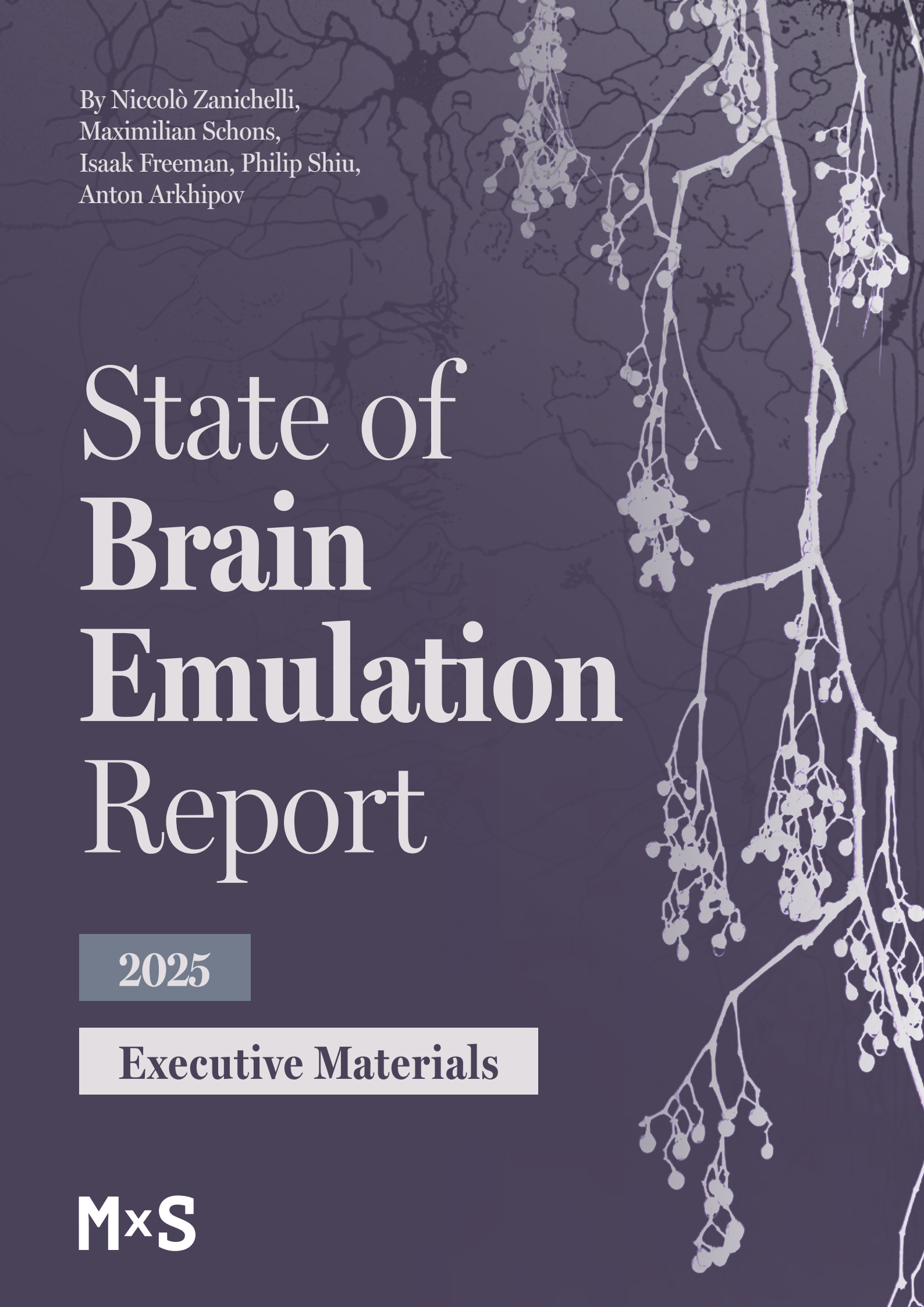
By Niccolò Zanichelli,
Maximilian Schons,
Isaak Freeman, Philip Shiu,
Anton Arkhipov

State of **Brain Emulation** Report

2025

Executive Materials



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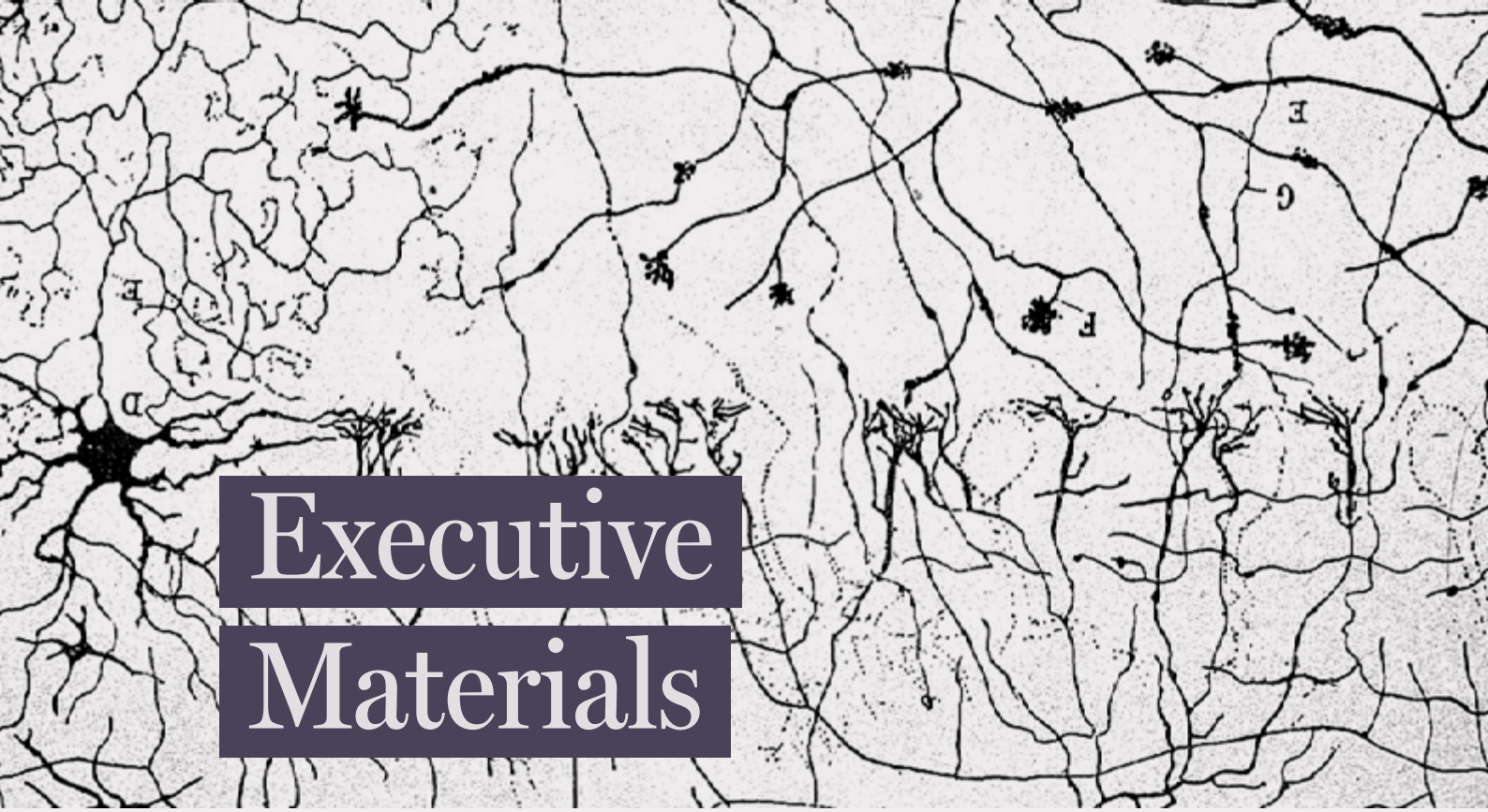


