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In Silico Neuroimmunology: Decoding the Systems Logic of Neuroinflammation in Neurodegenerative Disease

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ABSTRACT

Background: The human central nervous system (CNS) operates through a complex, non-linear dialogue with the innate immune system. This review delineates the emerging field of in silico neuroimmunology, which employs mathematical abstraction to resolve the "complexity crisis" and the "stiff timescale problem" inherent in neurodegenerative pathologies.

Materials and Methods: This expert narrative review utilizes a framework-driven methodology to synthesize diverse computational formalisms. Models were selected based on their mechanistic depth and relevance to diseases such as Alzheimer's, Parkinson's, and Multiple Sclerosis.

Results: By synthesizing frameworks ranging from ordinary differential equations (ODEs) to agent-based models (ABMs), we demonstrate how the transition to chronic neurotoxicity is a systems-level bifurcation. We highlight the role of hysteresis in creating self-sustaining inflammatory states and the necessity of modeling microglial plasticity as a continuous epigenetic landscape. We further address the "stiffness" of neuroimmune networks, which requires specialized solvers to bridge the 12-order-of-magnitude temporal gap between molecular events and clinical decline.

Conclusion: In silico neuroimmunology is no longer merely descriptive but offers the quantitative logic to design precision therapies. The advent of neurological digital twins and physics-informed neural networks (PINNs) marks a transition toward engineering control, allowing for the simulation of personalized therapeutic interventions and the optimization of immunomodulatory strategies.

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Introduction

The human central nervous system (CNS) operates through a complex, non-linear dialogue with the innate immune system [1]. Although once viewed as an "immune-privileged" organ, the CNS is now understood to be serviced by a dynamic innate immune system orchestrated primarily by resident glial cells [2-4]. This paradigm shift has given rise to the field of systems neuroimmunology [5], in which neuroinflammation is recognized as a critical, non-linear process governing the balance between CNS health and neurodegeneration [6].

The complexity of the neuroimmune network—arising from feedback loops, redundancy, and multiscale interactions—demands quantitative approaches [7-9]. In response, the emerging discipline of in silico neuroimmunology employs mathematical abstraction to resolve the complexity crisis inherent in neurodegenerative pathologies [5].

While several recent reviews have cataloged general biological markers of neuroinflammation or summarized specific computational models in isolation, there remains a critical gap in bridging multiple mathematical scales and frameworks. This integrative review aimed to systematically synthesize the diverse computational and mathematical formalisms used to decode the systems logic of neuroinflammation. We specifically focus on how mathematical abstractions—ranging from continuous differential equations to discrete agent-based models (ABMs) and network graph theory—can address the "stiff timescale problem" [9] and the "bifurcation" from protective homeostasis to chronic, self-perpetuating neurotoxicity [10, 11].

By analyzing the underlying dynamic principles (such as bistability, hysteresis, and multiscale connectivity), we provide a framework for translating these models into predictive, control-oriented clinical strategies [12-14].

The clinical need: The duality of acute vs chronic inflammation

The most critical clinical feature of neuroinflammation is its inherent duality. It functions as a "double-edged sword," capable of both profound neuroprotection and catastrophic neurotoxicity depending on the context, duration, and intensity of the response [15, 16].

The protective physiological response

In its acute, physiological form, neuroinflammation is an adaptive, homeostatic mechanism. When the brain encounters "danger signals"—such as pathogen-associated molecular patterns from infection or damage-associated molecular patterns (DAMPs) from trauma—microglia undergo a rapid phenotypic shift [17]. As described by Vaughan et al. (2018), this acute response serves three essential functions: The containment of infection, the phagocytic clearance of cellular debris and toxic protein aggregates (such as amyloid-beta), and the initiation of tissue repair through the release of neurotrophic factors [18].

Under healthy conditions, this inflammatory burst is transient and self-limiting; once the threat is neutralized, powerful resolution mechanisms (e.g. interleukin [IL]-10 and tumor necrosis factor [TNF]-β signaling) dampen the response, returning the system to homeostasis [19].

