Symposium

# Large-Scale Mechanistic Models of Brain Circuits with Biophysically and Morphologically Detailed Neurons

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**Understanding the brain requires studying its multiscale interactions from molecules to networks. The increasing availability of large-scale datasets detailing brain circuit composition, connectivity, and activity is transforming neuroscience. However, integrating and interpreting this data remains challenging. Concurrently, advances in supercomputing and sophisticated modeling tools now enable the development of highly detailed, large-scale biophysical circuit models. These mechanistic multiscale models offer a method to systematically integrate experimental data, facilitating investigations into brain structure, function, and disease. This review, based on a Society for Neuroscience 2024 MiniSymposium, aims to disseminate recent advances in large-scale mechanistic modeling to the broader community. It highlights (1) examples of current models for various brain regions developed through experimental data integration; (2) their predictive capabilities regarding cellular and circuit mechanisms underlying experimental recordings (e.g., membrane voltage, spikes, local-field potential, electroencephalography/magnetoencephalography) and brain function; and (3) their use in simulating biomarkers for brain diseases like epilepsy, depression, schizophrenia, and Parkinson's, aiding in understanding their biophysical underpinnings and developing novel treatments. The review showcases state-of-the-art models covering hippocampus, somatosensory, visual, motor, auditory cortical, and thalamic circuits across species. These models predict neural activity at multiple scales and provide insights into the biophysical mechanisms underlying sensation, motor behavior, brain signals, neural coding, disease, pharmacological interventions, and neural stimulation. Collaboration with experimental neuroscientists and clinicians is essential for the development and validation of these models, particularly as datasets grow. Hence, this review aims to foster interest in detailed brain circuit models, leading to cross-disciplinary collaborations that accelerate brain research.**

*Key words:* **biophysically detailed models; brain circuits; mechanistic models; modeling; morphologically detailed neurons; multicompartmental neuron models; network models; simulations**

## Introduction

Understanding the brain requires studying its multiscale interactions, from molecules to cells to circuits and networks. The neuroscience field is undergoing a qualitative change due to new rich and vast datasets describing the composition, connectivity, and functional activity of brain circuits across scales [BRAIN Initiative Cell Census Network (BICCN), 2021; MICrONS Consortium et al., 2021; Turner et al., 2022; Yao et al., 2023; Shapson-Coe et al., 2024]. However, integrating and interpreting this data remains a daunting challenge. Simultaneously, the accelerating development of supercomputing resources and sophisticated modeling software tools (reviewed below) is giving rise to highly detailed and large-scale biophysical circuit models. Such mechanistic multiscale modeling offers an unparalleled approach to systematically integrate and interpret experimental

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data and enable investigation of a multitude of questions about brain structure, function, and disease.

### Goal of the minisymposium and review article

This review is based on a minisymposium with the same title held at the Society for Neuroscience 2024 Meeting. The overarching goal of the review and minisymposium is to disseminate the recent advances in large-scale mechanistic modeling of brain circuits to the broader neuroscience community. More specifically, we aim to communicate (1) examples of large-scale mechanistic models currently available for different brain regions and how these were developed by integrating experimental data; (2) how these models can make predictions about the cellular and circuit mechanisms underlying experimental recordings [e.g., membrane voltage, spikes, local-field potential (LFP), electroencephalography (EEG), magnetoencephalography] and brain function; and (3) how these models can be used to simulate biomarkers of brain disease and disorders, such as epilepsy, depression, schizophrenia, or Parkinson's disease, to unravel their biophysical underpinnings and help develop and evaluate novel treatments.

### Characteristics, building pipeline, and challenges of these models

The event and this accompanying review aim to highlight a specific type of models within computational neuroscience: large-scale biophysical multiscale mechanistic models of brain circuits, which typically include (1) the major neuron types with experimentally constrained cell densities, ratios, and spatial distribution; (2) individual neuron models with multicompartment morphologies and multiple conductance-based spatially distributed ion channels (based on the Hodgkin–Huxley formalism and cable theory), fitted to reproduce cell-type–specific physiological responses (e.g., *F–I* curves); and (3) experimentally constrained synaptic connectivity, including different postsynaptic receptors with specific kinetics, cell-type–specific local connectivity properties (e.g., probability of connection and postsynaptic potential (PSP) amplitude), and external or long-range inputs. This level of detail makes these models ideally suited for addressing highly specific mechanistic research questions, which simpler or more abstract models may not be able to tackle. For example, accurately predicting how pharmacological manipulation of a specific ion channel in a specific cell type affects LFP oscillations likely requires a circuit model that includes that cell type with that ion channel properly distributed across dendrites, and a population of morphologically detailed neurons with realistic cell density and spatial distribution to rigorously simulate the LFP signals (Ness et al., 2018; Rimehaug et al., 2023).

As shown in the following sections on specific models, the modeling workflow typically follows common steps, with some variations depending on the project's needs: (1) Data gathering and preprocessing stage, where all the relevant parameter values for the model components described above, ranging from cell biophysics to long-range inputs, are derived from experiments, publications, or existing datasets. This may also involve preprocessing to estimate missing values or to convert the data to the correct units required by the model. (2) Model implementation, where the appropriate software tools (see below, Ecosystem of software tools, standards, and platforms) are used to instantiate cells, connections, and mechanisms in the network model based on the specifications extracted from the previous step. Importantly, the components, like cell and synapse models need to exist—meaning, in practice, leveraging existing publications or databases or developing such component models from scratch (Van Geit et al., 2016; Gouwens et al., 2018; Migliore et al., 2018). Note that a multitude of differing approaches and algorithms for converting available experimental data to specific model features can be employed at this stage—e.g., establishing connectivity based on precalculated probabilities (Billeh et al., 2020; Dura-Bernal et al., 2023a) versus using algorithmic implementation of synaptic touches followed by pruning (Reimann et al., 2015). (3) Model fitting and validation may cover a very broad range of observations, depending primarily on the data available and aims of the project. Most typically, circuit models are constructed (in the previous steps) based on in vitro data like cell-type properties, connectivity, etc. and are optimized and validated based on in vivo data, such as attempting to reproduce firing patterns or features of signals like LFP or EEG. (4) Model exploration, the stage at which the model is considered more or less "final" and one is then investigating how the model behaves under various conditions and stimuli, how this behavior is affected by changes in parameters or perturbations, and how it translates to signals that could be experimentally recorded. This is the stage where insights about biological mechanisms and principles are obtained and predictions might be formulated for potential experimental verification. (5) Model sharing, a stage that is increasingly recognized as crucial, in which the model and simulations are shared as computational resources (rather than simply a publication) leveraging the emerging standards and tools.

