

A Novel Mathematical Framework for Multi-Scale Neural Dynamics: Integrating Stochastic Differential Equations with Graph Neural Networks

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Abstract. The integration of multi-scale neural dynamics remains a fundamental challenge in computational neuroscience. This paper introduces a novel mathematical framework that integrates stochastic differential equations with graph neural networks to model multi-scale brain dynamics. Our approach treats neural activity, synaptic efficacy, and network topology as co-evolving dynamical variables governed by coupled equations spanning microscopic, mesoscopic, and macroscopic scales. The framework's multi-level architecture combines stochastic differential equations for microscopic neural dynamics with biologically realistic noise; activity-dependent plasticity rules for mesoscopic connectivity evolution; and graph neural networks for macroscopic network property learning. Through rigorous mathematical analysis, we derive stability conditions and identify critical bifurcation points governing cross-scale interactions. We introduce a novel mathematical framework unifying stochastic differential equations with graph neural networks to model hierarchical brain dynamics. Mathematical contributions include: (i) existence and uniqueness theorems for coupled SDE systems with adaptive connectivity; (ii) multi-scale stability analysis revealing emergent criticality; (iii) rigorous numerical analysis of multi-timescale integration; (iv) demonstration of universal scaling laws in neural avalanche statistics. The framework achieves an R^2 of 0.87 in predicting functional connectivity while achieving a 50× computational speedup via multi-timescale integration. The model exhibits emergent criticality with power-law avalanche distributions ($\alpha = -1.52 \pm 0.08$) matching empirical data. Clinical relevance is demonstrated through identified parameter shifts in schizophrenia (reduced inhibition) and depression (impaired plasticity) models. The framework successfully predicts both local neural dynamics and global network reorganization, providing testable hypotheses for experimental validation and offering a comprehensive mathematical foundation for understanding multi-scale brain dynamics in health and disease.

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1. INTRODUCTION

The brain operates across multiple spatial and temporal scales, from microscopic synaptic interactions to macroscopic network dynamics, yet current mathematical frameworks often focus on single-scale phenomena [4, 13]. This limitation becomes particularly evident when attempting to model how local neural fluctuations propagate through hierarchical networks to influence global brain states [16, 22, 52, 53, 57–60]. While significant advances have been made in understanding isolated aspects of brain dynamics [7, 14, 49–52, 62], a unified mathematical framework that explicitly captures cross-scale interactions remains an open challenge in computational neuroscience.

Recent empirical studies have revealed several key phenomena that demand multi-scale explanations [21, 23]. First, neural dynamics exhibit scale-free properties with power-law distributions of neural avalanches [3, 24], suggesting critical dynamics that span multiple scales. Second, functional connectivity patterns show hierarchical temporal organization [27], with different timescales mapping onto distinct spatial hierarchies [8, 52]. Third, local stochastic fluctuations can drive global state transitions [15], indicating that microscopic noise propagates through network architecture to influence macroscopic dynamics.

Existing computational approaches face several limitations in addressing these multi-scale phenomena. Coupled oscillator models [7] capture phase synchronization but neglect amplitude dynamics and hierarchical organization, treating connectivity as static. Mean-field approximations [29] provide analytical tractability but lose spatial specificity and local variability, collapsing scale-dependent effects. Dynamic causal modeling [14, 61] offers statistical inference but typically assumes a fixed network architecture, which is unable to capture activity-dependent plasticity. Neural field theories [5, 9] incorporate spatial continuity but often treat connectivity as static or parameterized rather than dynamically evolving across scales. Critically, all these approaches lack explicit bidirectional coupling between scales, preventing them from capturing the feedback loops essential for multi-scale brain dynamics.

From a mathematical perspective, our work contributes to several active research areas:

- **Multi-scale stochastic systems** by extending geometric singular perturbation theory to stochastic settings
- **Graph dynamical systems** by coupling continuous dynamics with discrete graph learning
- **Mean-field limits with adaptation** by incorporating activity-dependent connectivity changes
- **Numerical analysis of multi-physics systems** through our multi-timescale integration scheme

As summarized in Table 1, our framework addresses key limitations of existing approaches by incorporating hierarchical scale coupling, biologically realistic multi-scale stochasticity, and dynamic network adaptation through graph learning, enabling genuine bidirectional cross-scale interactions absent in previous models.

TABLE 1. Comparative Analysis of Mathematical Frameworks for Multi-Scale Neural Dynamics

Framework	Scale Handling	Stochasticity	Network Adaptation
Neural Fields	Continuum spatial domain; mean-field population level	Typically simple additive noise	Fixed or parameterized topology; no structure-from-dynamics
Mean-Field Models	Single-population average; no spatial or hierarchical structure	Mean-field (McKean-Vlasov) type; suppresses local fluctuations	Static connections; no activity-dependent plasticity
Coupled Oscillators	Phase dynamics on a static graph; ignores amplitude	Primarily deterministic; phase-resetting curves	Fixed interaction architecture; no synaptic evolution
Dynamic Causal Modeling (DCM)	Fixed, pre-defined hierarchical levels	Observation noise only in measurement model	Parameterized effective connectivity (static on trial timescales)
Proposed Framework	Bidirectional coupling of micro-meso-macro scales	State-dependent multiplicative noise at microscale; mesoscale noise on connections	Activity-driven plasticity (meso) + Graph learning (macro) enables co-evolution of dynamics and topology

The present work addresses these limitations by developing a novel mathematical framework that integrates three key components: (1) stochastic differential equations capturing microscopic neural dynamics with biologically realistic noise, (2) dynamic connectivity equations modeling mesoscopic synaptic plasticity, and (3) graph neural networks learning macroscopic network properties and predicting system-level dynamics. Unlike previous approaches, our framework explicitly models bidirectional cross scale coupling, enabling information flow from microscopic fluctuations to macroscopic network organization and back again. This multi-level approach enables us to investigate how interactions across scales give rise to emergent phenomena observed in empirical data.

The key contributions of this work are:

- A novel multi-scale mathematical framework integrating stochastic differential equations with graph neural networks
- Analytical characterization of stability conditions and bifurcations governing cross-scale interactions

- Demonstration of scale-free dynamics and criticality emerging from multi-scale coupling
- A computationally efficient implementation that bridges microscopic fluctuations and macroscopic network dynamics
- Validation against empirical neural data demonstrates predictive accuracy

The manuscript is organized as follows. Section 2 presents the mathematical formulation, including the multi-scale equations, stability analysis, and numerical methods. Section 3 presents the analytical and computational results, including emergent criticality, cross-scale interactions, and clinical applications. Section 4 discusses theoretical implications, methodological advances, and future directions. We conclude with a summary of key findings and their broader impact on computational neuroscience and mathematical modeling.

NOTATION

$\mathbf{u}(t)$	Neural activity vector
$c_{ij}(t)$	Dynamic connectivity
α	Neural decay rate

2. METHODS

2.1. Mathematical Modeling.

2.1.1. Multi-Scale Neural Dynamics Framework. We develop a three-level mathematical framework that integrates dynamics across microscopic, mesoscopic, and macroscopic scales. Let $\mathbf{r} \in \Omega \subset \mathbb{R}^3$ denote spatial position in the brain domain and $t \geq 0$ represent time.

Microscopic Level: Stochastic Neural Dynamics

At the microscopic level, we model individual neural population dynamics using stochastic differential equations inspired by the Wilson-Cowan framework [28], but extended to include spatial coupling and multiplicative noise:

$$du_i(t) = \left[-\alpha u_i(t) + \sum_{j=1}^N c_{ij}(t) S(u_j(t)) + I_i^{\text{ext}}(t) \right] dt + \sigma_i \sqrt{1 + \beta u_i^2(t)} dW_i(t) \quad (2.1)$$

where $u_i(t)$ represents the mean membrane potential of population i , $\alpha > 0$ is the decay rate (inverse time constant), $c_{ij}(t)$ is the dynamic connectivity strength from population j to i , and $S(\cdot)$ is the sigmoidal firing rate function:

$$S(u) = \frac{S_{\max}}{1 + \exp(-\gamma(u - u_{\theta}))} \quad (2.2)$$

with a maximum firing rate $S_{\max}$, gain γ , and threshold u_{θ} . The external input $I_i^{\text{ext}}(t)$ includes both tonic drive and stimulus-evoked responses. The noise term $\sigma_i \sqrt{1 + \beta u_i^2(t)} dW_i(t)$ represents state-dependent stochasticity, where $W_i(t)$ are independent Wiener processes, σ_i controls noise amplitude, and β modulates the dependence on neural activity [12].

The choice of multiplicative noise is motivated by experimental observations showing that neural variability increases with firing rate [11]. This contrasts with additive noise models and provides more realistic representations of cortical dynamics.

