapse details are maintained, the resulting microcircuit model is fine-grained and allows precise reconstruction of local

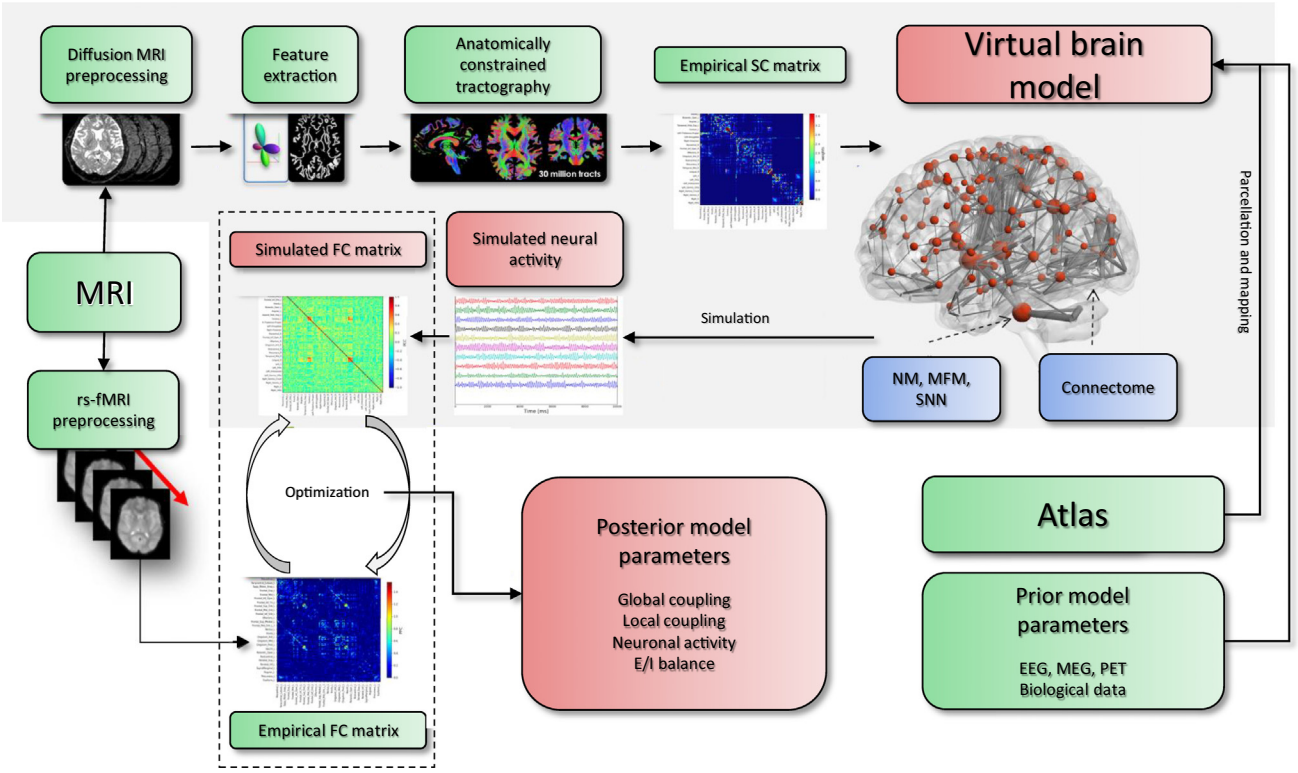

Figure 4. Top-down workflow: the virtual brain (TVB). This figure illustrates the main steps necessary to generate a virtual brain model in a single subject using the TVB platform [48,85,103–107]. (i) The structural connectivity matrix is obtained from diffusion-weighted MRI (dw-MRI) that allows the whole-brain connectome to be reconstructed. (ii) The empirical functional connectivity matrix is obtained from functional MRI (fMRI) through the elaboration of resting-state (rs) networks. (iii) The connectome, made of nodes and edges, is remapped in human MNI space using an atlas. Neural masses (or, in more advanced cases, MF models or SNNs) are then placed into the nodes. (iv) The model can be constrained in several ways using prior information (e.g., EEG, MEG, PET data) or through brain atlases (e.g., that provide data on receptor density, gene expression, ion channels, molecular properties). (v) The simulated functional connectivity matrix is obtained through model simulations which generate salient dynamics in the interconnected nodes. (vi) The model is inverted using optimization of functional connectivity as a target template. This implies that the simulated matrix is compared to empirical functional connectivity matrix and that the parameters are optimized through an iterative process. The best match (under the current objective function) is obtained when the Pearson correlation coefficient (PCC) between the matrices is maximized. The similarity between the matrices should attain statistical significance. The mapping of empirical onto simulated functional connectivity eventually yields the posterior model parameters that inform about the underlying (hidden) neuronal mechanisms. Abbreviations: EEG, electroencephalography; E/I balance; excitation/inhibition balance; FC, functional connectivity; MEG, magnetencephalography; MF, mean field; MFM, MF modeling; MNI, Montreal Neurological Institute standard brain template; NM, neural mass; PET, positron emission tomography; SC, structural connectome; SNN, spiking neural network.

