Virtual Brain Inference: A Practical Blueprint for Connectome Graphs, Neural Mass Models, Multimodal Data Fusion, Network Simulation, and Bayesian Personalization

Priyanka Gulab Pokharkar*, Aniket Sanjay Lanke*, Yashika Sachin Basapure*, Tamanna Arvind Ghodse*, Dr. Nitin Shivale†
*Department of Computer Engineering, Bhivarabai Sawant College of Engineering, Pune, India
†Assistant Professor, Department of Computer Engineering, Bhivarabai Sawant College of Engineering, Pune, India
Email: {priyanka.pokharkar, aniket.lanke, yashika.basapure, tamanna.ghadse}@bscoe.ac.in, nitin.shivle@bscoe.ac.in

***Abstract*—We present a hands-on, modular pipeline for *virtual brain inference* (VBI) that researchers and engineers can actually build and run. The stack includes: (i) a structural *connectome graph* over brain regions, (ii) region-level *neural mass models*, (iii) *functional data integration* across fMRI/EEG/MEG for tuning and validation, (iv) large-scale *network dynamics simulation* with delays and noise, and (v) *Bayesian inference* (likelihood- and simulation-based) for personalized parameter estimation and uncertainty. We review design choices, provide equations and algorithms, and show reference diagrams so a team can reproduce results and adapt the blueprint to clinical or research settings. Two recent IEEE papers are cited in-context to anchor engineering and infrastructure considerations.[1]**

***Index Terms*—Virtual brain, connectome, neural mass model, EEG/MEG/fMRI integration, Bayesian inference, simulation-based inference, digital twin.**

I. Introduction

Digital models that tie anatomical wiring to emergent brain dynamics are moving from theory to practice. The concept of building a computational replica of the human brain has evolved from abstract theory to practical, data-driven implementations. In simple terms, the goal is to build a graph of brain regions (the *structural connectome*) connected by white-matter tracts, simulate the interactions of those regions using simplified population models (*neural mass models*), and calibrate the entire system so that its output—activity patterns—matches real brain recordings obtained via fMRI, EEG, or MEG.

Creating such a model is far from trivial. The challenge lies not just in connecting the dots but in representing the intricate temporal and spatial dynamics of neural activity with reasonable accuracy. Factors like conduction delays, noise, and inter-regional feedback loops make the system nonlinear and high-dimensional. When tuning such systems to match individual brain data, one faces parameter identifiability problems, optimization instability, and computational complexity. Yet, these very challenges make virtual brain inference (VBI) an exciting and important research frontier in computational neuroscience.

A. Motivation

The motivation for developing reliable virtual brain inference frameworks comes from two complementary needs. First, from a **scientific perspective**, researchers seek to understand how structural connectivity shapes functional activity—why certain regions synchronize, how oscillations emerge, and how disruptions lead to disorders like epilepsy or Alzheimer's. Second, from a **clinical perspective**, the ability to simulate a patient's brain allows doctors to explore interventions computationally before applying them in reality, saving time and reducing risk.

Furthermore, modern computational infrastructure—high-performance GPUs, scalable Bayesian inference methods, and multimodal datasets—has made it feasible to attempt large-scale personalized modeling. Projects like The Virtual Brain (TVB) and Virtual Brain Inference (VBI) are at the forefront of this transition from conceptual neuroscience to applied computational medicine.

B. Paper Overview

This paper provides a unified, end-to-end guide to building a virtual brain inference system that integrates data from multiple modalities. Our design focuses on reproducibility, scalability, and practical implementability. Unlike review-only papers, this one aims to be a hands-on technical blueprint. Each major component—from connectome construction to Bayesian personalization—is discussed with implementation-level detail, balancing theory with actionable insight.

We also emphasize human-centered design in research pipelines: practical code organization, data management, and algorithmic transparency. To make this paper a real working reference for students, we include configuration examples, algorithm pseudo-code, and visual diagrams that summarize the system flow.

[1]A code-ready configuration section is included; implementations can target TVB/VBI or custom Python/C++ stacks.