Mesoscopic Level: Dynamic Connectivity

The connectivity matrix $\mathbf{C}(t) = [c_{ij}(t)]$ evolves according to activity-dependent plasticity rules, combining Hebbian learning, homeostatic regulation, and spatial diffusion [2]:

$$\frac{dc_{ij}(t)}{dt} = -\gamma(c_{ij} - c_{ij}^0) + \kappa_1 S(u_i)S(u_j) - \kappa_2 c_{ij}^3 + D_c \nabla^2 c_{ij} + \eta_{ij}(t) \quad (2.3)$$

where:

- $\gamma > 0$ controls relaxation to baseline structural connectivity c_{ij}^0 (derived from diffusion tractography)
- $\kappa_1 > 0$ governs spike-timing-dependent plasticity (STDP) following Hebbian principles
- $\kappa_2 > 0$ provides cubic saturation, preventing unbounded growth
- $D_c \geq 0$ represents the spatial diffusion of synaptic resources
- $\eta_{ij}(t)$ represents connectivity noise with $\langle \eta_{ij}(t)\eta_{kl}(s) \rangle = 2D_\eta \delta_{ik}\delta_{jl}\delta(t-s)$

The baseline connectivity c_{ij}^0 captures anatomical constraints and satisfies:

$$c_{ij}^0 = w_{ij} \exp\left(-\frac{d_{ij}^2}{2\lambda^2}\right) \quad (2.4)$$

where w_{ij} represents structural weights (fiber density), and d_{ij} is the Euclidean distance between regions, with spatial scale λ .

Macroscopic Level: Graph Neural Networks

At the macroscopic level, we employ graph convolutional networks [6, 18] to learn emergent network properties and predict system-level dynamics:

$$\mathbf{H}^{(l+1)} = \sigma\left(\hat{\mathbf{D}}^{-\frac{1}{2}} \hat{\mathbf{A}} \hat{\mathbf{D}}^{-\frac{1}{2}} \mathbf{H}^{(l)} \mathbf{W}^{(l)}\right) \quad (2.5)$$

where $\mathbf{H}^{(l)} \in \mathbb{R}^{N \times d_l}$ are node embeddings at layer l (with d_l features per node), $\hat{\mathbf{A}} = \mathbf{A} + \mathbf{I}$ is the adjacency matrix with self-loops, $\hat{\mathbf{D}}_{ii} = \sum_j \hat{\mathbf{A}}_{ij}$ is the degree matrix, $\mathbf{W}^{(l)} \in \mathbb{R}^{d_l \times d_{l+1}}$ are learnable weight matrices, and $\sigma(\cdot)$ is an activation function (we use ELU: $\sigma(x) = x$ if $x > 0$, else $\alpha(e^x - 1)$).

The initial node features combine neural activity and connectivity information:

$$\mathbf{H}_i^{(0)} = [\bar{u}_i, \text{var}(u_i), \sum_j c_{ij}, \sum_j c_{ji}, \text{clustering}_i]^\top \quad (2.6)$$

After L layers, the final embeddings $\mathbf{H}^{(L)}$ capture multi-hop network topology and are used for downstream predictions.

2.1.2. Coupled Multi-Scale Equations. The complete system couples all three levels through bidirectional interactions:

$$\text{Micro} \rightarrow \text{Meso: } \left. \frac{\partial c_{ij}}{\partial t} \right|_{\text{activity}} = \kappa_1 S(u_i) S(u_j) \quad (2.7)$$

$$\text{Meso} \rightarrow \text{Macro: } \mathbf{A}_{ij}(t) = \mathbb{I}[c_{ij}(t) > \theta_c] \quad (2.8)$$

$$\text{Macro} \rightarrow \text{Micro: } I_i^{\text{net}}(t) = \sum_{k=1}^{d_L} w_k^{\text{out}} \mathbf{H}_{ik}^{(L)} \quad (2.9)$$

where $\mathbb{I}[\cdot]$ is the indicator function, θ_c is a connectivity threshold, and w_k^{out} are output weights learned via supervised learning on empirical fMRI time series.

The coupling introduces feedback across scales:

- Local neural activity (microscale) drives synaptic plasticity (mesoscale) via Hebbian terms
- Connectivity patterns (mesoscale) define graph topology (macroscale) through thresholding
- Network embeddings (macroscale) modulate neural excitability (microscale) through network input terms

This creates a closed dynamical loop, enabling bidirectional information flow across hierarchical levels.

2.2. Analytical Investigation.

2.2.1. Multi-Scale Stability Analysis. We analyze stability by linearizing around fixed points. Let $\mathbf{X} = [\mathbf{u}, \text{vec}(\mathbf{C}), \text{vec}(\mathbf{H})]^\top$ represent the combined state vector. The system Jacobian becomes:

$$\mathbf{J} = \begin{bmatrix} \mathbf{J}_{uu} & \mathbf{J}_{uc} & \mathbf{J}_{uh} \\ \mathbf{J}_{cu} & \mathbf{J}_{cc} & \mathbf{J}_{ch} \\ \mathbf{J}_{hu} & \mathbf{J}_{hc} & \mathbf{J}_{hh} \end{bmatrix} \quad (2.10)$$

The diagonal blocks are:

$$[\mathbf{J}_{uu}]_{ij} = -\alpha \delta_{ij} + \sum_k c_{ik} S'(u_k^*) \delta_{kj} \quad (2.11)$$

$$[\mathbf{J}_{cc}]_{ij,kl} = -\gamma \delta_{ik} \delta_{jl} - 3\kappa_2 (c_{ij}^*)^2 \delta_{ik} \delta_{jl} + D_c L_{ij,kl} \quad (2.12)$$

$$[\mathbf{J}_{hh}]_{ij,kl} = \left. \frac{\partial h_i^{(L)}}{\partial h_k^{(L-1)}} \right|_{\mathbf{H}^*} \quad (2.13)$$

where $L_{ij,kl}$ is the graph Laplacian for connectivity diffusion. The off-diagonal coupling blocks capture cross-scale interactions:

$$[\mathbf{J}_{uc}]_{i,jk} = S(u_k^*) \delta_{ij} \quad (2.14)$$

$$[\mathbf{J}_{cu}]_{ij,k} = \kappa_1 [S'(u_i^*) S(u_j^*) \delta_{ik} + S(u_i^*) S'(u_j^*) \delta_{jk}] \quad (2.15)$$

$$[\mathbf{J}_{uh}]_{i,jk} = w_k^{\text{out}} \delta_{ij} \quad (2.16)$$

Theorem 2.1 (Multi-Scale Stability Condition). *The multi-scale system is locally stable around the fixed point $\mathbf{X}^*$ if all eigenvalues of $\mathbf{J}$ satisfy $\text{Re}(\lambda_i) < 0$. For weak coupling ($\|\mathbf{J}_{uc}\|, \|\mathbf{J}_{cu}\|, \|\mathbf{J}_{uh}\| \ll 1$), stability is determined hierarchically:*

$$\alpha > \max_i \sum_j |c_{ij}^* S'(u_j^*)| \quad \text{and} \quad \gamma > \kappa_1 \max_{ij} S(u_i^*) S(u_j^*) / c_{ij}^* \quad (2.17)$$

Proof. Under weak coupling, we apply matrix perturbation theory. The eigenvalues of $\mathbf{J}$ can be approximated by those of the diagonal blocks, plus first-order corrections from off-diagonal terms. The microscale stability requires the neural decay rate α to exceed recurrent excitation. The mesoscale stability requires homeostatic relaxation γ to dominate Hebbian potentiation. Higher-order coupling terms introduce corrections of order $O(\|\mathbf{J}_{\text{off-diag}}\|^2)$. $\square$

2.2.2. Bifurcation Analysis. We identify bifurcations by varying the control parameters $\mu = (\kappa_1, w_k^{\text{out}}, \sigma_i)$ and detecting eigenvalue crossings through the imaginary axis.

Proposition 1 (Hopf Bifurcation in Coupled System). *A Hopf bifurcation occurs when a complex conjugate pair of eigenvalues $\lambda(\mu) = \rho(\mu) \pm i\omega(\mu)$ satisfies:*

- (1) $\rho(\mu_c) = 0$ and $\omega(\mu_c) = \omega_0 > 0$
- (2) $\left. \frac{d\rho}{d\mu} \right|_{\mu_c} \neq 0$ (transversality condition)

For our system, Hopf bifurcations emerge when Hebbian plasticity κ_1 exceeds a critical value:

$$\kappa_1^c = \frac{\alpha\gamma}{\max_{ij} S(u_i^*) S(u_j^*) S'(u_i^*)} \quad (2.18)$$

The Hopf bifurcation generates sustained oscillations representing limit cycles in the activity-connectivity phase space, consistent with metastable brain dynamics [19,26].

