Approaching Brain Levels of Organization with Computational Neuroscience

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ABSTRACT

Computational neuroscience is uniquely positioned to address challenging questions about the brain. Modeling distinct levels of organization in a computer offers scientists the ability to access variables that are otherwise hidden in living systems and to experiment with scenarios that may be non-feasible in a wet lab. Since the seminal work of Hodgkin and Huxley, the understanding of how neurons process information and communicate has been explored by various scientists across different domains. With the recent developments in artificial intelligence, we once again see a new trend of tools being developed and new groups working on brain-related subjects. In this review, we discuss how different levels of organization can be approached through computational neuroscience. We point to common and recent techniques that are used both experimentally and computationally.

Keywords: Computational neuroscience, Ion channels, Synaptic plasticity, Simulation-based inference, Neural networks

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Introduction

A central impediment to understanding the brain has been an inability to experimentally test the effects of many different brain scales simultaneously. While several approaches try to create connections from data,[1] computational neuroscience emerges as a powerful tool to bridge between these levels.[2–4] Computational neuroscience is grounded and relies heavily on diverse experimental techniques, each targeting distinct spatial and temporal scales of neural function.[5] In fact, one can say that computational neuroscience works by creating *in silico* laboratories where hypotheses can be experimented. At the molecular and cellular levels, techniques such as patch-clamp recordings[6] and calcium imaging[7] allow for the detailed analysis of ion channel dynamics, synaptic transmission, and intracellular signaling pathways. These methods capture the minute activities that define individual neurons' behaviors and interactions, providing data essential for constructing accurate neuron and network models. Moving up to circuit and network levels, optogenetics and electrophysiology,[8] such as multi-electrode arrays (MEA)[9] and silicon probes,[10] enable the study of synchronous and asynchronous neural firing across larger populations of neurons. These approaches help elucidate how neuronal networks generate complex patterns like oscillations or synchronization,[11] critical for understanding functional organization at the mesoscopic scale.[12] At the macroscopic level, neuroimaging techniques like fMRI and EEG provide broader, large-scale views of brain regions and their interconnections, mapping network-wide activity across the cortex and subcortical areas.[13,14] These varying techniques, each with unique resolutions and timescales, are invaluable for computational models that strive to unify biological data across levels of brain organization, from single-cell dynamics to whole-brain networks.

A diversity of computational models exists for each level and for crossing these levels of organization. It is common to identify these models as "building blocks," and the action of building a proper computational model for the problem at hand as a building block approach.[15,16] By employing the building block approach, this review systematically discusses how to approach four brain scales: ion channels, single neurons, synapses, and networks. The employed methods include computational simulations and techniques derived from machine learning that allow for the identification of parameters that generate a reliable activity akin to what is to be observed *in vitro* or *in vivo* experiments.

This review is organized into four sections that each address a specific level of brain organization, highlighting how computational approaches integrate with experimental findings to deepen our understanding at each scale. We begin with the *channel level*, where we explore how computational models replicate ion channel dynamics observed through experimental techniques like patch-clamp electrophysiology. These models allow us to investigate ion conductance patterns and gating mechanisms critical to neuronal excitability and signaling. Next, in the *neuronal level* section, we examine the complexities of individual neuron models and ion channel distributions. In the *synaptic level* section, we focus on computational models that incorporate synaptic plasticity and neurotransmitter dynamics. Experimental techniques like paired recordings and optogenetics validate these models, helping to understand how synaptic interactions drive network function. Finally, we address the *network and population levels*, where computational simulations are paired with population-level experimental techniques such as MEA and neuroimaging. This section discusses how large-scale models of neural networks capture complex dynamics, such as oscillations and synchronization, reflecting the collaborative activity that drives cognition and behavior discovery. Together, these sections build a cohesive view of how computational neuroscience connects insights across levels to approach a more comprehensive understanding of brain function.