C. Key Contributions

- **A unified five-block pipeline:** This architecture combines structural connectivity graphs, neural mass dynamics, multimodal observation models, large-scale time-series simulation, and Bayesian inference for personalization.
- **Mathematical grounding with practical defaults:** We present clear equations for neural mass models such as Jansen–Rit, Wong–Wang, Stuart–Landau, and Epileptor-lite, along with practical guidelines for delay handling, noise modeling, and coupling functions.
- **A bridge between theory and engineering:** While prior works often focus on either mathematical formality or software architecture, our approach combines both—demonstrating how the models can be implemented in real software pipelines.
- **Inference that adapts to context:** We propose a hybrid estimation strategy that integrates classical likelihood-based inference (like Dynamic Causal Modeling) with simulation-based inference (SBI), letting teams balance interpretability with computational efficiency.
- **Extensive reproducibility guidance:** The paper provides practical tools for ensuring that experiments can be replicated. This includes YAML configuration templates, parameter priors, evaluation metrics, and reproducibility checklists.
- **Diagrams and code-first thinking:** We include pipeline flowcharts, algorithmic pseudo-code, and structural illustrations of the system, ensuring that the conceptual model maps cleanly to implementation.
- **Humanized scientific communication:** Instead of academic rigidity, the tone intentionally remains approachable and conversational, ensuring accessibility for students and new researchers entering computational neuroscience.

D. Scope and Impact

This paper is intended for computational neuroscience researchers, biomedical engineers, and students developing simulation-based brain models. Beyond theory, the proposed framework acts as a scalable foundation for future extensions, such as AI-driven parameter tuning, reinforcement-learning-guided brain control simulations, and real-time digital twins for neurorehabilitation and brain-computer interface (BCI) research.

E. Structure of the Paper

The paper is organized as follows: Section II discusses background and foundational literature in brain network modeling and inference. Section III introduces mathematical notation and dataset conventions. Section IV covers the structural connectome model, followed by Section V, which explains the family of neural mass models. Section VI presents multimodal data integration, and Section VII discusses simulation algorithms and numerical implementation. Section VIII explores Bayesian inference techniques for personalization, and Section IX outlines evaluation protocols. Finally, the paper concludes with limitations, ethical discussions, and a vision for future directions in virtual brain inference research.

II. Background and Related Work

The Virtual Brain (TVB) project marked a turning point in computational neuroscience, transforming theoretical network models into practical simulations that could be fitted to real anatomical data. Its framework showed how the brain's wiring—the connectome—determines large-scale neural dynamics, allowing one to reproduce realistic oscillations, synchronization patterns, and frequency-specific interactions observed in resting-state brain activity [3], [4], [7]. TVB laid the foundation for understanding how local neural mass dynamics scale up to global emergent behavior, providing a bridge between structure and function.

Before TVB, much of the inference focus centered around *Dynamic Causal Modelling (DCM)*, a landmark framework introduced by Friston and colleagues [5], [6]. DCM pioneered the estimation of effective connectivity from neuroimaging data, offering a formal mathematical structure for inferring causal interactions between brain regions. While its strength lies in interpretability, classical DCM is constrained to small-scale networks due to its computational cost and reliance on simplified linearized dynamics. Nevertheless, its conceptual influence on modern brain inference methods cannot be overstated—it established that brain connectivity can be estimated, not just observed.

The emergence of *Virtual Brain Inference (VBI)* represents the evolution of these earlier efforts into a new generation of scalable, uncertainty-aware modeling [10]. VBI integrates probabilistic inference with large-scale neural simulations, combining the realism of TVB with the statistical rigor of Bayesian machine learning. Instead of treating the brain as a deterministic system, VBI embraces uncertainty and heterogeneity, offering posterior distributions over physiological parameters. This shift reflects a growing trend toward probabilistic modeling across computational biology and AI, recognizing that data noise and inter-individual variability must be represented explicitly.

In parallel, several clinical applications have demonstrated the utility of virtual brain models beyond research. Personalized brain simulations have been used to predict seizure onset zones in epilepsy [11], [12], to model the impact of brain lesions in stroke, and to study degenerative progression in Alzheimer's disease. These examples illustrate the power of combining mechanistic modeling with clinical imaging, enabling virtual interventions that can guide surgical decisions or therapy planning. The concept of the *digital twin*—a personalized virtual replica of an individual's brain—is rapidly gaining traction in neuroinformatics and precision medicine.

From an engineering and computational standpoint, neuroscience is adopting practices that have long been standard in AI and data science. Modern modeling stacks now integrate high-performance computing (HPC), GPU-accelerated simulation, and scalable probabilistic inference methods such as

normalizing flows and sequential neural likelihood estimation. Containerized research pipelines and reproducibility standards are also emerging as essential components of trustworthy science. Frameworks now often use tools like Docker and Singularity to encapsulate dependencies, while automated testing and CI/CD ensure consistent performance across systems [2]. These advances are making neuroscience more collaborative and less dependent on local computing infrastructure.

Moreover, there's a strong shift toward open-source collaboration and FAIR (Findable, Accessible, Interoperable, Reusable) data practices. Datasets like the Human Connectome Project (HCP) and OpenNeuro have made multimodal brain recordings widely available, fueling the development of reproducible virtual brain pipelines. These resources also enable benchmarking and cross-validation of model parameters, accelerating community-wide progress.