Executive Materials

Executive Summary

Accurate brain emulations would occupy a unique position in science: combining the experimental control of computational models with the biological fidelity needed to study how neural activity gives rise to cognition, disease, and perhaps consciousness. A brain emulation is a computational model that aims to match a brain's biological components and internal, causal dynamics at a chosen level of biophysical detail. Building a brain emulation requires three core capabilities: 1) recording brain activity, 2) reconstructing brain wiring, and 3) digitally modelling brains with respective data. In this report, we explain how all three capabilities have advanced substantially over the past two decades, to the point where neuroscientists are collecting enough data to emulate the brains of sub-million neuron organisms, such as zebrafish larvae and fruit flies.

The first core technique required to build brain emulations is **Neural Dynamics**, in which electrodes are used to record how neurons — from a few dozen to several thousands — fire. Functional optical imaging transitioned from nascent technology to large-scale recordings: calcium imaging, where genetically encoded indicators report correlates of neural activity, now captures approximately one million cortical neurons in mice (though without resolving individual spikes), while voltage imaging resolves individual spikes in tens of thousands of neurons in larval zebrafish. Taking neuron count and sampling rate into account, these improvements represent about a two-order-of-magnitude increase in effective data bandwidth of neural recordings in the past two decades.

Causal perturbation methods, like optogenetics, have also improved. It is now feasible to propose systematic reverse-engineering of neuron-level input-output relationships across entire small nervous systems. Yet, neural activity recording today still faces significant trade-offs across spatial coverage, temporal resolution, recording duration, invasiveness, signal quality, and behavior repertoire. Even more challenging is recording of modulatory molecules like hormones and neuropeptides. Defining "whole-brain" as capturing more than 95 percent of neurons across 95 percent of brain volume simultaneously, no experiment to date has delivered that scale with single-neuron, single-spike resolution in *any* organism during *any* behavior. It seems plausible that this barrier will be overcome for sub-million neuron organisms in the upcoming years.

The second core technique, **Connectomics**, is used to reconstruct wiring diagrams for all neurons in a brain. Connectomics models have today moved past *C. elegans* worm brain mappings to produce, more recently, two fully reconstructed adult fruit fly brain connectomes. This is a big achievement because fruit flies have about three orders-of-magnitude more neurons than a *C. elegans* worm. Several additional scans in other organisms, such as larval zebrafish, have also been acquired and are expected to complete processing in the near future. Dataset sizes now increasingly reach petabyte scale, which challenges storage/backup infrastructure not only with costs, but also the ability to share and collaborate.

It is faster to make connectomics maps today than it was just a few years ago, in part because of how the actual images are acquired and "stitched" together. Progress is being enabled by a mix of faster electron microscopy, automated tissue handling pipelines and algorithmic image processing / neuron tracing. Each of these improvements have contributed to push cost per reconstructed neuron from an estimated $16,500 in the original *C. elegans* connectome to roughly $100 in recent larval zebrafish projects. Proofreading, the manual process of fixing errors from computerized neuron tracing, remains the most time- and cost-consuming factor. This holds particularly for mammalian neurons with large size and complex morphologies. Experts are optimistic that machine-learning will eventually overcome this bottleneck and reduce costs further. As of now, all reconstruction efforts are basically limited to contour tracing to reconstruct wiring diagrams, but lack molecular annotations of key proteins, limiting their direct utility for functional interpretation and computational modeling. Many experts are optimistic that, in the future, one might be able to build connectomes much more cheaply by using expansion microscopy, rather than electron microscopy, combined with techniques that enable molecular annotation, including protein barcoding for self-proofreading.

The final capability is **Computational Neuroscience**, or the ability to model brains faithfully. The capacity to simulate neural systems has advanced, enabled by richer datasets, more powerful software and hardware. In *C. elegans*, connectome-constrained and embodied models now reproduce specific behaviors, while in the fruit fly, whole-brain models recapitulate known circuit dynamics. At the other end of the spectrum, feasibility studies on large GPU clusters have demonstrated simulations approaching human-brain scale, albeit with simplified biophysical assumptions.

On the hardware side, the field has shifted from specialized CPU supercomputers toward more accessible GPU accelerators. For mammalian-scale simulations, the primary hardware bottlenecks are now hardware memory capacity and interconnect bandwidth, not raw processing power. On the software side, improvements come from automatically differentiable data-driven model parameter fitting, efficient simulation methods and the development of more rigorous evaluation methods. Still, many biological mechanisms like neuromodulation are still largely omitted. A more fundamental limitation is that models remain severely data-constrained. Experimental data are scarce in general, complementary structural and functional datasets from the same individual are rare, and where they exist, they lack sufficient detail. Moreover, passive recordings alone struggle to uniquely specify model parameters, highlighting the need for causal perturbation data.