Across all these steps, a set of common challenges is encountered. The primary among them is missing data—brain circuits are incredibly complex, and, so far, constraining all aspects of circuit models by high-quality data remains mostly an aspirational goal. As such, an important and typical part of the modelers' job is to "fill the gaps" in the data using reasonable assumptions and educated guesses, for example, adapting values from similar brain regions or species. Another challenge is computational cost, which is rather high for the models covered here, as they utilize complex biophysical mechanisms and detailed neuronal morphologies across many thousands of cells—simulation of one biological second can require hundreds to thousands of core hours on supercomputers. Yet another important challenge is the interpretation, that is, connecting what can be observed or learned from the model with tangible experimental reality. The model examples below illustrate how researchers approach these challenges to produce scientifically useful computational models.

### Ecosystem of software tools, standards, and platforms

There is also a large ecosystem of software tools, standards, and platforms that enables the development, simulation, and analysis of these large-scale biophysical circuit models. These include simulation engines such as NEURON (Carnevale and Hines, 2006; Awile et al., 2022), Arbor (Akar et al., 2019), MOOSE (Ray and Bhalla, 2008), EDEN (Panagiotou et al., 2022), NEST (10.4249/scholarpedia.1430), and Brian (Stimberg et al., 2019); modeling and analysis tools such as Brain Modeling Toolkit (BMTK; Dai et al., 2020a)/Bionet (Gratiy et al., 2018), BBP Neurodamus (Pereira et al., 2023), BluePyOpt (Van Geit et al., 2016; Reva et al., 2023), ConnectomeUtilities (Reimann et al., 2023), BlueRecording (Tharayil et al., 2024), NetPyNE (Dura-Bernal et al., 2019), Brain Scaffold Builder (De Schepper et al., 2022), pyNeuroML (Gleeson et al., 2010; Dai et al., 2020b), PyNN (Davison et al., 2009), LFPy (Hagen et al., 2018), and Human Neocortical Neurosolver (Neymotin et al., 2020); and standards and platforms such as

SONATA (Dai et al., 2020b), NeuroML (Sinha et al., 2024), Open Source Brain (Gleeson et al., 2019), and ModelDB (Hines et al., 2004; McDougal et al., 2016), among others.

### Other modeling approaches

Numerous other modeling approaches exist, each optimally suited to specific research questions and scales of interest. These range from smaller scale or simplified circuits with multicompartment neurons (Cutsuridis et al., 2010; Sherif et al., 2020; Medlock et al., 2022; Metzner et al., 2022; Herrera et al., 2023; Ponzi et al., 2023) to large-scale detailed circuits/networks with single-compartment or spiking point neurons (Schmidt et al., 2018; Peron et al., 2020; Marsh et al., 2024) to whole-brain mean–field models (Demirtaş et al., 2019; Meier et al., 2022; Cakan et al., 2023; Jirsa et al., 2023). Previous reviews provide an overview of some of these different modeling approaches (D'Angelo et al., 2013; Tikidji-Hamburyan et al., 2017; D'Angelo and Jirsa, 2022; Haufler et al., 2023).

### Models showcased in this review and other examples

This publication is not intended to provide a comprehensive review of this modeling subfield. To illustrate its broadness, we highlight several relevant circuit models across species and brain regions that will not be covered in detail here: rat thalamocortical circuit (Traub et al., 2005), rodent cerebellum (De Schepper et al., 2022), mouse striatum (Hjorth et al., 2020), mouse somatosensory thalamus and thalamic reticular nucleus (Iavarone et al., 2023), and human hippocampus epileptic circuitry (Buchin et al., 2022). Previous reviews and books provide further description of this modeling approach and discussion of its applications (Einevoll et al., 2019; Poirazi and Papoutsi, 2020; Haufler et al., 2023; Halnes et al., 2024).

The following section showcases several state-of-the-art large–scale mechanistic models of brain circuits, which were presented at the SfN Minisymposium. They cover multiple brain regions, including hippocampus and somatosensory, visual, motor, auditory cortical, and thalamic circuits across different species (Fig. 1; Table 1). These models provide insights into the biophysical mechanisms underlying sensation and motor behavior; the origins of brain signals such as LFP and EEG; disease such as depression, epilepsy, and schizophrenia; and the effects of pharmacological interventions and neural stimulation.

## Showcase of models

### Model of mouse, rat, and human hippocampus

In this section, we review the implementation pipeline and preliminary results on the intrinsic activity properties of a full-scale computational model of the rat hippocampus CA1 area (450,000 cells), using data-driven constraints on cell location, electrophysiological properties, and connectivity (Fig. 1), and implemented in NEURON (Romani et al., 2024).

Morphological reconstructions and electrophysiological recordings allowed us to reproduce in great details the morphoelectrical properties of several neuron types. At the same time, the wealth of literature data also allowed us to faithfully reconstruct the connectome and synaptome and validate the different components of the network model. The main scope of the model is to link the mechanisms acting at the subcellular scale (e.g., synaptic integration and plasticity, local dendritic activity) with phenomena at cellular and network scales (e.g., oscillations, LFP).

