

# The Scientific Case for Brain Simulations

Gaute T. Einevoll,<sup>1,2,\*</sup> Alain Destexhe,<sup>3,4</sup> Markus Diesmann,<sup>5,6,7</sup> Sonja Grün,<sup>5,8</sup> Viktor Jirsa,<sup>9</sup> Marc de Kamps,<sup>10</sup> Michele Migliore,<sup>11</sup> Torbjørn V. Ness,<sup>1</sup> Hans E. Plesser,<sup>1,5</sup> and Felix Schürmann<sup>12</sup>

<sup>1</sup>Faculty of Science and Technology, Norwegian University of Life Sciences, 1432 Ås, Norway

<sup>2</sup>Department of Physics, University of Oslo, 0316 Oslo, Norway

<sup>3</sup>Paris-Saclay Institute of Neuroscience (NeuroPSI), Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette, France

<sup>4</sup>European Institute for Theoretical Neuroscience, 75012 Paris, France

<sup>5</sup>Institute of Neuroscience and Medicine (INM-6), Institute for Advanced Simulation (IAS-6), and JARA-Institut Brain Structure-Function Relationships (INM-10), Jülich Research Centre, 52425 Jülich, Germany

<sup>6</sup>Department of Psychiatry, Psychotherapy, and Psychosomatics, RWTH Aachen University, 52074 Aachen, Germany

<sup>7</sup>Department of Physics, RWTH Aachen University, 52074 Aachen, Germany

<sup>8</sup>Theoretical Systems Neurobiology, RWTH Aachen University, 52074 Aachen, Germany

<sup>9</sup>Institut de Neurosciences des Systèmes (INS), INSERM, Aix Marseille Université, 13005 Marseille, France

<sup>10</sup>Institute for Artificial and Biological Intelligence, School of Computing, Leeds LS2 9JT, UK

<sup>11</sup>Institute of Biophysics, National Research Council, 90146 Palermo, Italy

<sup>12</sup>Blue Brain Project, École Polytechnique Fédérale de Lausanne (EPFL), Campus Biotech, 1202 Geneva, Switzerland

\*Correspondence: [gaute.einevoll@nmbu.no](mailto:gaute.einevoll@nmbu.no)

<https://doi.org/10.1016/j.neuron.2019.03.027>

**A key element of the European Union's Human Brain Project (HBP) and other large-scale brain research projects is the simulation of large-scale model networks of neurons. Here, we argue why such simulations will likely be indispensable for bridging the scales between the neuron and system levels in the brain, and why a set of brain simulators based on neuron models at different levels of biological detail should therefore be developed. To allow for systematic refinement of candidate network models by comparison with experiments, the simulations should be multimodal in the sense that they should predict not only action potentials, but also electric, magnetic, and optical signals measured at the population and system levels.**

Despite decades of intense research efforts investigating the brain at the molecular, cell, circuit, and system levels, the operating principles of the human brain, or any brain, remain largely unknown. Likewise, effective treatments for prevalent serious psychiatric disorders and dementia are still lacking (Hyman, 2012; Masters et al., 2015). In broad terms, one could argue that we now have a fairly good understanding of how individual neurons operate and process information, but that the behavior of networks of such neurons is poorly understood. Following the pioneering work of Hubel and Wiesel (1959) in mapping out receptive fields in the early visual system, similar approaches have been used to explore how different types of sensory input and behavior are represented in the brain. In these projects, the statistical correlation between recorded neural activity, typically action potentials from single neurons, and sensory stimulation or behavior of the animal is computed. From this, so-called descriptive mathematical models have been derived, accounting for, say, how the firing rate of a neuron in the visual system depends on the visual stimulus (for example, see Chapter 2 in Dayan and Abbott, 2001).

The qualitative insights gained by obtaining these descriptive receptive-field models should not be underestimated, but these models offer little insight into how networks of neurons give rise to the observed neural representations. Such insight will require mechanistic modeling in which neurons are explicitly modeled and connected in networks. Starting with the seminal work of Hodgkin and Huxley (1952), who developed a mechanistic model for action-potential generation and propagation in squid giant axons, biophysics-based modeling of neurons is now well estab-

lished (Koch, 1999; Dayan and Abbott, 2001; Sterratt et al., 2011). Numerous mechanistic neuron models tailored to model specific neuron types have been constructed, for example, for cells in the mammalian sensory cortex (Hay et al., 2011; Markram et al., 2015; Pozzorini et al., 2015), hippocampus (Migliore et al., 1995), and thalamus (McCormick and Huguenard, 1992; Hahné et al., 2011).

At the network level, most mechanistic studies have focused on generic properties and have considered stylized models with a single or a handful of neuronal populations consisting of identical neurons with statistically identical connection properties. Such studies have given invaluable qualitative insights into the wide range of possible network dynamics (see Brunel, 2000 for an excellent example), but real brain networks have heterogeneous neural populations and more structured synaptic connections. For small networks, excellent models aiming to mimic real neural networks have been developed, a prominent example being the circuit in the crustacean stomatogastric nervous system, which comprises tens of neurons (Marder and Goaillard, 2006). However, even though pioneering efforts to construct comprehensive networks with tens of thousands of neurons mimicking cortical columns in mammalian sensory cortices have been pursued (e.g., Traub et al., 2005; Potjans and Diesmann, 2014; Markram et al., 2015; Schmidt et al., 2018a; Arkhipov et al., 2018), the mechanistic modeling of biological neural networks mimicking specific brains or brain areas is still in its infancy.

A cubic millimeter of cortex contains several tens of thousands of neurons, and until recently, limitations in computer technology



have prohibited the mathematical exploration of neural networks mimicking cortical areas, even in the smallest mammals. With the advent of modern supercomputers, simulations of networks comprising hundreds of thousands or millions of neurons are becoming feasible. Thus, several large-scale brain projects, including the European Union's Human Brain Project (HBP) and MindScope at the Allen Brain Institute, have endeavored to create large-scale network models for the mathematical exploration of network dynamics (Kandel et al., 2013). In the HBP, in which all of the authors of this article participate, the goal is not so much to create models for specific brain areas, but rather to create general purpose brain simulators. These brain simulators, which also aptly are called brain-simulation engines, will not be tied to specific candidate models but rather be applicable for the execution of many candidate models, both current and future. As such, their use by the scientific community for the mathematical exploration of brain function is expected to go well beyond the planned end of the HBP project in 2023.

In this article, we present the scientific case for brain simulations—in particular, the development and use of multi-purpose brain simulators—and argue why such simulators will be indispensable in future neuroscience. Furthermore, the long-term maintenance and continued development of such simulators are neither feasible for individual researchers nor individual research groups. Rather, community efforts as exemplified by the brain-simulator developments in the HBP are required.

### Brain Simulations

Brain function relies on the activity of many spatial scales, from the nanometer scale of atoms and molecules to the meter scale of whole organisms (Devor et al., 2013), and these scales are intimately connected, unlike, for example, in a canister of gas. While the replacement of a single gas molecule with another has no effect on the overall behavior of the gas, a change in a DNA molecule can change the brain dramatically, as in Huntington disease (Gusella et al., 1983). Mechanistic models can act as “bridges between different levels of understanding” (Dayan and Abbott, 2001), as, for example, in the Hodgkin-Huxley model, in which axonal action-potential propagation is explained in terms of the properties of ion channels (i.e., molecules [proteins] embedded in the cell membrane). Today's most impressive multiscale simulations are arguably the weather simulations that provide, with increased accuracy year by year, weather forecasts (Bauer et al., 2015). These physics- and chemistry-based simulations bridge scales from tens of meters to tens of thousands of kilometers, the size of our planet, and are in computational complexity comparable to whole-brain simulations (Koch and Buice, 2015).