The destructive pathological transformation

However, in the context of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), this regulatory logic fails. The system transitions into a state of chronic, dysregulated inflammation [20, 12]. Instead of resolving, glial activation becomes sustained and self-perpetuating.

As detailed in recent reviews, this chronic state is characterized by the continuous release of neurotoxic mediators—including TNF-α, IL-1β, and reactive oxygen species (ROS)—which cause collateral damage to healthy neurons [21, 22]. This neuronal damage releases additional DAMPs, which, in turn, re-activate microglia, creating a "vicious cycle" of inflammation and degeneration that drives disease progression over decades [23].

Distinguishing between the protective (acute) and the destructive (chronic) phases is the central clinical challenge, as therapies that broadly suppress inflammation may inadvertently hinder beneficial repair processes if administered at the wrong time [24].

The systems-level failure: Defining the "bifurcation"

From the perspective of dynamical systems theory, the transition from health to disease can be rigorously conceptualized as a bifurcation [10]. A bifurcation occurs when a small change in the parameters of a system (such as the gradual accumulation of amyloid plaque or

oxidative stress) causes a sudden qualitative change in its long-term behavior [11].

In systems neuroimmunology, the transition from acute, protective neuroinflammation to a chronic, self-perpetuating state can be understood through this same dynamical systems framework. The nervous system maintains homeostasis by balancing pro-inflammatory and anti-inflammatory signals. However, when an external pathological stimulus—such as DAMPs or protein aggregates—exceeds a critical threshold, the system undergoes a bifurcation, transitioning from a low-inflammation state to a high-inflammation state.

To formalize this behavior, we can represent the inflammatory state variable (which can denote the concentration of pro-inflammatory cytokines or the activation level of microglia) using the following canonical ordinary differential equation (ODE) *(Equation 1)*:

1. $$\frac{dx}{dt} = S + \frac{x^n}{K^n + x^n} - \gamma x$$

Here, the dynamic components are defined as follows:

1) S represents the baseline external pathological stimulus driving the system away from homeostasis. 2) The Hill function x^n/K^n+x^n $\frac{x^n}{K^n+x^n}$ models the non-linear auto-amplification, or positive feedback, of the inflammatory response. Here, n is the Hill coefficient (where n>1 introduces switch-like, sigmoidal behavior), and K is the activation threshold constant. 3) The term represents the linear clearance rate of the inflammatory mediators by the surrounding tissue or homeostatic pathways.

As illustrated in the system's phase plane and bifurcation diagrams, when the stimulus exceeds a critical threshold, the stable homeostatic equilibrium disappears, and the system is drawn toward the high-activity, pathological steady state.

The concept of bistability

Building on this mathematical formulation, models reveal that the neuroimmune system often exhibits bistability, meaning it possesses two distinct stable equilibrium states:

1) The healthy state (basin of attraction A): Characterized by low cytokine levels and ramified, surveillance-mode microglia. Perturbations (such as a minor injury) are quickly dampened, and the system returns to its baseline.

2) The chronic disease state (basin of attraction B): Characterized by high, sustained cytokine levels and amoeboid, phagocytic microglia. Once the system enters this state, it is "locked in" by self-reinforcing feedback loops [25].

Tipping points and hysteresis

The shift between these states is not linear. As highlighted by Jenner et al. (2025) in the context of MS, the system possesses a "tipping point" or separatrix [26]. Once the inflammatory stimulus exceeds this critical threshold, the system crosses the bifurcation point and collapses into the chronic disease state.

Crucially, this transition often exhibits hysteresis, a phenomenon where the system's state depends on its history. Consequently, simply removing the initial trigger (e.g. clearing the infection or reducing amyloid load) may be insufficient to restore homeostasis; the system remains trapped in the high-inflammation state due to the established internal feedback dynamics [27]. This mathematical concept explains the clinical observation that neurodegeneration often continues even after the primary insult has been addressed.