neuronal dynamics, as first demonstrated for the isocortex [67]. The process of network reconstruction and simulation is intrinsically complex and requires specific modeling platforms such as the Brain Modeling ToolKit (BMTK) [97–99], NetPyNE [100], PyCabnn [101], Snudda [68], and Brain Scaffold Builder (BSB) [65,66]. BSB, initially developed for the cerebellum, uses general rules that can be applied to any brain microcircuit and can be optimally guided by anatomical atlases such as the Allen Mouse Connectivity Brain Atlas [18,19]. In all these models, neurons maintain realistic morphologies, the dendrites and axons are oriented, and their intersections are tracked. In these models the microcircuit connectome is generated using constructive rules that extract information from the interdependence of structural parameters.

Virtual brain models

Virtual brain models [48,52,84–88] implement a top-down strategy that instantiates the inverse problem, $p = F^{-1}\, d_{obs}$, and extract parameter values informing about brain properties that

would otherwise remain undetermined. Because of neurodegeneracy, these parameters pertain to neuronal ensembles and connection tracts, and include global coupling, local coupling, firing spectrum, and excitatory/inhibitory balance (Figure 4). Thus, instead of addressing the activity of single neurons and synapses, these macroscale parameters address the probability that particular microscale events occur. Virtual brain models have been available since the early 1970s (e.g., the Nunez model [102]); these initially emphasized temporal features and only later (with the advent of diffusion weighted MRI and tractography in the late 1990s) addressed the connectivity between brain areas through the connectome [9–14,48,85,103]. This approach today provides data-driven models informed by subject-specific connectomes allowing the formulation of theories and concepts about how global brain parameters change as a function of ecological or pathological contexts and over long timescales linked to learning, plasticity, and development.

Virtual brain models are primarily constrained by structural data and simulate functional data from various imaging modalities (fMRI, EEG, MEG, PET). In **inference and model inversion**, the inference of parameters from empirical data by use of a generative model (termed model inversion) is the instantiation of the inverse problem (see preceding text and Box 1). Virtual brain models used in TVB are closely related to the generative models in DCM [88], which are mostly used to unravel the causal or psychophysiological relationship between active brain areas. Thus, TVB is best suited to reproduce large-scale brain dynamics in resting state (e.g., rs-fMRI) and its pathological alterations (e.g., in epilepsy), whereas DCM is often used to address causality in task-dependent fMRI.