Channel Level

Since the seminal experiments of Hodgkin and Huxley in the 1950s[17] (but see[18]), which provided a biophysical understanding of how electrical excitable cell voltage works and is shaped by ionic channels,

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by delivering the first quantitative description of ion channel behavior in the giant axon of the squid, the field of neuroscience has progressively expanded its experimental and computational repertoire to probe the brain's complexity.[19,20] Hodgkin and Huxley's model, although containing only sodium, potassium, and leaky currents, is markedly a revolutionary moment by which a phenomenon observed in neuroscience now had a counterpart in physics (equivalent electrical circuit) and mathematics (differential equations). The Hodgkin-Huxley models can accurately describe the electrical properties of neurons, specifically action potential generation through the so-called voltage-gated ion channels.

More specifically, the Hodgkin-Huxley biophysical model is based on the understanding of how electricity propagates in neurons and how the membrane and the ion channels that are embedded in it contribute to this propagation, inspiring decades of research where the mechanisms of neural signaling at various levels could be uncovered. This approach from the 1950s has since evolved considerably, integrating more sophisticated experimental techniques and computational methods to study other aspects of neural function. Today, researchers leverage tools such as high-resolution imaging, genetic manipulation, and electrophysiological recordings, complemented by computational models, to investigate brain organization from ion channels to neural circuits.

In Figure 1 (top), we see how a fundamental representation of the channel-level dynamics can be captured by an equivalent electrical circuit. The passive properties of the membrane are given by a capacitive circuit, and each additional ionic channel is added to this circuit through a parallel and non-ohmic component.

Each ion and ionic conductance that is added to the circuit shapes the neuron's membrane potential over time in a different manner. Interestingly, frequency-dependent mechanisms also arise from the combination of ionic currents. This is the case of subthreshold voltage dynamics in neurons and, more interestingly, the resonant property that some neurons demonstrate.[21] As represented in Figure 1 (bottom), some neurons can be tested for resonance by applying