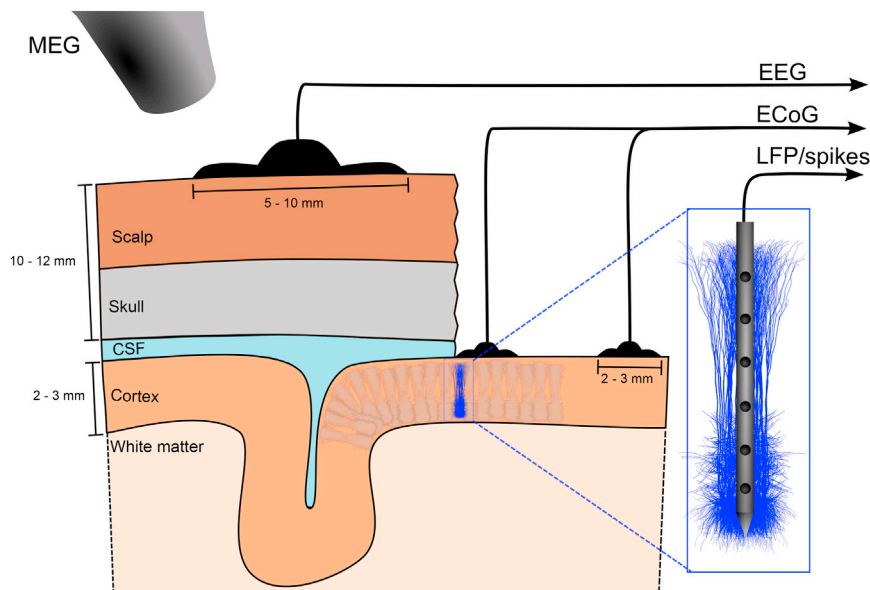
### Brain Network Simulations

Large-scale brain-simulation projects have until now predominantly focused on linking the neuron level to the network level, that is, simulating synaptically connected networks of hundreds, thousands, or more neurons. One obvious reason is that at present such networks, whose properties presumably lie at the heart of our cognitive abilities, are particularly difficult to understand with qualitative reasoning alone—in other words, without the aid of mathematics. Another reason is that starting with the seminal works of Hodgkin and Huxley (1952) and Rall (Segev et al., 1994), we now have a biophysically well-founded scheme

for simulating how individual neurons process information (i.e., how they integrate synaptic inputs from other neurons and generate action potentials). This scheme is covered in all textbooks in computational neuroscience (e.g., Koch, 1999; Dayan and Abbott, 2001; Sterratt et al., 2011) and typically also in computational neuroscience courses offered at universities. Numerous neuron models are now available for reuse and further development and can be downloaded from databases such as ModelDB (<https://senselab.med.yale.edu/modeldb/>), the Neocortical Microcircuit Collaboration (NMC) Portal (<https://bbpteam.epfl.ch/nmc-portal>), the Brain Observatory at the Allen Brain Institute (<http://observatory.brain-map.org/visualcoding/>), and Open Source Brain ([opensourcebrain.org](https://opensourcebrain.org)). Mathematical models for synaptic function, including synaptic plasticity, have also been developed, and all of the necessary building blocks for creating models for networks of neurons are thus available.

Some large-scale network models have been based on morphologically detailed neuron models (Reimann et al., 2013; Markram et al., 2015; Arkhipov et al., 2018), some have used stylized spatially extended neuron models (Traub et al., 2005; Tomsett et al., 2015; Migliore et al., 2015), some have used point neurons of the integrate-and-fire type (Lumer et al., 1997; Izhikevich and Edelman, 2008; Potjans and Diesmann, 2014; Hagen et al., 2016; van Albada et al., 2018; Schmidt et al., 2018a, 2018b), and some have used firing-rate units representing population activity (Schirner et al., 2018). More biological detail does not by itself mean that the model is more realistic. In fact, point neurons, that is, neuron models in which the membrane potential is assumed to be the same across dendrites and soma, have been found to be excellently suited to reproduce experimentally recorded action potentials following current stimulation (Jolivet et al., 2008; Pozzorini et al., 2015). The various neuron models have different pros and cons, and the choice of which to use depends on the question asked (Herz et al., 2006). We thus argue that a set of brain simulators for the simulation of models at different levels of biological detail should be developed.

For weather simulations, the goal is clear: to accurately predict temperature, precipitation, and wind at different geographical locations. Likewise, brain simulations should predict what can be experimentally measured, not only action potentials but also population-level measures such as local field potentials (LFPs), electrocorticographic signals (ECoGs) and voltage-sensitive dye imaging (VSDI) signals, as well as systems-level measurements such as signals recorded by electroencephalography (EEG) or magnetoencephalography (MEG) (Brette and Destexhe, 2012) (Figure 1). For these electrical, magnetic, and optical measures the “measurement physics” seem well established; in other words, the mathematical models for the biophysical link between electrical activity in neurons and what is measured by such recordings have been developed (see the references in the Figure 1 legend). Simulation tools such as LFPy ([lfp.py.github.io](https://github.com/epfl-lfp/py)) and BIONET (<https://alleninstitute.github.io/bmtk/bionet.html>) for the prediction of such electrical and magnetic signals from simulated network activity, both using biophysically detailed multicompartment models (Lindén et al., 2014; Gratiy et al., 2018; Hagen et al., 2018) and point-neuron models of the integrate-and-fire type (Hagen et al., 2016), are now publicly available. For fMRI, the biophysical link between



**Figure 1. Electric and Magnetic Signals to Be Computed in Brain Network Simulations**

Measures of neural activity in cortical populations: spikes (action potentials) and LFPs from a linear microelectrode inserted into cortical gray matter, ECoG from electrodes positioned on the cortical surface, EEG from electrodes positioned on the scalp, and MEG measuring magnetic fields stemming from brain activity by means of superconducting quantum interference devices (SQUIDS) placed outside the head. For reviews on the biophysical origin and link between neural activity and the signals recorded in the various measurements, see Hämäläinen et al. (1993); Nunez and Srinivasan (2006); Brette and Destexhe (2012); Buzsáki et al. (2012); Einevoll et al. (2013); Pesaran et al. (2018); and Hagen et al. (2018).

the activity in individual neurons and the recorded blood oxygen level-dependent (BOLD) signal is not yet established (Uhlirova et al., 2016a, 2016b), and a mechanistic forward-modeling procedure linking microscopic brain activity to the measurements is not yet available.

