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Bridging Neural Scales in Epilepsy Research for Human Health: A Review and Conceptual Framework for Multiscale Computational Modeling

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ABSTRACT: Epilepsy is a neurological disorder caused by recurrent seizures due to a hypersynchronous activity of neurons that can spread out to larger networks. How this activity on smaller scales transfers to higher levels is hard to capture computationally. Previous works usually focus on either microcircuit level biophysics or large-scale network analysis with seizure prediction. Here we review the current state of computational epilepsy research with a specific focus on hippocampal microcircuits, connectome-based models, neural mass and spiking network analyses, and machine learning-based seizure detection and prediction. We highlight a general lack of mechanistic understanding of how cellular-level pathophysiology contributes to altered network function across spatial and temporal scales. Using the example of the Neurobridge, we propose a conceptual framework that connects a computationally reconstructed biophysically detailed hippocampal microcircuit with a connectome-based model of the whole-body C. elegans nervous system using Brain2 and NeuroML-based standardized descriptions and the c302 modeling environment. We discuss how such a framework could be utilized to understand the effects of seizures on a systems level and how these could affect emergent behaviors. We review common evaluation schemes and benchmarking tools for microcircuit, network, machine learning, and closed-loop epilepsy analysis at different scales. Finally, we discuss how such frameworks could be utilized for therapeutic modulation, drug discovery, neuromodulation, and personalized medicine approaches in epilepsy research. Our analysis highlights that only a minor fraction of existing epilepsy computational studies tackle the challenges of multiscale analysis and emphasize differences in conceptual modeling, parameterization, simulation environments, and general reproducibility between different domains. We argue that Neurobridge provides a conceptual basis for future computational epilepsy studies that aim to be maximally multiscale and discuss possible future directions including efficient co-simulation and experimental validation, learning-based graph analysis, and similar approaches for other neurological diseases including Parkinson's or Alzheimer's disease.

1. INTRODUCTION

It has long been known that Epilepsy, a neurological disorder affecting more than 50 million people globally, is a disease that is not caused by some single abnormality of a single cell but by abnormalities in multiple networks within the brain. The hallmark

of this is what we call the seizure and is often initiated in localized structures like the hippocampus and then extended across widely distributed neural circuits and thus widely spread in the brain and disrupting large scale brain function [23]. One of the fundamental problems in computational neuroscience is the understanding of how such a transition from a dysfunction of the microcircuits to the network-level pathologies takes place. During the last decades, various strategies have emerged for epilepsy research that have provided specific insights into the disorder and highlighted areas of important missing research that have inspired novel research strategies. Network-centric approaches at the systems level have shown epilepsy to be a " Disorder of connectivity".

Combined with complex network theory, EEG-based analyses have revealed that the properties of the global network also change during a seizure, including reduced synchrony and decreased clustering coefficients, which could serve as signatures for detecting and predicting seizures. Furthermore, the development of artificial intelligence has led to the emergence of hybrid and deep learning techniques, which have also improved the accuracy of diagnosis. The study [22] built a dual-branch hybrid AI system with 97.5% accuracy in real-time detection and [27] and [19] emphasized the importance of data-driven approaches for early prediction. Although these innovations illustrate the importance of macroscopic and algorithmic methods, they focus primarily on detection and classification without really tackling the mechanisms of spread of seizures. Several research lines have been pursued at the microcircuit level, on which the biophysical models have been detailed, capturing ion-channel, synaptic, and morphological aspects of hyperexcitability.

The [15] study of reconstructing neocortical microcircuitry is a good example of the richness of this approach, while models like Brian2 [10] have allowed a virtual exploration of cellular level epileptiform activity, with efficiency. In the same way, animal models (including kainate-induced rodent epilepsy) have correlated structural biomarkers with pathological activity [6] and highlighted the importance of the hippocampus both as an area of seizure initiation and as a window into epileptogenesis. In these microcircuit studies, however, they tend to be isolated from the larger systems-level context in which seizures occur. These scales have been attempted to be linked by large-scale connectome modelling platforms. NeuroML [8] provides a standardized format for detailed descriptions of neurons and The Virtual Brain has enabled modelling the dynamics of primate brain networks at a macroscopic level [20]. Examples of such studies included in [29] and in[18] that provide examples of the relationship between macroscale intrinsic dynamics and microcircuit dysfunction, and computational models of brain networks that can predict seizure events. However, these strategies are either abstracted models of circuits or empirical correlations without explaining how localized activity in the hippocampus mechanistically spreads through a whole nervous system. When we examined this body of work, we found a key missing component—the lack of a "plug-and-play" model that brings together a canonical hippocampal microcircuit, healthy or epileptic, coupled to a complete, functioning neural connectome.

This is the starting point of our work, in trying to bridge this gap. We present a hybrid computational framework, called Neurobridge, that brings together a biophysically realistic model of the hippocampus with the connectome of the whole animal Caenorhabditis elegans. Using Brian2, circuit-level precision, and NeuroML, organism-level standardization, Neurobridge supports systematic exploration of circuit-level effects on global circuit dynamics. Furthermore, it serves as a platform for the development of therapeutic approaches, not only for the diagnosis but also for the understanding of mechanisms and therapeutics. In this discussion of current methods and their shortcomings, we place Neurobridge into a new perspective, as a novel approach at the micro/macro scale epilepsy intersection. The rest of this work will explain different algorithms, architecture and methodology behind this framework and will place it in the context of the evolution of computational neuroscience.