The multiscale challenge: The "stiff timescale problem"

A major impediment to understanding and treating neuroinflammation is the "stiff timescale problem." This term, borrowed from computational physics, refers to systems that operate simultaneously on vastly different temporal horizons, making them notoriously difficult to simulate and understand.

Bridging microseconds to decades

The biology of neuroinflammation spans a temporal magnitude of over 12 orders of magnitude (from 10^{-3} to 10^9 seconds):

1) Molecular Scale (10^{-3} to 10^0 seconds): Receptor-ligand binding events (e.g. LPS binding to Toll like receptor 4 [TLR4], with association rates typically 10^6 to 10^7 M^{-1} s^{-1}) and ion channel gating occur in milliseconds to seconds [28].

2) Cellular scale (10^1 to 10^4 seconds): Signal transduction cascades (e.g. NF-κB nuclear translocation occurring within minutes) and subsequent gene expression, protein synthesis, and cytoskeletal rearrangement for microglial migration occur over minutes to hours [29].

3) Tissue/organ scale (10^5 to 10^6 seconds): The formation of glial scars, the infiltration of peripheral T-cells across the compromised blood-brain barrier (BBB), and the resolution of edema occur over days to weeks [30].

4) Disease Scale (10^7 to10^9 seconds): The gradual accumulation of misfolded proteins (e.g. amyloid-β (Aβ) aggregation kinetics), progressive synaptic loss, and clinical cognitive decline in AD or PD unfold over years to decades [31].

In computational physics, "stiffness" is defined by the stiffness ratio S, which is the ratio of the largest to the smallest eigenvalue magnitude of the Jacobian (Equation 2):

2. $$S = \frac{\max|\mathrm{Re}(\lambda)|}{\min|\mathrm{Re}(\lambda)|}$$

In neuroimmune networks, S routinely exceeds 10^9. Simulating such systems requires explicit solvers to take time steps smaller than the fastest dynamics (Δt 10^{-3} s) to maintain stability, making it computationally prohibitive to simulate the slow dynamics (10^8 s). To simulate such systems without numerical instability, specialized implicit numerical solvers or timescale separation methods are required. While the quasi-steady-state approximation is often used to eliminate fast variables by assuming they rapidly reach equilibrium, this approximation can break down in multistable systems, particularly near bifurcation points where timescale separation is not uniform. Fast variables can influence the system's trajectory toward different attractors. Therefore, modern in silico neuroimmunology requires implicit stiff solvers (e.g. backward differentiation formulas) or multiscale hybrid algorithms (e.g. the "slow-scale SSA") that partition the system into fast and slow subsets without destroying the dynamic feedback loops essential for bifurcation.

The role of in silico modeling: From description to control

In response to the "complexity crisis" and the multiscale challenges described above, the field of in silico neuroimmunology has emerged as an indispensable pillar of modern neuroscience. As defined by Vodovotz et al. (2008), this discipline employs mathematical modeling and computational simulation to reconstruct the complex landscape of inflammation [5].

Beyond description:

While early models served primarily to describe observed phenomena, modern computational frameworks serve three transformative functions:

1) Formalization: They force researchers to explicitly define their hypotheses. By converting a biological diagram into a set of differential equations, vague assumptions are replaced by precise mathematical relationships [12].

2) Prediction: They allow for the simulation of "What if?" scenarios. For example, models can predict the "window of opportunity" for a therapeutic intervention—identifying the precise timeframe in which blocking TNF-α is neuroprotective versus when it might inhibit necessary repair [13].

3) Control: Ultimately, the goal is to apply engineering control theory to the brain. By understanding the topology of the cytokine network, models can identify the specific "control nodes" (parameters) that, if perturbed, will force the system out of the chronic disease basin and back toward the healthy attractor [14].

Through the integration of ODEs for temporal dynamics, Partial differential equations (PDEs) for spatial propagation, and ABMs for emergent behavior, in silico neuroimmunology provides the quantitative logic necessary to decipher the immune system of the brain.