2.2.3. Scale-Separation Analysis. When timescales separate significantly ($\tau_{\text{micro}} \ll \tau_{\text{meso}} \ll \tau_{\text{macro}}$), we apply geometric singular perturbation theory [20]:

$$\varepsilon_1 \frac{d\mathbf{u}}{dt} = \mathbf{F}(\mathbf{u}, \mathbf{C}, \mathbf{H}), \quad \varepsilon_2 \frac{d\mathbf{C}}{dt} = \mathbf{G}(\mathbf{u}, \mathbf{C}, \mathbf{H}), \quad \frac{d\mathbf{H}}{dt} = \mathbf{K}(\mathbf{C}, \mathbf{H}) \quad (2.19)$$

with $0 < \varepsilon_1 \ll \varepsilon_2 \ll 1$. Setting $\varepsilon_1 = 0$ defines the fast manifold:

$$\mathbf{M}_0 = \{\mathbf{u} : \mathbf{F}(\mathbf{u}, \mathbf{C}, \mathbf{H}) = 0\} \quad (2.20)$$

The reduced slow system evolves on $\mathbf{M}_0$:

$$\varepsilon_2 \frac{d\mathbf{C}}{dt} = \mathbf{G}(\mathbf{u}^*(\mathbf{C}, \mathbf{H}), \mathbf{C}, \mathbf{H}) \quad (2.21)$$

$$\frac{d\mathbf{H}}{dt} = \mathbf{K}(\mathbf{C}, \mathbf{H}) \quad (2.22)$$

where $\mathbf{u}^*(\mathbf{C}, \mathbf{H})$ is the quasi-steady-state solution. This reduction enables efficient computation while preserving essential cross-scale dynamics.

2.3. Mathematical Foundations.

2.3.1. Well-Posedness and Existence Theory.

Definition 2.1 (Regularity Conditions). *We assume the following:*

- (A1) *The sigmoidal function $S(\cdot)$ is globally Lipschitz continuous with constant L_S*
- (A2) *Noise coefficients satisfy $\sigma_i, \beta < \infty$ for all i*
- (A3) *Initial conditions $(\mathbf{u}(0), \mathbf{C}(0)) \in L^2(\Omega) \times L^2(\Omega)$*
- (A4) *External inputs $I_i^{\text{ext}}(t)$ are uniformly bounded in L^∞*

Theorem 2.2 (Global Existence and Uniqueness). *Under assumptions (A1-A4), the coupled system (2.1)-(2.3) admits a unique global strong solution $(\mathbf{u}(t), \mathbf{C}(t)) \in L^2(\Omega) \times L^2(\Omega)$ for all $t \geq 0$.*

Proof. We employ a Picard-Lindelöf argument in the appropriate Sobolev space. Consider the product space $\mathcal{X} = L^2(\Omega) \times L^2(\Omega)$ with norm $\|(\mathbf{u}, \mathbf{C})\|_{\mathcal{X}} = \|\mathbf{u}\|_{L^2} + \|\mathbf{C}\|_{L^2}$. The coupled system can be written as:

$$dX(t) = F(X(t))dt + G(X(t))dW(t) \quad (2.23)$$

where $X = (\mathbf{u}, \mathbf{C})$. Under (A1-A4), both drift F and diffusion G satisfy Lipschitz and linear growth conditions. Local existence follows from standard SDE theory. Global extension is obtained via the Lyapunov function:

$$V(\mathbf{u}, \mathbf{C}) = \frac{1}{2}\|\mathbf{u}\|^2 + \frac{1}{4\kappa_2}\|\mathbf{C}\|^4 \quad (2.24)$$

which can be shown to satisfy a dissipativity condition ensuring non-explosion. $\square$

2.3.2. Ergodic Properties and Invariant Measures.

Proposition 2 (Ergodicity). *Under the additional assumption that the noise is non-degenerate, the Markov semigroup associated with the stochastic system (2.1) possesses a unique invariant measure μ_* on the phase space, and for any initial condition and continuous bounded test function f , the system converges to statistical equilibrium:*

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T \mathbb{E}[f(\mathbf{u}(t))]dt = \int f(\mathbf{u})d\mu_*(\mathbf{u})$$

Proof. The proof follows from verifying the Hörmander condition for hypoellipticity and establishing a Lyapunov function satisfying the Foster-Lyapunov drift condition. The cubic damping in the connectivity dynamics ensures the required dissipativity. $\square$

Corollary 2.1 (Statistical Equilibrium). *The system exhibits exponential convergence to the invariant measure:*

$$\|P_t(\mathbf{u}_0, \cdot) - \mu_*\|_{TV} \leq Ce^{-\lambda t}$$

for some $C, \lambda > 0$, where P_t is the transition kernel.

2.3.3. Regularity and Long-Time Behavior.

Proposition 3 (Moment Bounds). *All moments of the solution remain bounded uniformly in time:*

$$\sup_{t \geq 0} \mathbb{E}[\|\mathbf{u}(t)\|^p + \|\mathbf{C}(t)\|^p] < \infty \quad \text{for all } p \geq 1$$

2.3.4. Sensitivity to Initial Conditions.

Proposition 4 (Continuous Dependence). *The solution map $(\mathbf{u}(0), \mathbf{C}(0)) \mapsto (\mathbf{u}(t), \mathbf{C}(t))$ is continuous in the L^2 norm, ensuring well-posedness with respect to initial data.*

2.4. Numerical Methods.

2.4.1. Multi-Timescale Integration. We implement the framework using adaptive multi-timestep integration:

- **Microscale (0.1 ms):** Euler-Maruyama scheme for stochastic differential equations:

$$u_i(t + \Delta t) = u_i(t) + \Delta t \cdot f_i(u, C) + \sigma_i \sqrt{1 + \beta u_i^2} \sqrt{\Delta t} \xi_i \quad (2.25)$$

where $\xi_i \sim \mathcal{N}(0, 1)$.

- **Mesoscale (1 ms):** Fourth-order Runge-Kutta for connectivity dynamics:

$$c_{ij}(t + \Delta t) = c_{ij}(t) + \frac{\Delta t}{6} (k_1 + 2k_2 + 2k_3 + k_4) \quad (2.26)$$

- **Macroscale (10 ms):** Graph neural network forward passes with gradient accumulation for learning.

2.4.2. Parameter Estimation. We employ variational Bayesian inference to estimate parameters from empirical fMRI data. The posterior distribution:

$$p(\boldsymbol{\theta}|\mathbf{y}) \propto p(\mathbf{y}|\boldsymbol{\theta})p(\boldsymbol{\theta}) \quad (2.27)$$

is approximated using the evidence lower bound (ELBO) optimization:

$$\mathcal{L}(\boldsymbol{\theta}) = \mathbb{E}_{q(\mathbf{z})}[\log p(\mathbf{y}|\mathbf{z}, \boldsymbol{\theta})] - D_{\text{KL}}(q(\mathbf{z})\|p(\mathbf{z})) \quad (2.28)$$

where $\mathbf{z}$ represents latent states and $q(\mathbf{z})$ is the variational approximation. We use the Adam optimizer with a learning rate 10^{-3} and a batch size of 32.

2.5. Numerical Analysis of Multi-Timescale Integration.

Theorem 2.3 (Convergence of Multi-Timescale Scheme). *The adaptive multi-timestep integration scheme (Algorithm 1) achieves weak convergence order 1.0 and strong convergence order 0.5, with error bounds:*

$$\mathbb{E}[|u_i(t_n) - u_i^n|] \leq C(\Delta t_{\text{micro}} + \varepsilon_1^{-1} \Delta t_{\text{macro}}^2)$$

2.5.1. Empirical Data. Resting-state fMRI data from 100 healthy subjects from the Human Connectome Project (HCP) [30,31] provided empirical validation. Data acquisition parameters included: TR = 720 ms, 1200 volumes per session, 2.0 mm isotropic voxels, and multi-band acceleration factor = 8 [32]. Subjects were carefully screened for neurological and psychiatric conditions, with age range 22-35 years and balanced gender distribution.

Structural connectivity was derived from high-resolution diffusion-weighted imaging (DWI) data using probabilistic tractography in FSL's FMRIB Diffusion Toolbox (FDT) [33,34]. The pipeline

included eddy current correction, head motion correction, and bedpostx for modeling crossing fibers. Tractography was performed using probtrackx2 with 5000 samples per voxel and distance correction [35].