Figure 2 illustrates the use of brain network simulators for a so-called barrel column in the somatosensory cortex. Each column primarily processes sensory information from a single whisker on the snouts of rodents, and in rats, a barrel column contains tens of thousands of neurons. A column can be modeled as a network of interconnected neurons based on biophysically detailed multicompartiment models (here referred to as level I), point-neuron models of the integrate-and-fire type (level II), or firing-rate units in which each unit represents the activity in a neuronal population (level III). Regardless of the underlying neuron type, the simulator should preferably be multimodal, meaning that it should simultaneously predict many types of experimental signals stemming from the same underlying network activity. Ideally, the neuron models at the different levels of detail should be interconnected in the sense that the simpler neuron models should be possible to reduce from (or at least be compatible with) the more detailed neuron models. The field of statistical physics addresses such scale bridging. A prime example of its application is the development of the thermodynamic ideal-gas law, which describes the macroscopic properties of gases in terms of variables such as temperature or pressure from the microscopic Newtonian dynamics of the individual gas molecules. Several neuroscience projects have aimed to derive firing-rate models (level III) from spiking neuron models (level II) (de Kamps et al., 2008; Deco et al., 2008; Ostojic and Brunel, 2011; Bos et al., 2016; Schwalger et al., 2017; Heiberg et al., 2018).

**One Simulator, Many Models**

When discussing simulations, it is important to distinguish between the model and the simulator. Here, “Model” refers to the equations with all of the parameters specified. “Simulator” refers to the soft-

ware tool that can execute the model (e.g., NEURON, NEST, The Virtual Brain used in HBP). “Simulation” refers to the execution of a model in a simulator.

In some fields of science, simulators are intimately tied to solving a particular

model. One example is atomic physics, in which there is consensus about both what equation to solve (the Schrödinger equation) and the numerical values of the few parameters involved (e.g., electron mass, Planck’s constant). In contrast, for simulations of brain networks, we can and should have a clear separation. The simulators used in HBP are accordingly designed to execute many different models, just as calculus can be used in many different physics calculations. Also, if possible, one should, as a control, execute the same model on different simulators to check for the consistency of the results (van Albada et al., 2018; Shimoura et al., 2018). To facilitate this, software packages for simulator-independent specification of neuronal network models have been developed (Davison et al., 2009).

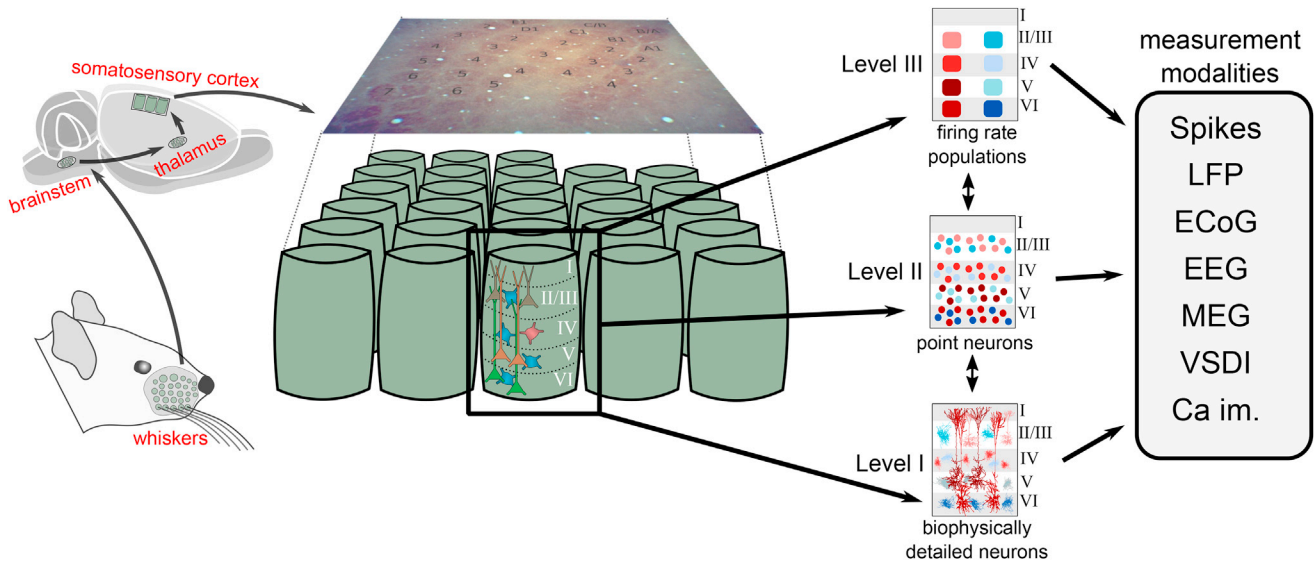
**Network Simulators Not Tailored to Specific Brain Function Hypotheses**

In experimental neuroscience, the method is often intimately tied to the hypothesis being tested. In electrophysiological experiments, for example, the experimental setup and execution protocols are tailored to most efficiently answer the biological question asked. In contrast, brain network simulators should not be designed to test a particular hypothesis about brain function; rather, they should be designed so that they can test many existing and future hypotheses.

**Discovery of Newton’s Law of Gravitation: An Analogy**

As the tools for testing a hypothesis can easily be confused with the hypothesis itself, we present an analogy from physics, Isaac Newton’s discovery of the law of gravitation. While one could argue that the establishment of a mechanistic understanding of brain function—understanding our cognitive abilities on the basis of neuronal action—would be a breakthrough of similar magnitude as discovering this law, this is not the point. Here, this example is used only to illustrate the role of network simulators in brain research.

Before Newton formulated his theory, planetary orbits had, since ancient times, been described using the Ptolemaic model.



**Figure 2. Illustration of Multimodal Modeling with Brain Simulators**

Network dynamics in a cortical column (barrel) processing whisker stimulation in rat somatosensory cortex (left) can be modeled with units at different levels of detail. In the present example, we have a level organization with biophysically detailed neuron models (level I), simplified point-neuron models (level II), and firing-rate models with neuron populations as fundamental units (level III). Regardless of level, the network simulators should aim to predict the contribution of the network activity to all available measurement modalities. In addition to the electric and magnetic measurement modalities illustrated in Figure 1, the models may also predict optical signals—for example, signals from voltage-sensitive dye imaging (VSDI) signals and two-photon calcium imaging (Ca im.).

This model assumed that Earth was the center of the universe and the planets moved in trajectories described as a complicated arrangement of circles within circles (so-called epicycles). The model predicted the planetary orbits accurately and was used for >1,500 years to make astronomical charts for navigation. It was a successful descriptive model, but it shed little light on the underlying physical mechanisms governing planetary movement. As such, it had a similarly useful role as the present descriptive, receptive-field-like models that account for neural representations in the brain.

Newton’s theory of gravitation provided a mechanistic understanding of planetary movement based on his two hypotheses: (1) how masses attract one another and (2) how the movement of masses is changed when forces act on them. The theory went beyond planetary orbits, however, in that it also successfully predicted the kinematic laws of falling apples, the trajectories of cannonballs, and high and low tides due to gravitational attraction between the moon and the water in Earth’s oceans.

The first hypothesis of Newton was that two masses  $m$  and  $M$  with a separation distance  $r$  attract each other with a force  $F_g$  given by

$$F_g = G \frac{mM}{r^2}, \tag{Equation 1}$$

where  $G$  is the gravitational constant. The second hypothesis was that when a force  $F$ ,  $F_g$  in Equation 1, is acting on a mass  $m$ , the mass will be accelerated with an acceleration  $a$  according to

$$a = \frac{F_g}{m}. \tag{Equation 2}$$

To test the validity of these hypotheses, Newton had to compare them with the available measurements of planetary orbits. However, the connection between the mathematically formulated hypotheses in Equations 1 and 2 and the shapes of predicted planetary orbits is not obvious. In fact, Newton developed a new type of mathematics, calculus, to make testable predictions from his theory that allowed for its validation (Leibniz independently developed calculus around the same time). Without the appropriate type of mathematics, it would have been impossible for Newton to test whether nature behaved according to his hypotheses.