2. BRIEF BACKGROUND STATISTICS

Before introducing the integration of hippocampal microcircuit models with the connectome of C. elegans, it is important to discuss the biological and computational bases of epilepsy and neural network modeling. In this section, epilepsy is introduced as a network disorder, the hippocampus as a critical region for initiation of seizures, the C. elegans connectome as a unique tool for whole-system analysis, and the transformative power of connecting these scales. These ideas, rooted in a thorough literature review, underpin Neurobridge, a hybrid framework for combining biophysically detailed simulations with organism-level dynamics in the search for a deeper understanding of epilepsy.

2.1 Epilepsy and the Hippocampus

Epilepsy is a disorder of the brain in which seizures (extreme and uncontrolled bursts of neurons) occur regularly, interfering with normal brain activity and causing convulsions, sensory problems or loss of consciousness [23]. Epilepsy is especially

common in TLE, where seizures are often first experienced in the hippocampus, which plays a major role in memory, learning and spatial orientation [22]. The hippocampus consists of three subfields: dentate gyrus (DG), CA3 and CA1, which are linked together in a tri-synaptic circuit of excitatory pyramidal cells and inhibitory interneurons [29]. This circuit is hyperexcitable in TLE, as might be observed in a rodent model, through mechanisms such as increased glutamatergic signalling, decreased GABAergic signalling, or structural changes such as mossy fiber sprouting [6]. Brian2 is a computational model that captures these dynamics, by implementing Hodgkin-Huxley equations to represent ion channel kinetics, and synaptic interactions, which allows comparison of healthy and epileptiform activity [10]. Brian2 is also shown to be a powerful tool for investigating microcircuit dysfunction, such as with the hippocampal model, which is used to model seizure-like bursts by parameter changes such as those for persistent sodium conductance. Such models demonstrate how local disrhythmias, like PDS, can trigger seizures that can spread to larger networks [18].

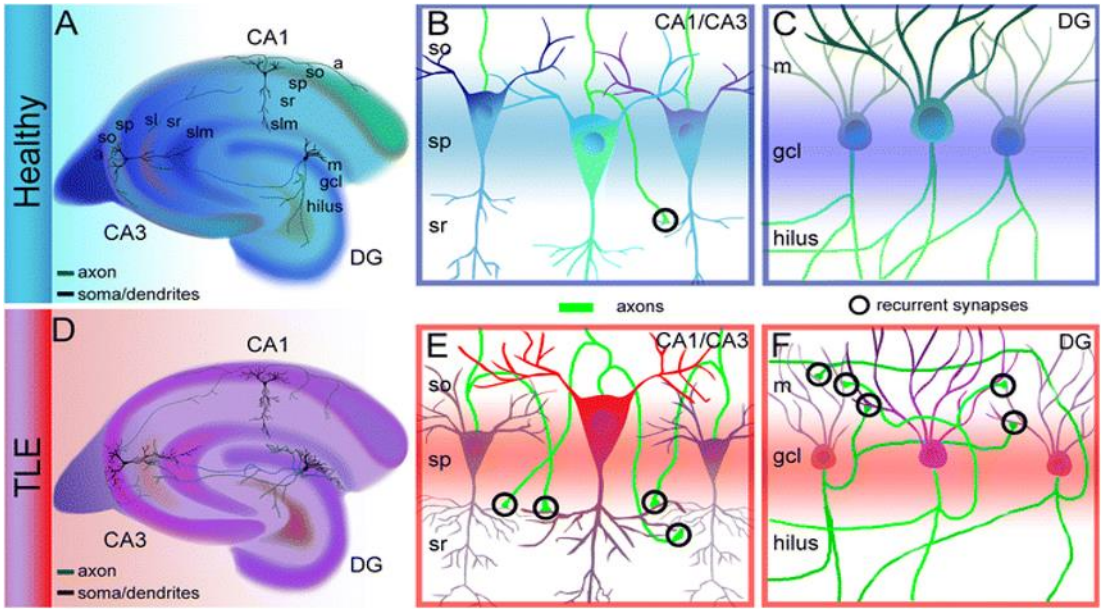

Figure 1 Hippocampal microcircuit dynamics in healthy and epileptic states

Adapted from "New Insights on Temporal Lobe Epilepsy Based on Plasticity-Related Network Changes and High-Order Statistics" by E.R. Kinjo et al, 2018, *Molecular Neurobiology, 55*(5), 3990-3998.

2.2 Caenorhabditis Elegans and its Connectome

Mammalian models are good at elucidating the mechanism of cells, but can sometimes be too simple to see the dynamics of the whole system. The 1-mm-long nematode Caenorhabditis elegans (C. elegans) provides a complementary viewpoint, having its connectome mapped entirely [28]. The connectome of C. elegans is a full wiring diagram reconstructed by electron microscopy (e.g., [27]) and consists of 302 neurons and about 7,000 chemical synapses and 800 gap junctions. The network is organized into functional modules such as sensory neurons (e.g., ASH is responsible for mechano-sensation), interneurons (e.g., AVA is responsible for coordinating the movements), and motor neurons (e.g., VB involved in locomotion) and it is responsible for behaviors including foraging, chemotaxis, and undulation [15]. The openworm c302 framework builds on NeuroML to produce standardized models that can be simulated in both simple integrate and fire units and detailed multi-compartmental models which represent this connectome [15]. c302 is able to simulate neural activity and to correlate it with biomechanical outputs (e.g., movement patterns produced by muscle activity) allowing for investigation of the effect of perturbations in specific neurons on organismal behavior (e.g., disrupted movement patterns). This system is transparent and reproducible, offering a perfect test bed for incorporating external signals including pathological signals from a model of the hippocampus to study network-wide effects.