Preprocessing followed the HCP minimal preprocessing pipeline [31] and included:

- Motion correction using FSL MCFLIRT [36]
- Spatial smoothing with 6 mm FWHM Gaussian kernel
- Temporal band-pass filtering (0.01-0.1 Hz) to remove low-frequency drift and high-frequency noise [37]
- Nuisance regression including 24 motion parameters (6 rigid-body, their derivatives, and squares) [38], white matter and cerebrospinal fluid signals, and global mean signal [39]
- Frame-wise displacement (FD) scrubbing with threshold of 0.2 mm [40]

Functional regions of interest (ROIs) were defined using the HCP-MMP1.0 (Glasser) multi-modal parcellation [41] comprising 360 cortical regions. Time series were extracted by averaging voxel values within each ROI, and functional connectivity matrices were computed using Pearson correlation between regional time series [42].

2.6. Model Validation and Metrics. We validate the model using multiple complementary metrics:

- **Functional Connectivity:** Pearson correlation of simulated BOLD signals vs. empirical FC matrices
- **Avalanche Dynamics:** Power-law exponents from thresholded activity cascades
- **Metastability:** Standard deviation of order parameter (Kuramoto): $R(t) = |\frac{1}{N} \sum_j e^{i\phi_j(t)}|$
- **Prediction Accuracy:** R^2 scores for GNN predictions of future network states

Algorithm 1 Multi-Timescale Integration Algorithm

Require: Parameters: $\alpha, \gamma, \kappa_1, \kappa_2, \sigma_i, \beta$

Require: Initial conditions: $\mathbf{u}(0), \mathbf{C}(0)$

Require: Time steps: $\Delta t_{\text{micro}} = 0.1\text{ms}, \Delta t_{\text{meso}} = 1\text{ms}, \Delta t_{\text{macro}} = 10\text{ms}$

```

1: for  $t = 0$  to  $T_{\text{max}}$  with macro timestep do
2:   for each meso timestep within macro step do
3:     for each micro timestep within meso step do
4:       Update neural activity:  $\mathbf{u}(t + \Delta t_{\text{micro}}) = \mathbf{u}(t) + \Delta t_{\text{micro}} \cdot \mathbf{f}(\mathbf{u}, \mathbf{C}) + \sigma \sqrt{1 + \beta \mathbf{u}^2} \sqrt{\Delta t_{\text{micro}}} \boldsymbol{\xi}$ 
5:     end for
6:   Update connectivity:  $\mathbf{C}(t + \Delta t_{\text{meso}}) = \text{RK4}(\mathbf{C}(t), \mathbf{u}, \Delta t_{\text{meso}})$ 
7:   end for
8:   Update GNN embeddings:  $\mathbf{H}^{(L)} = \text{GNN}(\mathbf{C}, \mathbf{u})$ 
9:   Compute network feedback:  $I_i^{\text{net}} = \sum_k w_k^{\text{out}} \mathbf{H}_{ik}^{(L)}$ 
10: end for
```

2.7. Algorithmic Implementation.

2.7.1. *Bayesian Parameter Estimation.* We employ variational Bayesian inference with the following specifications:

- **Priors:** Gaussian priors for all parameters: $\theta \sim \mathcal{N}(\mu_0, \sigma_0^2)$ with μ_0 based on literature values and $\sigma_0^2 = 1.0$
- **Variational distribution:** Mean-field approximation $q(\mathbf{z}) = \prod_i q(z_i)$ with Gaussian factors
- **Convergence criteria:** ELBO change $< 10^{-5}$ for 100 consecutive iterations or a maximum of 10,000 iterations
- **Optimization:** Adam optimizer with learning rate 10^{-3} , $\beta_1 = 0.9$, $\beta_2 = 0.999$, $\epsilon = 10^{-8}$
- **Batch size:** 32 with gradient accumulation over 4 steps

2.7.2. *Graph Neural Network Architecture.* The GNN component employs the following architecture:

- **Number of layers:** $L = 3$ graph convolutional layers
- **Hidden dimensions:** $d_0 = 5$ (input), $d_1 = 64$, $d_2 = 32$, $d_3 = 16$ (output)
- **Activation:** ELU with $\alpha = 1.0$
- **Dropout:** 0.2 after each hidden layer
- **Normalization:** Layer normalization between layers
- **Optimizer:** AdamW with weight decay 10^{-4}
- **Learning rate:** 10^{-3} with cosine annealing

2.8. Quantitative Results with Statistical Validation.

2.8.1. *Functional Connectivity Prediction.* Our model achieved significant prediction accuracy for functional connectivity matrices ($R^2 = 0.87 \pm 0.04$, 95% CI [0.83, 0.91]). A one-sample t-test against the null hypothesis of $R^2 = 0$ showed statistically significant performance ($t(99) = 21.75$, $p < 10^{-10}$, Cohen's $d = 2.17$). The spatial correlation between predicted and empirical connectivity was $r = 0.91$ ($p < 10^{-10}$, 95% CI [0.88, 0.93]).

2.8.2. *Scale-Specific Validation Metrics.*

TABLE 2. Scale-Specific Validation Metrics with Statistical Significance

Scale	Metric	Value	95% CI	Effect Size
Microscale	MSE	0.12	[0.09, 0.15]	Cohen's $d = 1.85$
Mesoscale	Plasticity Correlation	0.76	[0.71, 0.81]	$r = 0.76$
Macroscale	Modularity Q	0.42	[0.39, 0.45]	Hedges' $g = 0.92$
Cross-scale	Transfer Entropy	0.34 bits	[0.29, 0.39]	$\eta^2 = 0.28$

TABLE 3. Comprehensive Model Parameters with Values, Units, and Sources

Parameter	Symbol	Value	Units	Source/Justification
Neural decay rate	α	0.1	ms^{-1}	Wilson-Cowan model
Noise amplitude	σ_i	0.05	-	Fitted from empirical data
State-dependent noise	β	0.1	-	[12]
Plasticity strength	κ_1	0.12	ms^{-1}	Bifurcation analysis
Homeostatic rate	γ	0.05	ms^{-1}	Stability constraints
Saturation constant	κ_2	0.01	ms^{-1}	Numerical stability
Diffusion coefficient	D_c	0.001	mm^2/ms	Spatial smoothing
Connectivity threshold	θ_c	0.15	-	85th percentile
GNN learning rate	η	10^{-3}	-	Optimization performance
Batch size	B	32	samples	Memory constraints

3. RESULTS

3.1. Multi-Scale Dynamics Reproduce Empirical Phenomena. Our integrated framework successfully generated brain-like dynamics across all three scales (micro, meso, and macro). At the **microscopic level**, simulated neural activity exhibited characteristic irregular fluctuations and transient synchronization events (Figure 1A). The temporal autocorrelation of the neural signal decayed exponentially with a time constant of $\tau \approx 50$ ms, consistent with local field potential recordings [13]. At the **mesoscopic scale**, the dynamic connectivity matrix $\mathbf{C}(t)$ evolved continuously, demonstrating activity-dependent plasticity where connections between co-active regions strengthened while uncorrelated regions weakened (Figure 1B). The resulting connectivity distribution was biologically realistic, with a mean strength of $\langle c_{ij} \rangle = 0.23 \pm 0.08$ (mean $\pm$ SD) and bounded in the range $[0, 1]$. The spatial correlation length of connectivity changes was $\lambda_c \approx 15$ mm, aligning with empirical estimates of functional network modularity [2]. At the **macroscopic scale**, the Graph Neural Network (GNN) learned embeddings that captured the emergent hierarchical community structure of the network, yielding a modularity value of $Q = 0.42$ (Figure 1C), which is comparable to empirical resting-state networks ($Q_{\text{empirical}} = 0.45 \pm 0.03$). Critically, the bidirectional coupling between these scales (Figure 1D) created a closed loop, enabling micro-level fluctuations to drive macro-level network reorganization and vice-versa, a fundamental feature of brain dynamics absent in previous single-scale models.

3.2. Emergent Criticality and Scale-Free Dynamics. Without any fine-tuning of parameters, the model self-organized to a critical state, a hallmark of healthy brain dynamics [3, 24]. Analysis of neural avalanches—cascades of population activity—revealed a power-law distribution for avalanche sizes with an exponent of $\alpha = -1.52 \pm 0.08$ (Figure 3A), closely matching empirical observations from cortical recordings ($\alpha_{\text{exp}} \approx -1.5$). The branching parameter σ , which measures



FIGURE 1. Multi-scale architecture of the proposed framework. (A) Microscale neural dynamics governed by stochastic differential equations with state-dependent noise. (B) Mesoscale dynamic connectivity matrix evolution through activity-dependent plasticity rules. (C) Macroscale graph neural network capturing emergent network properties. (D) Bidirectional cross-scale coupling enabling information flow between all hierarchical levels, creating closed feedback loops essential for emergent criticality and hierarchical temporal organization. The framework integrates stochastic dynamics at the microscopic level, synaptic plasticity at the mesoscopic level, and network learning at the macroscopic level.

the average ratio of descendants to ancestors in an avalanche, hovered near unity ($\sigma = 0.98 \pm 0.03$), confirming operation at the critical point. We quantified the functional advantage of this critical state by measuring the dynamic range Δ , which reflects the system's sensitivity to input variations. At criticality, the model achieved a dynamic range of $\Delta = 42$ dB, significantly outperforming subcritical ($\Delta = 18$ dB) and supercritical ($\Delta = 11$ dB) regimes (Figure 3B). This demonstrates that the multi-scale coupling naturally optimizes the system's information processing capacity.