Comparison with the available measurements of planetary orbits demonstrated that Newton’s hypotheses were correct, and Newton’s theory of gravitation is now one of the pillars of physics. However, if it had turned out that the predictions of planetary orbits were not in accordance with the observational data, Newton could have tried other mathematically formulated hypotheses than those in Equations 1 and 2. Then, with the aid of calculus, he could have made new planetary orbit predictions and checked whether these were in better agreement with the measurements.

The point is that calculus was a tool to test Newton’s hypotheses regarding the movement of masses; it was not a part of the hypotheses themselves. Likewise, we argue that brain network simulators should, analogous to calculus, be designed to be tools for making precise predictions of brain measurements for any candidate hypothesis for how brain networks are designed and operate.

**Hypothesis Underlying Brain Network Simulators**

At present, we do not have a well-grounded, and certainly not generally accepted, theory about how networks of millions or billions of neurons work together to provide salient brain functions in animals or humans. We do not even have a well-established

model for how neurons in the primary visual cortex of mammals work together to form the intriguing neuronal representations with, for example, the orientation selectivity and direction selectivity that were discovered by Hubel and Wiesel 60 years ago (Hubel and Wiesel, 1959). Moreover, we do not have an overview of all of the neuron types in the brain. However, we do know the biophysical principles of how to model electrical activity in neurons and how neurons integrate synaptic inputs from other neurons and generate action potentials. These principles, which go back to the work of Hodgkin and Huxley (1952) and Rall (Segev et al., 1994) and are described in numerous textbooks (e.g., Koch, 1999; Dayan and Abbott, 2001; Sterratt et al., 2011), are the only hypotheses underlying the construction of brain network simulators. This is the reason why many models can be represented in the same simulator and why it is possible to develop generally applicable simulators for network neuroscience.

While we know the principles for how to model neuronal activity, we do not *a priori* know all of the ingredients needed to fully specify network models. To construct candidate network models, information on the anatomical structure, electrophysiological properties, and spatial positions of neurons, as well as information on how these neurons are connected, are needed. The MindScope project at the Allen Brain Institute as well as the HBP are gathering these data, and the first large-scale models are constructed on the basis of these and other sources (Arkhipov et al., 2018). Although the primary goal in the HBP is to create general purpose brain simulators, such initial models are needed to guide the construction of these simulators and to demonstrate their performance and potential usefulness. However, given the present lack of data on, for example, the strength and plasticity of synaptic connections between the neurons, it is clear that these initial models can be nothing more than plausible skeleton models to be used as starting points for further explorations. Experimental data are collected to have a starting point for mathematical exploration, not in the belief that brain function will be understood simply by collecting these data and putting them into a large simulator.

Each candidate network model with specified neuron models, network structure, and synaptic connections precisely defined by a set of model parameters can be thought of as a candidate hypothesis. Brain network simulators should be designed to allow for the computation of predictions of relevant experimental measures from any such candidate model (Figure 2) so that the merit of each model can be assessed by comparison with experiments.

In passing, we note that the use of mathematical simulators has a proud history in neuroscience. The accurate model prediction of the speed and shape of propagating action potentials in the squid giant axon by Hodgkin and Huxley in the early 1950s required numerical solution of the equations on a hand-operated calculation machine, since the newly installed Cambridge computer was inoperative for 6 months in 1951 (Hodgkin, 1976).

### Use of Brain Network Simulators *Biological Imitation Game*

When the physicist Richard Feynman died in 1988, a statement on his blackboard read, “What I cannot create, I do not understand.” In the present context, an interpretation of this is that unless we can create mechanistic mathematical models that

mimic the behavior of real brains, our understanding will have to remain limited. An obvious use of brain network simulators is to contribute to building such models. In particular, the simulators should test candidate network models against experiments so that over time, network models improve and move closer to the networks that are realized in real biological systems. This would amount to identifying the models that perform best in the biological imitation game (Koch and Buice, 2015)—that is, the models whose predictions best mimic experimental recordings of the same system.

In general, a unique winner of this imitation game will not be found. Such a winner would be a specific network model with a specific set of model parameters. Rather, classes of candidate models with similar structures and model parameters will likely do equally well, but as more experiments become available, the class of models jointly leading this game will expectedly be reduced in size. At all times, the leading models can be considered as the currently most promising hypotheses for how the specific biological network is designed and operates, and these will be challenged by new experiments and new candidate models.

For Newton it was clear what should be compared: the observed planetary orbits and the corresponding orbits predicted by his theory. In brain science the comparison is less clear. Action potentials are clearly the key carrier of information, but what aspects of the trains of action potentials should be mimicked by brain simulations? Detailed temporal sequences of action potentials from individual neurons, coefficients of variation, or firing rates of individual neurons (Jolivet et al., 2008; Gutzen et al., 2018)? Or perhaps the target should be only the average firing rates of populations of neurons? Likewise, it is unclear what aspects of the LFP or VSDI signals should be compared—the full temporal signals or perhaps the power spectral densities? The question of what criteria should be used to select the best model cannot be fully settled at present. The answer will also depend, for example, on whether one believes that information is coded in firing rates or in the detailed temporal structure of action potential trains. Perhaps the realistic behavior of a robot following motor commands produced by a model network could be one success criterion when such models become available? Such uncertainties regarding modeling targets should not preclude the initiation of a biological imitation game; they mean only that different rules of the game may be considered or that the rules may change over time.

Overarching ideas on how computations are performed by the brain can also inspire candidate models. For example, predictive coding (Rao and Ballard, 1999) has emerged as a contender to the more traditional idea that the brain integrates information from the outside world from feature detectors through predominantly feedforward processes. Instead, predictive coding suggests that the brain is constantly updating hypotheses about the world and predicting sensory information by feedback mechanisms. These two competing ideas could, when instantiated as specific network models, make different predictions about neurophysiological experiments.

### *Validation of Data Analysis Methods*

Another important application of brain simulations is to create benchmarking data for the validation of the methods used to analyze experimental data. This approach has already been

used to generate benchmarking data for testing automatic spike-sorting algorithms (Hagen et al., 2015), methods for detecting putative synfire chains (Schrader et al., 2008), and methods used to estimate current-source densities (CSDs) from recorded LFPs (Pettersen et al., 2008). Several statistical methods have been developed for estimating functional connectivities between neural populations and cortical areas based on population-level and systems-level measures such as LFP, EEG, MEG, and fMRI signals (Einevoll et al., 2013; Pesaran et al., 2018). These statistical analysis methods should be validated on “virtual” benchmarking data computed by brain network simulators in which the ground-truth neuron and network activity are known (Denker et al., 2012). Even if these model-based benchmarking data do not correspond in detail to any specific biological system, data analysis methods claimed to be generally applicable should also perform well on these simulated data.

### Use by the Wider Research Community

Anyone who has tried knows that learning the calculus that is needed to derive planetary orbits from Newton’s hypotheses is demanding, and for most, formal training in mathematics is required. Likewise, the development of brain simulators requires extensive training in mathematics, computer science, and physics, as well as a significant coordinated effort involving many developers. Fortunately, just as a practicing neuroscientist does not need to construct a confocal microscope to use it in research, simulators can be used without knowing all of the technical inner workings. Some simulators such as NEURON (Carnevale and Hines, 2006) even come with a graphical user interface, and plug-and-play programs in which neural networks can be created and simulated by pulling elements with a finger onto a canvas have also been made (Dragly et al., 2017).