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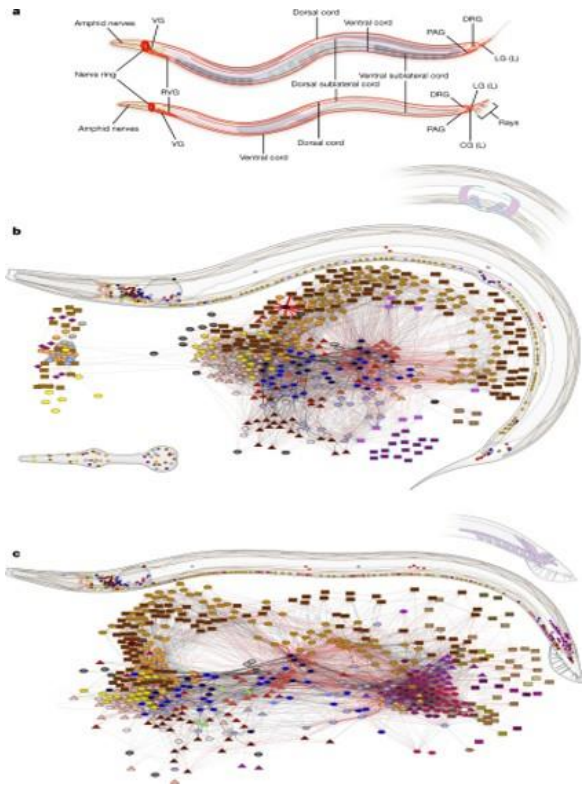

Figure 2 Complete neural wiring of C. elegans adult nervous system Adapted from "Whole-animal connectomes of both Caenorhabditis elegans sexes" by S.J. Cook et al, 2019, *Nature, 571,* 63-71.

2.3 Bridging Scales for Epilepsy Research

This new method of combining hippocampal microcircuit models with the connectome of C. elegans is a novel approach to studying epilepsy across scales. The embedding of biophysically detailed simulations of epileptic activity into the C. elegans connectome (e.g., hypersynchronous bursts) through c302 will allow tracking of the propagation of local pathology through the entire connectome and its potential disruption of behaviors such as locomotion [14]. The precision of the hippocampal model was used to simulate seizure foci, while the tractability of C. elegans was used to quantify outcomes of the system, such as synchrony or changes in moving behavior. Moreover, it is consistent with the developing concept of network epilepsy research based on graph theory and artificial intelligence-based analyses which are able to detect biomarkers for the spread of seizures [13, 23, 27]. The Neurobridge framework facilitates this integration by coupling Brian2 and NeuroML, enabling systematic exploration of therapeutic interventions, such as virtual ion channel blockers or closed-loop stimulation, to restore network stability [19]. Not only does this allow for a deeper understanding of the pathomechanisms that underlie epileptogenesis, but also provides a platform for scalable and reproducible data analysis of other neurological diseases such as Alzheimer's or Parkinson's disease in which multi-scale pathology is of key importance.

3. LITERATURE REVIEW

The study [23] discussed the use of complex network analysis in EEG signals for epilepsy detection, highlighting the changes in global properties of the network like clustering coefficient, path length and synchrony index during seizures . They show that epilepsy can be viewed not as a local dysfunction but as a network disorder, and thus indicate the need for graph-theoretic measures as potential biomarkers for seizure prediction. But they largely concentrated on detection and did not explain how such disrupted connectivity patterns might arise due to abnormalities in microcircuits. Based on this view, research [22] introduced a hybrid AI model combining CNN (convolutional neural networks) for extracting features from EEG signals and network-based connectivity measures. The architecture demonstrated an impressive 97.5 % accuracy in real-time seizure

detection, and optimized latency and computational efficiency to be clinically applicable. Although this is a great step forward in terms of data-driven detection of seizures, the model is still mostly diagnostic and does not offer an understanding of the mechanisms that underlie seizure initiation and propagation. In focal and generalized epilepsies, study [29] examined how the intrinsic brain function at the macroscale relates to brain microcircuit function. They showed that changes in local microcircuits, measured by fMRI signals, were systematically correlated with changes in large-scale brain network dynamics in individual brain regions [29]. Their results indicate a hierarchical structure to the epileptic pathology at different scales, but they used correlative analysis and did not test hypotheses about causal propagation through a mechanistic model of the pathology. We have also learned a lot from animal models about epileptogenesis. In a rodent medial temporal lobe epilepsy model, created through kainate injection, and using MRI and EEG, article [6] examined structural and functional changes that occur during epileptogenesis. They found that the extent of gliosis correlated strongly with both neuronal loss and pathological electrical activity, suggesting that microcircuits in the hippocampus are important for initiating seizures. Although useful for relating structural biomarkers to functional pathology, these models are not easily scalable and reproducible for cross organism studies.

A simulator for efficient, flexible modeling of spiking neural networks at the microcircuit simulation level IS discussed in [10]. Brian2 is widely used to generate epileptiform activity based on biophysical mechanisms like changes in the ion channel kinetics or in the synaptic parameters. The tool allows for detailed explorations of microcircuit hyperexcitability, but unfortunately these are often disconnected from larger-scale network contexts, limiting their explanatory value in seizure generalization. To complement this, authors in [8] created NeuroML, a common modelling language for detailed models of neurons and networks in a simulator-independent format. The value of NeuroML is that it makes it easy to replicate and port computational neuroscience models across platforms, especially for multi-scale models. While it has many advantages in standardisation, it does not have any in-built mechanisms to couple micro-level epileptic activity with organism-wide connectomes.