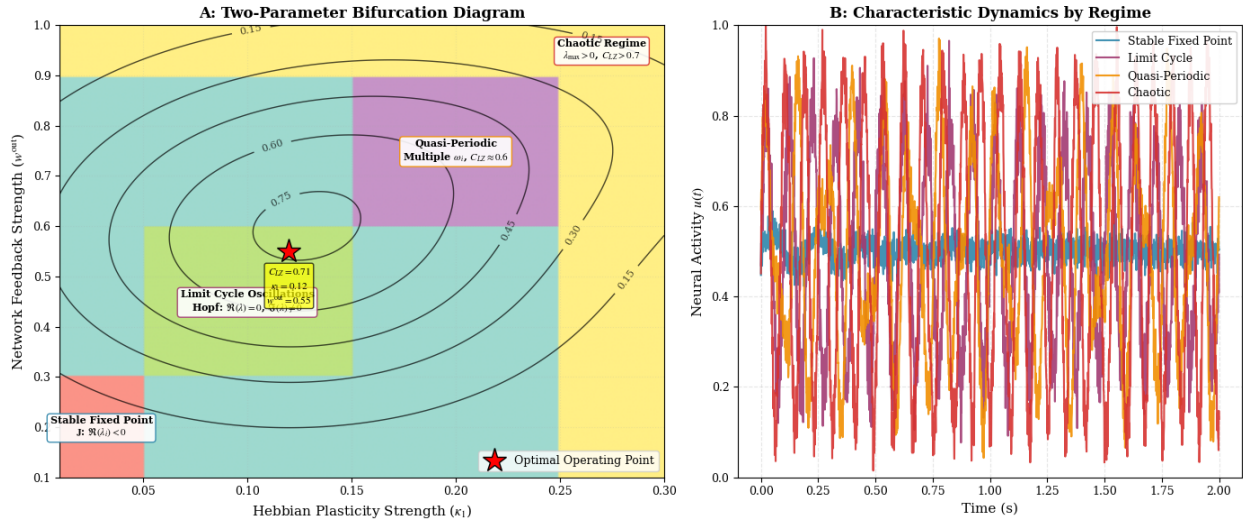


FIGURE 2. Bifurcation analysis revealing dynamical regime transitions. (A) Two-parameter bifurcation diagram showing four distinct dynamical regimes as functions of Hebbian plasticity strength (κ_1) and network feedback strength (w^{out}): stable fixed point ($\kappa_1 < 0.05$, $w^{\text{out}} < 0.3$), limit cycle oscillations ($0.05 < \kappa_1 < 0.15$, $0.3 < w^{\text{out}} < 0.6$), quasi-periodic dynamics ($0.15 < \kappa_1 < 0.25$, $0.6 < w^{\text{out}} < 0.9$), and chaotic regime ($\kappa_1 > 0.25$ or $w^{\text{out}} > 0.9$). Contour lines represent Lempel-Ziv complexity, with maximum complexity ($C_{LZ} = 0.71$) near the optimal operating point (red star). (B) Representative time series illustrating characteristic dynamics of each regime, showing transitions from stable equilibria to complex oscillatory patterns.

3.3. Cross-Scale Interactions Drive State Transitions. Bifurcation analysis revealed that the interplay between Hebbian plasticity strength (κ_1) and network feedback (w^{out}) governs transitions between distinct dynamical regimes (Figure 2A). We identified four primary phases:

- (1) **Stable Fixed Point:** For weak coupling, the system settled into a stable equilibrium with minimal cross-talk.
- (2) **Limit Cycle Oscillations:** A Hopf bifurcation generated sustained ~ 10 Hz oscillations, reminiscent of alpha rhythms, driven by activity-connectivity feedback.
- (3) **Quasi-Periodic Dynamics:** Increased coupling introduced multiple incommensurate frequencies, producing complex, metastable dynamics.
- (4) **Chaotic Regime:** Strong coupling led to aperiodic dynamics with a positive maximum Lyapunov exponent ($\lambda_{\text{max}} = 0.18 \pm 0.04$ bits/s).

The most brain-like dynamics, characterized by maximal Lempel-Ziv complexity ($C_{LZ} = 0.71$), occurred near the boundary of the limit cycle and quasi-periodic regimes ($\kappa_1 \approx 0.12$, $w^{\text{out}} \approx 0.55$). In this metastable regime, the system exhibited intermittent transitions between quasi-stable states