Conclusion The past two decades delivered meaningfully improved methods and a new era of scale for data acquisition. Two challenges will shape the next phase of research: first, determining which biological features (from gap junctions to glial cells and neuromodulators) are necessary to produce faithful brain emulation models. Empirically answering such questions calls for more comprehensive evaluation criteria to include neural activity prediction, embodied behaviors and responses to controlled perturbations.

Second, there is a widening gap between our ability to reconstruct ever-larger connectomes and our much more limited capacity to record neural activity across them. This discrepancy necessitates that the neuroscience community develops better methods to infer functional properties of neurons and synapses primarily from structural and molecular data. For both challenges, sub-million neuron organisms — where whole-brain recording is already feasible — present a compelling target. Here, comprehensive functional, structural, and molecular datasets are attainable at scale, making it possible to empirically determine which biological details are necessary for a faithful emulation. Furthermore, the cost-efficient collection of aligned structural and neural activity datasets from multiple individuals provides the essential ground truth for developing and rigorously evaluating methods to predict functional properties from structure alone. The evidence this generates, defining what is needed for emulation and validating methods that infer function from structure, will be critical to guide and justify the large-scale investments required for mammalian brain projects.

In short, faithful emulation of small brains is the necessary first step toward emulating larger ones. To make that happen mammalian brain projects will also require parallel progress in cost-effective connectomics. The deeply integrated, end-to-end nature of this research calls for integrated organizational models to complement the vital contributions of existing labs at universities and research campuses.

Technical Overview

This Technical Overview gives a compact, data focused map of the rest of the report. While the Executive Summary presents the main conclusions at a high level, this section summarizes, for each major technical chapter, the key quantitative facts, scaling relationships, and bottlenecks that define the current state of brain emulation. Readers who want a single, technically informed snapshot of where the field stands, before diving into the detailed chapters, should be able to find it here.

Organism Scale Overview

The magnitude of the emulation challenge scales non-linearly with organism complexity. The following table summarizes the physical dimensions and component counts for the five primary model organisms discussed in this report.

TABLE 1 **Physical dimensions and component counts for the five model organisms**

Organism	Developmental Stage	Approx. Brain Volume	Neuron Count	Synapse Count
C. elegans	Adult	0.002 mm^3	~300	~5,600 (chemical) ~600 (gap junctions)
Larval Zebrafish	~5-7 days post fertilization (dpf)	0.08 mm^3	~1 x 10^5	(Not yet fully quantified)
Drosophila	Adult	0.04 mm^3	~1.4 x 10^5	~5 x 10^7
Mouse	Adult	420 - 460 mm^3	~7 x 10^7	(not fully quantified; for scanned cubic millimeters ~5 x 10^8 per mm^3)
Human	Adult	1,000,000 - 1,500,000 mm^3	~8.6 x 10^{10}	(not quantified)

Neural dynamics:
Recording brain activity

Despite impressive progress in neuron recording capabilities, neuroscience has not yet achieved whole-brain recording (≥ 95% of neurons and brain volume) at single-neuron resolution in any organism. The closest achievements include larval zebrafish with approximately 80% brain coverage and C. elegans with roughly 50% of nervous system neurons recorded at single-cell resolution. Even these figures, however, come with substantial limitations: temporal resolution is typically well below neuronal firing rates (often 1-30 Hz for calcium imaging), recording durations remain short (minutes to hours), and the need for head-fixation severely constrains behavior repertoires. In larger organisms like mice, recordings focus on cortical regions or specific brain areas rather than whole-brain coverage, while human recordings are either non-invasive and thus not single-neuron resolution or restricted to clinical settings and sample from extremely localized volumes of hundreds of thousands of neurons.

FIGURE 1, an aggregation of all studies available for this report, visualizes these: smaller organisms have more data available and are more likely to have significant data without fixation. Also, recording duration in all organisms is at least 2-3 orders of magnitude away from the entire life span. Finally, recording modalities with strong performance in one dimension will likely have poor performance in another.

Current single-cell resolution neural activity recording methods fall into two broad categories, each with distinct trade-offs. Optical fluorescence microscopy approaches, primarily calcium imaging, excel at capturing activity from large populations of neurons simultaneously (up to approximately one million in mouse cortex or tens of thousands in zebrafish and *Drosophila*) but suffer from slow temporal resolution that misses individual spikes in many neuron types. Electrophysiological methods like Neuropixels offer millisecond-precision spike detection but sample sparsely, typically recording from hundreds to a few thousand neurons along electrode trajectories. Voltage imaging with genetically encoded voltage indicators is emerging as a potential bridge between these extremes, with recent demonstrations approaching tens of thousands of neurons at spike-relevant speeds in larval zebrafish, though this technology remains in active development and recording durations are limited.

A fundamental challenge is that these methods primarily track electrical activity. Monitoring the broader chemical context (neurotransmitters, neuropeptides, and other signaling molecules that critically shape circuit function) remains difficult. While genetically encoded neurotransmitter indicators have been developed for select molecules, they cover only a small fraction of the hundreds of neuromodulatory signals known to exist in these brains.

Obtaining comprehensive, single-neuron resolution recordings of whole mammalian brains faces severe physical constraints, and as a result will likely remain extremely challenging for the foreseeable future (see FIGURE 2). Single-cell recording capabilities are currently at about 1 million cells at 2 Hz (calcium

imaging), equivalent to $2x10^6$ bits per second. In the 1980s about 5 cells could be sampled at 200 Hz (electrophysiology), equivalent to 10^3 bits per second. For context, recording a mouse brain at single-neuron resolution recordings at 200 Hz (sufficient to resolve individual spikes) would generate about 1.4×10^9 bits/s, while doing the same for a whole human brain would generate about 1.7×10^{15} bits/s.

The path forward requires progress on several fronts. First, maturing voltage imaging to achieve spike-resolution whole-brain recordings in smaller organisms remains a primary goal, with extending recording durations being a particular challenge. Second, expanding behavioral freedom requires lighter microscopes, less invasive surgical preparations, and creative experimental setups that permit more natural movement patterns. Third, greater emphasis on causal rather than merely correlational data is needed to reduce the otherwise prohibitive data requirements. This means integrating large-scale recording with systematic perturbations experiments of neural activity, most likely using optogenetic approaches. Such experiments then measure the effectome, a quantitative map of causal influence between neurons and would ground computational models in measured functional interactions rather than inferred ones. Finally, developing molecular sensors for the broader range of neurotransmitters and neuropeptides present in these organisms will add the chemical dimension necessary to understand how circuit dynamics emerge.