While the complexity of many neural network models will make the use of solely graphical user interfaces difficult, it should nevertheless be a goal to design brain simulators so that they also can be used by the general neuroscience community. One aspect of this is that the developers of widely used simulators should regularly offer tutorial and training courses, for example, in connection with major neuroscience conferences. Furthermore, high-quality user-level documentation and support systems for personal inquiries by users must be set up. However, even the best user-level documentation will not enable the general neuroscience community to easily set up large-scale network models. Extracting all of the necessary neurobiological data from experiments, literature, and databases and specifying reliable executable model descriptions, generally requires many years of effort, as exemplified by recent studies (e.g., Potjans and Diesmann, 2014; Markram et al., 2015; Schmidt et al., 2018a; Arkhipov et al., 2018). It is therefore essential that executable descriptions of such models are made publicly available as examples and starting points for the community.

The publishing of executable model descriptions may require procedures and tools that go beyond standard scientific publishing practices. For example, the recent publication of a comprehensive multi-area model of the macaque visual cortex (Schmidt et al., 2018a, 2018b) was accompanied by detailed model descriptions expressed by technologies such as GitHub (<https://inm-6.github.io/multi-area-model/>) and Snakemake (Köster

and Rahmann, 2012) and supplemented with an introductory video (<https://youtu.be.com/watch?v=YsH3BcyZBcU&feature=youtu.be>). Furthermore, the authors also provided the digitized workflow leading from the underlying experimental data to the model specification.

With a plausible candidate network model for a part of V1 in a mouse as a starting point, for example, scientists with modest training in mathematics, physics, and computer science should be able to use brain simulations to ask questions such as the following:

- What is the predicted spiking response of various neuron types to different types of visual stimuli?
- What is the predicted effect on network activity with pharmacological blocking of a particular ion channel in a particular neuron type?
- What does the visually evoked LFP signal recorded inside the cortex look like, and what neuron populations are predicted to contribute most to this signal?
- Can the EEG signal recorded by electrodes on the scalp positioned outside the visual cortex distinguish between two candidate network models for V1?

The application of brain simulators can be computationally demanding and require the use of supercomputers, especially if many model parameter combinations are to be investigated. Not everyone has access to such supercomputers, nor the experience to install or maintain large computer programs. One option would be to make brain network simulators available through web-based services so that all computations are done remotely on centralized supercomputer centers, as is the plan for HBP.

In the long run, network neuroscience can only approach a mechanistic systems-level understanding if we overcome the complexity barrier by learning how to build on the work of others, by eventually combining models of smaller brain networks components to larger structures of more relevance for cognition. Newton said that he had seen further than others because he was “standing on the shoulders of giants.” Likewise, we argue that we need to find a way to stand on the shoulders of each other’s mathematical models to hope to gain a detailed understanding of the functioning of brain networks.

### Discussion and Outlook

We have presented arguments for why brain network simulators are not only useful but also likely critical for advancing systems neuroscience. By drawing an analogy to Newton’s law of gravitation, we have argued that brain simulators should not be made to test specific hypotheses about brain function. Rather, like Newton’s development of calculus to allow for the testing of the validity of his physical hypotheses regarding planetary movement (Equations 1 and 2), brain simulators should be viewed as “mathematical observatories” to test various candidate hypotheses. A brain simulator is thus a tool, not a hypothesis, and can as such be likened to tools used to image brain structure or brain activity.

In computational neuroscience, one has to “learn to compute without knowing all the numbers” (as quoted from a talk by John Hopfield at a conference in Sigtuna, Sweden, some 20 years

ago). What is meant by this is that unlike in quantum-mechanical computations of atomic properties, in which the handful of model parameters are known to many digits, the model parameters specifying brain networks are numerous, uncertain, and may change over time. The effects of uncertain model parameters and the uncertainty of model predictions can be systematically studied, although such uncertainty quantification requires repeated evaluations of the model of interest and is typically computationally demanding (Tennøe et al., 2018).

We need a set of different brain network simulators describing the neurons at different levels of resolution, different levels of biological detail, as exemplified by the three levels depicted in Figure 2. Simulators based on biophysically detailed, multicompartmental neuron models (level I) can explore in detail how the dendritic structures affect the integration of synaptic inputs and, consequently, the network dynamics (Reimann et al., 2013; Markram et al., 2015; Migliore et al., 2015; Arhipov et al., 2018). Simulators based on point neurons of the integrate-and-fire type (level II) are much less computationally demanding, so that larger networks can be studied (Potjans and Diesmann, 2014). Furthermore, the number of model parameters is much smaller and the fitting of single-neuron models to experimental recordings easier (Pozzorini et al., 2015). Population firing-rate models (level III) model the dynamics of entire populations, which makes the models computationally, and often also conceptually, much easier (de Kamps et al., 2008; Cain et al., 2016; Schwalger et al., 2017). With population firing-rate models describing a small patch of cortex, the neural-mass models, one can derive spatially extended models, the neural-field models, covering cortical areas and even complete human cortices (Deco et al., 2008; Ritter et al., 2013; Sanz Leon et al., 2013; Breakspear, 2017; Schirner et al., 2018). While at present most neural-field models are based on largely phenomenological neural-mass models (Jansen and Rit, 1995; Deco et al., 2008), the goal should be to derive such neural-mass building blocks from population network models based on individual neurons (Zerlaut et al., 2018) or from fitting to experiments (Blomquist et al., 2009).

Brain network simulation is still in its infancy, and the simulators and associated infrastructure should be developed to allow for the study of larger networks and fully exploit the capabilities of modern computer hardware (Akar et al., 2019; Kumbhar et al., 2019). They should also allow for the study of longer timescale processes such as homeostatic and synaptic plasticity (Turrigiano and Nelson, 2004; Keck et al., 2017). With plausible biophysics-based rules for, for example, spike-timing-dependent long-term synaptic plasticity included in the models, studies of learning will also be possible. Brain simulators should eventually also be extended beyond the modeling of networks of neurons alone to incorporate extracellular space and interaction with glia cells (Solbrå et al., 2018). Likewise, they should allow for studies of the effects of electrical or magnetic stimulation of the brain, either with intracranial electrodes as in deep-brain stimulation (Perlmutter and Mink, 2006), with surface electrodes (Bosking et al., 2017), or transcranially (Wassermann et al., 2008).

The present article has focused on brain simulators for studying networks of neurons. While not addressed here, there is clearly also a need for simulators for studying brain activity at

the subcellular scale, both for modeling molecular signaling pathways governed by reaction-diffusion dynamics (Bhalla and Wils, 2010) and for modeling molecular dynamics by Newtonian mechanics (Rapaport, 2004). We have also focused on the bottom-up-type network models typically pursued in the computational neuroscience community, in which model predictions can be compared directly with physiological experiments. However, network models can also be very useful for concisely and precisely representing ideas on how the brain may implement cognitive processes. An early example of such work is the so-called Hopfield model, describing how associative memory can be achieved in recurrent networks of binary neurons (Hopfield, 1982). During the last several decades such modeling work has grown to include visual attention (Reynolds and Desimone, 1999; Deco and Rolls, 2004), language representation (van der Velde and de Kamps, 2006), decision making (Gold and Shadlen, 2007), and learning (Brader et al., 2007). While none of these works immediately predict specific detailed outcomes of neurophysiological experiments, they state ideas about cognitive phenomenon in a concise manner that allows scrutiny and critique.