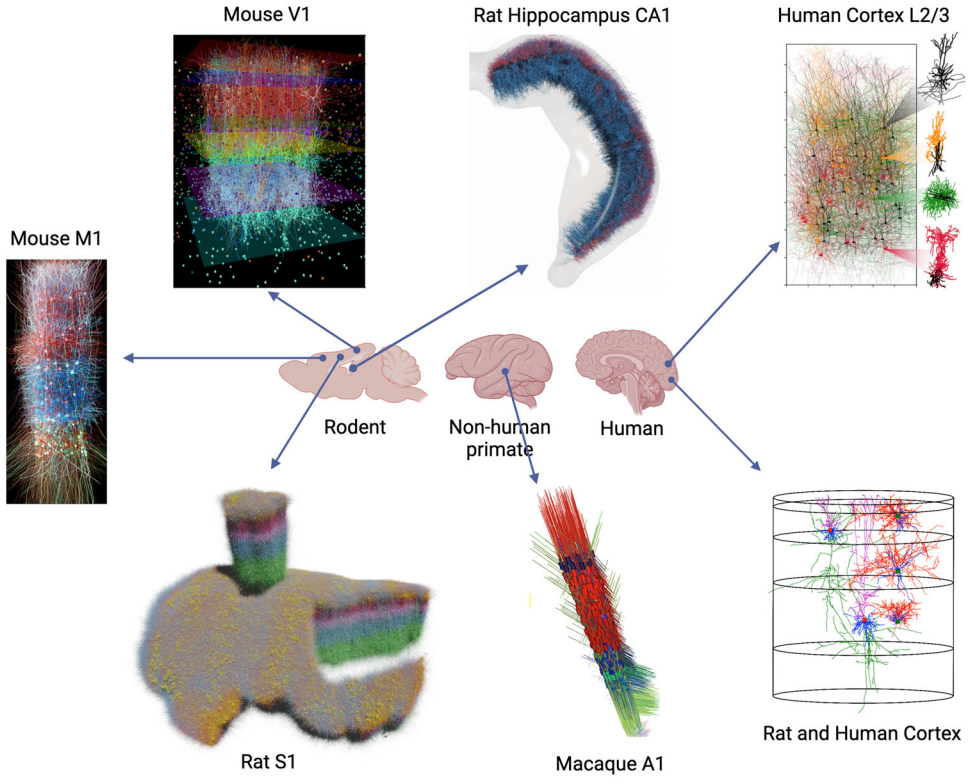


**Figure 1.** Overview of large-scale mechanistic brain circuit models showcased in this review. *Clockwise from top-left*: 3D spatial representation of neural circuit models of mouse primary visual cortex (V1) column (Billeh et al., 2020); rat full hippocampus CA1 (Gandolfi et al., 2022, 2023; Romani et al., 2024); human cortex Layer 2/3 (Guet-McCreight et al., 2024); rat (Halgren et al., 2023) and human (Marsh et al., 2024) cortical column; macaque primary auditory cortex (A1) column (Dura-Bernal et al., 2023a); full rat nonbarrel somatosensory cortex S1 (Reimann et al., 2024); and mouse primary motor cortex (M1) column (Dura-Bernal et al., 2023b). See details in the main text.

**Table 1. List of repositories and publications for the showcased models**

| Model | Model repository | Publication |
|---|---|---|
| Rat hippocampus CA1 | www.hippocampushub.eu | Romani et al., 2024 |
| Rat nonbarrel somatosensory cortex (S1) | https://zenodo.org/records/11113043 https://zenodo.org/records/11108303 | Isbister et al., 2024; Reimann et al., 2024 |
| Mouse primary visual cortex (V1) | https://portal.brain-map.org/explore/models/mv1-all-layers | Billeh et al., 2020 |
| Mouse primary motor cortex (M1) | https://github.com/suny-downstate-medical-center/S1_Thal_NetPyNE_Frontiers_2022 | Dura-Bernal et al., 2023b |
| Macaque auditory cortex (A1) | https://github.com/NathanKlineInstitute/Macaque_auditory_thalamocortical_model_data | Dura-Bernal et al., 2023a |
| Human cortex L2/3 depression pharmacology | https://github.com/agmccrei/HumanL23Circuit_a5PAM_AGM2023 | Guet-McCreight et al., 2024 |
| Human cortex electrical stimulation | Will be made available after peer-reviewed publication. | In preparation; Halgren et al., 2023; Marsh et al., 2024 |

The CA1 volume was first defined adapting a publicly available atlas reconstruction of the hippocampus (Ropireddy et al., 2012); then it was populated with single-cell models respecting experimental constraints on cell composition, including 1 type of excitatory neuron, pyramidal (PY) cell, and 11 types of inhibitory (IN) neurons. Cell positions were determined according to rules describing how neurites target the different layers (Romani et al., 2024).

The connectome algorithm previously described in Reimann et al. (Reimann et al., 2015) was used to find all potential synapses and a pruning procedure to consider experimental data on bouton density and number of synapses. Synaptic transmission and electrophysiological neuron/interneuron properties were those obtained in Ecker et al. (Ecker et al., 2020), implemented with a double-exponential synaptic transmission model encompassing stochastic neurotransmitter release and short-term plasticity. Electrophysiological properties of neurons and interneurons were based on experimental features extracted from rat recordings (Migliore et al., 2018), with a full set of morphologically detailed cells created by cloning a set of 3D reconstructions, optimizing channel densities/distributions against experimental traces, and obtaining an ensemble of individual cell models reproducing the experimentally observed variability in the response to constant somatic current injections.

This model, implemented with morphologically detailed neurons, is computationally very expensive but more accurate in directly reproducing experimental results. For example, it can be "cut" to reproduce in vitro slice experiments, and extracellular ion concentrations (e.g., $K^+$, $CA^{2+}$, $Mg^{2+}$) can be changed to mimic different in vitro baths or in vivo conditions which can then impact cellular and synaptic properties (e.g., neuron excitability, release probability, NMDAR block).

Taking advantage of these capabilities, a series of in vitro experiments were reproduced, for example, to test feedforward inhibition of the Schaffer collaterals (Sasaki et al., 2006) or to study the influence of acetylcholine at neuronal, synaptic, and network level (see Romani et al., 2024 for all the citations). Similarly, the model was used to investigate the onset and maintenance of theta oscillations in vitro and in vivo (Fig. 2*A*) and the transmission of a wide range of oscillations through Schaffer collaterals.

We have also implemented full-scale CA1 models of mouse (288,000 cells) and human (5,280,000 cells), using single-point neurons and implemented in NEST. The choice of point-neuron models and therefore the different simulation environments was dictated by the trade-off between the computational load and the characteristics of the simulation (e.g., duration, output to be mapped, etc.). In particular, mouse and human models were built to study and compare network and signal propagation properties, including cells' oscillation and synchronization along the transversal and longitudinal directions in response to localized stimulations in these two systems. Models were implemented following the pipelines introduced in Gandolfi et al. (2022) for the mouse and in Gandolfi et al. (2023) for the human CA1. For both models, individual cells were simulated with a generalized integrate-and-fire model (Marasco et al., 2023) able to quantitatively reproduce the response of CA1 PY neurons and interneurons to synaptic inputs (Marasco et al., 2024a). A custom algorithm to generate an arbitrary number of copies (Marasco et al., 2024b) was developed to reproduce the full range of experimental variability.