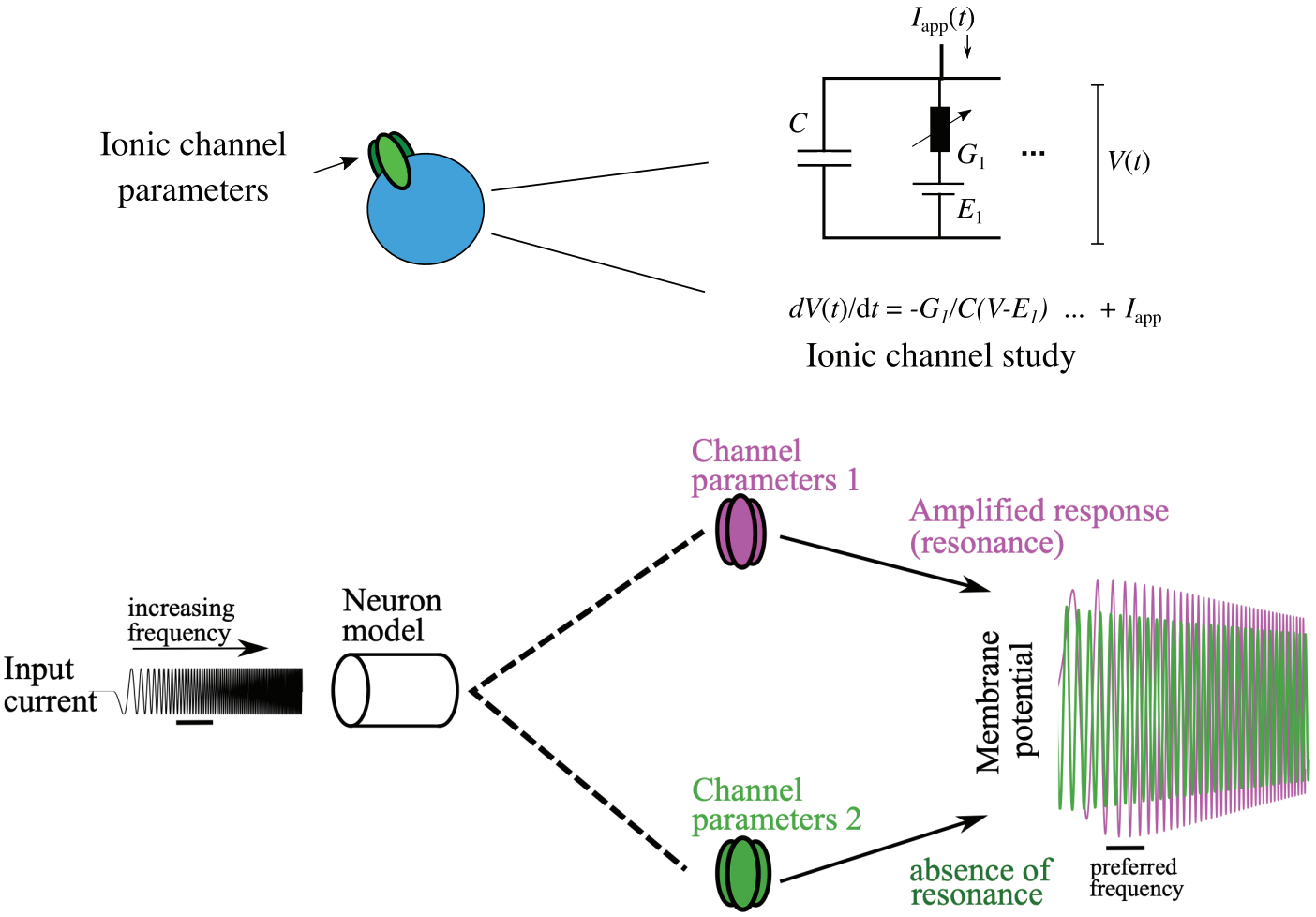

Fig 1 | A model for studying ionic channels. Upper panel: Ionic currents are modeled by adding more voltage-dependent components in parallel to the equivalent circuit proposed by Hodgkin and Huxley. The differential equation describes the rate of change of the membrane potential $V(t)$ over time, governed by the conductance and driving force of a single ionic channel, along with an applied current I_{app}. Bottom panel: A current with increasing frequency applied to a neuron model delivers a different output depending on the embedded ionic channels. Pink: An ionic channel where the channel parameters allow for subthreshold resonance. Green: An ionic channel where the channel parameters allow for low-pass filtering behavior

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a current in which the frequency content increases over time, also known as chirp or ZAP (Impedance Amplitude Profile; Z = Impedance) currents. This can either be done with a real neuron model through dynamic clamp or with computational simulation.[22] The combination of ionic currents that are embedded in the neuron will cause frequency-dependent patterns that are identified in the membrane voltage of the neuron, in the example depicted in Figure 1 (bottom), two colors are shown, pink for a resonant pattern. The resonance is identified when a non-zero input frequency causes an amplification of the response in the output of the neuron. The green color demonstrates the complementary case where a low-pass filter pattern emerges, lower frequencies are preferred, and the neuron does not peak or respond well to higher frequencies. The latter is an inheritance from the membrane's passive properties or particular ion channels.[23]