TVB provides the workflows needed for the construction and simulation of virtual brains integrated into an open-source neuroinformatic platform [104]. TVB makes it possible to reconstruct the connectome from diffusion MRI data, to remap it in a virtual brain space, to use resting-state fMRI as functional template, to embed other datasets (EEG, MEG, PET) as priors, to use different NMs, and finally to simulate brain dynamics (Figure 4). TVB offers a large spectrum of developments to improve the matching between simulated and empirical data, and therefore the reliability of parameter extraction. First, because the direction of signal communication is not unveiled by tractography and false positive/negative tracts may occur, curating the directionality and precision of tracts can overcome the lack of equivalent information derived from the MRI connectome [105]. Second, mapping the properties of nodes onto brain atlases can help to account for the heterogeneity of neuronal structures and spectral properties across different areas [84,106,107]. Third, the performance of TVB can be enhanced by increasing the number of nodes toward a fine-grained representation of brain properties. Finally, more precise representations of local neural activities can be obtained substituting NM with MF models [108] or, in perspective, with SNNs [109–111]. This means, *de facto*, that a bottom-up strategy can be used to obtain the model to be inserted into the top-down flow, thereby generating a hybrid simulation on mixed scales (*cf* Figures 2 and 3).

Unavoidably, TVB at mixed scales poses a greater challenge for humans than for mice [112] because data about mouse neurons and connectivity are far more advanced [14,18–21] and allow, in principle, reconstruction of a fine-grained brain model (Figure 3) by leveraging biophysically detailed neuron and microcircuit models [66], SNNs [78], axonal tractography [18], and a large set of multiscale data for reconstruction and validation [3,49]. In principle, a hybrid TVB [109–111] would allow an understanding of single neuron dynamics in the whole-brain context and exploration of the impact of single neurons and single spikes on brain dynamics [40–42,44,45].

Task-driven models

Although virtual brain models can mechanistically explain resting-state brain dynamics (TVB) or causal relationships between active brain areas (DCM), they are still unable to explain how the

brain operates during sensorimotor or cognitive tasks [24,25]. Addressing aspects such as learning, cognition, embodiment, and behavior requires the problem to be addressed from a different angle and a change of strategy – the target task must first be defined in terms of functions, and then different (often abstract) representations of neural mechanisms can be used to generate such functions (Figure 2). The reference datasets are also different because they address functional measurement of electrophysiological and imaging correlates of behavior [113]. The main problem here is that higher aspects of behavior (including cognition, ideation, decision-making, planning) remain out of reach on mechanistic grounds because they would require understanding how the brain gives rise to mental experience [114]. Thus, task-driven models are used to cast light on the mechanisms (most often in terms of hierarchical interacting brain regions; e.g., [115–117]) that might implement such functions. This system-level view of brain modeling allows the fundamental questions [118] asked through the model to be extended by linking internal brain circuits to the body–environment interaction (e.g., through tools placed in the external space). One of the best-documented cases is illustrated by closed-loop motor controllers [78–80] in which an artificial sensorimotor system embeds a cerebellar SNN with cellular and learning mechanisms that faithfully reproduce those of the corresponding biological network. These cerebellar SNNs can easily learn Pavlovian conditioning tasks which associate conditioned and unconditioned stimuli through experience-driven learning, thereby providing important cues to how brain circuits generate behavior (Box 2 and Figure 3) [50]. This approach has been able to demonstrate how synaptic plasticity regulates neuronal discharge during sensorimotor tasks [119,120] (discussed further in the following text).

Task-driven modeling has been extended to include several brain functions remapped onto cortical and subcortical areas, with the aim of bridging the gap between neural activity and cognitive functions such as calculation, question answering, variable creation, and fluid reasoning [121]. Simplified SNNs are connected to generate the functions specified by a group of internal operators regulating information flow (i.e., information encoding, transform calculation, reward evaluation, information decoding, motor processing) that control action selection and working memory. Salient operations are predefined and remapped onto neuronal discharges. This approach, although lacking biological details on SNNs, casts light on psychophysiological correlates of behavior at a very large scale.