Since the intrinsic properties of a hippocampal CA1 network cannot be conveniently studied experimentally, the availability of full-scale networks constrained by experimental data can have a significant role in understanding how the hippocampus relays signals to other brain regions under physiological and pathological conditions.

All models and tools for model building and analysis are available through the hippocampus facility hub (www.hippocampushub.eu), the EBRAINS Knowledge Graph (https://search.kg.ebrains.eu/instances/7fb22b04-5fe1-4f18-b0d0-dc1386f90f83) for the rat model, the EBRAINS-Italy infrastructure website (https://www.ebrains-italy.eu) for the human model, and the EBRAINS live paper section (https://ebrains.eu/service/live-papers/) for the mouse model.

### Model of the full rat nonbarrel somatosensory cortex micro- and mesocircuitry

The EPFL BBP team has developed a large-scale, biophysically detailed model of rat nonbarrel somatosensory regions (Reimann et al., 2024; Figs. 1, 2*B*) recreating cellular and subcellular targeting of IN connectivity observed in electron microscopy data (Schneider-Mizell et al., 2024), atlas-based geometry, and local and long-range connectivity and used it to study plasticity, how spike sorting obscures our view into neural coding, and the structure–function relationship (Santander et al., 2024; Ecker et al., 2024a,b). Building upon an earlier version of such a model (Markram et al., 2015), they increased the spatial scale of the model and enhanced its biological realism. The most salient improvements were as follows: First is the construction of realistic synaptic connectivity as the union of two algorithms, one for local connections up to 750 µm (Reimann et al., 2015) and another for longer-range connections (Reimann et al., 2019). Second is the introduction of methods to build a model inside a standardized voxel atlas (Bolaños-Puchet et al., 2024). These points allow models of brain regions to be developed separately and then easily integrated. Third is improvements in the methods to compensate for missing extrinsic inputs and to validate an in vivo-like activity regime.

Furthermore, we outline several examples of the model being used to investigate specific scientific questions, commenting on the reasons why biophysically detailed modeling is well suited to address the topics and the specific modeling and analysis techniques developed to address them. BBP researchers investigated plasticity at the population level using a biophysically detailed model of functional plasticity (Ecker et al., 2024a). They found