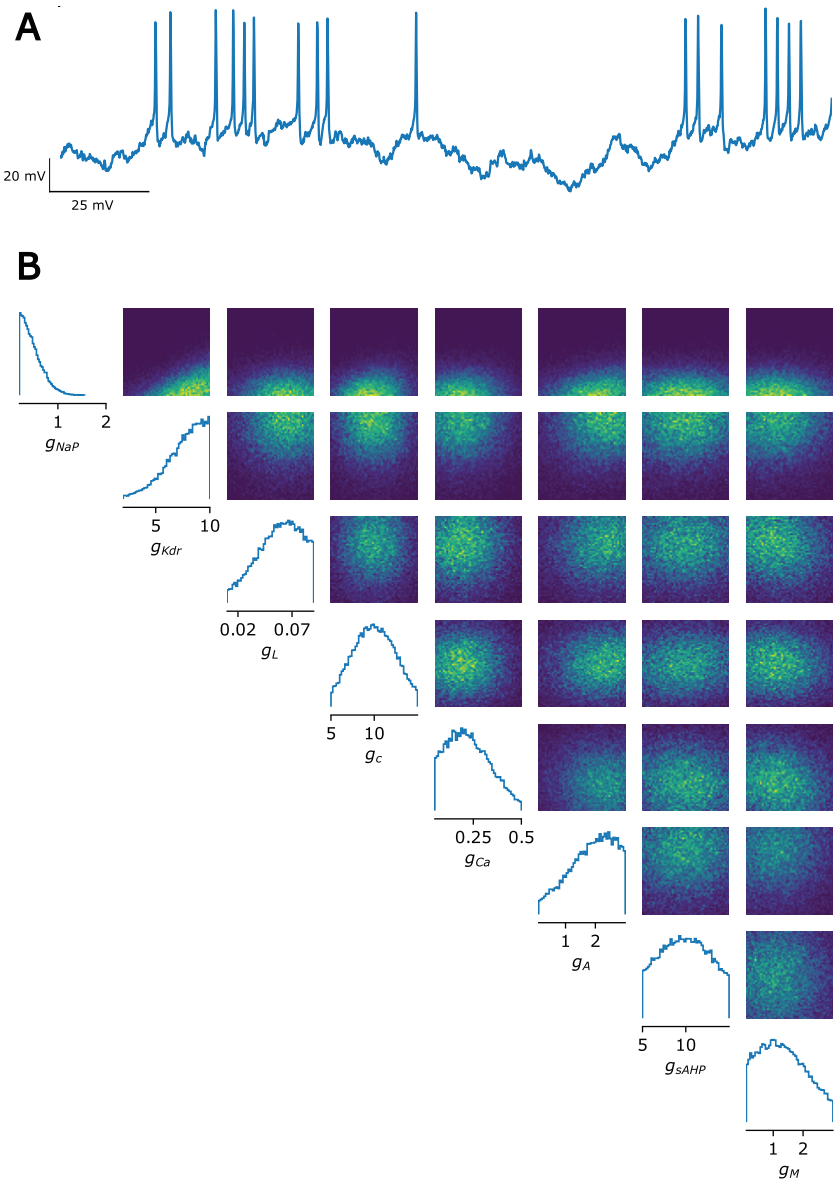

Fig 2 | Application of SBI to infer ionic channel conductance parameters. (A) Sample voltage trace showing the observed neuronal response to an applied stimulus, serving as the target signal for parameter inference. (B) Inferred conductance values for various ion channels, including persistent sodium g_{NaP}, delayed rectifier potassium g_{Kdr}, leak g_L, calcium g_{Ca}, A-type potassium g_A, slow afterhyperpolarization potassium g_{sAHP}, and M-type potassium g_M. SBI optimizes these conductances to produce a simulated response that closely aligns with the observed voltage trace, illustrating the method's ability to uncover precise channel contributions to neuronal behavior

Temporal and frequency-dependent studies can be easily accessed through computational techniques. This highlights the importance of conductance-based models in which ionic currents flow based on the membrane potential's difference from the reversal potential of a specific ion. The equation presented in Figure 1 is central to channel-level studies, as it enables researchers to explore how different ion channel properties, such as changes in conductance or reversal potential, affect neuronal excitability for varying temporal- and frequency-dependent inputs.

Neuronal Level

At the neuronal level, computational techniques help decipher the diversity of ion channels that shape neuronal function and its membrane voltage dynamics. Neurons rely on a variety of voltage-gated and ligand-gated ion channels, each contributing to the cell's excitability, firing patterns, and signal processing capabilities.[24] Techniques such as patch-clamp recordings, paired with pharmacological manipulations, allow researchers to isolate and characterize individual ion channel types. However, to truly understand how various channels work together within a neuron, we turn to computational approaches like conductance-based models, which integrate multiple channels into a cohesive simulation of neuronal behavior.