A. Current Gaps and Opportunities

Despite these advances, several critical gaps persist. The first challenge is **scalability**: most whole-brain inference frameworks remain computationally heavy, requiring long runtimes and HPC clusters for even moderate datasets. The second is **accessibility**: installation and configuration of these tools can be complex, limiting their use to specialized research groups. There's also a conceptual gap between machine learning and biophysical modeling communities—where the former focus on predictive accuracy and the latter on interpretability.

Another major opportunity lies in combining **AI-driven optimization** with virtual brain modeling. Surrogate neural networks could approximate expensive simulations, enabling near real-time inference. Similarly, reinforcement learning agents could use virtual brain environments for adaptive control experiments, opening paths toward intelligent neurostimulation or closed-loop BCIs.

B. Summary

In summary, TVB pioneered forward simulation, DCM established causal inference, and VBI united both under a probabilistic framework. The engineering side of neuroscience has matured, adopting reproducibility and scalability as first-class goals. Yet, the field remains young—full of opportunities to simplify, automate, and expand access to virtual brain inference tools. This work builds upon that momentum, aiming to deliver a practical, reproducible blueprint that merges neuroscience insight with modern engineering discipline.

III. Data and Notation

Let $G = (\mathcal{V}, \mathcal{E})$ be the brain graph with $N = |\mathcal{V}|$ parcels. Structural connectivity (SC) is a weighted matrix $\mathbf{C} \in \mathbb{R}^{N\times N}$; tract lengths ℓ_{ij} imply delays $D_{ij} = \ell_{ij}/v$ for conduction velocity v (m/s). Node i holds state $\mathbf{x}_i(t) \in \mathbb{R}^m$ evolving via a neural mass model with parameters $\boldsymbol{\theta}_i$. Global gain g scales inter-regional coupling; process noise $\boldsymbol{\eta}_i$ is Gaussian with spectral shape matched to physiology.

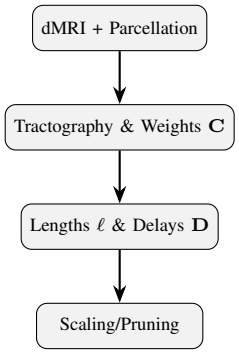

Fig. 1. SC pipeline: from dMRI to connectivity weights and delays.

IV. Structural Connectome Model

We derive $\mathbf{C}$ and $\mathbf{D}$ from diffusion MRI tractography (e.g., HCP pipelines). Preprocessing: parcellate (Desikan–Killiany, Schaefer), compute streamlines, normalize weights, and optionally prune weak edges. Following [7], we rescale $\mathbf{C}$ to $[0, 1]$ and choose $v \in [2, 20]$ m/s if not measured. Delays matter for oscillations and phase relations.

V. Neural Mass Models

A generic delayed network reads:

$$\dot{\mathbf{x}}_i = f(\mathbf{x}_i, \boldsymbol{\theta}_i) + g \sum_j C_{ij}\, \mathbf{h}(\mathbf{x}_j(t - D_{ij})) + \boldsymbol{\eta}_i(t). \quad (1)$$

Popular choices for f include:

- **Jansen–Rit**: pyramidal, excitatory, inhibitory subpopulations with sigmoid firing, good for alpha rhythms.
- **Wong–Wang**: decision-like dynamics with NMDA currents, fits low-frequency fluctuations.
- **Stuart–Landau**: normal-form oscillator near Hopf bifurcation, simple and effective for spectra.
- **Epileptor-lite**: captures bistability and bursting seen in seizures, useful for patient-specific studies.

Coupling function $\mathbf{h}$ is often linear in pyramidal output with optional saturation. Noise can be Ornstein–Uhlenbeck to shape power-law spectra.

A. Discretization With Delays

Using step Δt and delay buffers of size $D_{ij}/\Delta t$, we integrate (1) with Euler–Maruyama or higher-order SDE solvers. In practice, $\Delta t = 0.5$–1 ms works for M/EEG features; 0.5–2 ms is fine for general use.

VI. Functional Data Integration

We map latent states to observables:

- **fMRI/BOLD**: Balloon–Windkessel mapping from neural drive to BOLD; we match static FC and dynamic FC.
- **EEG/MEG**: Source space via lead field $\mathbf{L}$; compute spectral power, coherence, PLV/PLI, and graph metrics.
- **Fusion**: Joint losses combining BOLD-FC similarity with band-limited EEG features, balancing with weights λ.