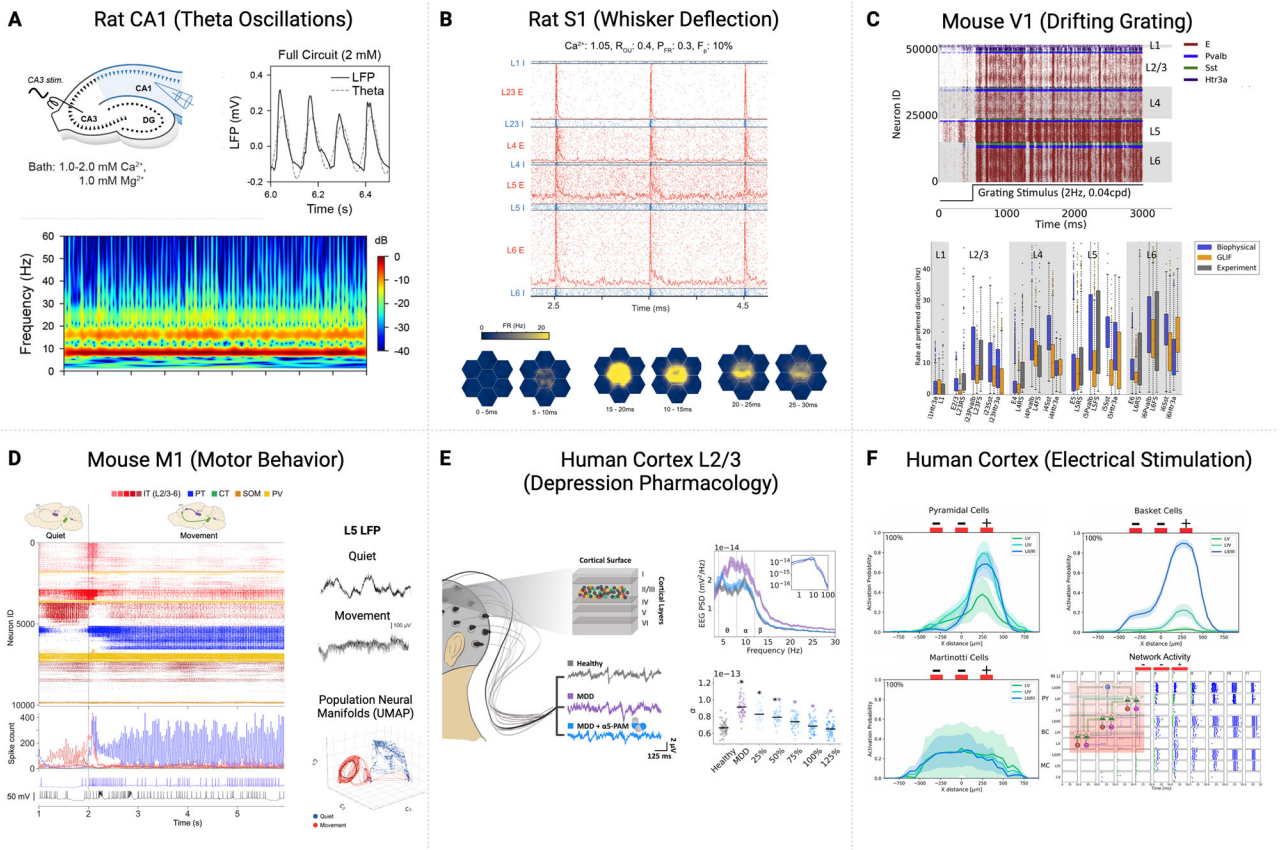


**Figure 2.** Example simulation outputs of large-scale mechanistic brain circuit models showcased in this review. ***A***, CA3 theta (8 Hz) oscillatory input entrains CA1 to matched theta oscillation across different scales of circuit. Top-left, Schema showing the in silico experimental setup. Top-right and bottom, Full circuit model LFP recordings from stratum PY neurons and corresponding spectrogram (Romani et al., 2024). ***B***, Layer-wise population responses to single whisker deflection closely match in vivo millisecond dynamics and response amplitudes. Top, Spiking activity for each layer-wise E and I population for a 2.5 s section of the 10 whisker deflection test protocol. Bottom, Spatiotemporal evolution of the trial-averaged stimulus response in flat space (Isbister et al., 2024). ***C***, Neural response in the V1 mouse model to a drifting grating stimulus. Top, The raster plot of neural activity, with neurons grouped by layer and type. Bottom, The firing rate at preferred direction of the grating, by population, compared with the biophysical model, point-neuron (GLIF) model, and experimental in vivo recordings (Billeh et al., 2020). ***D***, M1 cell type- and layer-specific firing dynamics during quiet wakefulness and movement. Left, The raster plot of activity transitioning from quiet to movement; spike count histogram for excitatory populations; and an example model (blue) and experiment (black) PT5B somatic membrane voltage. Top-right, M1 simulated L5 LFP signals during quiet and movement. Bottom-right, Neural manifold (UMAP low-dimensional representation) of the 10 ms binned mean firing rates of the 16 populations during quiet and movement (Dura-Bernal et al., 2023b). ***E***, Left, Simulated EEG from human cortical microcircuits in health and depression (major depressive disorder) and under application of alpha5-PAM pharmacology for depression. Top-right, Power spectral density of simulated EEG in the different conditions. Bottom-right, Simulated alpha (8–12 Hz) power in health and depression and under different doses of the pharmacology (Guet-McCreight et al., 2024). ***F***, Top and bottom-left, Probability of spiking as a function of horizontal distance from the center of the electrode array for each cell type and cortical layer in the rat cortical column. Average (solid line) cell spiking probability and 95% confidence intervals (shaded region) for each cell reconstruction were calculated for soma locations across the entire *X-Z* plane of the corresponding cortical layer. Activation probabilities were calculated for 150 mA anodal and 75 mA cathodal stimulation currents over a 200 ms stimulation period. Bottom-right, A raster plot displaying network behavior during and after stimulation in one trial of the microcircuit simulation across all rat cortical columns at maximum applied current. Each cell within the microcircuit has its own coordinate on the *y* axis. Each dot is an action potential. Green dots indicate spikes that are directly triggered by electrical stimulation (occurs during first 5 ms). Blue dots indicate spikes triggered via synaptic input (Halgren et al., 2023).

that a model that describes plasticity at the pairwise level can also lead to realistic results at the population level without additional stabilizing mechanisms. They further characterized the signatures left in the synaptic weights as a circuit is exposed to repeated stimuli. Finally, they found ways to predict the outcome of plasticity based on membership of neurons in structurally or functionally defined groups of neurons. This is a decidedly nonlocal view of plasticity that considers neurons beyond the pair that is directly forming a synaptic connection—population-dependent plasticity.

The model was also used to investigate the accuracy of spike sorting algorithms (Laquitaine et al., 2024). The authors applied the most common algorithms to extracellular potentials calculated in simulations of population activity and compared their outputs with the true spiking activity. They found great increases in accuracy for the most recently released algorithms over their older versions but with remaining inaccuracies. They characterized the biases resulting from the inaccuracies and how they impact the outcome of common population-level analyses, such as dimensionality reduction of spiking activity and stimulus–response curves. They found that results based on sorted spike trains captured most of the trends present on the population level, although they misrepresent responses of a small number of individual neurons. These results have relevance for the future directions of improvements to spike sorting. Building the model in a brain atlas allowed them to embed it in a detailed model of the rat skull and perform accurate simulations of the EEG signal generated by somatosensory regions (Tharayil et al., 2024).

Connectivity in the model is based on appositions between axons and dendrites or somata, a necessary, though not sufficient, condition for the formation of a synapse. Consequently, the model could be used to investigate how the morphology of individual

neurons constrains the possible wiring of the connectome. They found a highly nonrandom higher-order structure emerging in the connectome (Reimann et al., 2024). Such structure is equally—or even more strongly—present in biologically measured cellular connectomes, such as *Drosophila*, the worm, and electron-microscopic reconstructions of the cortex, but it cannot be captured by more simplified models of synaptic connectivity (Egas-Santander et al., 2024), highlighting that neuron morphology plays an important role in constraining a connectome. Egas-Santander et al. (2024) further explored the role of such complexity, asking the question whether it is relevant for the function of a cortical circuit using simulations of connectomes that enhance or reduce specific nonrandom trends. They defined a measure of connectome complexity as the distance of degree distributions between a network and its randomized control and measured it in subnetworks of the model centered around individual neurons. They found a great diversity of the metric across subnetworks with distinct functional consequences. Specifically, high complexity subnetworks promote neurons acting as parts of a reliable, but less efficient, population code, predominately in input layers. Conversely, low complexity parts promote neurons spiking more independently of the population, thus enhancing the efficiency of the neural code. Parts of these predictions were already testable using an electron-microscopic reconstruction of a cortical connectome with coregistered functional data and thus confirmed.

### Model of the mouse primary visual cortex

The Allen Institute developed and shared publicly a detailed data-driven model of the mouse primary visual cortex (V1; Billeh et al., 2020), comprising ~230,000 neurons and 17 cell classes represented by 112 unique cell models from the Allen Cell Types Database (Gouwens et al., 2018), illustrated schematically in Figure 1. The model's core features multicompartment neuron models with somatic Hodgkin–Huxley dynamics and passive dendrites. As we mention below, this level of biophysically detailed description is useful for capturing electrical signals like LFP, whereas its role in reproducing the biological spiking dynamics of the network remains to be understood. Surrounding the core column is an annulus of leaky-integrate-and-fire neurons to avoid boundary artifacts. Layers 2/3 to 6 (L2/3–6) are composed of an excitatory population and three IN populations (PV, parvalbumin; SST, somatostatin; and Htr3a neurons), while L1 only includes Htr3a interneurons. The visual stimulus in the form of movies is conveyed via a filter-based model of the thalamic lateral geniculate nucleus, projecting to V1 cells (Fig. 2*C*).