In this regard, inferring the multitude of parameters from particular ion channels is an important task for reproducing neuronal characteristics. Most importantly, the task becomes more difficult for *in vivo* recordings, given the stochasticity of the signals.[25] A powerful technique in this domain that can address this challenge is simulation-based inference (SBI),[26] which leverages artificial intelligence and computational models to infer the conductance parameters of diverse ion channels based on experimental data. By simulating numerous possible channel configurations and comparing them with empirical recordings, SBI can estimate the most likely channel conductances that produce observed neuronal responses. This method allows researchers to explore the complex interplay between ion channels and understand how specific conductance profiles contribute to diverse neuronal behaviors, such as bursting, adaptation, or high-frequency firing. The insights gained from SBI enhance our understanding of how different ion channels integrate at the neuronal level, offering an interesting view of how individual neurons support network-level dynamics.[27]

In Figure 2, we effectively illustrate how SBI can be used to extract detailed conductance profiles from data, offering insights into the individual and combined roles of specific ion channels. The target signal is based on recent work[28] where CA1 pyramidal cells from the hippocampus are performing transitions from single spikes to bursting behavior, as depicted

in the figure. These transitions are important for several brain functions but are still under investigation.[29] Moreover, this pattern is highly stochastic and, in general, not easy to reproduce when models are based on *in vitro* experiments (with less external stimulation) or contain a limited number of ion channels (constrained models). Therefore, we relied on SBI to infer the parameters that can re-create these patterns in simulations on this highly dimensional system.

The SBI algorithm applied in Figure 2B shows a diverse range of ion channel conductance parameters associated with different channel types, which include persistent sodium conductance (g_{NaP}), delayed rectifier potassium conductance (g_{Kdr}), leak conductance (g_L), fast calcium conductance (g_c), calcium conductance (g_{Ca}), A-type potassium conductance (g_A), slow afterhyperpolarization conductance potassium (g_{sAHP}), and M-type potassium conductance (g_M). Each heatmap contains a range for the pairwise conductance values in which the observed or target pattern is most likely to be found, and the corners of the diagram contain histograms where the single parameters are distributed. There is no unique solution; rather, it is a combination of parameters where the ion channels can be identified. To use the SBI package, we refer the reader to github.com/sbi-dev/sbi.

Recent advances in artificial intelligence, particularly in SBI, have significantly impacted computational neuroscience. These methods enhance our ability to apply and estimate parameters critical for modeling complex neuronal behaviors, enabling more accurate simulations of neural dynamics based on experimental data.

Synaptic Level

At the synaptic level, computational models capture the mechanisms of synaptic transmission and plasticity, which are fundamental to learning, memory, and information processing in the brain.[30,31] Synapses are highly dynamic structures where neurotransmitters are released in response to action potentials on the presynaptic terminal, leading to postsynaptic currents that either excite or inhibit the receiving neuron.[32] The neurotransmitter coupled to the reversal potential and its time scale determine the different effects that can emerge.[24] Experimentally, techniques such as paired recordings and optogenetics provide detailed descriptions of synaptic function by measuring postsynaptic responses to controlled presynaptic stimulation.[33] These data enable computational models to replicate synaptic dynamics, accounting for variables such as neurotransmitter release probability, receptor kinetics, and calcium dynamics within the synapse.

A significant and interesting aspect of synaptic modeling is the ability to include plasticity mechanisms, such as long-term potentiation and long-term depression, which adjust synaptic strength based on the history of activity (Figure 3). Models that incorporate Hebbian and spike-timing-dependent plasticity (STDP) rules allow researchers to simulate how experience and repeated stimulation modify synaptic connectivity over time.[34,35] STDP works by strengthening or weakening the postsynaptic signal depending on the time difference between presynaptic and postsynaptic action potentials: if the postsynaptic fires before presynaptic, a weakening is expected. Otherwise, a strengthening is expected.