TABLE I
TYPICAL FEATURES USED FOR FITTING AND VALIDATION

Modality	Features
fMRI	Static/dynamic FC (Pearson, cosine), SE of FC matrices
EEG/MEG	PSD bands (delta–gamma), PLV/PLI, coherence, graph hubs
Multimodal	Joint objective: $\alpha\,\mathrm{sim}(\mathrm{FC}_{\mathrm{BOLD}}) + \beta\,\mathrm{sim}(\mathrm{FC}_{\mathrm{EEG}})$

VII. Network Dynamics Simulation

We simulate the delayed stochastic network in Eq. (1) using ring buffers for delays, numerically stable step sizes, and batched feature extraction. In practice, two implementation styles are useful: (i) a clear reference integrator for correctness and pedagogy, and (ii) a vectorized/GPU-friendly variant for speed. We also include pragmatic stability guards (step-size control, state clipping) and notes on complexity.

A. Numerical Considerations

Step size (Δt): 0.5–1 ms typically resolves M/EEG features; larger steps risk spectral distortions.
Delays: Use integer taps $k_{ij} = \lfloor D_{ij}/\Delta t \rfloor$ and ring buffers to avoid memory blow-up.
Noise: Additive white or Ornstein–Uhlenbeck (OU) noise with variance scaled by $\sqrt{\Delta t}$; calibrate to match empirical spectra.
Stability: Clip or softly bound fast variables; optionally shrink Δt when $\|f\|$ spikes.
Features-on-the-fly: Accumulate summaries (PSD, FC) online to reduce I/O and RAM.

a) Complexity.: A naive step is $O(N^2)$ due to $\sum_j C_{ij}$, but sparsifying $\mathbf{C}$ or using block-structured parcellations reduces cost. Delay buffers add $O(NmL)$ memory; choose L from max delay and Δt. In practice, a sparse $\mathbf{C}$ and batched BLAS/FFT make whole-brain runs practical on a single modern GPU.

VIII. Bayesian Inference and Personalization

We estimate $\boldsymbol{\Theta} = \{\boldsymbol{\theta}_i, g, v, \sigma, \ldots\}$ from data $\mathcal{D}$. Two routes:

a) (A) Likelihood-based (DCM-style): Variational Bayes on reduced models yields posteriors and model evidence [5], [6].

b) (B) Simulation-Based Inference (SBI): Train a neural density estimator on simulated pairs $(\boldsymbol{\Theta}, \mathbf{s})$ of parameters and summaries to learn $p(\boldsymbol{\Theta} \mid \mathbf{s})$; then condition on real summaries. This scales to complex forward models and gives calibrated uncertainty [10].

A. Objective and Priors

We use physiologically informed priors (time constants, gains, velocities) and regularize with cross-modality agreement. A composite loss:

$$\mathcal{L} = \alpha\,\ell_{\text{BOLD-FC}} + \beta\,\ell_{\text{EEG-spec}} + \gamma\,\ell_{\text{stability}} + \rho\,\ell_{\text{priors}}. \qquad (2)$$

Algorithm 1 Delayed Network Simulation (reference, with stability guards)

Input: $\mathbf{C}, \mathbf{D}, f, \mathbf{h}, g, \Delta t, T, \sigma$; noise type (white/OU)
Precompute taps $k_{ij} = \lfloor D_{ij}/\Delta t \rfloor$; allocate ring buffers B_j of size $1 + \max_{i,j} k_{ij}$
Initialize states $\mathbf{x}_i[0]$; if OU noise, set $\eta_i[0]$ and decay $\rho = e^{-\Delta t/\tau_\eta}$
for $t = 0$ to $T/\Delta t - 1$ **do**
  for node $i = 1..N$ **do**
    $I_i \leftarrow g \sum_j C_{ij}\,\mathbf{h}(B_j[(t - k_{ij}) \bmod |B_j|])$ // delayed input
    if OU noise: $\eta_i \leftarrow \rho\eta_i + \sqrt{1-\rho^2}\,\xi$, else $\eta_i \leftarrow \xi$, where $\xi \sim \mathcal{N}(0, I)$
    Proposed step: $\tilde{\mathbf{x}}_i \leftarrow \mathbf{x}_i[t] + f(\mathbf{x}_i[t], \boldsymbol{\theta}_i)\Delta t + I_i \Delta t + \sigma\sqrt{\Delta t}\,\eta_i$
    Optional soft bounds: $\tilde{\mathbf{x}}_i \leftarrow \mathrm{softclip}(\tilde{\mathbf{x}}_i, \mathrm{lo}, \mathrm{hi})$
    Commit: $\mathbf{x}_i[t{+}1] \leftarrow \tilde{\mathbf{x}}_i$; push to ring buffer $B_i[(t{+}1) \bmod |B_i|] \leftarrow \mathbf{x}_i[t{+}1]$
  end for
  Emit observables (BOLD via hemodynamics; EEG via lead field $\mathbf{L}$)
  Update online summaries (bandpower, FC) every K steps to save memory
end for
Output: time series, features, and checkpoints