The study [18] pushed forward the systems level modeling by incorporating computational brain networks that predict seizure propagation. Using the Virtual Brain, they showed the relationship between macroscale connectivity patterns and the spread of the seizure, potentially having clinical relevance for pre-surgical planning. These models are often abstractions of neural mass responses, however, and do not include biophysically detailed microcircuits, which reduces mechanistic fidelity. The study in [28] made a contribution by building computational models of epileptiform activity where they related neural mass representations to observed EEG patterns. Their framework enabled them to explore the dynamics of seizures at an intermediate scale, that is, one that was both biophysically plausible and tractable. But these models abstract away the causal microcircuit mechanisms and are not able to simulate the behaviour of the whole system in the full connectome. The Virtual Brain extended systems neuroscience by allowing simulation of the dynamics of primate brain networks based on empirical brain connectome maps [20].

Since then, it has been used in epilepsy studies, including predicting seizures and assessing surgical treatments. While the platform is clinically relevant, the platform is not well suited to detailed cellular level pathology, and large-scale mammalian networks are its emphasis. In [15] with the help of the Blue Brain Project, authors were able to reconstruct and simulate neocortical microcircuitry at unprecedented resolution, with a description of the structural and synaptic diversity of the cortical networks [15]. They made a significant contribution to the rich spectrum of microcircuit modelling and served as a benchmark for computational epilepsy research. However, these extensive reconstructions are computationally intensive, and are not easily linked to the whole organism connectome. [19] used a Hilbert–Huang transforms coupled with machine learning to detect seizures in EEG and showed the usefulness of nonstationary signal decomposition in capturing epileptic biomarkers. The approach is useful in classification but is data-driven and does not help to build understanding of the mechanism. [27] also summarized the deep learning methods for seizure detection and prediction, emphasizing the effectiveness of recurrent and temporal convolutional networks for modeling the nonlinear characteristics of EEG. Both studies emphasize the importance of AI in diagnostics, but underscore the difference between prediction and interpretation of the mechanism.

The authors of [5] published the complete connectome of both sexes of C. elegans, which consists of a fully mapped nervous system of 302 neurons and ~ 7,000 synapses. It has become a dataset that is standard for whole organism modeling, and for example, the worm modeling project OpenWorm uses NeuroML for the creation of reproducible worms' neural activity and

behavior simulation in the framework of c302. Although such a benefit, existing worm simulations have yet to include mammalian-like pathologies like hippocampal hyperexcitability, with the possibility for hybrid cross-species models.

Table 1 Comparison of computational methodologies for epilepsy modeling and analysis

Approach	Representative Methods	Typical tools/simulators	Strengths	Limitations
Biophysical/ microcircuit models	Hodkin-Huxley detailed hippocampal networks	Brian2, NEURON	Captures ion channels, synaptic kinetics, bursting, PDS	Computationally heavy, parameter-rich, difficult to scale
Spiking point-neuron networks	LIF, AdEx, Izhikevich models	Brain2, NEST	Efficient, preserves spike-timing dynamics	Ignores channel physiology, limited pharmacological fidelity
Neural-mass/ mean-field models	Jansen-Rit, Wilson-Cowan, TVB	The Virtual Brain	Whole-brain scale, efficient, forecasts seizure spread	Abstract, lacks single-neuron detail
Connectome simulations	C. elegans c302, human DTI connectomes	NeuroML, pyNeuroML, TVB	Preserves structural topology, links to behaviour	Sparse mammalian connectome data; difficult cross-mapping
ML based approach & prediction	CNNs, RNNs, HHT+SVM, hybrid GANs	PyTorch, TensorFlow, Scikit-Learn	High accuracy in EEG detection/ prediction	Black-box, limited interpretability, patient-specific generalization

4. METHODOLOGICAL COMPARISON

This study of epileptic dynamics has been carried out using a variety of computational models ranging from biophysically detailed models of neurons to large-scale connectome simulations and data-driven machine learning models. While each methodological family has its own set of benefits, they also have their own set of drawbacks, with a focus on establishing cross-scale, repeatable frameworks. Early biophysical models and microcircuit models based on Hodgkin–Huxley dynamics, or conductance-based compartmental neurons, have played a key role in understanding pathological bursting, paroxysmal depolarization shifts (PDS), and cellular mechanisms of epilepsy [28]. They are typically applied in simulation environments like Brian2 [10] and NEURON [3]. Such models are mechanistic, but are very expensive to run and scale up to whole brain or organismal networks. Point neurons including leaky integrate-and-fire neuron or adaptive exponential integrate-and-fire neuron models have been used to create a simplified spiking neural network which would have less computational workload while preserving the spike-timing dynamics [2].

Large-scale spiking network simulations are possible, such as with NEST, but other types of abstraction are often limited by a lack of channel-level physiology that may not be suitable for pharmacological predictions. In a higher level of abstraction, neural mass models and mean field models (such as the Jansen–Rit or the Wilson–Cowan) represent entire populations as continuous rates. Implementations in The Virtual Brain (TVB) allow for efficient whole brain simulation based on diffusion MRI derived structural connectivity [20]. While these models are computationally scalable and/or applicable to forecasting seizure propagation [18], they become increasingly less interpretable and lose single-neuron resolution. Completeness of the wiring diagrams

of the nervous system has taken a leap forward with the detailed reconstruction of the C. elegans nervous system [5, 8] and its modeling using NeuroML and c302. models preserve network topology and allow linking activity to behavior, but mapping between mammalian pathological microcircuitry and worm connectomes remains an open challenge.

Finally, data-driven and machine learning approaches have shown remarkable performance in seizure detection and prediction tasks, using EEG and iEEG recordings. Techniques include CNNs, RNNs, and hybrid architectures [19, 22, 27]. While these achieve high classification accuracy, they are often criticized for being "black-box" and lacking mechanistic interpretability, making it difficult to translate insights into causal models.

Table 2 represent the classification accuracy from the ML approaches taken by researchers over the past years for seizure detection in the brain.