The development of high-quality brain simulators requires a long-term commitment of resources. Both NEURON and NEST, two key brain simulators in the HBP, have been developed over >25 years. Likewise, the continued development, maintenance, and user support of key brain simulators used by the research community requires long-term funding. These simulation tools can be likened to other joint research infrastructures such as astronomical observatories or joint international facilities for studies of subatomic particles. While the expenses for the operation of brain simulators will be much smaller than these experimental facilities, they should nevertheless be considered necessary research infrastructure and preferably be funded as such.

Until we learn how the wide range of spatial and temporal scales involved in brain function are connected, our understanding of our brains will be limited. Bridging these scales with mathematical modeling will be a daunting challenge, but encouragingly, there are examples from other branches of science in which many scales have been bridged, the most visible likely being numerical weather prediction (Bauer et al., 2015). Another impressive example of scale bridging is the engineering underlying cellular telephones. Tailored materials made of selected semiconductor and metal atoms are assembled into numerous transistors (in some sense, analogous to neurons) connected in networks on a chip (“brain”), which together with other components make up the cellular telephone (“organism”). These examples have been totally dependent on mathematics and simulations to bridge models at different scales; therefore, a natural question is, do we have a chance of ever understanding brain function without brain simulations?

#### ACKNOWLEDGMENTS

Funding was received from the European Union Seventh Framework Program (FP7/2007/2013) under grant agreement no. 604102 (HBP); the European Union’s Horizon 2020 Framework Programme for Research and Innovation under grant agreements 720270 (HBP SGA1), 785907 (HBP SGA2), and 754304 (DEEP-EST); the Research Council of Norway (DigiBrain 248828

and CoBra 250128); Deutsche Forschungsgemeinschaft grants GR 1753/4-2 and DE 2175/2-1 of the Priority Program (SPP 1665); the Helmholtz Association Initiative and Networking Fund under project nos. ZT-I-0003 (HAF) and SO-902 (ACA); RTG 2416 “Multi-senses Multi-scales”; VSR Computation Time Grant Brain-Scale Simulations JINB33; and the Swiss ETH Domain for the Blue Brain Project.

## REFERENCES

- Akar, A.N., Cumming, B., Karakasis, V., Küsters, A., Klijin, W., Peyser, A., and Yates, S. (2019). Arbor – a morphologically-detailed neural network simulation library for contemporary high-performance computing architectures. arXiv, arXiv, 1901.07454 <https://arxiv.org/abs/1901.07454>.
- Arkipov, A., Gouwens, N.W., Billeh, Y.N., Gratiy, S., Iyer, R., Wei, Z., Xu, Z., Abbasi-Asl, R., Berg, J., Buice, M., et al. (2018). Visual physiology of the layer 4 cortical circuit in silico. *PLoS Comput. Biol.* *14*, e1006535.
- Bauer, P., Thorpe, A., and Brunet, G. (2015). The quiet revolution of numerical weather prediction. *Nature* *525*, 47–55.
- Bhalla, U.S., and Wils, S. (2010). Reaction-diffusion modeling. In *Computational Modeling Methods for Neuroscientists*, E. de Schutter, ed. (MIT Press), pp. 61–92.
- Blomquist, P., Devor, A., Indahl, U.G., Ulbert, I., Einevoll, G.T., and Dale, A.M. (2009). Estimation of thalamocortical and intracortical network models from joint thalamic single-electrode and cortical laminar-electrode recordings in the rat barrel system. *PLoS Comput. Biol.* *5*, e1000328.
- Bos, H., Diesmann, M., and Helias, M. (2016). Identifying anatomical origins of coexisting oscillations in the cortical microcircuit. *PLoS Comput. Biol.* *12*, e1005132.
- Bosking, W.H., Sun, P., Ozker, M., Pei, X., Foster, B.L., Beauchamp, M.S., and Yoshor, D. (2017). Saturation in phosphene size with increasing current levels delivered to human visual cortex. *J. Neurosci.* *37*, 7188–7197.
- Brader, J.M., Senn, W., and Fusi, S. (2007). Learning real-world stimuli in a neural network with spike-driven synaptic dynamics. *Neural Comput.* *19*, 2881–2912.
- Breakspear, M. (2017). Dynamic models of large-scale brain activity. *Nat. Neurosci.* *20*, 340–352.
- R. Brette and A. Destexhe, eds. (2012). *Handbook of Neural Activity Measurement* (Cambridge University Press).
- Brunel, N. (2000). Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *J. Comput. Neurosci.* *8*, 183–208.
- Buzsáki, G., Anastassiou, C.A., and Koch, C. (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nat. Rev. Neurosci.* *13*, 407–420.
- Cain, N., Iyer, R., Koch, C., and Mihalas, S. (2016). The computational properties of a simplified cortical column model. *PLoS Comput. Biol.* *12*, e1005045.
- Carnevale, N.T., and Hines, M.L. (2006). *The NEURON Book* (Cambridge University Press).
- Davison, A.P., Brüderle, D., Eppler, J., Kremkow, J., Müller, E., Pecevski, D., Perrinet, L., and Yger, P. (2009). Pynn: a common interface for neuronal network simulators. *Front. Neuroinform.* *2*, 11.
- Dayan, P., and Abbott, L. (2001). *Theoretical Neuroscience* (MIT Press).
- de Kamps, M., Baier, V., Drever, J., Dietz, M., Mösenlechner, L., and van der Velde, F. (2008). The state of MIND. *Neural Netw.* *21*, 1164–1181.
- Deco, G., and Rolls, E.T. (2004). A neurodynamical cortical model of visual attention and invariant object recognition. *Vision Res.* *44*, 621–642.
- Deco, G., Jirsa, V.K., Robinson, P.A., Breakspear, M., and Friston, K. (2008). The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLoS Comput. Biol.* *4*, e1000092.
- Denker, M., Einevoll, G., Franke, F., Grün, S., Hagen, E., Kerr, J., Nawrot, M., Ness, T.B., Ritz, R., Smith, L., et al. (2012). Report from 1st INCF workshop on validation of analysis methods. ResearchF1000. Published online August 9, 2018. <https://doi.org/10.7490/f1000research.1115887.1>.
- Devor, A., Bandettini, P.A., Boas, D.A., Bower, J.M., Buxton, R.B., Cohen, L.B., Dale, A.M., Einevoll, G.T., Fox, P.T., Franceschini, M.A., et al. (2013). The challenge of connecting the dots in the B.R.A.I.N. *Neuron* *80*, 270–274.
- Dragly, S.-A., Hobbi Mobarhan, M., Våvang Solbrå, A., Tennøe, S., Hafreager, A., Malthé-Sørensen, A., Fyhn, M., Hafting, T., and Einevoll, G.T. (2017). Neuronify: an educational simulator for neural circuits. *eNeuro* *4*, ENEURO.0022-17.2017.
- Einevoll, G.T., Kayser, C., Logothetis, N.K., and Panzeri, S. (2013). Modelling and analysis of local field potentials for studying the function of cortical circuits. *Nat. Rev. Neurosci.* *14*, 770–785.
- Gold, J.I., and Shadlen, M.N. (2007). The neural basis of decision making. *Annu. Rev. Neurosci.* *30*, 535–574.
- Gratiy, S.L., Billeh, Y.N., Dai, K., Mitelut, C., Feng, D., Gouwens, N.W., Cain, N., Koch, C., Anastassiou, C.A., and Arkipov, A. (2018). BioNet: a Python interface to NEURON for modeling large-scale networks. *PLoS One* *13*, e0201630.
- Gusella, J.F., Wexler, N.S., Conneally, P.M., Naylor, S.L., Anderson, M.A., Tanzi, R.E., Watkins, P.C., Ottina, K., Wallace, M.R., Sakaguchi, A.Y., et al. (1983). A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* *306*, 234–238.
- Gutzen, R., von Papen, M., Trensche, G., Quaglio, P., Grün, S., and Denker, M. (2018). Reproducible neural network simulations: statistical methods for model validation on the level of network activity data. *Front. Neuroinform.* *12*, 90.
- Hagen, E., Ness, T.V., Khosrowshahi, A., Sørensen, C., Fyhn, M., Hafting, T., Franke, F., and Einevoll, G.T. (2015). ViSAPy: a Python tool for biophysics-based generation of virtual spiking activity for evaluation of spike-sorting algorithms. *J. Neurosci. Methods* *245*, 182–204.
- Hagen, E., Dahmen, D., Stavrinou, M.L., Lindén, H., Tetzlaff, T., van Albada, S.J., Grün, S., Diesmann, M., and Einevoll, G.T. (2016). Hybrid scheme for modeling local field potentials from point-neuron networks. *Cereb. Cortex* *26*, 4461–4496.
- Hagen, E., Næss, S., Ness, T.V., and Einevoll, G.T. (2018). Multimodal modeling of neural network activity: computing LFP, ECoG, EEG and MEG signals with LFPy 2.0. *Front. Neuroinform.* *12*, 92.
- Halnes, G., Augustinaite, S., Heggelund, P., Einevoll, G.T., and Migliore, M. (2011). A multi-compartment model for interneurons in the dorsal lateral geniculate nucleus. *PLoS Comput. Biol.* *7*, e1002160.
- Hämäläinen, M., Hari, R., Ilmoniemi, R., Knuutila, J., and Lounasmaa, O.V. (1993). Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev. Mod. Phys.* *65*, 413–497.
- Hay, E., Hill, S., Schürmann, F., Markram, H., and Segev, I. (2011). Models of neocortical layer 5b pyramidal cells capturing a wide range of dendritic and perisomatic active properties. *PLoS Comput. Biol.* *7*, e1002107.
- Heiberg, T., Kriener, B., Tetzlaff, T., Einevoll, G.T., and Plesser, H.E. (2018). Firing-rate models for neurons with a broad repertoire of spiking behaviors. *J. Comput. Neurosci.* *45*, 103–132.
- Herz, A.V.M., Gollisch, T., Machens, C.K., and Jaeger, D. (2006). Modeling single-neuron dynamics and computations: a balance of detail and abstraction. *Science* *314*, 80–85.
- Hodgkin, A.L. (1976). Chance and design in electrophysiology: an informal account of certain experiments on nerve carried out between 1934 and 1952. *J. Physiol.* *263*, 1–21.
- Hodgkin, A.L., and Huxley, A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* *117*, 500–544.
- Hopfield, J.J. (1982). Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl. Acad. Sci. USA* *79*, 2554–2558.
- Hubel, D.H., and Wiesel, T.N. (1959). Receptive fields of single neurones in the cat's striate cortex. *J. Physiol.* *148*, 574–591.