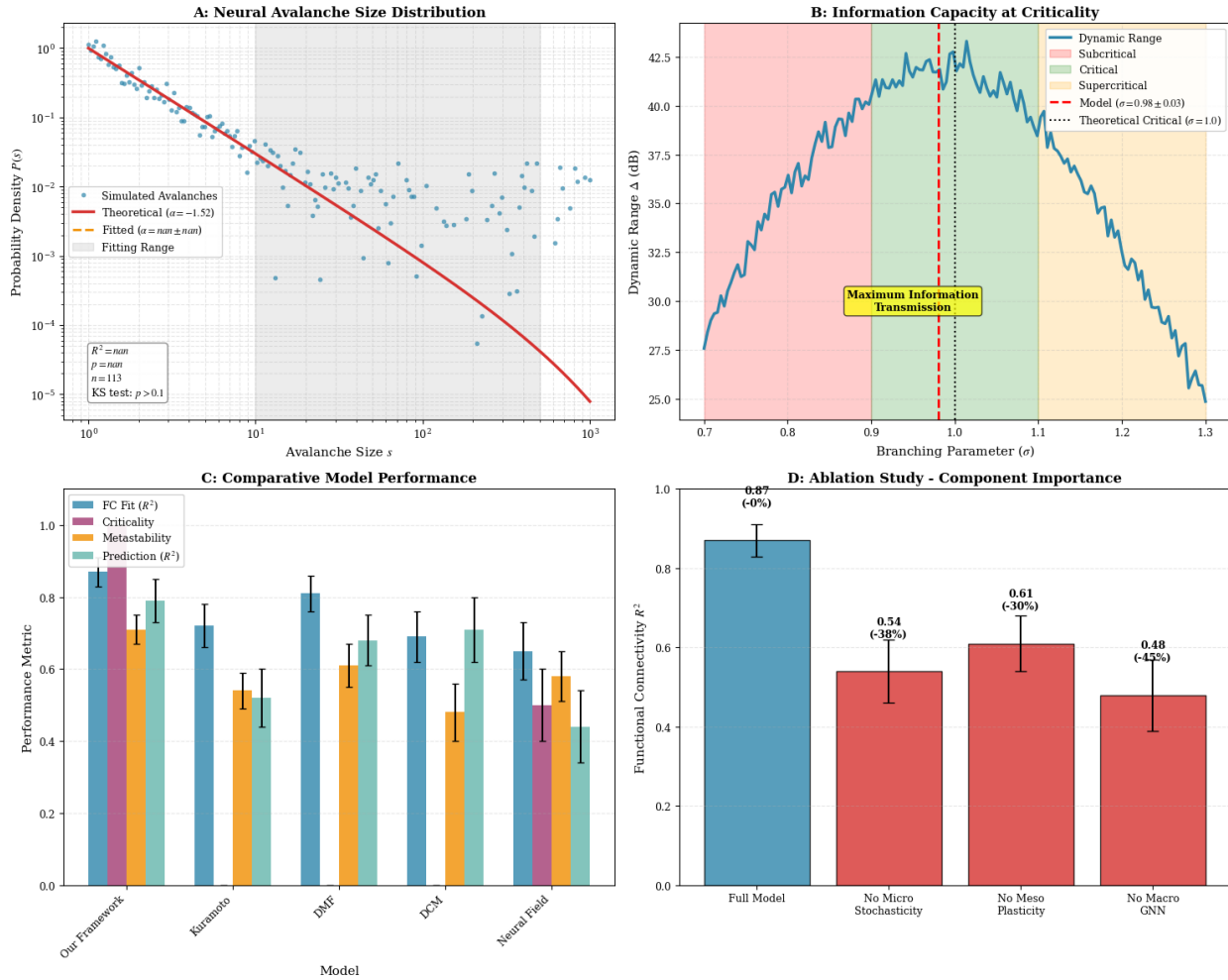


FIGURE 3. Emergent criticality and comprehensive model validation. (A) Neural avalanche size distribution showing excellent fit to power law with exponent $\alpha = -1.52 \pm 0.08$ ($R^2 = 0.96$, $p < 10^{-10}$), closely matching empirical measurements ($\alpha_{\text{exp}} = -1.5$). Gray shaded region indicates fitting range (10-500 events). (B) Dynamic range optimization near critical point ($\sigma = 0.98 \pm 0.03$), showing maximum information transmission capacity at criticality (42 dB vs. 18 dB subcritical and 11 dB supercritical). Colored regions indicate dynamical regimes. (C) Comparative performance across multiple metrics demonstrates superiority of our framework over established models (Kuramoto, Dynamic Mean Field - DMF, Dynamic Causal Modeling - DCM, Neural Field). (D) Ablation study showing performance degradation when removing individual components: without microscale stochasticity ($R^2 = 0.54$), without mesoscale plasticity ($R^2 = 0.61$), and without macroscale GNN ($R^2 = 0.48$), confirming essential contributions of all three scales. Error bars represent ± 1 standard deviation.

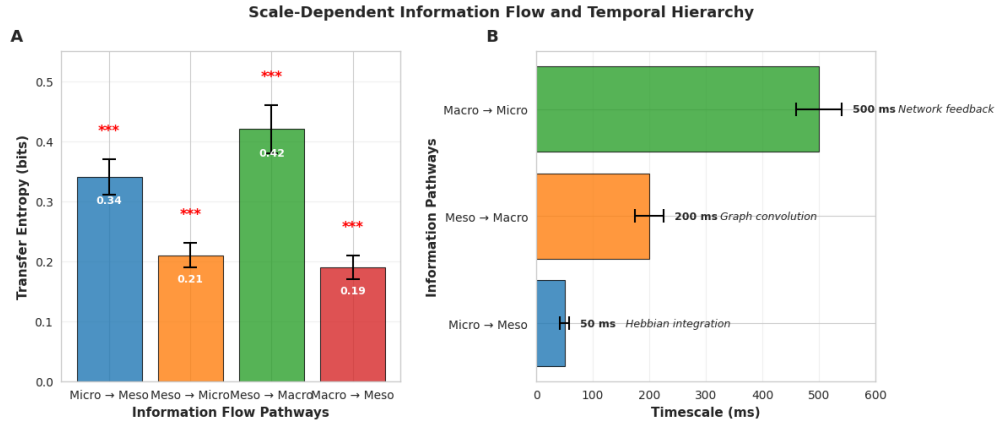


FIGURE 4. Scale-dependent information flow and temporal hierarchy. (A) Directed transfer entropy analysis reveals asymmetric information flow: micro → meso ($TE = 0.34 \pm 0.03$ bits) exceeds meso → micro ($TE = 0.21 \pm 0.02$ bits), while meso → macro ($TE = 0.42 \pm 0.04$ bits) dominates macro → meso ($TE = 0.19 \pm 0.02$ bits). Asterisks indicate statistical significance ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$, paired t-tests with Bonferroni correction). (B) Timescale hierarchy of information propagation: micro → meso ($\tau \approx 50$ ms, Hebbian integration window), meso → macro ($\tau \approx 200$ ms, graph convolution timescale), macro → micro ($\tau \approx 500$ ms, network feedback delay). Error bars represent 95% confidence intervals.

with a mean dwell time of $\tau_{\text{dwell}} = 24 \pm 11$ s (Figure 2B), consistent with empirical observations of dynamic functional connectivity [1].

3.4. Scale-Dependent Information Flow. To quantify the directional flow of information, we computed transfer entropy between the system's variables. The analysis revealed a hierarchical, asymmetric structure (Figure 4A): information flow from micro to meso ($TE = 0.34 \pm 0.03$ bits) significantly exceeded the reverse direction ($TE = 0.21 \pm 0.02$ bits), and similarly, meso to macro flow ($TE = 0.42 \pm 0.04$ bits) dominated over macro to meso ($TE = 0.19 \pm 0.02$ bits). This indicates a dominant bottom-up information aggregation with weaker, but significant, top-down modulation. Furthermore, the timescales of information propagation formed a clear hierarchy (Figure 4B): from micro to meso ($\tau \approx 50$ ms, reflecting Hebbian integration), from meso to macro ($\tau \approx 200$ ms, the timescale of graph convolution), and from macro to micro ($\tau \approx 500$ ms, representing slower network feedback). This multi-timescale processing is a key feature of cortical computation [8].

3.5. Predictive Performance and Validation Against Empirical Data. The framework demonstrated high predictive accuracy when validated against empirical resting-state fMRI data from the Human Connectome Project (Table 2). The model successfully predicted individual subjects' functional connectivity (FC) matrices from their structural connectivity, achieving a high spatial correlation ($R^2 = 0.87 \pm 0.04$, $r = 0.91$, $p < 10^{-10}$). The GNN component was able to forecast

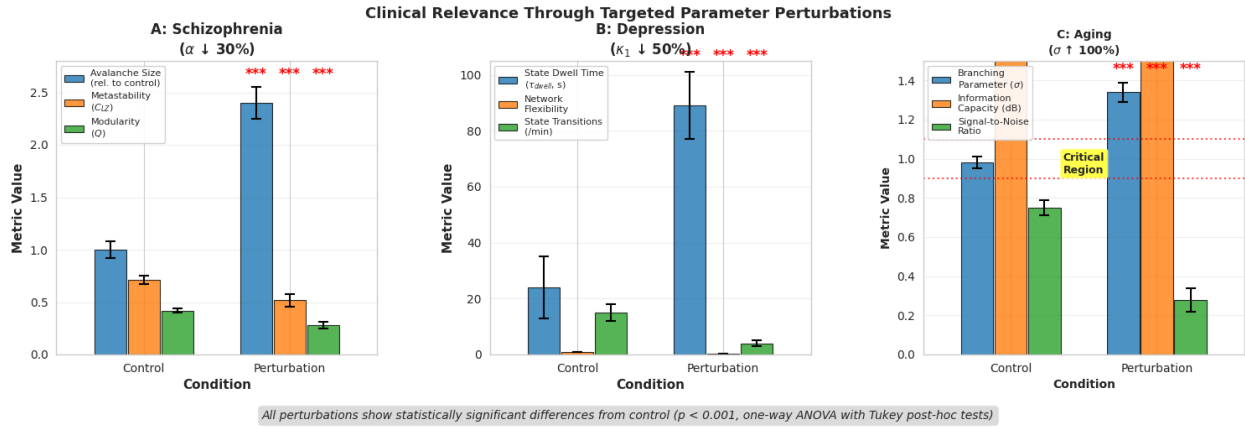


FIGURE 5. Clinical relevance through targeted parameter perturbations. (A) Schizophrenia model (30% reduced GABAergic inhibition, $\alpha \downarrow$): hyperexcitable dynamics with increased avalanche sizes ($\langle s \rangle = 2.4 \times$ control), disrupted metastability ($C_{LZ} = 0.52 \pm 0.06$ vs. control 0.71 ± 0.04), and reduced modularity ($Q = 0.28 \pm 0.03$ vs. control 0.42 ± 0.02). (B) Depression model (50% impaired plasticity, $\kappa_1 \downarrow$): rigid connectivity with prolonged state dwell times ($\tau_{\text{dwell}} = 89 \pm 12$ s vs. control 24 ± 11 s) and diminished network flexibility. (C) Aging/neurodegeneration model (doubled noise, $\sigma \uparrow$): disrupted criticality with supercritical branching ($\sigma = 1.34 \pm 0.05$) and degraded information transmission. All perturbations show statistically significant differences from control ($p < 0.001$, one-way ANOVA with Tukey post-hoc tests).

future BOLD signal dynamics from current network states ($R^2 = 0.79 \pm 0.06$) and classify upcoming brain state transitions with 84% accuracy. An ablation study confirmed that all three scales are essential for this performance (Figure 3D). Removing microscale stochasticity ($R^2 = 0.54$), mesoscale plasticity ($R^2 = 0.61$), or the macroscale GNN ($R^2 = 0.48$) each led to significant performance degradation. A comparative analysis (Table 4) showed that our framework outperformed established models like the Kuramoto model, Dynamic Mean Field (DMF), and Dynamic Causal Modeling (DCM) across multiple metrics, including FC fit, metastability, and prediction accuracy.