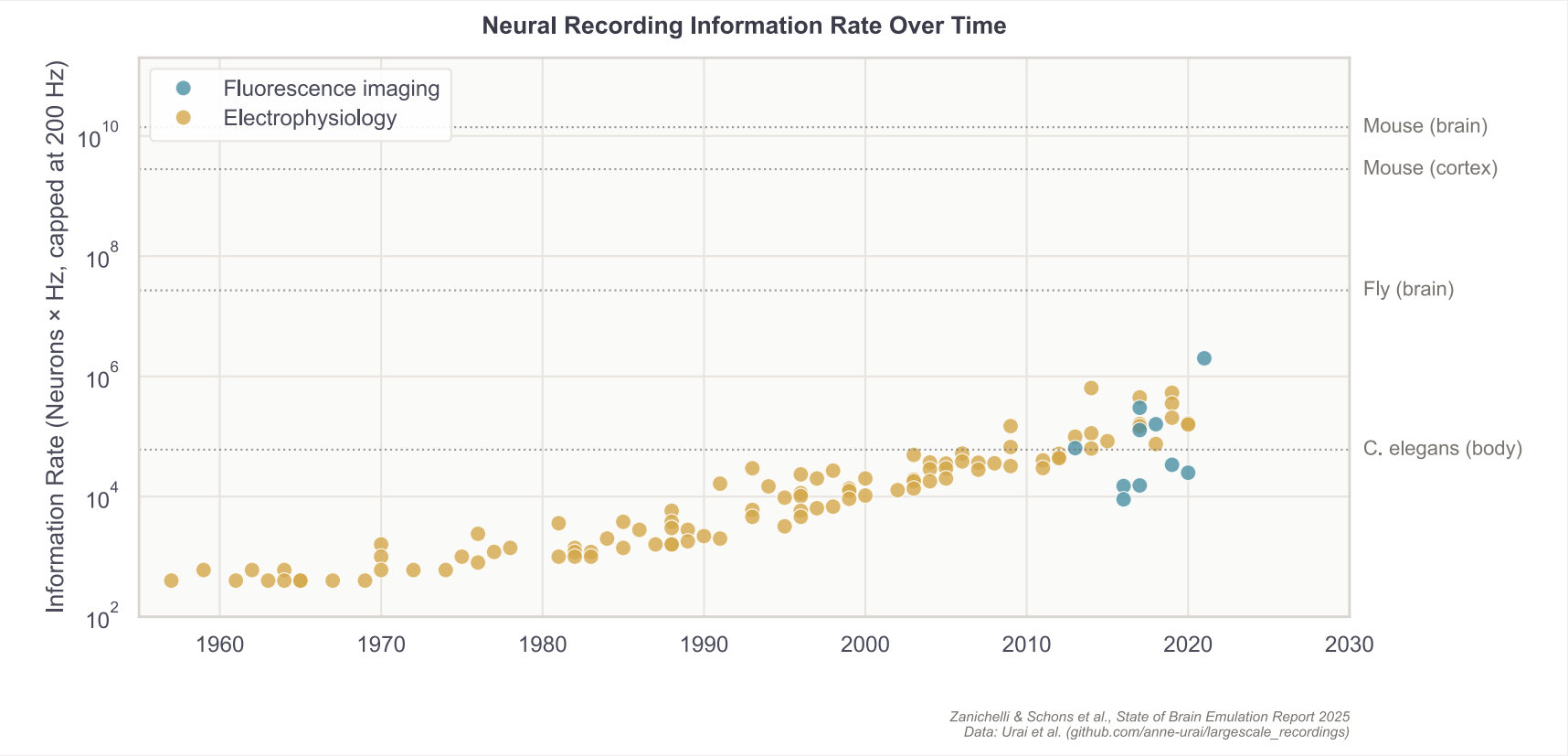
> “Despite impressive progress in neuron recording capabilities, neuroscience has not yet achieved whole-brain recording at single-neuron resolution in any organism.”

FIGURE 1 **Heatmap plot of significant brain recording publications across different organisms.**

The figure plots the relative distance from the respective organism's maximum value in a set of recording dimensions for a given publication. All papers referenced in the report and other noteworthy papers are listed. (data)

FIGURE 2 **Estimated instantaneous information rate of neural recordings over time.**

Adaptation of Urai et al., 2022. This metric is defined as the number of simultaneously recorded neurons multiplied by their effective temporal resolution, capped at 200 Hz. This capped rate serves as a proxy for the instantaneous data bandwidth and provides a more consistent basis for comparison across different recording modalities. The 200 Hz cap balances the high-frequency capabilities of electrophysiology with the typical temporal dynamics of calcium imaging methods. Data points distinguish between Imaging (e.g., calcium imaging, light-sheet; blue circles) and Ephys (extracellular electrophysiology; red triangles), illustrating technological advancements. While this plot focuses on the simultaneous recording capacity, the total information acquired in an experiment also critically depends on the recording duration, a factor that varies widely and could be incorporated into future editions of this report. Horizontal dashed lines indicate theoretical maximum information rates for selected nervous systems (*C. elegans* body, fly brain, mouse cortex, whole mouse brain), calculated by multiplying their respective total neuron counts by the 200 Hz cap. These lines offer benchmarks for current experimental capabilities against the scale of these neural systems. (data)



Connectomics:
Reconstructing brain wiring

Complete connectomes at synaptic resolution currently exist only for small organisms. C. elegans has multiple whole-nervous-system reconstructions from individual specimens, with approximately ten datasets available. Adult Drosophila has fully proofread connectomes for both the male central nervous system and the female brain, with another female CNS reconstruction in progress. Larval zebrafish has had its whole brain imaged at synaptic resolution multiple times, with reconstruction and proofreading efforts ongoing. For larger organisms, progress remains at the proof-of-concept stage. In mice, the largest densely reconstructed volume is a cubic millimeter of visual cortex, containing approximately 120,000 neurons and 523 million automatically detected synapses, with ongoing proofreading of a small fraction of neurons. Current efforts funded by the NIH target 10 mm^3 volumes, representing roughly 2-3% of the mouse brain. In humans, the largest synaptic-resolution volume is approximately 1 mm^3 of the temporal cortex (0.00007% of the whole brain), with only 104 neurons fully proofread from approximately 16,000 identified cells. TABLE 2 lists the different connectomes for the organisms discussed in our report.