Box 2. Brain models, robotic controllers, and gravitation

As illustrated in Box 1, model inversion requires specific mathematical strategies. We consider here how a closed-loop controller can naturally face (and solve) the inverse problem. In an adaptive sensorimotor controller, for example one including a cerebellar circuit [49], the problem of finding model parameters translates into that of adapting synaptic weights in the embedded cerebellar SNN. The free parameters p of the model are the synaptic weights, and d_{obs} are the properties of the external world, and the controller works as the agent extracting the parameter values through an iterative adaptation process. Gravitation provides a straightforward example of how model inversion applies to closed-loop controllers. Newton's law of gravitation (the mathematical model) allows the gravitational field (state of the system) to be directly calculated given model parameters (the distribution of mass): $d_{obs} = F(p) = Gp/r^2$, where d_{obs} is the acceleration, G is the universal gravitation constant, p is the mass, and r is the distance from the mass to the observation point. By model inversion, one can extract the Newton's equation parameters from a group of measurements, for example by using a set of gravitometers to measure the gravitational acceleration of the Earth at different positions and to calculate the underlying mass. Once d_{obs} is obtained at different positions on the Earth's surface, we can obtain an equivalent number of equations setting up a system that can be solved (inverted), yielding the corresponding values of $p = F^{-1}\, d_{obs}$. This reasoning reflects in the cases illustrated in Figure 1 where special mathematical methods are necessary to invert the $p \times d_{obs}$ matrix. In an adaptive sensorimotor cerebellar controller applied to a robot, when an arm lifts an object with a given mass, the cerebellum makes an estimate of its weight (d_{obs}) and therefore of the force of gravity. Synaptic plasticity at circuit synapses generates an implicit and distributed representation of p. Thus, the closed-loop circuit exploits sensory feedback to implicitly solve the inverse problem of extracting $p = F^{-1}\, d_{obs}$ using the desired trajectory as the target template. Eventually, the cerebellar SNN generates an internal model of the body–object system and, along with parameters, acquires the physical rules governing kinematics and dynamics of masses in the gravitational field along with apparent (centrifugal and Coriolis) forces and frictions [125–129].

An interesting workflow for embedding task-driven models into TVB has recently been presented [122]. A large-scale neural model of visual object processing consisting of interconnected neural populations (representing primary and secondary visual, inferotemporal, and prefrontal cortex) was embedded into corresponding nodes of the TVB connectome. Interestingly, this hybrid TVB effectively performed the task, suggesting that TVB can be used to understand how interacting neural populations give rise to behavioral functions.

An exemplar case: multiscale cerebellar models

An exemplar case of how the different modeling strategies can be integrated derives from cerebellar studies [3,49]. The cerebellum benefits from a solid theory that links structure to function and behavior – the motor learning theory [123] – and its mechanisms are expressed by core structural network modules [124]. The cerebellum has long been the object of models aiming to explain the adaptation of sensorimotor control by error learning and to investigate the impact of a predictive forward controller architecture on brain circuits [125–129]. Recently, all the principal cerebellar neuron types (e.g., [64,92–94]), as well as their synapses and microcircuits (e.g., [65,66]). have been modeled in detail with the support of rich datasets for construction and validation. These models have been simplified, while maintaining the salient aspects of spike discharge (but not so far of dendritic processing; e.g., [130]), and have been used to generate SNNs [78]. Finally, these SNNs have been embedded into hybrid closed-loop controllers [50,78–80,119,120] and transformed into neuromorphic hardware [81] that is capable of running very large-scale simulations [131]. As a whole, these controllers are providing remarkable support to cerebellar theory, physiology, and pathology [41,119,125]. SNNs may now be used to generate MF models that can improve TVB by including specific representations of the cerebellar nodes [105].