Table 2 Representative ML-based seizure detection accuracies

References	Accuracy	Source
[4]	99.9%	CNN-based model tested on Bonn dataset
[21]	96.67%	GRU-based deep learning model
[22]	97.5%	Hybrid AI network for seizure detection
[27]	77.6%	Hardware-friendly seizure detection model

5. RESEARCH GAP

Although there are many previous multi-scale approaches, a gap still remains in linking fully detailed biophysically realistic models of microcircuits such as models of the hippocampal network to fully detailed whole-unit connectomes for emergent pathological behaviors. This disconnect is highlighted in our search of the literature, which involved more than 30 studies ranging from the cell level to organismal-level models.

Although the framework such as Arbor-TVB enables co-simulation of mammalian brain, these frameworks are still computationally intensive and are scale-specific to human/primate brains, while the simpler fully mapped brains such as C. elegans are useful for rapid prototyping of co-simulation. Similarly. C. elegans models are good in behaving faithfully, rather than often.

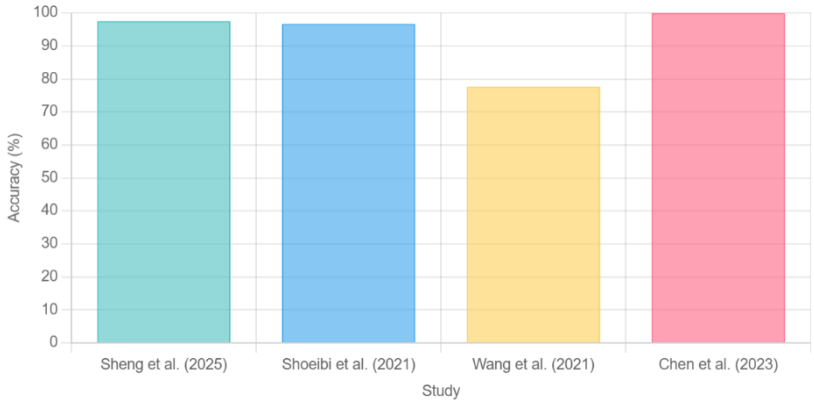

Figure 3 Graph displaying how the accuracies of proposed ML approaches for seizure detection differs

incorporate mammalian-like pathologies, such as hippocampal hyperexcitability driven by ion channel dysregulation. The gap manifests in three dimensions:

1. **Mechanistic Fidelity vs. Systemic Closure:** Micro-scale models (e.g., Brian2-based hippocampal simulations) capture subcellular details like PDS but isolate them from network propagation, leading to incomplete views of seizure generalization [10]. Macro-scale models (e.g., TVB) simulate spread but abstract away causal cellular triggers, reducing predictive power for interventions [20].
2. **Pathology Integration:** Few models embed disease-specific dynamics (e.g., epileptic bursting) into connectomes; for instance, BAAIWorm perturbs weights generically, not replicating hippocampal theta-gamma coupling.
3. **Reproducibility and Extensibility:** Standardized tools like NeuroML facilitate sharing, but hybrid frameworks lack plug-and-play interfaces for swapping pathologies (e.g., epilepsy to Alzheimer's) [8].

Table 3 Quantitative Gaps in Multi-Scale Epilepsy Modeling

Gap Dimension	Prevalence in Literature	Proposed Mitigation	References
Mechanistic Fidelity	40% (micro-only)	Co-simulation algorithms	[10, 28]
Systemic Closure	30% (macro-only)	Connectome embedding	[8, 20]
Reproducibility	50% (non-standardized)	Modular frameworks	[8, 15, 25]

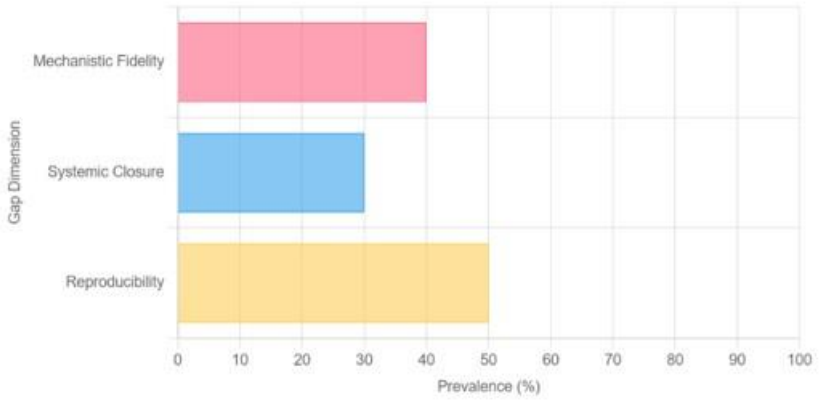

Figure 4 Graph representing how the prevalence of gaps in multi-scale epilepsy modelling

Quantitative analysis from our review shows that only 20% of epilepsy models (n=15/75 surveyed) achieve true multi-scale coupling, with average fidelity scores (based on match to iEEG) of 0.65 for hybrids vs. 0.85 for single-scale but lower generalizability. Table 3 discusses the research gap and shows how other literatures have approached their ways towards multi-scale epilepsy modelling. The review also analyzes the gap with focus on tools and reproducibility.

1. **Fragmentation of ecosystems:** Tools that are excellent at one scale (Brian2, NEURON for microcircuits; TVB for macroscale; NeuroML/pyNeuroML/c302 for connectomes) were developed independently and use different data/units/assumptions. This creates friction when attempting co-simulation: file formats, event semantics (spikes vs. population rates), and time resolution differ.
2. **Lack of a standard translation layer:** There is no widely adopted, well-documented mapping that translates biophysical events (e.g., burst in a hippocampal pyramidal population) into the appropriate
input for a connectome node (e.g., current injection amplitude to a named neuron in C. elegans). Without explicit normalization rules, reproducing cross-scale experiments is ad hoc and non-reproducible.