Electron microscopy provides the imaging foundation for nearly all existing synaptic-resolution connectomes. Over past decades technical advances include multi-beam systems that parallelize acquisition, achieving higher throughput for large volumes. However, EM workflows remain slow for mammalian-scale projects and provide minimal molecular information. Expansion microscopy is advancing rapidly on two fronts: high-expansion protocols have demonstrated effective lateral resolutions of approximately 20 nm, sufficient for dense reconstruction in mouse cortex while enabling protein-specific labels. X-ray microscopy offers another path to rapid, large-volume imaging. Synchrotron-based efforts have demonstrated cellular-resolution imaging of whole brains, and separate work has achieved the sub-40 nm resolution capable of resolving individual synapses under specialized laboratory conditions.

FIGURE 3 shows how the average costs per quality-controlled reconstructed neuron fell from ~$16,500 for C. elegans in the 1980s, to ~$214 for the Drosophila and ~$100 for zebrafish larvae as of 2025 . Improved neuron tracing and new imaging methods like expansion microscopy could continue this trend. Larger animals, however, often have larger and more complex neurons. For rodent neurons the average price is often still about $1,000 per neuron. To reconstruct a connectome at 1 billion dollars, prices need to fall to $10/neuron for the mouse and $0.01/neuron for humans. As part of this report we created a detailed model for connectomics cost-estimates interested users can consult (see data repository). Given the numerous variables involved—resolution requirements, imaging modalities, storage setups, and methodological trade-offs—we plottet data only from past or ongoing projects for FIGURE 3.

Irrespective of imaging modality, synaptic-resolution connectomics produces vast datasets that pose significant storage and analysis challenges. A mouse brain at 10 nm isotropic resolution would require without further lossless or lossy compression approximately 1 exabyte of storage, while a human brain would require 1-1.4 zettabytes. These volumes necessitate specialized infrastructure and advanced, AI-based compression algorithms, with recent methods demonstrating storage reductions of up to 128x. Automated reconstruction has been a second major bottleneck. The latest AI-driven methods have improved key error rates by an order of magnitude or more compared to previous approaches, dramatically reducing the need for manual correction. This brings proofreading costs down to a level comparable with image acquisition, making exhaustive reconstruction of cubic-millimeter-scale mammalian brain volumes economically feasible. Expansion microscopy has also demonstrated proof-of-concept molecular barcoding techniques that enable automated matching of neuron fragments across spatial gaps, offering an alternative route to reducing manual proofreading requirements.

The path forward for connectomics requires advances on multiple fronts. Continued improvement in AI for automated segmentation, proofreading, intelligent imaging strategies, and data compression is essential for scaling to mammalian brains. Expansion microscopy holds significant promise for scalable, molecularly-annotated connectomics by integrating its demonstrated capabilities: high-throughput imaging, dense reconstruction with high expansion factors, and molecular barcoding for automated proofreading. These technical pursuits are particularly important because ex vivo structural mapping benefits from a key advantage over in vivo functional imaging: it is not constrained by the same physical limitations. Tissue can be chemically fixed, sectioned, expanded, and imaged over arbitrarily long timescales without the constraints imposed by maintaining a living organism. This makes mammalian-scale connectomics technically challenging but not fundamentally limited in the way that whole-brain functional imaging appears to be.

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TABLE 2 **Synaptic resolution Electron microscopy connectome reconstructions**

Complete overview of connectome reconstructions in the four model organisms. Additionally, multiple expansion and x-ray experiments are ongoing. Blue: scanned. Red: Scanned and traced.

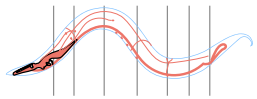
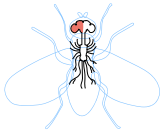
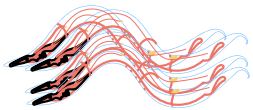
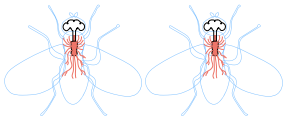
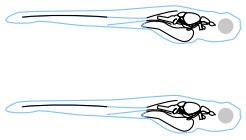
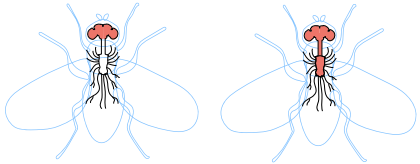
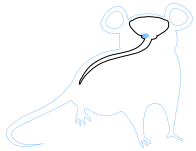
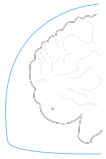
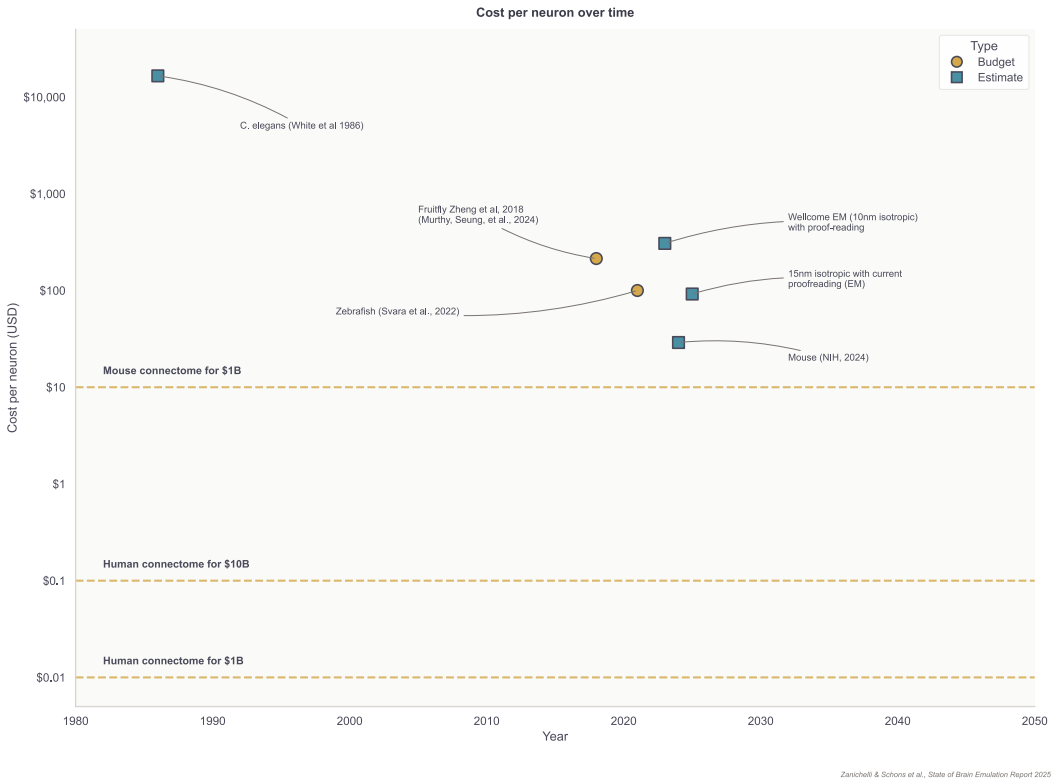
	"Original" composite *C. elegans* connectome. (EM). Synaptic resolution. (White et al, 1986)		*Drosophila*: One half-brain female individual. Synaptic resolution via EM (Scheffer et al 2020)
	*C. elegans*: 10 complete connectomes, one composite, including both sexes and five different developmental stages (EM). (Varshney et al., 2011, Cook et al., 2019, Brittin et al., 2020, Witvliet et al., 2021)		*Drosophila*: Ventral nerve cord in female (Azevedo et al., 2024) and male individuals (Takemura et al., 2024)
	Zebrafish: 10% of the spinal cord in an individual before sex differentiation. Brainstem (Vishwanathan et al., 2024) and spinal cord have also been reconstructed (Svara et al., 2018)		*Drosophila*: One whole brain and one half of the central brain – in different female individuals (Zheng et al, 2018, Dorkenwald et al., 2024 and Schlegel et al., 2024). The entire male brain and nerve cord (Berg et al., 2025) Additionally, there is a complete connectome of the Drosophila larvae (Winding et al, 2023)
	Zebrafish: One whole brain in an individual before sex differentiation. (Svara et al., 2022)		Mouse: 1mm3 male mouse brain cortex (0.2% total brain volume). Synaptic resolution. (Microns, 2025)
	Additional efforts are ongoing (Lueckmann et al., 2025). Note: during the editing process two additional projects were published:		1 mm^3 female human brain cortex (not proofread, 0.000001% total brain volume). (Shapson-Coe et al, 2024)