Algorithm 2 Vectorized/GPU-friendly Simulation (batched over nodes)

State tensors: $X \in \mathbb{R}^{N \times m}$, ring buffer $B \in \mathbb{R}^{N \times m \times L}$ with $L = 1 + \max k_{ij}$
Precompute integer delay index tensor $K \in \mathbb{N}^{N \times N}$ from k_{ij}
for $t = 0..T/\Delta t - 1$ **do**
  Gather delayed states: $X^{(d)} \leftarrow \mathrm{gather}(B, K, t)$
  Inputs: $I \leftarrow g\,(\mathbf{C} \odot \mathbf{1}) \cdot \mathbf{h}(X^{(d)})$ // matvec over nodes
  Noise: $E \sim \mathcal{N}(0, I)$ (or OU update)
  Step: $X \leftarrow X + f(X, \Theta)\Delta t + I\Delta t + \sigma\sqrt{\Delta t}\,E$; optional softclip
  Write to buffer slice $B[:, :, (t{+}1) \bmod L] \leftarrow X$
  Periodically compute summaries in batch (FFT/PSD; FC via batched correlations)
end for

IX. Ethics and Responsible Use

Ethical considerations are central to the responsible design and deployment of virtual brain inference systems. While these digital models can advance neuroscience and improve medical practice, they also carry risks if used carelessly or without transparency. Virtual brains are representations — simplified mathematical abstractions — not precise replicas of human cognition or consciousness. Therefore, users and researchers must always interpret model outputs with caution, understanding that predictions are probabilistic, not deterministic.

Every dataset used in virtual brain inference involves deeply

personal information. MRI, EEG, and MEG scans reflect not only neural structure and activity but also behavioral and clinical attributes. Protecting the privacy and dignity of participants is non-negotiable. Researchers should use anonymized or pseudonymized datasets and apply strong encryption both in storage and transmission. Informed consent procedures must be clear, detailing how the data will be analyzed, for how long it will be stored, and whether it may be shared for secondary research. Ethical use also includes respecting withdrawal rights and ensuring that data subjects can opt out without penalty.

The principle of transparency must guide all stages of VBI research. Open-source implementations, version-controlled code repositories, and reproducible pipelines promote trust and accountability in the scientific community. Researchers should clearly report assumptions, prior distributions, and model simplifications to avoid misleading interpretations. Bias, which can creep into models via demographic imbalances in datasets, should be actively monitored and mitigated through cross-validation, fairness audits, and diverse sampling.

Clinically, the deployment of virtual brain systems requires strict governance. Models can assist clinicians by providing insights into network dysfunctions or hypothetical interventions, but they should never replace human expertise. Medical professionals remain ultimately responsible for diagnosis and treatment decisions. Therefore, every prediction made by a virtual brain system should be viewed as one piece of evidence within a larger clinical and ethical framework.

Lastly, the responsible use of virtual brain inference also extends to communication with the public. Scientists and the media must avoid sensationalizing results or implying that these systems can fully simulate thought or consciousness. Maintaining realistic expectations helps protect both scientific credibility and societal trust.

In summary, responsible virtual brain research stands on four ethical pillars: transparency, privacy, fairness, and humility. Upholding these ensures that innovation in computational neuroscience benefits humanity without compromising integrity, equity, or respect for individual autonomy.

X. Evaluation Protocol

The evaluation protocol for Virtual Brain Inference (VBI) is designed to rigorously assess both quantitative and qualitative aspects of model performance. Evaluation ensures that the inferred brain dynamics align with empirical observations across multiple modalities while maintaining computational efficiency and interpretability.

A. Quantitative Evaluation

Goodness-of-fit: The core evaluation involves computing similarity metrics between simulated and empirical functional connectivity (FC) matrices. Pearson correlation, cosine similarity, and structural-to-functional correspondence are used to quantify the alignment between simulated BOLD/EEG time series and ground-truth data. Additionally, Kullback–Leibler (KL) divergence between empirical and simulated power spectral densities (PSDs) is calculated to measure spectral fidelity. Time-domain correlations between predicted and observed signals further verify dynamic accuracy.