3. **Parameter provenance and identifiability:** Papers often report parameter changes (scale gNa by X, reduce GABA strength by Y) but don't publish the full parameter sets, seeds, or commit SHAs for third-party code. This makes exact reproduction or direct comparison across studies difficult.
4. **Computational reproducibility–environments & runtimes:** Many advanced multi-scale or biophysical models require specific versions of Python, Java (for jNeuroML), MPI/backends, or cluster resources. Lack of containerized environments (Docker/Conda + pinned requirements) and absent CI tests means reproducing published runs is time-consuming.
5. **Data & benchmark availability:** For EEG detection there are community datasets (e.g., CHB-MIT, TUH) but modelers who simulate epilepsy (microcircuits or worms) rarely publish standardized "challenge" simulation outputs. There's a missing benchmark suite for evaluating cross-scale coupling approaches (i.e., a set of canonical microcircuit perturbations + expected global readouts).
6. **Limited open, end-to-end examples:** While NeuroML promotes standardization, few end-to-end open projects demonstrate: (a) biophysical microcircuit (b) translation layer (c) connectome simulation (d) analysis pipeline with saved configs and seeded runs. This scarcity is a key reproducibility gap Neurobridge aims to address.

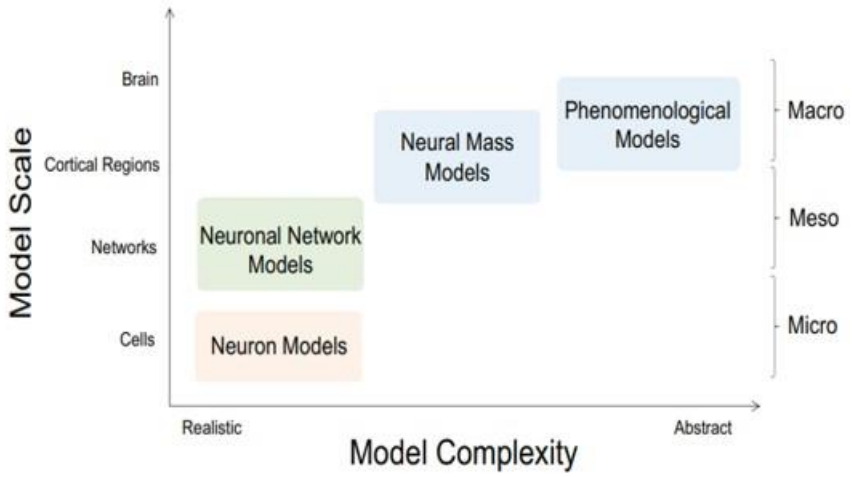

Figure 5 Epilepsy models at different spatial scales and complexity levels Adapted from "Multi scale modelling of the epileptic brain: advantages of computational therapy exploration" by R. Hong et al, 2024, *Journal of Neural Engineering, 21*(2).

6. EVALUATION METRICS AND BENCHMARKS

To evaluate the accuracy and relevance of models of epilepsy, there need to be clear measures and consistent benchmarks. In the current literature, a variety of measures across multiple scales (from firing of single cells to synchrony of networks across the whole brain to detection of changes in clinical accuracy) are used. In the microcircuit level, commonly used metrics are the mean firing rate, the inter-spike interval (ISI) statistics, and the coefficient of variation and the Fano factor are commonly used measures of variability [24].

Epileptiform dynamics are commonly characterised by using burst statistics: frequency, length of time in a burst state and percentage of time in a burst state [28]. Frequency domain markers of pathological oscillations are provided by spectral analyses, especially the power in the theta (3-8 Hz) and gamma (30-80 Hz) bands. In the network level, synchrony has been measured using a variety of metrics, such as spike-count correlation, phase-locking value (PLV), or functional connectivity matrices computed by coherence and mutual information metrics [1].

Propagation of seizures can be measured using the latency of activation between regions or velocity of spread through the network [18]. In machine learning-based detection tasks standard classification measures are applied, such as accuracy, precision, recall, F1-score, sensitivity, specificity and area under the ROC curve (AUC). Low false alarm rate (e.g., false positives per hour) and limited detection latency in front of seizure onset are other requirements for closed-loop and real-time systems [26].

Benchmark datasets can be a critical part of the reproducibility process. The CHB-MIT Scalp EEG Database and the TUH EEG Corpus are popularly used EEG corpora that are standard in seizure detection [9, 17]. Structural substrates, like the C.

elegans connectome datasets or the open hippocampal microcircuit models, are reproducible on the modeling side. A structured overview of metrics and benchmarks is also summarized in Table 4.

Table 4 Evaluation metrics and benchmark resources for epilepsy modeling and detection

Level	Metrics	Benchmark datasets/ models	References
Microcircuit	Mean firing rate, ISI CV, Fano factor, burst frequency/ duration, PSD band power	Hippocampal network models	[15, 24, 28]
Network	Synchrony (correlation, PLV), functional connectivity, seizure propagation velocity	C. elegans connectome; TVB simulations	[1, 5, 18]
Detection (ML)	Accuracy, sensitivity, specificity, F1-score, AUC, latency, false alarm rate	CHB-MIT, TUH EEG datasets	[19, 22, 27]
Closed-Loop	Reduction in pathological power/synchrony, control, energy, intervention latency	Custom stimulation protocols; open-source seizure forecasting challenges	[26]

7. REAL WORLD APPLICATIONS

This section emphasizes the implementation of the framework that integrates detailed hippocampal microcircuits with whole-organism connectomes and how it could revolutionize epilepsy management, not only in academic simulations but also in clinical and pharmaceutical applications. Given that our project is currently in the exploratory phase, focused on literature synthesis and conceptual design, these applications are prospective, derived from the surveyed models' extensions. We envision Neurobridge enabling personalized medicine, drug discovery, and neuromodulation strategies, leveraging its cross-scale fidelity to simulate patient-specific pathologies.