- Hyman, S.E. (2012). Revolution stalled. *Sci. Transl. Med.* *4*, 155.
- Izhikevich, E.M., and Edelman, G.M. (2008). Large-scale model of mammalian thalamocortical systems. *Proc. Natl. Acad. Sci. USA* *105*, 3593–3598.
- Jansen, B.H., and Rit, V.G. (1995). Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biol. Cybern.* *73*, 357–366.
- Jolivet, R., Schürmann, F., Berger, T.K., Naud, R., Gerstner, W., and Roth, A. (2008). The quantitative single-neuron modeling competition. *Biol. Cybern.* *99*, 417–426.
- Kandel, E.R., Markram, H., Matthews, P.M., Yuste, R., and Koch, C. (2013). Neuroscience thinks big (and collaboratively). *Nat. Rev. Neurosci.* *14*, 659–664.
- Keck, T., Toyozumi, T., Chen, L., Doiron, B., Feldman, D.E., Fox, K., Gerstner, W., Haydon, P.G., Hübener, M., Lee, H.-K., et al. (2017). Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* *372*, 20160158.
- Koch, C. (1999). *Biophysics of Computation* (Oxford University Press).
- Koch, C., and Buice, M.A. (2015). A biological imitation game. *Cell* *163*, 277–280.
- Köster, J., and Rahmann, S. (2012). Snakemake—a scalable bioinformatics workflow engine. *Bioinformatics* *28*, 2520–2522.
- Kumbhar, P., Hines, M., Fouriaux, J., Ovcharenko, A., King, J., Delalandre, F., and Schürmann, F. (2019). CoreNEURON - an optimized compute engine for the NEURON simulator. *arXiv, arXiv, 1901.10975* <https://arxiv.org/abs/1901.10975>.
- Lindén, H., Hagen, E., Leski, S., Norheim, E.S., Pettersen, K.H., and Einevoll, G.T. (2014). LFPy: a tool for biophysical simulation of extracellular potentials generated by detailed model neurons. *Front. Neuroinform.* *7*, 41.
- Lumer, E.D., Edelman, G.M., and Tononi, G. (1997). Neural dynamics in a model of the thalamocortical system. I. Layers, loops and the emergence of fast synchronous rhythms. *Cereb. Cortex* *7*, 207–227.
- Marder, E., and Goaillard, J.-M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.* *7*, 563–574.
- Markram, H., Müller, E., Ramaswamy, S., Reimann, M.W., Abdellah, M., Sanchez, C.A., Ailamaki, A., Alonso-Nanclares, L., Antille, N., Arsever, S., et al. (2015). Reconstruction and simulation of neocortical microcircuitry. *Cell* *163*, 456–492.
- Masters, C.L., Bateman, R., Blennow, K., Rowe, C.C., Sperling, R.A., and Cummings, J.L. (2015). Alzheimer's disease. *Nat. Rev. Dis. Primers* *1*, 15056.
- McCormick, D.A., and Huguenard, J.R. (1992). A model of the electrophysiological properties of thalamocortical relay neurons. *J. Neurophysiol.* *68*, 1384–1400.
- Migliore, M., Cook, E.P., Jaffe, D.B., Turner, D.A., and Johnston, D. (1995). Computer simulations of morphologically reconstructed CA3 hippocampal neurons. *J. Neurophysiol.* *73*, 1157–1168.
- Migliore, M., Cavarretta, F., Marasco, A., Tulumello, E., Hines, M.L., and Shepherd, G.M. (2015). Synaptic clusters function as odor operators in the olfactory bulb. *Proc. Natl. Acad. Sci. USA* *112*, 8499–8504.
- Nunez, P.L., and Srinivasan, R. (2006). *Electric Fields of the Brain: The Neurophysics of EEG*, Second Edition (Oxford University Press).
- Ostojic, S., and Brunel, N. (2011). From spiking neuron models to linear-nonlinear models. *PLoS Comput. Biol.* *7*, e1001056.
- Perlmutter, J.S., and Mink, J.W. (2006). Deep brain stimulation. *Annu. Rev. Neurosci.* *29*, 229–257.
- Pesaran, B., Vinck, M., Einevoll, G.T., Sirota, A., Fries, P., Siegel, M., Truccolo, W., Schroeder, C.E., and Srinivasan, R. (2018). Investigating large-scale brain dynamics using field potential recordings: analysis and interpretation. *Nat. Neurosci.* *21*, 903–919.
- Pettersen, K.H., Hagen, E., and Einevoll, G.T. (2008). Estimation of population firing rates and current source densities from laminar electrode recordings. *J. Comput. Neurosci.* *24*, 291–313.
- Potjans, T.C., and Diesmann, M. (2014). The cell-type specific cortical microcircuit: relating structure and activity in a full-scale spiking network model. *Cereb. Cortex* *24*, 785–806.
- Pozzorini, C., Mensi, S., Hagens, O., Naud, R., Koch, C., and Gerstner, W. (2015). Automated high-throughput characterization of single neurons by means of simplified spiking models. *PLoS Comput. Biol.* *11*, e1004275.
- Rao, R.P., and Ballard, D.H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci.* *2*, 79–87.
- Rapaport, D.C. (2004). *The Art of Molecular Dynamics Simulation* (Cambridge University Press).
- Reimann, M.W., Anastassiou, C.A., Perin, R., Hill, S.L., Markram, H., and Koch, C. (2013). A biophysically detailed model of neocortical local field potentials predicts the critical role of active membrane currents. *Neuron* *79*, 375–390.
- Reynolds, J.H., and Desimone, R. (1999). The role of neural mechanisms of attention in solving the binding problem. *Neuron* *24*, 19–29, 111–125.
- Ritter, P., Schirner, M., McIntosh, A.R., and Jirsa, V.K. (2013). The virtual brain integrates computational modeling and multimodal neuroimaging. *Brain Connect.* *3*, 121–145.
- Sanz Leon, P., Knock, S.A., Woodman, M.M., Domide, L., Mersmann, J., McIntosh, A.R., and Jirsa, V. (2013). The Virtual Brain: a simulator of primate brain network dynamics. *Front. Neuroinform.* *7*, 10.
- Schirner, M., McIntosh, A.R., Jirsa, V., Deco, G., and Ritter, P. (2018). Inferring multi-scale neural mechanisms with brain network modelling. *eLife* *7*, e28927.
- Schmidt, M., Bakker, R., Hilgetag, C.C., Diesmann, M., and van Albada, S.J. (2018a). Multi-scale account of the network structure of macaque visual cortex. *Brain Struct. Funct.* *223*, 1409–1435.
- Schmidt, M., Bakker, R., Shen, K., Bezgin, G., Diesmann, M., and van Albada, S.J. (2018b). A multi-scale layer-resolved spiking network model of resting-state dynamics in macaque visual cortical areas. *PLoS Comput. Biol.* *14*, e1006359.
- Schrader, S., Grün, S., Diesmann, M., and Gerstein, G.L. (2008). Detecting synfire chain activity using massively parallel spike train recording. *J. Neurophysiol.* *100*, 2165–2176.
- Schwalger, T., Deger, M., and Gerstner, W. (2017). Towards a theory of cortical columns: from spiking neurons to interacting neural populations of finite size. *PLoS Comput. Biol.* *13*, e1005507.
- I. Segev, J. Rinzel, and G.M. Shepherd, eds. (1994). *Theoretical Foundations of Dendritic Function: The Collected Papers of Wilfrid Rall with Commentaries* (MIT Press).
- Shimoura, R.O., Kamiji, N.L., de Oliveira Pena, R.F., Cordeiro, V.L., Ceballos, C.C., Romaro, C., and Roque, A.C. (2018). Reimplementation of the potjansmann cortical microcircuit model: from nest to Brian. *ReScience* *4*, 2.
- Solbrå, A., Bergersen, A.W., van den Brink, J., Malthe-Sørensen, A., Einevoll, G.T., and Halnes, G. (2018). A Kirchhoff-Nernst-Planck framework for modeling large scale extracellular electrodiffusion surrounding morphologically detailed neurons. *PLoS Comput. Biol.* *14*, e1006510.
- Sterratt, D., Graham, B., Gillies, A., and Willshaw, D. (2011). *Principles of Computational Modelling in Neuroscience* (Cambridge University Press).
- Tennøe, S., Halnes, G., and Einevoll, G.T. (2018). UncertainPy: a python toolbox for uncertainty quantification and sensitivity analysis in computational neuroscience. *Front. Neuroinform.* *12*, 49.
- Tomsett, R.J., Ainsworth, M., Thiele, A., Sanayei, M., Chen, X., Gieselmann, M.A., Whittington, M.A., Cunningham, M.O., and Kaiser, M. (2015). Virtual Electrode Recording Tool for Extracellular potentials (VERTEx): comparing multi-electrode recordings from simulated and biological mammalian cortical tissue. *Brain Struct. Funct.* *220*, 2333–2353.
- Traub, R.D., Contreras, D., Cunningham, M.O., Murray, H., LeBeau, F.E.N., Roopun, A., Bibbig, A., Wilent, W.B., Higley, M.J., and Whittington, M.A. (2005). Single-column thalamocortical network model exhibiting gamma oscillations, sleep spindles, and epileptogenic bursts. *J. Neurophysiol.* *93*, 2194–2232.