FIGURE 3 **Cost per quality-controlled reconstructed Neuron (inflation adjusted to 2025).**

This plot uses best estimates on the end-to-end reconstruction costs (sample preparation & slicing, scanning, reconstruction & proofreading) for the three major connectomics initiatives of the past 40 years, *C. elegans*, Fruitfly, Zebrafish, and the estimates from experts for current costs. (see data repository)



Computational Neuroscience: Modelling brains faithfully

Meaningful progress toward whole-brain emulation is currently confined to small organisms where comprehensive datasets are becoming available. In C. elegans, multi-scale, closed-loop simulations now reproduce basic behaviors by integrating neural dynamics, body mechanics, and environmental interaction. For Drosophila, the adult connectome has enabled models spanning the entire brain, successfully predicting neural responses and circuit functions for behaviors like feeding and grooming. Larval zebrafish modeling, while often circuit-specific, is driven by readily available whole-brain functional data, with proof-of-concept connectome-constrained simulations demonstrating accurate prediction of oculomotor integration dynamics, and embodied models replicating optomotor responses. With a full connectome for this organism expected soon, the field is poised for more integrated structural-functional models. In larger organisms like mice and humans, however, comprehensive emulation remains at the proof-of-concept stage. These efforts demonstrate building biophysically detailed cortical circuits by algorithmically inferring connectivity, or running human-scale simulations on supercomputers as feasibility tests.

As part of this report, simulation attempts for different organisms were rated on the following 0-3 point scale across 10 dimensions. No simulation attempt scores highly across all dimensions, and some cannot be found in any simulation attempt at all. FIGURE 4 shows a respective heatmap plot across the dimensions we introduce in detail in the Definition chapter.

Two fundamental challenges constrain progress at larger scales. First and foremost is data scarcity: fitting the vast number of parameters required for accurate neural models (a single biophysically detailed neuron can require tens of thousands of parameters) requires dense, high-quality functional and structural datasets. While large neural data repositories exist, lack of standardization and variable data quality often limit their usability for parameter fitting. Moreover, in larger organisms, comprehensive whole-brain recordings remain infeasible, further compounding this challenge.

Second, computational demands are substantial. Even with simplified neuron and synapse models, real-time mammalian-scale simulation strains available resources. Assuming approximately 10 KB memory and 1 MFLOP/s per neuron with synapses, a mouse brain simulation requires 1-2 TB memory and 5-10 PFLOP/s; a human brain simulation requires 1-3 PB memory and approximately 10 EFLOP/s. For comparison, an H100 GPU (80 GB, 67 TFLOP/s) can store roughly 8 million neurons before hitting memory limits; devices in the 1980s (~0.5 GB, 2 GFLOP/s) could handle only about 2,000 neurons (see FIGURE 5). While hardware will continue to improve, it cannot compensate for insufficient training data; data constraints set a hard upper bound on model quality.

The path forward involves three coordinated strategic objectives. First, achieve high-fidelity emulations in small, tractable organisms by fully integrating complete connectomes with rich, whole-brain functional and causal perturbation datasets. Activity prediction benchmarks in C. elegans and larval zebrafish already demonstrate that model performance improves with increased data availability, suggesting a productive feedback loop, as benchmark results can guide experimentalists on what types of data (passive recordings, targeted perturbations, molecular annotations) and in what quantities would most improve computational models. Second, within these same systems, develop and validate generative models that can compensate for the lack of whole-brain activity data, for instance by inferring functional parameters from anatomical data alone, mapping molecularly-annotated structure to function. For mammalian nervous systems, such structure-to-function mappings will likely be indispensable. Third, in parallel, optimize simulation software (leveraging modern accelerators and event-driven paradigms) and develop specialized hardware to reduce computational and memory requirements for mammalian-scale emulations.