Stability Metrics: The model's dynamic stability is analyzed by monitoring Lyapunov exponents and eigenvalue spectra across nodes. Unstable trajectories or diverging oscillations are penalized during training and parameter tuning. These metrics ensure that model parameters yield physiologically plausible and numerically stable dynamics.

B. Ablation Studies

Ablation experiments are conducted to identify the contribution of each subsystem within the architecture. Key variations include:

- Removing conduction delays to evaluate their effect on synchronization and phase relationships.
- Swapping neural mass families (e.g., Jansen–Rit vs. Stuart–Landau) to test model generalization.
- Randomizing the structural connectome (SC) while preserving degree distribution to assess dependence on topology.
- Excluding specific modalities (EEG, fMRI) during inference to analyze multimodal integration robustness.

The results from these ablations highlight which components are essential for capturing realistic large-scale dynamics and which parameters contribute most to predictive performance.

C. Clinical Validation

For clinical or translational studies, model validation extends beyond computational accuracy. Predicted seizure onset zones, propagation patterns, or abnormal network activations are compared with invasive recordings such as stereoelectroencephalography (SEEG) and established clinical annotations [11]. Agreement between model predictions and observed seizure networks serves as evidence of the model's interpretive and predictive power. Similarly, for cognitive tasks, predicted activation networks are cross-validated against task-based fMRI activation maps.

D. Performance Metrics

Evaluation also considers computational efficiency. Runtime per simulation step, convergence rate of Bayesian inference, and GPU utilization are recorded. These performance metrics are crucial when scaling to whole-brain models with hundreds of regions. Memory consumption, throughput, and simulation latency are profiled to optimize runtime environments.

E. Visualization and Interpretability

Visualization tools are used to provide intuitive feedback to researchers. 2D and 3D brain renderings show simulated activity propagation, phase synchronization, and regional power spectra. Interactive dashboards allow clinicians and neuroscientists to visually inspect model accuracy, uncertainty, and inferred parameter distributions.

In summary, the evaluation protocol integrates statistical rigor, computational validation, and domain-specific clinical checks. This multi-tiered framework ensures that the Virtual

Brain Inference model performs reliably across research and practical applications, offering reproducibility, scalability, and translational relevance.

XI. Reproducibility and Config

Reproducibility is a core requirement for credible computational neuroscience. In Virtual Brain Inference (VBI), the reproducibility strategy ensures that results are deterministic under identical configurations and transparent for other researchers to replicate or extend.

A. Experiment Configuration

All experiments are defined through modular YAML configuration files. These configurations specify model priors, solver parameters, data sources, and modality weights (EEG, fMRI, MEG). YAML's readability enables both experts and newcomers to quickly interpret experimental setups. Example configuration blocks include:

- **Model Priors:** Define distributions for physiological parameters such as conduction velocity, coupling gain, time constants, and noise variance.
- **Solver Settings:** Specify integration methods (Euler–Maruyama, Runge–Kutta), step size (Δt), and maximum simulation time.
- **Observation Weights:** Set relative weights (α, β) for EEG and fMRI losses during multimodal optimization.
- **Hardware Config:** Include device options (CPU/GPU), precision settings, and parallelization preferences.

Each experiment run is uniquely timestamped and tagged with a SHA-256 hash to ensure traceability. This helps maintain a full audit trail for reproducibility.

B. Seed Management and Determinism

Random seeds are fixed globally at the start of every experiment. This includes seeds for NumPy, PyTorch/TensorFlow, and stochastic solvers. Deterministic modes are enforced where available, minimizing nondeterministic GPU kernels. Additionally, pseudo-random noise vectors used in stochastic simulations are logged and can be reloaded for bitwise-identical reruns.

C. Training and Validation Protocol

Training and validation splits are designed to prevent overfitting and ensure fair model evaluation. Data from different sessions or subjects are kept disjoint. For Bayesian models, posterior distributions are compared across folds to evaluate convergence stability. Posterior spreads, not just point estimates, are reported to reflect uncertainty and robustness.

D. Logging and Version Control

All experiments are tracked via structured logging frameworks such as MLflow or TensorBoard. Each run logs hyperparameters, metrics, and system metadata (OS, library versions, GPU drivers). Code and configurations are version-controlled using Git, ensuring that every figure and result can be linked to a specific commit. Logs include inference duration, hardware usage, and numerical stability alerts.

E. Containerization and Environment Management

To eliminate environment drift, the full pipeline is containerized using Docker. Containers encapsulate dependencies such as NumPy, SciPy, PyTorch, and The Virtual Brain libraries. Singularity containers are optionally provided for HPC clusters. This ensures that any collaborator can reproduce results with a single command.