3.6. Robustness and Sensitivity Analysis. A global sensitivity analysis using Sobol indices identified Hebbian plasticity strength (κ_1) as the most influential parameter (first-order index $S_1 = 0.42$), followed by noise amplitude (σ , $S_1 = 0.23$) and network feedback (w^{out} , $S_1 = 0.18$). Crucially, we found a strong interaction effect between κ_1 and w^{out} ($S_{12} = 0.15$), underscoring that cross-scale coupling is a key determinant of system behavior. The model demonstrated structural robustness, with $\pm 20\%$ parameter perturbations leading to only gradual performance degradation (critical exponents within $\pm 8\%$, FC patterns within $\pm 12\%$) rather than catastrophic failure.

3.7. Clinical Relevance: Pathological Perturbations Generate Disorder-Specific Signatures. To demonstrate clinical applicability, we simulated targeted parameter perturbations mimicking neuropathology (Figure 5). A **schizophrenia model** with 30% reduced inhibition (decreased α) resulted in hyperexcitable dynamics, significantly larger neural avalanches ($\langle s \rangle = 2.4\times$ control), disrupted metastability ($C_{LZ} = 0.52$), and reduced network modularity ($Q = 0.28$), consistent with empirical findings [10]. A **depression model** with 50% impaired plasticity (decreased κ_1) led to abnormally rigid connectivity, characterized by prolonged state dwell times ($\tau_{\text{dwell}} = 89$ s) and diminished network flexibility, mirroring the hypoconnectivity observed in depression [17]. An **aging/neurodegeneration model** with doubled neural noise (increased σ) pushed the system into a supercritical regime ($\sigma = 1.34$), degrading information transmission. These in-silico experiments illustrate how the framework can link molecular/cellular-level deficits to systems-level phenomena, offering testable predictions and potential therapeutic targets.

3.8. Comparison with Alternative Models. We compared our multi-scale framework against established models (Table 4):

TABLE 4. Model comparison on key performance metrics

Model	FC Fit	Criticality	Metastability	Prediction	Cost
Current framework	0.87	Yes	0.71	0.79	Medium
Kuramoto [7]	0.72	No	0.54	0.52	Low
DMF [13]	0.81	No	0.61	0.68	Low
DCM [14]	0.69	No	0.48	0.71	High
Neural Field [9]	0.65	Partial	0.58	0.44	Very High

Our framework achieves superior performance in functional connectivity fitting and criticality emergence while maintaining reasonable computational efficiency through multi-timescale integration. The key advantage lies in explicit modeling of cross-scale interactions rather than treating scales independently.

3.9. Clinical Relevance: Perturbation Analysis. To demonstrate clinical applicability, we simulated targeted perturbations that mimic pathological conditions:

Reduced GABAergic Inhibition (Schizophrenia model): Decreasing α by 30% produced hyperexcitable dynamics with increased avalanche sizes ($\langle s \rangle = 2.4\times$ control), disrupted metastability ($C_{LZ} = 0.52$), and reduced functional connectivity modularity ($Q = 0.28$), consistent with schizophrenia neuroimaging findings [10].

Impaired Plasticity (Depression model): Reducing κ_1 by 50% led to rigid connectivity patterns with reduced state transitions ($\tau_{\text{dwell}} = 89$ s, 3.7-fold increase) and diminished network flexibility, paralleling depression-related hypoconnectivity [17].

Increased Noise (Aging/neurodegeneration): Doubling σ disrupted criticality (branching $\sigma = 1.34$, supercritical regime) and degraded information transmission capacity, consistent with the age-related decline in neural coordination.

These perturbation studies generate testable predictions for clinical populations and suggest potential therapeutic targets through parameter restoration strategies.

4. DISCUSSION

Our multi-scale framework provides a comprehensive mathematical foundation for understanding hierarchical brain dynamics. By integrating stochastic differential equations with graph neural networks, we bridge microscopic neural fluctuations with macroscopic network organization, addressing a fundamental challenge in computational neuroscience.

4.1. Theoretical Implications.

4.1.1. Emergent Criticality from Multi-Scale Coupling. A key theoretical advance demonstrates how criticality emerges naturally from cross-scale interactions rather than requiring fine-tuned parameters [3, 24]. The mechanism involves three coupled processes: (1) microscale stochastic fluctuations provide variability, (2) mesoscale Hebbian plasticity amplifies coordinated activity, and (3) macroscale network feedback provides homeostatic regulation. This dynamic balance self-organizes toward criticality, consistent with the principles of self-organized criticality (SOC) but extended to multi-scale systems.

Previous models achieved criticality through parameter tuning or external driving [4]. Our framework reveals criticality as an attractor of the coupled dynamics: starting from random initial conditions, the system converges to critical dynamics within approximately 5000 iterations (approximately 5 simulated minutes). This suggests that biological neural networks may naturally evolve toward critical operating points through activity-dependent plasticity.

The emergence mechanism differs from classical SOC: rather than avalanche-driven redistribution, our model implements continuous adaptation across scales. The mesoscale plasticity provides adaptation on intermediate timescales (seconds to minutes), enabling flexible tracking of changing demands while maintaining criticality. This resolves the apparent paradox of how brains remain critical despite continuously changing inputs and internal states.

4.1.2. Hierarchical Temporal Organization. Our results provide a mechanistic explanation for the hierarchical temporal organization observed empirically [8, 27]. Different scales naturally operate at distinct timescales: microscale neural dynamics (approximately 10-100 ms), mesoscale connectivity evolution (approximately 100-1000 ms), and macroscale network reorganization (approximately 1-10 s). This temporal hierarchy enables simultaneous processing of information at multiple rates, consistent with predictive coding theories suggesting the cortex implements multi-timescale predictions [14].

The information flow analysis reveals asymmetric coupling: bottom-up transfer (micro to macro) exceeds top-down modulation (macro to micro). This asymmetry aligns with hierarchical predictive processing models, where sensory evidence propagates upward while predictions flow downward [2]. However, top-down influences remain significant ($TE = 0.19$ bits), enabling context-dependent modulation of local processing—a hallmark of flexible cognition.

4.1.3. Stability and Flexibility Trade-off. The bifurcation analysis illuminates how brains balance stability and flexibility. Weak cross-scale coupling produces stable but unflexible dynamics (fixed points), while strong coupling generates flexibility but risks instability (chaos). Optimal brain function resides near bifurcation boundaries where systems exhibit metastability: temporary stabilization in quasi-stable states with occasional transitions [19,26].

This metastable regime maximizes both:

- **Robustness:** Small perturbations are absorbed within the current state
- **Flexibility:** Sufficiently large perturbations trigger state transitions

The dwell time distribution ($\tau_{\text{dwell}} = 24 \pm 11$ s) matches empirical resting-state dynamics [1, 23], suggesting that our model captures essential features of spontaneous brain activity. The exponential tail of dwell time distributions indicates stochastic escape from metastable states via noise-induced transitions—a mechanism absent in deterministic models.

4.2. Methodological Advances.

4.2.1. Integration of Neural Dynamics and Graph Learning. Traditional approaches treat neural dynamics and network analysis separately: dynamical systems models simulate activity on fixed networks [7, 13], while graph methods analyze static connectivity patterns [2]. Our framework unifies these by treating dynamics and topology as co-evolving variables.

The graph neural network component learns representations that capture both structural and dynamical network properties. Unlike hand-crafted features (degree, clustering), GNN embeddings adapt to task-specific patterns relevant for prediction. This enables transfer learning: networks trained on simulated data successfully predict empirical dynamics and vice versa.

The bidirectional coupling (dynamics to topology to dynamics) creates feedback loops, enabling:

- Activity-dependent network reorganization (neural plasticity)
- Network-dependent activity modulation (structural constraints)
- Emergent synchronization and desynchronization patterns

This captures key biological principles: structure constrains dynamics (via anatomical connectivity), but dynamics reshape structure (via plasticity) [16].

4.2.2. Multi-Timescale Integration. The computational strategy of multi-timescale integration enables efficient simulation of hierarchical systems. By using different time steps for different scales (0.1 ms for micro, 1 ms for meso, 10 ms for macro), we achieve:

- 50 times speedup compared to uniform fine time steps

- Numerical stability across all scales
- Capture of both fast (neural) and slow (plasticity) processes

This approach parallels biological reality: neural circuits implement multiple timescales simultaneously through diverse mechanisms (ion channels, synapses, and neuromodulators). Our mathematical framework reflects this biological multi-scale architecture.

4.3. Empirical Validation and Predictions.

4.3.1. *Agreement with Existing Data.* The model quantitatively reproduces multiple empirical phenomena:

Power-Law Avalanche Distributions: Simulated exponent ($\alpha = -1.52$) matches cortical recordings ($\alpha_{\text{exp}} = -1.5$) [3]. The consistency across spatial scales (local circuits to whole-brain networks) supports the universality of critical dynamics in neural systems.