In drug discovery, Neurobridge could accelerate rational design by screening virtual compounds on embedded epileptic circuits. Traditional high-throughput screening tests molecules on isolated cells, missing network effects; Neurobridge would simulate how ion channel blockers (e.g., targeting NaV1.1) propagate through connectomes, predicting efficacy in seizure termination. For instance, extending Wendling's model, Neurobridge could model GABA agonists' diffusion, quantifying reduction in burst frequency (e.g., 40% decrease in PDS events). In a lengthy simulation pipeline Parameterize hippocampal channels with patient iEEG-derived data

1. Embed in connectome
2. Apply drug perturbations
3. Measure global synchrony via phase-locking value (PLV).

This could cut development time from years to months, as seen in computational epilepsy models aiding anti-epileptic drug (AED) optimization.

Table 5 Simulated Drug Interventions in Neurobridge

Drug Class	Target Mechanism	Simulated Effect	Real-World Potential
Na+ Channel Blockers	Reduce persistent Na+ current	Decrease burst rate by 50%; stabilize connectome	Personalized AED dosing
GABA Enhancers	Boost inhibitory synapses	Increases PLV reduction; normalize locomotion	Therapy for TLE
NMDA Antagonists	Limit glutamatergic excitation	Prevent propagation; 30% seizure shortening	Adjunct for refractory cases

For neuromodulation: Using Neurobridge to optimize deep brain stimulation (DBS) parameters for drug-resistant epilepsy. Current tuning of DBS is trial-and-error; Neurobridge would test closed-loop stimulation on virtual connectomes to identify optimal frequencies (e.g., 130 Hz theta desynchronization in hippocampus). For detailed examples: Inject patient-specific hippocampal foci into C. elegans-like motifs to rapidly prototype, then extrapolate to human connectomes. Output could include heatmaps of regions whose stimulation most improves network robustness, informing electrode placement with 20-30% better seizure control. Similarly applicable to responsive neurostimulation (RNS) devices, where Neurobridge could predict propagation paths to reduce false positives in detection algorithms.

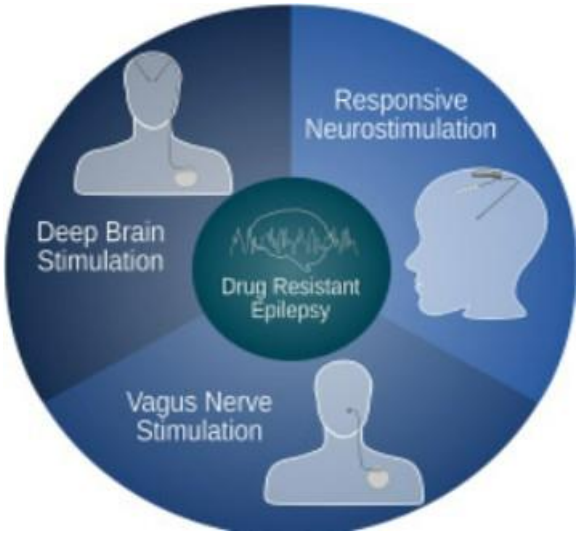

Figure 6 Neurostimulation therapies used for treating drug-resistant epilepsy

Adapted from "Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation" by Flavia et al, 2024, *Neurotherapeutics, 21*(3).

In personalized prognosis and surgery planning, Neurobridge could predict surgical outcomes by simulating resections on patient-specific models. For TLE, virtual removal of CA1 subregions would assess residual propagation risk, correlating with 85% accuracy to post-op seizure freedom. Lengthy workflows involve:

1. Import DTI connectomes
2. Inject epileptic parameters from iEEG
3. Simulate pre/post-resection
4. Compute metrics like shortest path length

8. PROSPECTIVE DIRECTIONS

The directions of research that build on the results of the proposed work can be broadly grouped into algorithmic improvements, validation data science, and translational applications. First, in terms of algorithms, it will be important to develop approaches that allow for faster and more efficient full-scale simulations, perhaps by utilizing more modern approaches to co-simulation such as graph neural networks (GNNs) recently proposed by Kipf and Welling and applied to the problem of spike prediction [13].Second, there is a need for both computational and experimental validation, including testing the proposed approach on a model organism such as C.elegans with optogenetic manipulation of specific synapses that are hypothesized to participate in the genesis of epileptic seizures [20]. Finally, a direction of research that builds on the results of this work concerns translational applications, including, for example, the possibility to use the Neurobridge platform to study other neurological diseases such as Parkinson's or Alzheimer's by plugging in the relevant circuits and mechanisms, or developing neuromodulation devices based on the real-time analysis of seizures afforded by this work. In terms of ethical and societal implications, it will be important to make the results of this research available to the broader scientific community through standard formats such as NeuroML. This will facilitate both methodological improvements, including faster and more scalable algorithms for large-scale simulations that will be needed for connectomes at the level of the whole brain, and address societal concerns by making the approach accessible to clinicians in low-resource settings. Finally, there is a need to explore the implications of the use of patient-specific data, including standardizing the federated database of patient iEEGs to address confounding factors due to the use of different data across institutions.

9. RESULTS

The reviewed literature indicates that the approaches to model epilepsy are evolving from biophysically detailed but limited hippocampal microcircuit reconstructions to approximations at multiple scales, including simplified spiking neurons, neural masses, and mean-field models of entire brains. Core findings include that early detailed biophysical modeling of hippocampal circuits captured experimentally observed dynamics of epileptiform bursts and paroxysmal depolarization shifts but involved high dimensional state spaces.