These plasticity mechanisms are critical for encoding memory traces within neural circuits and adapting to changes in network activity.[36] By combining experimental data and computational modeling at the synaptic level, we gain a better understanding of how individual synapses shape neuronal responses, influence network dynamics, and drive adaptive behaviors. This level of modeling bridges single-neuron activity with larger-scale network computations, highlighting the essential role of synaptic interactions in generating functional connectivity across brain regions.

Network and Populational Levels

At the network and population levels, computational models aim to capture the collective dynamics of interconnected neurons, offering insights into how large-scale neural activity supports complex cognitive processes and behaviors. Networks of neurons exhibit diverse behaviors, such as oscillations,[11] synchronization, and spontaneous activity patterns, which emerge from the interaction of thousands or even millions of individual neurons. Currently, we know that the brain has, on average, 86 billion neurons.[37] Techniques like MEA, calcium imaging, and neuroimaging modalities such as fMRI provide experimental data on population-level activity, allowing researchers to study how neural circuits behave *in vivo* and *in vitro*. These

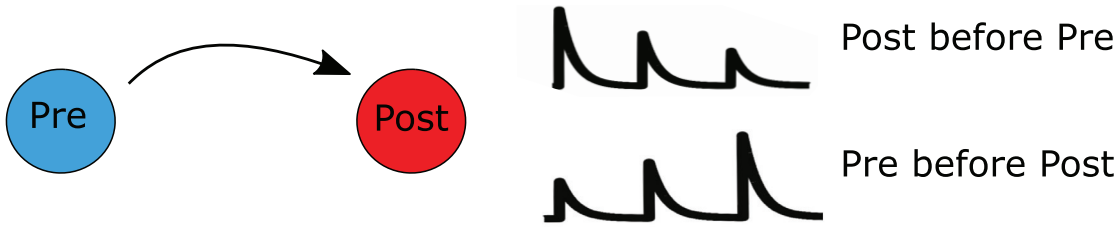

Fig 3 | Illustration of various timing conditions between presynaptic and postsynaptic events. The conditions include: *Pre*, representing successive presynaptic events; *Post*, depicting a standard postsynaptic response following presynaptic activation; *Post before Pre*, indicating an unusual sequence where a postsynaptic event occurs before a presynaptic one; and *Pre before Post*, showing the conventional timing of a presynaptic event preceding a postsynaptic response. These timing variations provide insights into the dynamics of synaptic interactions and the influence of temporal patterns on neuronal communication and plasticity

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experimental insights enable the construction of network models that can replicate observed population dynamics, shedding light on the organization and function of brain circuits.

A starting point for the description of network dynamics is Brunel's network[38] (Figure 4). In Brunel's network, neurons are connected randomly independently of being excitatory or inhibitory. There is a balance between excitatory and inhibitory synapses that, coupled with external stimulation, generates a diversity in network firing. Extensions from Brunel's work have found more patterns that are helpful in describing the brain's dynamics.[39]

A powerful theoretical tool for studying population-level activity is the mean-field approximation.[40] This approach simplifies complex neural networks by describing the average behavior of large groups of neurons rather than modeling each neuron individually. Mean-field models are particularly useful in understanding how global network properties emerge from interactions at the cellular and synaptic levels. For example, mean-field approximations can model the transition between asynchronous and synchronous firing states or capture network-wide oscillatory dynamics[38] that are critical for processes like attention and working memory.[41] By bridging individual neuron models with population-level behavior, mean-field models offer a tractable way to explore the conditions under which large-scale phenomena arise, enabling us to infer how networks operate under different physiological or pathological conditions.