An ensemble view: toward mixing scales

In aggregate, brain modeling can best be conceived as mixing bottom-up and top-down strategies facing the direct and inverse problems, respectively. The detailed single neuron and microcircuit models reproducing biological data can be seen, *de facto*, as the physical description of brain processing. These models can produce the observed ensemble activity, $d_{obs} = F(p)$ once the parameters (single neuron and connectivity properties) are known. The same models can be simplified and used, based on ensemble activity measurements (fMRI, EEG etc.), to cast light on the parameters needed by the brain model, $p = F^{-1}\, d_{obs}$, to generate its output. Clearly, because of neurodegeneracy, it is impossible to discern between the possible states of the system that generate the ensemble signals. Nonetheless, the models can inform us about the activity and connectivity of local neuronal populations that would otherwise remain undetermined. In essence, virtual brain modeling allows the extraction of hidden information contained in the correlation between structural and functional connectivity through the simulation of brain dynamics [1]. An interesting attempt to bridge scales by inserting microscale into macroscale models has been reported to simulate the effects of deep brain stimulation in which a spiking basal ganglia model has been cosimulated with a whole brain mean-field model using TVB [109–111]. Hybrid closed-loop controllers are another category of models that allow cosimulations by embedding bottom-up microscale models into a top-down macroscale architecture. These can be configured in different ways to extract information about the body–environment interaction through learning, and can be used to elaborate brain functional theories (Box 2 and Outstanding questions) [50,78–80,119,120]. Finally, TVB can also embed task-driven models [122] consisting of interconnected SNNs to simulate behavioral tasks.

Pros and cons

Although computational neuroscience is growing toward its highest standards ever, it is also facing inherent limitations [69,132]. First, it is rarely possibly to integrate the molecular scale,

although the laws of mass representation of chemical kinetics (e.g., the Hodgkin–Huxley scheme for ion channel gating) and Markovian schemes for transitions among chemical states are potential exceptions. Second, details of the neurons and microcircuits are often missing, and cellular-level model reconstructions have only been done for the cerebral cortex, cerebellum, basal ganglia, and hippocampus over a limited spatial scale [65–68,97–101]. Thus, reconstructing a whole-brain model fully bottom-up is currently out of reach. The use of brain atlases may help to fill neuroanatomical and neurophysiological gaps for the remaining brain regions through constructive rules [15–21]. Third, even in the best case, inverse modeling cannot retrieve individual neuron properties and the submillisecond spike patterns and dendritic computations that are crucial for brain activity (although it can retrieve collective parameters related to connectivity and population dynamics). Because of neurodegeneracy, single neuron activity at a given time remains undetermined. On top of this, brain plasticity and neuromodulation continuously modify the brain functional state, and this, as well as ontogenetic and pathogenetic aspects, cannot easily be integrated into existing models. Fourth, brain models such as TVB are currently designed to reproduce brain dynamics rather that task-dependent activity, and are still far from explaining behavior. Finally, the speed and power of current computing systems are still insufficient for simulations of neural activities along timescales compatible with lifespan, making it difficult to address issues such neural developmental plasticity, learning, and aging [69]. It has been estimated that simulating a whole human brain at cellular resolution would require up to ~4×10^{29} TFLOPS, whereas the Fugaku Supercomputer at RIKEN 8 (Japan) has a peak performance of ~5×10^{5} TFLOPS [6]. One open perspective is to transform digital brain simulators in neuromorphic hardware to bring computation close to real time [79,81,131]. Overall, personalizing a brain model remains difficult, thus impacting on the challenging perspective of generating **brain digital twins** [22,133], as discussed in the following text.

Fortunately, however, several approaches can make brain modeling effective by solving the multiscale issue [69]. For example, detailed SNNs can now be inserted into robotic controllers [50,78–80,119,120] to generate hybrid simulations at mixed scales. Hybrid closed-loop robotic controllers are making progress by combining function, structure, and dynamics in a single simulator and by embodying the simulator into an artificial agent that can interact with the environment and learn from this interaction [1,50]. In this sense, hybrid robotic controllers are emerging as a sophisticated tool for investigating the neural correlates of behavior (Box 2). The process might be brought forward by combining SNNs [109–111] and functional modules [122] with virtual brains. Further, some molecular properties (e.g., extracted from genomic, proteomic, or metabolomic analyses) can be placed in the virtual space of brain atlases and remapped onto virtual brains and local microcircuits, that allowing model fitness to be improved by importing low-level biological features into high-level constructs [106]. Brain modeling thus increasingly appears to be a workbench that allows the assembly of different modules that neuroscientists can combine depending on their needs (e.g., Figure 1).