Recurrent connectivity was established from the Allen Institute data (Seeman et al., 2018) and available literature, constraining the following features: connection probability as a function of distance, magnitude of synaptic weights (based on the experimentally recorded PSP and PSC distributions), synaptic delays, synaptic kinetics, and dendritic targeting rules. Excitatory-to-excitatory (E-to-E) connections followed "like-to-like" rules within and across layers, i.e., cells preferring similar stimuli were preferentially connected. After incorporating this information, a layer-by-layer optimization procedure determined the final synaptic strengths within constraints imposed by data.

Comparing simulations of multiple model versions with in vivo electrophysiology recordings (Siegle et al., 2021) suggested synaptic organization rules that supported the observed computational properties of the circuit, such as orientation and direction selectivity. These included the like-to-like rules for synaptic weights of all cell classes, in addition to E-to-E like-to-like connection probabilities. Another rule involved the dependence of the recurrent E-to-E weights on the alignment of source neurons' receptive fields with the target neurons' preferred direction and response phase, which was concurrently demonstrated experimentally (Rossi et al., 2020). Additionally, a spatially asymmetrical weight organization in the V1 circuit compensated for the asymmetry of cortical magnification in the vertical versus horizontal directions.

Recent studies have utilized this model to investigate the underlying mechanisms of visually evoked LFPs and current source densities (CSDs; Rimehaug et al., 2023, 2024). According to Rimehaug et al. (Rimehaug et al., 2023), adjusting the synaptic weights to replicate the observed population firing rates did not significantly impact the LFP and CSD sink/source patterns. In contrast, the placement of the synapses along the neurons significantly impacted the CSD sink/source patterns while having a minimal impact on the population firing rates. Importantly, adding feedback from a higher cortical area to the V1 model was necessary to reproduce the CSD pattern fully. Building on these findings and using the mouse V1 model as a benchmark, Rimehaug et al. (Rimehaug et al., 2024) proposed a laminar population analysis method for elucidating the population contributions to LFP/CSD.

While the biophysically detailed V1 model provides valuable insights into the origin of LFPs/CSDs, its point-neuron model variant might be better suited for studying circuit mechanisms underlying cell responses (Billeh et al., 2020), due to much lower computational cost. The V1 point-neuron model consists of 111 unique generalized leaky-integrate-and-fire neuron models representing 17 cell classes with the same network graph as the detailed mouse V1 model. Several studies have taken advantage of its computational benefits, investigating topics ranging from the circuit mechanisms underlying visual flow (Galván Fraile et al., 2024) and optogenetic perturbations (Cai et al., 2020) to its visual processing capabilities for improving AI applications (Chen et al., 2022).

Both variants of the mouse V1 model are freely available at https://portal.brain-map.org/explore/models/mv1-all-layers. They use the BMTK (https://alleninstitute.github.io/bmtk/; Dai et al., 2020a), which facilitates simulations with NEURON and NEST and supports Python, and the SONATA format (https://github.com/AllenInstitute/sonata; Dai et al., 2020b) for saving the model and simulation outputs.

### Model of mouse primary motor cortex circuits

The primary motor cortex (M1) plays a central role in motor control. Despite this, efforts to model M1 circuitry in detail have been limited, particularly compared with other sensory cortical regions. Computational neuroscientists at State University of New York (SUNY) Downstate, in close collaboration with experimentalists, developed a detailed biophysical model of M1 circuits (Dura-Bernal et al., 2023b) by integrating experimental data on neuronal physiology, morphology, laminar density, cell-type distribution, dendritic distribution of synapses, and local and long-range synaptic connectivity (Fig. 1). The model simulated a cylindric cortical volume with over 10,000 neurons and 30 million synapses, including the major classes of excitatory and inhibitory cell types [see Neymotin et al. (2016b) for details on the corticospinal neuron model]. The M1 circuit model was validated by reproducing mouse M1 in vivo cell-type and layer-specific firing rates across different behavioral states (Fig. 2*D*) and experimental conditions (Schiemann et al., 2015). The model was developed using the NetPyNE tool (http://netpyne.org) and is available via GitHub and ModelDB.

The goal of the M1 model was to gain insights into the cellular and circuit mechanisms underpinning sensorimotor neural activity, function, and behavior (Dura-Bernal et al., 2023b). Movement

behavior was simulated by altering long-range and neuromodulatory inputs. The model captured the effects of experimental manipulations like noradrenaline receptor blockade and motor thalamus inactivation, offering multiscale mechanistic hypotheses for the observed behavioral deficits (Schiemann et al., 2015). LFP oscillations emerged spontaneously at physiological frequencies such as delta, beta, and gamma and exhibited behavior-related alterations consistent with in vivo data. Analysis of the M1 simulations generated multiple testable predictions: (1) a link between a decrease in noradrenaline-driven HCN current in PY tract (PT)-projecting corticospinal cells and impaired motor response, (2) a PV-mediated switching mechanism between intratelencephalic- and PT-predominant activity associated with behavior, (3) the cell-type–specific presynaptic inputs driving L5 populations for different behaviors, and (4) the cell-type–specific sources of LFP delta and gamma oscillations.

The authors generated low-dimensional neural manifolds (Gallego et al., 2017) associated with different behaviors and manipulations in the simulated data (Dura-Bernal et al., 2023b). They now aim to characterize the different cell types and circuit mechanisms underlying these latent dynamics (Baravalle et al., 2024). The M1 model is also being utilized to study the effect of channelopathies in Layer 5 PY neurons and their role in neurodevelopmental disorders such as epilepsy (Leitner et al., 2024). Additionally, the M1 model, or an earlier version, has also been used to study neuronal avalanches (Sivagnanam et al., 2020), dystonia (Neymotin et al., 2016a), Parkinson's disease (Doherty et al., 2024), and transcranial magnetic stimulation (Yu et al., 2024).

The latest M1 model version has been extended to include thalamic circuits and interconnected with a NetPyNE implementation of the (Markram et al., 2015) BBP S1 model (Borges et al., 2022; Moreira et al., 2022). The NetPyNE S1 model was expanded by incorporating thalamic circuits [VPL/VPM, PO, thalamic relay nucleus (TRN)] and corticothalamocortical connectivity (Borges et al., 2022; available via GitHub).