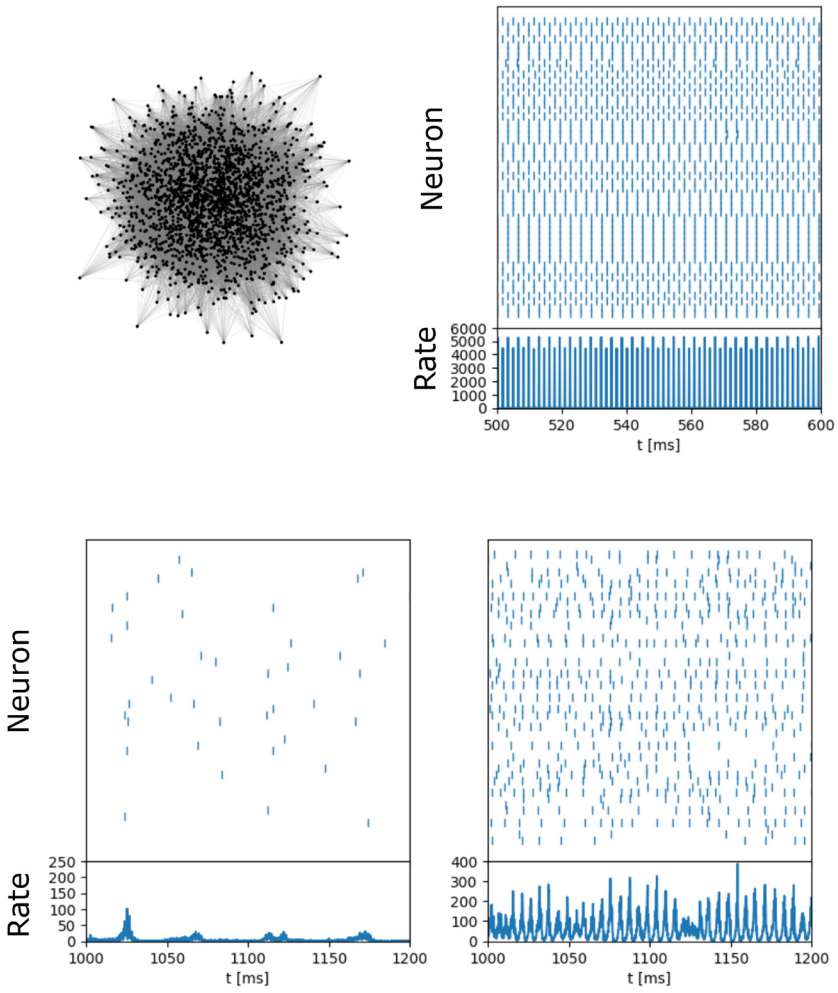

Fig 4 | Representation of neuronal firing rates and their interactions for a random network. The figure shows neuronal activity patterns and rate measurements, comparing different excitatory/inhibitory balance and input conditions. In the top right corner, there is a sketch of a random network. The remaining patterns show how the network goes from synchronous to asynchronous and irregular firing

Firing rate models are a type of mean-field model that derives from a simplification of spiking neuron models, capturing the average firing activity of a neuron or group of neurons over time.[42] Instead of tracking individual spikes as in Figure 4 (upper panels), firing rate models describe neural activity in terms of a continuous rate variable (bottom panels). This abstraction is particularly useful for analyzing large networks where the precise timing of each spike or even the precise nature of the underlying biophysical processes is less critical than the overall level of activity. Firing rate models are governed by equations that define the rate $r(t)$ as a function of inputs, reflecting how external stimuli or interactions with other neurons influence the neuron's firing activity. Such models are also important in the study of network dynamics, oscillations, and phenomena like synchronization across neuron populations. The equation for a simple firing rate model can be written as:

$$\frac{\tau dr(t)}{dt} = -r(t) + \phi(I(t))$$

where:

- τ is a time constant that determines the rate at which the firing rate adapts,
- $r(t)$ is the firing rate at time t,
- $I(t)$ is the input to the neuron at time t, and
- ϕ is a nonlinear function (often a sigmoid or threshold-linear function) that converts the input into a firing rate.
- This equation shows how the firing rate responds to input over time, decaying toward a new value based on the input $I(t)$ and the chosen activation function ϕ, thereby modeling the neuron's response to both external stimuli and the surrounding network environment.