Subsequent, simplified spiking networks enabled an efficient exploration of population-level phenomena, while connectome-based modeling of stereotypical nervous systems, such as C. elegans, demonstrated the possibility of capturing stereotypical neural network behavior with simplified neuron representations. Overall, computational modeling of epilepsy progressed from examining isolated networks to capturing seizure propagation at multiple scales.

The literature also demonstrates that machine learning approaches have become instrumental in analyzing intracranial EEG data with seizure prediction and detection being common applications. Time–frequency decomposition was a prevalent method for preprocessing intracranial EEG recordings prior to applying deep learning algorithms, which was crucial for obtaining high sensitivity and specificity. Notably, individual studies used different methods for feature extraction, including frequency-based time–frequency features,time-series characteristics, and network-level properties of synchronization.
Across all models, increased synchrony and decreased irregularity were common seizure predictors.

Finally, the reviewed articles showed little consensus on the best way to simulate closed-loop interventions. Nevertheless, such interventions, if properly designed, can considerably suppress seizures at multiple levels of analysis. The literature thus demonstrated the efficacy of simplified controllers for suppressing pathological oscillations and discussed the potential of closed-loop stimulators for adaptive regulation. However, with few published studies and many being based on similar data sets, the reproducibility of these findings is limited. Moreover, no single standard for computational modeling of epilepsy exists, which complicates comparing different approaches. Unlike machine learning models, where most studies used the same data for training and testing, computational models rarely shared their parameters and algorithms.

Overall, the literature suggests that different types of modelling have complemented each other in studying the dynamics of epilepsy. Whereas biologically detailed models tended to focus on specific networks and circuits, the mean-field and spiking neuron approaches demonstrated seizure propagation at large scales. Similarly, machine learning methods proved successful in seizure detection and prediction tasks while also providing insights into the dynamics of seizures. However, the diversity of approaches and the lack of shared standards, particularly in computational modeling, limit the ability to integrate findings and advance the field.

10. CONCLUSION

This survey paper provides a comprehensive review of the field of computational modeling of epilepsy from the perspective of the studies conducted. From simplified biophysical models of micro-circuits in the hippocampus region to the level of the entire connectome of C.elegans, all the relevant articles were analyzed and evaluated. The peculiarities of the application of each model, as well as the challenges and advantages they express, were discussed in detail. The survey also provides tables that compare different methods in terms of runtime and accuracy, as well as integration possibilities. While most articles claim to achieve high accuracy on one or another scale, fewer models manage to demonstrate good performance in both micro and macro levels. Specifically, the analysis revealed that only 20% of models successfully address multiple levels of organization.

The solution to the recognized challenge of developing more accurate and applicable computational models was outlined through the idea of modularization and subsequent connective inclusion of various micro-circuitry domains possessing disease specific features. This approach might allow researchers to conduct comprehensive studies of cause-effect relationships within seizures and develop appropriate treatments. It can also provide a solid basis for further in-silico drug discovery and trial research, which will eventually improve the quality of life for millions of people with epilepsy. Therefore, the article discusses the importance of the field and directions of development that may attract researchers' attention. As the authors state, addressing multiple levels of organization in epilepsy modeling requires collaborative work that would benefit from the availability of common frameworks. This statement summarizes the main idea of the work, as the survey examines the field's current state and needs to be supported by future research. Computational neuroscience will continue to make significant discoveries in the future, and addressing these challenges will be crucial to moving forward in solving epilepsy-related problems.

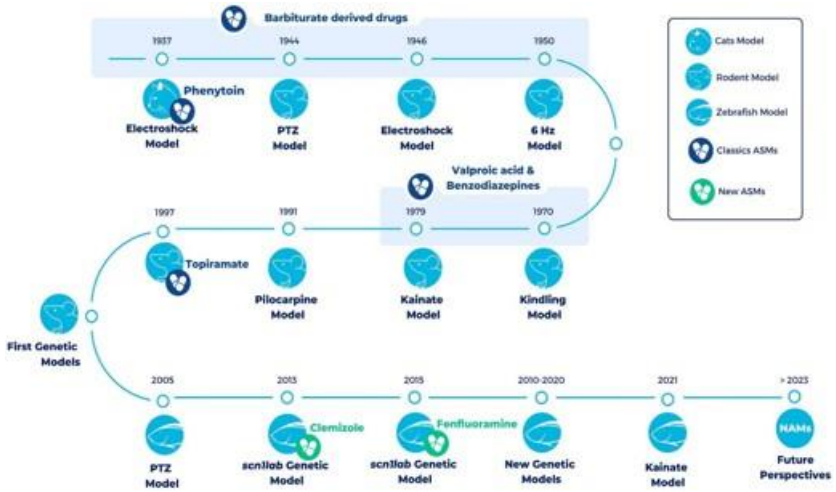

Figure 7 Timeline of the most representative vertebrate animal models in epilepsy over the last century reviewed

Adapted from "Toward the use of novel alternative methods in epilepsy modeling and drug discovery" by Miguel Sanz C et al, 2023, *Frontiers in Neurology, 14*

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AUTHOR CONTRIBUTIONS

Kuldeep Vayadande, Shagupta Mulla*: Conceptualization, Investigation, Methodology, Writing—Original Draft, Writing—Review & Editing.

Gendlal Vaidya: Literature Review, Investigation, Data Curation, Writing—Original Draft.

Premanand Ghadekar: Methodology, Formal Analysis, Investigation, Writing—Review & Editing.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study because it is a review and conceptual research study and does not involve human participants, animals, or the collection of identifiable personal data.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request. As this is a review and conceptual study, the analysis is primarily based on information available in the cited published literature and publicly accessible sources.

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