FIGURE 4 **Heatmap plot of computational brain models across different organisms.**

The figure plots the score of a brain model across various dimensions. All papers referenced in the report and other noteworthy papers are listed. (data)

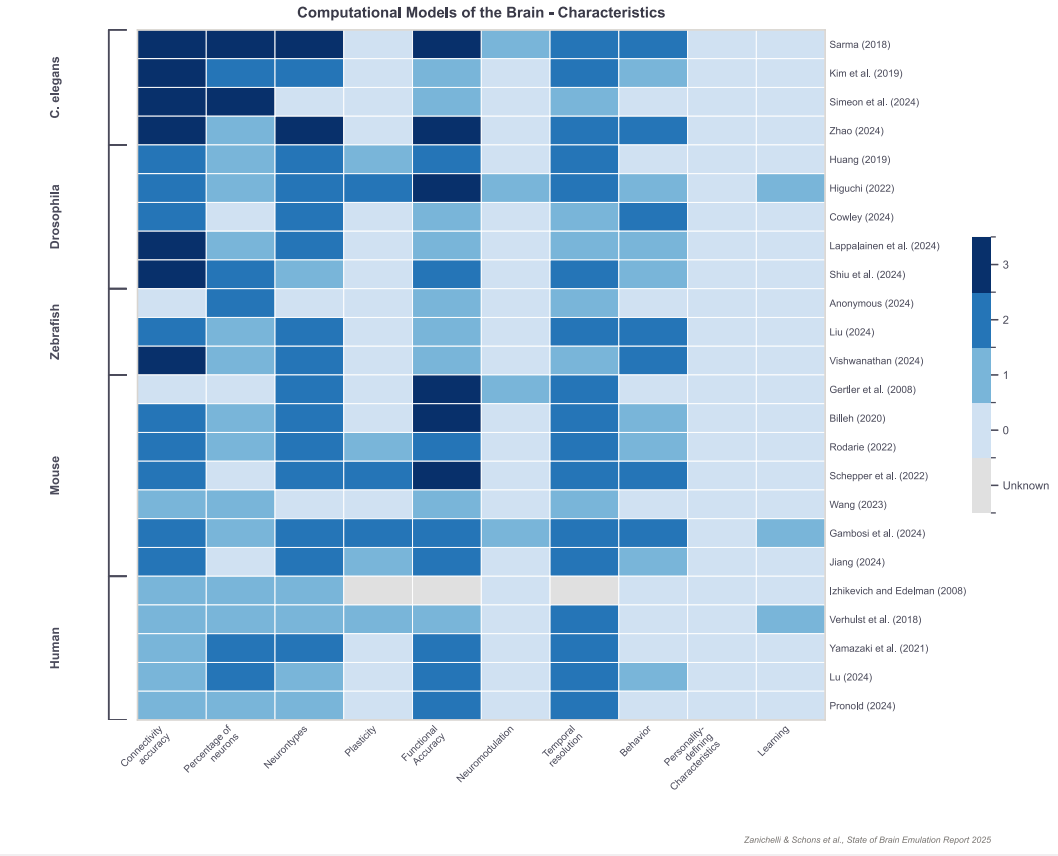
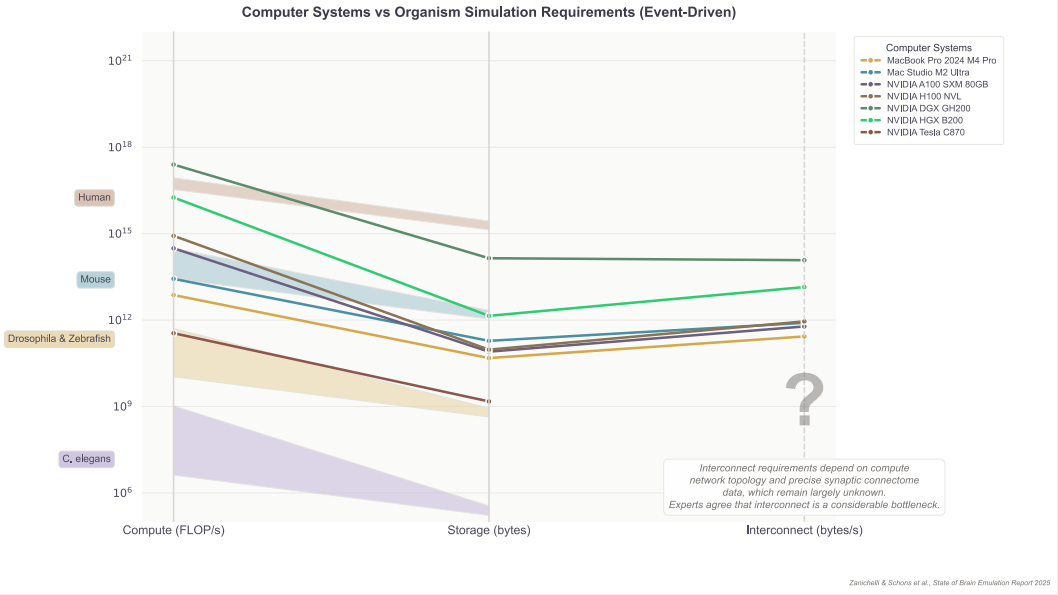


FIGURE 5 **Computational demands across organisms**

This figure illustrates the computational demands across compute and storage for various organisms and compares current state-of-the-art hardware against it. It uses point neurons and 5-compartment neurons estimates. For mice, a neuron is between 0.3 to 4 million FLOP/s and 15-30KB. This totals around 0.1 PetaFLOP/s and 1-2 TB of memory. Single GPUs like the Blackwell Ultra can calculate this fast, but as of today, they max out at 288 GB memory. Interconnect speeds depend on many setup variables and accurate connectomes, which is why the figure does not include estimates.(data)