Concluding remarks and future perspectives

The main proposal of this paper is that the integration of bottom-up into top-down modeling workflows, by providing the effective models that are necessary to solve the inverse problem, could have remarkable practical consequences. Modeling the relationship between microscopic phenomena and large-scale brain functions could allow us to predict how a drug that binds to specific receptors modifies local and distributed circuit activity, or how genetic alterations to membrane ion channels or receptors will modulate brain functions and dynamics. This in turn would allow the identification of potential targets for pharmacological and physical therapy – for example through electrical or magnetic stimulation of specific circuits – or precision surgery [108–111,134–136]. Clearly, these applications open new perspectives on personalized and

Outstanding questions

What are the main obstacles toward a full brain simulation based on detailed neuron models? In detailed models, each neuron has ~10^3 electrotonic compartments with about 10 ionic mechanisms requiring 4 ordinary differential equations (ODE) each, and each synapse has ~4 ODEs. These ODEs need to be integrated numerically. A local network involves in the order of 10^6 neurons and 10^9 synapses, the mouse brain has about $65*10^6$ neurons and 10^{10} synapses, and the human brain roughly 10^{12} neurons and 10^{15} synapses. It has been estimated that simulating a whole human brain would require up to ~$4*10^{29}$ TFLOPS, while the Fugaku Supercomputer at RIKEN 8 (Japan) has a peak performance of ~$5*10^5$ TFLOPS. Therefore, a human brain simulation remains out of reach even for the most powerful HPC systems. SNNs, made of simplified models maintaining some of the non-linear properties of neuron and synapses (1-3 ODEs each), may help addressing the issue.

How to choose between closed-loop controllers and virtual brains? Virtual brain models are mostly designed to simulate spatio-temporal brain dynamics, whereas closed-loop controllers are designed to govern tasks through the interaction of an agent (a robot) with the environment. Robotic controllers typically embed explicit representations of the functions to be implemented (e.g., motor commands), learning mechanisms, and actuators and sensors emulating motor and sensory functions.

How far are effective Brain Digital Twins applications in neurology? Virtual brain models, as personalized digital representations of the patient's brain, are already being tested for model-guided biomedical applications including surgical therapy of pharmaco-resistant epilepsy, neurostimulation in Alzheimer disease, and deep brain stimulation in Parkinson disease. Progress in connectome resolution, node diversification, and biological feature mapping, are likely to bring toward effective brain digital twins in the next few years.

precision medicine (see Outstanding questions), for example the generation of brain digital twins [22,133]. These aim to be personalized replicas of a subject's brain that can be used to simulate specific functionalities and anticipate the consequences of, for example, neurorehabilitation or surgical intervention.

Scientists are only beginning to unveil the computational properties that have allowed brain circuits to control and differentiate animal behavior during evolution. Multiscale brain modeling not only has breakthrough potential in fostering this aspect of science but we can also envisage applications in information technologies and artificial intelligence. Examples of SNN transformation in neuromorphic hardware are now available ([81,132]). Moreover, SNN networks are already operating inside closed-loop controllers, both in simulated and physical robots [79,80,119], with the perspective of incorporating adaptive behaviors and promoting the generation of autonomous robots (see Outstanding questions). In conclusion, brain models in mixed configuration are not only fundamental to understanding brain functioning but also in promoting digital technologies for society and health in ways that remain to be worked out and exploited in full.

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Declaration of interests

The authors declare no competing interests.

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