### Model of macaque auditory cortical and thalamic circuits

Researchers from the Nathan Kline Institute for Psychiatric Research and SUNY Downstate developed an experimentally grounded detailed mechanistic model of the macaque auditory thalamocortical circuits, including A1, medial geniculate body (MGB), and TRN (Dura-Bernal et al., 2023a), with the goal of better understanding oscillations, their mechanisms and role in auditory function and disease. The A1 model simulates a cortical column with over 12,000 neurons and 25 million synapses (Fig. 1), incorporating data on cell-type–specific neuron densities, morphology, and connectivity across six cortical layers (four types of excitatory neurons; four types of interneurons; six types of synaptic receptors). A1 was reciprocally connected to the MGB thalamus, which includes interneurons and core and matrix layer and cell-type–specific projections to A1. Inputs to the thalamus were generated through a phenomenological model of cochlea and inferior colliculus, enabling naturalistic auditory inputs, i.e., the same input sounds used during animal experiments. The model simulated realistic measures across scales, including physiological firing rates, LFP, CSD, and EEG signals (Mackey et al., 2024). Simulated spontaneous activity and responses to auditory stimuli were tuned to reproduce macaque in vivo experimental recordings (Neymotin et al., 2022). The model's highly detailed cell-specific connectivity patterns, and constraints on cellular dynamics, were selected in order to allow accurate linkage of neurophysiological recordings to the underlying cell-type- and layer-specific dynamics that generate them. The authors demonstrated this by identifying the major population contributing to an LFP/CSD oscillatory event and unraveling the presynaptic input spikes causing the dendritic synaptic currents captured in the LFP/CSD signal, leading to a circuit-level hypothesis of the source of the recorded LFP neural oscillation. The macaque auditory thalamocortical model was developed using NetPyNE and is available via GitHub and ModelDB.

This multiscale model is now being used to study the specific cellular and circuit mechanisms underlying multiple auditory EEG biomarkers associated with schizophrenia, including $1/f$ slope and broadband gamma power of resting-state activity, the 40 Hz auditory steady-state response, mismatch negativity, and the P300 event-related potential component (McElroy et al., 2023). Each of these biomarkers is hypothesized to originate from dynamic interactions between specific subpopulations of neurons, again justifying the relatively high level of biophysical detail used to build the model. Since the model generates neuroelectric signals comparable with those recorded in vivo, the model developers have also begun using the model to investigate and optimize a novel electrode designed for improving the resolution and localization of neuroelectric signals recorded for brain machine interface applications (Abrego et al., 2023).

### Testing new pharmacology for depression using detailed models of human cortical microcircuits

Recent years have seen the advent of detailed models of human cortical microcircuits in health and mental disorders such as depression or schizophrenia (Yao et al., 2022; Rosanally et al., 2024), which integrated the increasing human data of neuronal firing (Gouwens et al., 2018; Moradi Chameh et al., 2021) and synaptic properties (Obermayer et al., 2018; Seeman et al., 2018; Peng et al., 2019) together with postmortem data of altered neuronal mechanisms (Hashimoto et al., 2003). These detailed microcircuit models enable linking altered cellular and circuit mechanisms to impaired function (Yao et al., 2022) and biomarkers in clinically relevant brain signals such as EEG (Mazza et al., 2023; Rosanally et al., 2024), which is currently not possible to do in living humans. Another emerging application is the utilization of the detailed depression microcircuit models for testing new pharmacology and dose prediction in silico (Guet-McCreight et al., 2024; Figs. 1, 2*E*).

The depression microcircuit models implemented reduced SST interneuron inhibition as indicated by reduced expression in SST interneurons (Seney et al., 2015) in the postmortem brain tissue from depression patients (Seney et al., 2015). SST interneurons play an important role in maintaining baseline cortical firing (Gentet et al., 2012) via a lateral "blanket of inhibition" on PY neurons (Silberberg and Markram, 2007; Karnani et al., 2014; Obermayer et al., 2018), so that a reduced inhibition in depression would lead to increased baseline firing (noise) and thus reduced signal-to-noise ratio of cortical processing (Northoff and Sibille, 2014). This was demonstrated by detailed microcircuit models (Yao et al., 2022) and supported by studies that silenced SST interneurons in rodents (Fee et al., 2021).

The biophysical detail of the microcircuit models enables simulating the EEG resulting from the neuronal activity using NEURON (Carnevale and Hines, 2006) with LFPy (Hagen et al., 2018). The detailed models reproduced key properties of resting-state human EEG such as peak power in theta (4–8 Hz) and alpha (8–12 Hz) frequency bands. This provided a validation of the model, since these EEG properties were not explicitly constrained for but emerged from the model's physiological

firing, synaptic, and connectivity properties (Mazza et al., 2023). Importantly, these depression microcircuit models enabled identifying EEG biomarkers of reduced SST interneuron inhibition, which can serve to stratify depression patients who may benefit from new treatments targeting this mechanism.

A recent study applied the detailed microcircuit models to test in silico such new targeted pharmacology treatment for depression (Guet-McCreight et al., 2024). The pharmacology is a selective positive allosteric modulator of α5-$GABA_A$ receptors (α5-PAM) on PY neuron apical dendrites, which boosts the SST interneuron inhibition pathway and yields improved procognitive and antidepressant effects in rodents (Prevot et al., 2019) but remains to be tested and translated to humans. To facilitate the translation process, the study modeled the modulation of inhibition by the pharmacology as measured in single human PY neurons in vitro and integrated the effects into the detailed human microcircuit models (Guet-McCreight et al., 2024). Simulating pharmacology application on the microcircuits indicated that it would effectively recover EEG profile to a healthy level and recover cortical function as exemplified by signal detection metrics. The study systematically characterized the relationship between α5-PAM dose and EEG features, identifying biomarkers that could be used for monitoring treatment efficacy.

Future directions may include a more systematic dose prediction given EEG biomarkers of depression severity in terms of SST interneuron inhibition loss, with the aid of machine learning trained and validated on the ground-truth simulated data. Detailed microcircuit models are thus becoming relevant for clinical applications in mental health, by providing diagnostic biomarkers and facilitating translation of new treatments.