Together, network- and population-level models help contextualize how local synaptic and cellular properties translate into the collective dynamics that underpin brain function, advancing our understanding of the principles governing large-scale neural activity.

Conclusion and Future Directions

In conclusion, this review highlights the role of computational models across various levels of brain organization, from ion channels and single neurons to synapses and large-scale networks, in advancing our understanding of neural dynamics. By integrating data from diverse experimental techniques with sophisticated modeling approaches, computational neuroscience provides a comprehensive framework for linking

cellular mechanisms to systems-level brain function. Emerging methods, such as SBI, underscore the potential of artificial intelligence to refine parameter estimation and improve model accuracy, offering insights into complex neuronal behaviors and network interactions.

Computational neuroscience has significant real-world applications, particularly in the domains of disease modeling and brain-computer interfaces (BCIs). In disease modeling, computational neuroscience is used to simulate and understand the progression of neurological disorders such as Alzheimer's, Parkinson's, and epilepsy. By creating detailed models of neural networks and their interactions, researchers can predict how these diseases affect brain function over time, which can lead to the development of more effective treatments and interventions. For instance, models can help identify potential drug targets or simulate the effects of therapeutic interventions on disease progression.

In the realm of BCIs, computational neuroscience plays a crucial role in translating neural signals into actionable commands for devices that can assist individuals with motor impairments or communication difficulties. BCIs can enable paralyzed individuals to control prosthetic limbs or communicate through computer interfaces by decoding their brain activity. Advances in computational models have improved the accuracy and responsiveness of these systems, making them more practical for everyday use.

Combined with these approaches, datasets for computational modeling in neuroscience can be sourced from several specialized databases. The Allen Cell Types Database offers a comprehensive collection of neuronal cell types characterized through multimodal approaches, including electrophysiological data from whole-cell current-clamp recordings, image data, morphological reconstructions, and both abstract point and detailed compartmental models. Similarly, the Blue Brain Cell Atlas serves as an extensive online resource detailing the number, types, and positions of cells across various regions of the mouse brain, utilizing imaging data from the Allen Institute for Brain Science to facilitate statistical analysis, modeling, and visualization of brain areas. Additionally, Channelpedia provides a valuable knowledge base focused on genetically expressed ion channel models, offering free access to 187 annotated ion channels and 50 Hodgkin-Huxley models. These resources, along with initiatives like CRCNS (Collaborative Research in Computational Neuroscience), which promotes data sharing, are pivotal for researchers engaged in computational modeling within the field of neuroscience.

A particular model that was not addressed in this review constitutes glial cells. There are many types of glial cells in the brain, and the most abundant are the astrocytes.[43,44] They are traditionally viewed as supportive glial cells and are increasingly recognized as active participants in brain function, playing critical roles in synaptic regulation, metabolic support, and neural plasticity. In computational neuroscience, the modeling of astrocytes has evolved to reflect their dynamic contributions to neuronal network activity. Current models incorporate key astrocytic mechanisms, such as calcium signaling, neurotransmitter uptake, and gliotransmitter release, enabling the exploration of their influence on network synchronization, oscillatory behavior, and information processing.[45] These models reveal that astrocytes can modulate neuronal excitability, enhance coherence in synchronous states, and contribute to the maintenance of homeostasis in complex systems. Advances in computational techniques, including agent-based models, hybrid neuron-glia networks, and machine learning approaches, have further expanded our ability to study astrocytic influence at multiple scales, from single synapses to whole-brain dynamics. By integrating these models with experimental data, computational neuroscience is uniquely positioned to uncover novel insights into neuron-glia interactions, providing a foundation for innovations in artificial intelligence and potential therapeutic strategies targeting glial dysfunction in neurological disorders.[46–48]

Together, these approaches allow for numerous and important future discoveries, offering valuable tools for bridging theoretical models with experimental neuroscience in a way that principles of the brain can be derived.

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