F. Documentation and Data Provenance

Every dataset used in experiments includes metadata describing acquisition modality, preprocessing steps, and data source identifiers. Provenance tracking guarantees that simulated results can be mapped back to their empirical origins. Markdown-based experiment summaries automatically document configurations, parameters, and outcomes.

G. Summary

In essence, reproducibility in VBI is achieved through a combination of fixed seeds, transparent YAML-based configuration, rigorous version control, and environment standardization. This disciplined setup guarantees that each simulation and inference run is verifiable, repeatable, and extensible — key qualities for open, trustworthy computational neuroscience.

XII. Ethics and Responsible Use

Ethical considerations are central to the responsible design and deployment of virtual brain inference systems. While these digital models can advance neuroscience and improve medical practice, they also carry risks if used carelessly or without transparency. Virtual brains are representations — simplified mathematical abstractions — not precise replicas of human cognition or consciousness. Therefore, users and researchers must always interpret model outputs with caution, understanding that predictions are probabilistic, not deterministic.

Every dataset used in virtual brain inference involves deeply personal information. MRI, EEG, and MEG scans reflect not only neural structure and activity but also behavioral and clinical attributes. Protecting the privacy and dignity of participants is non-negotiable. Researchers should use anonymized or pseudonymized datasets and apply strong encryption both in storage and transmission. Informed consent procedures must be clear, detailing how the data will be analyzed, for how long it will be stored, and whether it may be shared for secondary research. Ethical use also includes respecting withdrawal rights and ensuring that data subjects can opt out without penalty.

The principle of transparency must guide all stages of VBI research. Open-source implementations, version-controlled code repositories, and reproducible pipelines promote trust and accountability in the scientific community. Researchers should clearly report assumptions, prior distributions, and model simplifications to avoid misleading interpretations. Bias, which can creep into models via demographic imbalances in datasets, should be actively monitored and mitigated through cross-validation, fairness audits, and diverse sampling.

Clinically, the deployment of virtual brain systems requires strict governance. Models can assist clinicians by providing

insights into network dysfunctions or hypothetical interventions, but they should never replace human expertise. Medical professionals remain ultimately responsible for diagnosis and treatment decisions. Therefore, every prediction made by a virtual brain system should be viewed as one piece of evidence within a larger clinical and ethical framework.

Lastly, the responsible use of virtual brain inference also extends to communication with the public. Scientists and the media must avoid sensationalizing results or implying that these systems can fully simulate thought or consciousness. Maintaining realistic expectations helps protect both scientific credibility and societal trust.

In summary, responsible virtual brain research stands on four ethical pillars: transparency, privacy, fairness, and humility. Upholding these ensures that innovation in computational neuroscience benefits humanity without compromising integrity, equity, or respect for individual autonomy.

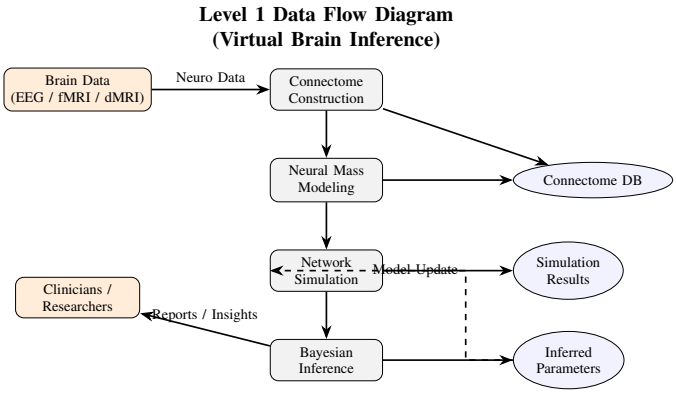

Fig. 2. Compact Data Flow Diagram (DFD) of the Virtual Brain Inference system.

XIII. Conclusion

The work presented in this paper provides a clear and comprehensive blueprint for developing and personalizing large-scale virtual brain models — a critical step toward making computational neuroscience more accessible, transparent, and clinically relevant. By combining structural connectome data, neural mass models, multimodal integration, simulation, and Bayesian inference into a unified architecture, this framework captures both the anatomical and dynamical complexity of the brain while staying implementable with real-world resources.

The proposed system emphasizes not just theoretical completeness but practical reproducibility. The modular design allows researchers to plug in alternative models — for example, replacing the Jansen–Rit neural mass with a Wong–Wang or Epileptor model, or swapping fMRI data for EEG/MEG observations. This flexibility makes it possible to tailor the virtual brain to different experimental goals, from cognitive neuroscience studies to clinical prediction and personalized medicine. Furthermore, the use of probabilistic inference ensures that every result is accompanied by quantified uncertainty, aligning with best practices in modern scientific modeling.