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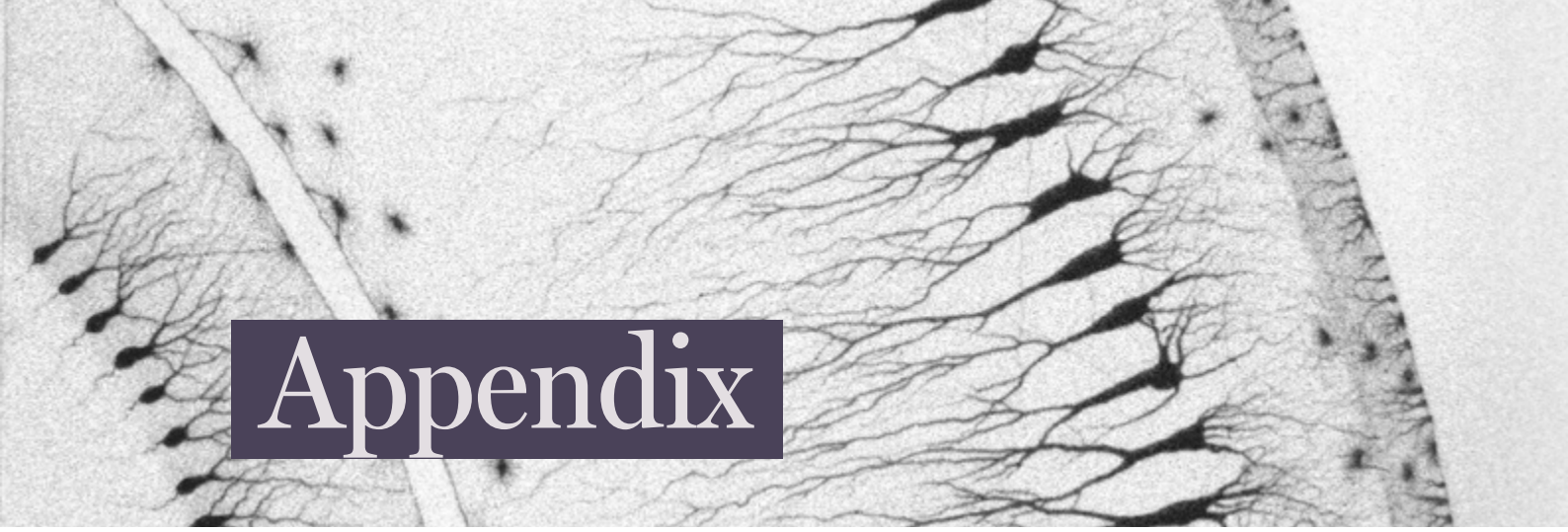

Appendix

Data repository

Data: State of Brain Emulation Report 2025 Data Repository

Author Contributions

Niccolò Zanichelli and Maximilian Schons are shared first authors and contributed equally to this work.

Maximilian Schons and Niccolò Zanichelli conducted the primary research, literature review, and drafted the initial manuscript. Maximilian Schons led the overall project coordination, expert consultation process, and finalization of the report. Isaak Freeman contributed to initial research and drafting. Philip Shiu and Anton Arkhipov provided scientific guidance and oversight throughout the project. All authors contributed to writing, editing, and reviewing the manuscript.

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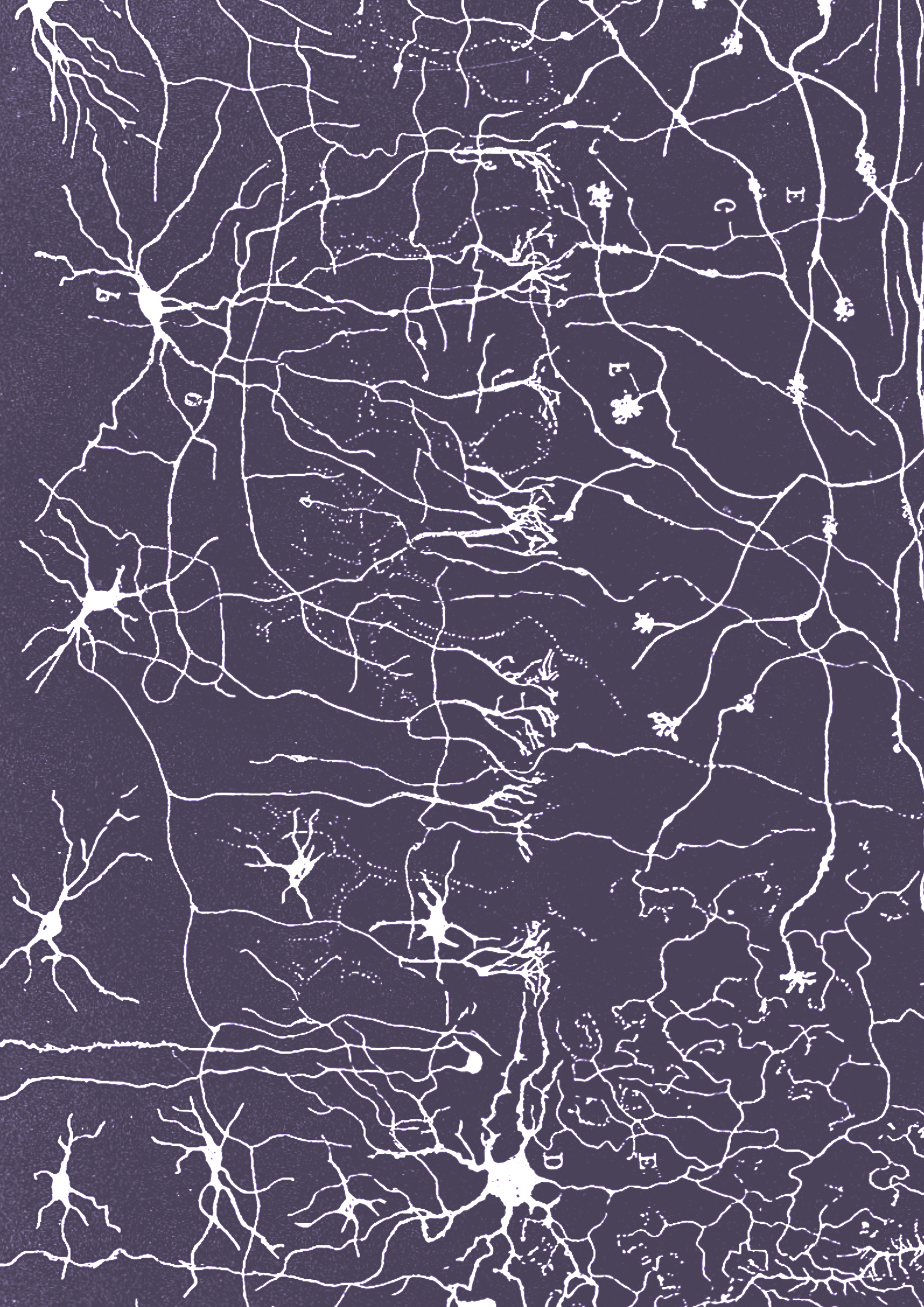
Statement on AI use: We used large language models (ChatGPT GPT-4/5, Google Gemini 2.5 Pro, and Anthropic Claude 3.7/4/4.5) to assist with literature search and summarization, to generate sections of the initial draft text, and for data extraction from papers. All AI-generated content was thoroughly reviewed, verified, and edited by the authors, who take full responsibility for the final content.

Competing Interests: Philip Shiu is an equity holder in Eon Systems PBC. Maximilian Schons is the owner of MxSchons GmbH, which coordinated this project and administered funds for the authors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