- Turrigiano, G.G., and Nelson, S.B. (2004). Homeostatic plasticity in the developing nervous system. *Nat. Rev. Neurosci.* *5*, 97–107.
- Uhlirva, H., Kılıç, K., Tian, P., Sakadžić, S., Gagnon, L., Thunemann, M., Desjardins, M., Saisan, P.A., Nizar, K., Yaseen, M.A., et al. (2016a). The road-map for estimation of cell-type-specific neuronal activity from non-invasive measurements. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* *371*, 20150356.
- Uhlirva, H., Kılıç, K., Tian, P., Thunemann, M., Desjardins, M., Saisan, P.A., Sakadžić, S., Ness, T.V., Mateo, C., Cheng, Q., et al. (2016b). Cell type specificity of neurovascular coupling in cerebral cortex. *eLife* *5*, e14315.
- van Albada, S.J., Rowley, A.G., Senk, J., Hopkins, M., Schmidt, M., Stokes, A.B., Lester, D.R., Diesmann, M., and Furber, S.B. (2018). Performance comparison of the digital neuromorphic hardware spinnaker and the neural network simulation software nest for a full-scale cortical microcircuit model. *Front. Neurosci.* *12*, 291.
- van der Velde, F., and de Kamps, M. (2006). Neural blackboard architectures of combinatorial structures in cognition. *Behav. Brain Sci.* *29*, 37–70, discussion 70–108.
- Wassermann, E., Epstein, C., Ziemann, U., Walsh, V., Paus, T., and Lisanby, S. (2008). *Oxford Handbook of Transcranial Stimulation* (Oxford University Press).
- Zerlaut, Y., Chemla, S., Chavane, F., and Destexhe, A. (2018). Modeling mesoscopic cortical dynamics using a mean-field model of conductance-based networks of adaptive exponential integrate-and-fire neurons. *J. Comput. Neurosci.* *44*, 45–61.