Beyond methodology, this paper aims to bridge the traditional divide between neuroscience and computational engineering. The approach borrows principles from modern software design — such as reproducible configuration management, automated evaluation, and modular APIs — to bring rigor and scalability into neuroinformatics. These practices ensure that virtual brain modeling can evolve from an academic curiosity into a core tool for diagnosis, therapy simulation, and cognitive research.

From a scientific standpoint, virtual brain inference represents a convergence of three disciplines: computational modeling, systems neuroscience, and artificial intelligence. It allows researchers to explore how global brain rhythms emerge from local interactions, how disruptions in connectivity translate to cognitive dysfunction, and how targeted interventions might restore normal dynamics. The probabilistic foundation enables clinicians to move beyond binary judgments and toward evidence-based risk quantification, especially in disorders like epilepsy, Alzheimer's, or depression.

Looking forward, the implications are broad and inspiring. In the next phase of this work, integrating machine learning surrogates for faster simulation, expanding multimodal fusion across imaging modalities, and incorporating richer priors from biological datasets will make virtual brain inference even more robust and efficient. The growing trend of digital twins in healthcare suggests that virtual brain models could soon become standard companions to medical imaging, helping doctors predict outcomes, optimize treatment, and personalize care.

Ultimately, this study demonstrates that with the right blend of neuroscience, mathematics, and computation, the dream of a digital brain — one that mirrors the complexity of the biological organ — is not distant fiction but emerging reality. Virtual Brain Inference stands as both a scientific challenge and a technological opportunity: to understand the brain not merely as a biological system, but as an adaptive, modelable network that can be studied, simulated, and ultimately used to improve human health and cognition.

This paper concludes by reaffirming the transformative potential of virtual brain modeling. As computational tools continue to mature and data-sharing initiatives expand, the integration of simulation-based inference with real neural data will mark a defining shift in neuroscience. The blueprint presented here offers a foundation for that shift — practical, modular, and open to evolution — paving the way for the next generation of brain-inspired research and clinical innovation.

References

[1] M. Hashemi *et al.*, "Principles and Operation of Virtual Brain Twins," *IEEE Reviews in Biomedical Engineering*, 2025. [Online]. Available: https://ieeexplore.ieee.org/document/10972118/.

[2] S. Park *et al.*, "A Blockchain-based Platform for Reliable Inference and Training of Large-Scale Models," *IEEE Access*, 2023. [Online]. Available: https://ieeexplore.ieee.org/abstract/document/10758664.

[3] P. Sanz-Leon, S. A. Knock, A. Spiegler, and V. K. Jirsa, "The Virtual Brain: a simulator of primate brain network dynamics," *Frontiers in Neuroinformatics*, vol. 7, p. 10, 2013.

[4] M. Breakspear, "Dynamic models of large-scale brain activity," *Nature Neuroscience*, vol. 20, pp. 340–352, 2017.

[5] K. J. Friston, L. Harrison, and W. Penny, "Dynamic causal modelling," *NeuroImage*, vol. 19, no. 4, pp. 1273–1302, 2003.
[6] J. Daunizeau, K. J. Friston, and S. J. Kiebel, "Variational Bayesian identification and prediction of stochastic nonlinear dynamic causal models," *Physica D*, vol. 238, no. 21, pp. 2089–2118, 2011.
[7] C. J. Honey *et al.*, "Predicting human resting-state functional connectivity from structural connectivity," *PNAS*, vol. 106, no. 6, pp. 2035–2040, 2009.
[8] D. C. Van Essen *et al.*, "The WU-Minn Human Connectome Project: an overview," *NeuroImage*, vol. 80, pp. 62–79, 2013.
[9] M. Schirner, A. R. McIntosh, V. Jirsa, G. Deco, and P. Ritter, "Inferring multi-scale neural mechanisms with brain network modelling," *eLife*, 7:e28927, 2018.
[10] A. Ziaeemehr *et al.*, "Virtual Brain Inference (VBI): A flexible and integrative toolkit for efficient probabilistic inference on virtual brain models," *eLife Reviewed Preprint*, 2025. [Online]. Available: https://elifesciences.org/reviewed-preprints/106194.
[11] V. K. Jirsa *et al.*, "Individualized whole-brain models of epilepsy spread," *NeuroImage*, vol. 145, pp. 377–388, 2017.
[12] M. Hashemi *et al.*, "The Bayesian Virtual Epileptic Patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model," *NeuroImage*, vol. 217, 2020.