### Effects of electrical stimulation in cortical circuits across species

Electrical brain stimulation is becoming increasingly useful to probe the workings of the brain and to treat a variety of neuropsychiatric disorders. However, determining the effects of electrical stimulation on individual neurons and neuronal circuits is a complex problem. Even when experimental data on individual neurons are available, this data is most often from rodent sources; determining the effects of stimulation on human neurons is an even more elusive task. To address this problem, researchers Marsh, Wilson, Halgren, and Bazhenov aimed to combine physics, biology, and computer science to simulate the effect of electrical stimulation on individual neurons, depending on their type, orientation, and location within the brain. Specifically, they used morphological reconstructions of cortical pyramidal (PY) neurons and inhibitory interneurons (IN) across multiple cortical layers from rats, mice, and humans (Fig. 1). These neuron reconstructions were individually subjected to a range of currents from a (simulated) square cortical electrode (or array of electrodes), and average activation probabilities were calculated across a range of horizontal and vertical distances from the electrode. This approach allowed to compare response probabilities across cell types, layers, and species; importantly, it could be done very quickly and over a large combination of possible stimulation parameters for any given cell type (Halgren et al., 2023; Komarov et al., 2019). Finally, the estimated cell responses probabilities were integrated into a cortical network model to analyze interaction and propagation of spiking activity as a result of electrical stimulation (Fig. 2*F*).

To illustrate the level of detail and complexity of this study, its modeling methods are briefly summarized. Morphological neuron reconstructions across three species (rat, mouse, and human) were collected from NeuroMorpho (Ascoli et al., 2007) (neuromorpho.org) and the Allen Institute Cell Atlas (brain-map.org). Cells taken from the Allen Institute (here including all human cells, all mouse IN cells, and mouse excitatory Layer 2/3 cells) were labeled only as spiny versus aspiny; here spiny cells were labeled as PY and aspiny as IN (Costa and Müller, 2015). Individual reconstructions were subjected to a computational simulation of single pulse anodal and cathodal current from a square surface electrode. Cells were shifted in 2D plane under the electrode: ±1 mm horizontally and within respective biological layer bounds vertically. Cell response probability was calculated, using the activating function approach (Rattay, 2013), as the probability of the activated segment of an axon (i.e., axonal segment where effective current exceeds a given threshold) to contain a node of Ranvier. Species-specific layer depths (Mohan et al., 2015; Durand et al., 2016; Narayanan et al., 2017) and distances between nodes of Ranvier (Uzman and Nogueira-Graf, 1957; Arancibia-Cárcamo et al., 2017) were used. Rodent cells were stimulated by a small electrode with up to ±500 μA, while human cells were stimulated by a large electrode with up to ±1.5 mA. Species-specific network connectivity was constructed based on Campagnola et al. (2022) and Halgren et al. (2023), including seven columns of PY and IN cells across five (rodent) or six (human) layers. Cell activation probabilities for each species (rat, mouse, and human) were then input to the network model, and network activity was allowed to propagate.

Preliminary results showed that cell response probability for a given stimulation strength decreased with increasing layer depth and species size, as well as generally stronger responses to anodal than cathodal stimulation of the same strength. While rat and human neurons show similar response magnitudes between their respective PY and IN cells, mouse PY neurons show a significantly stronger response than mouse IN neurons. Furthermore, mouse PY L2/3 neurons showed the weakest response among PY layers, where rat and human response strength followed logically from distance to electrode (L2/3, L4, L5, L6). Rat neuron reconstructions simulated with human parameters (cortical depths, current amplitudes, etc.) further provided a more reasonable estimate of the responses of human neurons, as determined by multilevel model statistical analysis. Network models using these response probabilities show marked differences between rat and mouse models, and rat cells can again be used under human conditions as the closest predictive model.

This study suggests that much more accessible rat cells can be used to accurately predict human cell response probabilities under a variety of experimental conditions. This approach could further be used by experimental scientists to test species-specific hypotheses in silico to select the appropriate subset of parameters for the expensive (and time-consuming) in vivo work. This project both builds new knowledge of cross-species cell response probabilities and contributes to tool building for more informed and efficient experimental protocols.

## Conclusion

Recent availability of brain data and advances in supercomputing and modeling tools have yielded mechanistic brain circuit models with an unprecedented level of detail and spatial scale. We emphasize that close collaboration with experimental neuroscientists and clinicians has been, and will remain, essential for the development and validation of such models, particularly as datasets grow in size and complexity. Below we highlight several promising future directions.

We are particularly excited about the prospect of integrating the massive new genomics and transcriptomics data, for example, on different brain cell types (BRAIN Initiative Cell Census Network (BICCN), 2021; Yao et al., 2023). We believe mechanistic models will be essential for linking these molecular-level datasets to brain function, cognition, and behavior. Furthermore, integrating these mechanistic circuit models with other modeling approaches will be pivotal in answering complex neuroscience questions. This is already happening, for example, through integration or interaction with whole-brain network models (Meier et al., 2022; Bragin et al., 2023), machine learning models and analysis methods (Chen et al., 2022; Dura-Bernal et al., 2023b), and functional/task-driven/robotics models (Dura-Bernal et al., 2016; Vannucci et al., 2020; Pimentel et al., 2021; Haşegan et al., 2022).

Large-scale mechanistic models hold promise in unraveling the multiscale interactions within brain circuits, crucial for understanding the biological mechanisms underlying various brain diseases and disorders. They are already being applied to gain insights into conditions like depression (Mazza et al., 2023), schizophrenia (Sherif et al., 2020; Metzner et al., 2022; McElroy et al., 2023), epilepsy (Lytton et al., 2017; Buchin et al., 2022), autism, Parkinson's disease (Cutsuridis, 2019), dystonia (Neymotin et al., 2016a), and chronic pain (Medlock et al., 2022), among others, potentially leading to the development of targeted treatments, for example, through gene editing therapy (Deverman et al., 2018; Ingusci et al., 2019) and neural stimulation devices (Polanía et al., 2018; Krauss et al., 2020; Roeder et al., 2024).

In sum, these models offer an unparalleled approach to integrate and interpret experimental findings across virtually all brain regions, scales (molecular, cellular, circuit, system), brain functions (sensory perception, motor behavior, learning, etc.), recorded signals (intracellular voltage, spikes, LFP, EEG, fMRI, etc.), and brain diseases and disorders. Consequently, these models are of interest to the broad neuroscience community, including experimental, clinical, and computational neuroscientists, as well as students and educators. We hope this review will help foster increased adoption of biophysically and morphologically detailed models of brain circuits leading to increased cross-disciplinary collaborations to accelerate brain research.

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