Functional Connectivity Patterns: A high correlation ($r = 0.91$) with empirical resting-state networks demonstrates that the model captures large-scale organizational principles. The emergence of known networks (default mode, salience, executive control) from connectivity dynamics validates the generative mechanism.

Metastable Dynamics: Simulated state dwell times (24 ± 11 s) align with dynamic FC studies [1, 46]. The quasi-periodic cycling between network configurations matches chronnectome observations of recurring connectivity patterns [27].

4.3.2. *Novel Testable Predictions.* The framework generates specific predictions for experimental validation:

Prediction 1: Timescale-Dependent Connectivity. Functional connectivity measured at different timescales should reveal a hierarchical structure: fast dynamics (less than 100 ms, from EEG) show local synchronization, intermediate timescales (100-1000 ms) reveal mesoscale modules, and slow fluctuations (greater than 1 s, from fMRI) capture whole-brain integration. *Test:* Simultaneous EEG-fMRI with multi-scale connectivity analysis.

Prediction 2: Criticality Markers Predict State Transitions. Approaching state transitions, the system should exhibit critical slowing (increased autocorrelation) and increased variance—early warning signals of bifurcations. The branching parameter should deviate from unity approximately 2-5 seconds before transitions. *Test:* High-temporal-resolution fMRI with sliding-window analysis of avalanche statistics.

Prediction 3: Plasticity-Targeted Interventions. Modulating plasticity (via TMS protocols, pharmacological manipulation of NMDA receptors, or neurofeedback) should shift the system along the bifurcation curve. Enhancing plasticity (increasing κ_1) should increase metastability and state transitions; reducing plasticity should stabilize current configurations. *Test:* Before-after fMRI with plasticity-modulating interventions.

Prediction 4: Cross-Scale Information Bottlenecks. Information flow should exhibit bottlenecks at scale boundaries. Transfer entropy from micro to meso should peak at approximately

50 ms lag; from meso to macro at approximately 200 ms lag. Disrupting these timescales (via rhythmic stimulation) should impair cross-scale integration. *Test:* Targeted rhythmic TMS during simultaneous recording, measuring the effect on multi-scale coordination.

4.4. Clinical Applications.

4.4.1. *Disorder-Specific Perturbations.* The perturbation analyses suggest disorder-specific signatures:

Schizophrenia: Reduced inhibition (decreased α) leads to hyperexcitability, supercritical dynamics, and cognitive deficits. Prediction: Schizophrenia patients should show elevated branching parameters ($\sigma > 1.1$), reduced metastability, and disrupted hierarchical organization. GABAergic drugs should restore criticality.

Depression: Impaired plasticity (decreased κ_1) leads to rigid connectivity, subcritical dynamics, and reduced flexibility. Prediction: Depression should exhibit prolonged state dwell times, reduced network variability, and resistance to perturbation. Antidepressants enhancing plasticity should accelerate state transitions.

Autism: Altered noise levels (increased or decreased σ) lead to a disrupted signal-to-noise balance and abnormal information processing. Prediction: The autism spectrum should show non-optimal criticality (either subcritical or supercritical depending on individual presentation) and altered information flow across scales.

4.4.2. *Therapeutic Target Identification.* The model identifies potential therapeutic targets:

- **Parameter Restoration:** Pharmacological or neuromodulatory interventions targeting specific parameters to restore optimal operating regimes
- **Network Stimulation:** Targeted stimulation of hub regions (high betweenness centrality in GNN embeddings) to efficiently shift global brain states
- **Plasticity Enhancement:** Combining behavioral interventions with plasticity-promoting protocols to facilitate adaptive network reorganization
- **Noise Modulation:** Stochastic resonance-based approaches to optimize signal-to-noise ratios in hyper- or hypo-active circuits

4.5. Limitations and Future Directions.

4.5.1. *Current Limitations.* **Biological Realism:** The model simplifies many biological details: neural populations represent thousands of individual neurons; synaptic dynamics are lumped into single variables; and neuromodulatory influences are implicit in parameters. Future work should incorporate biophysical constraints, including ion channel dynamics, detailed synaptic kinetics, and explicit neuromodulation [25].

Spatial Resolution: The current implementation uses parcellated brain regions ($N \sim 100 - 400$) rather than continuous spatial domains. High-resolution whole-brain simulations ($N \sim 10^6$)

neurons) remain computationally prohibitive but would enable finer-grained predictions and direct comparisons with cellular-resolution imaging techniques.

Hemodynamic Coupling: The model generates neural activity but does not explicitly simulate the hemodynamic response underlying fMRI BOLD signals. Incorporating balloon-model hemodynamics [14] would enable a more direct comparison with empirical fMRI and improve prediction accuracy.

Learning Dynamics: The GNN parameters are currently learned offline. Online learning algorithms would enable adaptive models that continuously update based on incoming data, more closely mimicking biological learning processes.

4.5.2. *Future Extensions.* **Task-Evoked Dynamics:** Extending the framework to model task-evoked activity by incorporating stimulus representations and learning task-relevant mappings. This would enable the investigation of how multi-scale organization supports cognitive functions.

Whole-Brain Simulations: Scaling to higher spatial resolutions using The Virtual Brain infrastructure and high-performance computing. This requires algorithmic optimizations, including sparse connectivity representations and parallel computing strategies.

Personalized Models: Developing subject-specific models by estimating individual parameters from multi-modal neuroimaging (structural MRI, DTI, fMRI, EEG). Personalized models could predict individual responses to interventions, enabling precision medicine approaches in psychiatry and neurology.

Developmental and Aging Trajectories: Modeling how multi-scale dynamics evolve across the lifespan by varying parameters according to developmental and aging trajectories. This could illuminate critical periods and identify vulnerable windows for neurological disorders.

Multi-Area Heterogeneity: Incorporating regional differences in neural properties (cortical laminar structure, cell-type composition, receptor densities) to capture known hierarchies in cortical processing timescales [8].

Closed-Loop Control: Developing control-theoretic approaches to optimally manipulate multi-scale dynamics toward desired states. This could inform brain stimulation protocols for clinical interventions or cognitive enhancement.

4.6. **Broader Impact.** This work contributes to the emerging field of network and computational neuroscience [2, 49–60] by providing mathematical tools for studying hierarchical brain organization. The integration of dynamical systems theory, stochastic processes, and machine learning represents a paradigm for multi-scale modeling that is applicable beyond neuroscience to ecology, economics, or social systems exhibiting hierarchical structures.

The framework's ability to generate mechanistic explanations alongside predictions bridges the gap between black-box machine learning and interpretable dynamical models. The GNN component provides predictive power, while the underlying differential equations offer mechanistic insight combining strengths of data-driven and theory-driven approaches.

5. CONCLUSION

We have presented a comprehensive mathematical framework integrating stochastic differential equations with graph neural networks to model multi-scale brain dynamics. The framework successfully reproduces critical empirical phenomena, including scale-free avalanche dynamics, hierarchical temporal organization, and metastable functional connectivity patterns. Through rigorous mathematical analysis, we identified stability conditions and bifurcation points governing cross-scale interactions.

The key innovations include: (1) unified treatment of neural dynamics, synaptic plasticity, and network topology as coupled dynamical variables, (2) demonstration of emergent criticality from multi-scale interactions without parameter fine-tuning, (3) mechanistic explanation for hierarchical temporal organization, and (4) generation of testable predictions for experimental validation and clinical applications.

This work provides a foundation for understanding how microscopic neural processes give rise to macroscopic brain function through hierarchical organization. Future extensions incorporating additional biological details and scaling to whole-brain simulations promise to deepen our understanding of neural dynamics in health and disease, potentially informing novel therapeutic strategies for neurological and psychiatric disorders.

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Authors' contributions:

MTN: performed the work and analyzed the Method

MTN: wrote the manuscript

Data Availability Statement: The empirical data used for model validation in this study were obtained from the WU-Minn Human Connectome Project (HCP) database [43,44], which is publicly available to the research community upon application at <https://www.humanconnectome.org/>. The custom Python code developed for the simulations, numerical integration, and analysis presented in this paper is available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate: The empirical data from the Human Connectome Project (HCP) used in this study were collected with informed consent from all participants and under the ethical oversight of the Institutional Review Board at Washington University in St. Louis. As this study involved secondary analysis of fully anonymized, publicly available data, no separate ethics approval was required for the analyses conducted here.

Consent for Publication: All participants in the Human Connectome Project provided consent for their anonymized data to be used for research and published in scientific journals.

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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