Scope and methodology

This review is structured as an expert narrative review aimed at conceptual synthesis rather than an exhaustive systematic mapping of the literature. Given the vast and interdisciplinary nature of in silico neuroimmunology, a purely systematic approach focused on keyword prevalence would likely obscure the conceptual bridges between biology and mathematics that underpin this work. Instead, we employ a targeted, framework-driven methodology.

The following criteria guided the selection of literature and computational models:

1) Conceptual illustrativeness: Priority was given to seminal and paradigm-shifting models that most clearly demonstrate a specific mathematical principle (e.g. bistability, hysteresis, Turing patterns, or prion-like network diffusion) in the context of neuroimmune dynamics.

2) Mechanistic depth: Models were selected based on their ability to mechanistically link biological variables (e.g. cytokines, microglia, Aβ) to dynamical systems behaviors, rather than purely statistical or correlative "black-box" predictions.

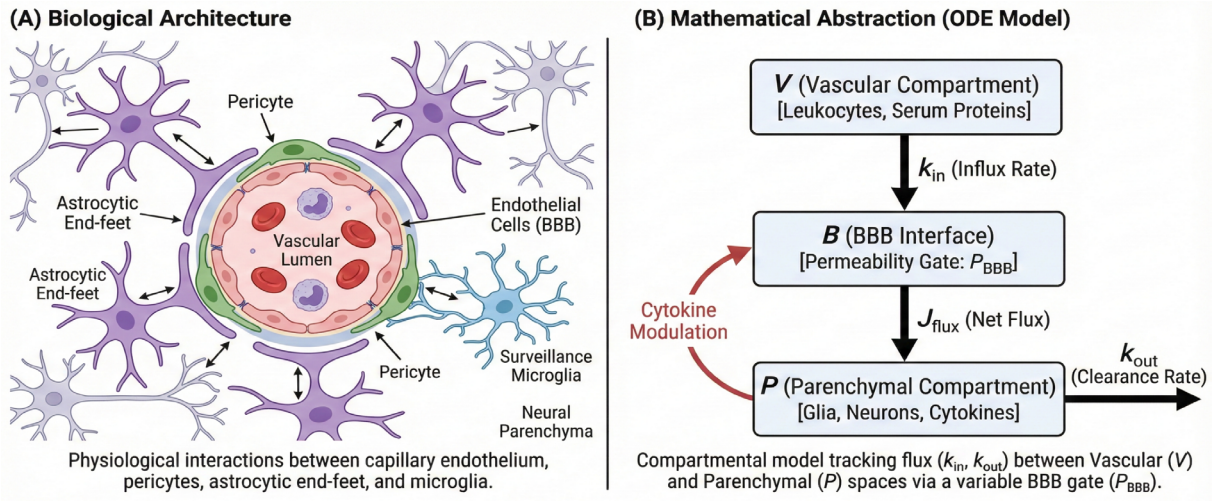

Figure 1. From anatomy to abstraction: Modeling the neurovascular unit

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3) Disease relevance: The review focuses on neurodegenerative and acute neurological conditions in which multiscale computational modeling has provided critical insights into clinical phenomena, such as the irreversibility of chronic inflammation and the spatial patterning of lesions.

By synthesizing these selected paradigms, we aim to construct a coherent “systems logic” framework that identifies the quantitative principles governing the transition from physiological homeostasis to pathological neurodegeneration.

Biological foundations for mathematical abstraction

To construct effective mathematical models, the immense biological complexity of the CNS must be abstracted into quantifiable variables and logical rules. This process of abstraction requires a rigorous definition of the system’s boundaries, its constituent actors, and the topology of their communication networks. As detailed in the review by Foster-Powell & Krishnan (2024), the foundational unit for this abstraction is the neurovascular unit (NVU), which serves as the interface between the immune, nervous, and vascular systems [9, 32].

NVU as a system

In computational terms, the NVU is rarely modeled as a monolithic entity. Instead, it is treated as a multi-compartmental system, defined by distinct spatial domains and flux rates.

According to the structural definitions provided in recent reviews, the NVU is mathematically compartmentalized into three primary domains [33], which are visually contrasted in Figure 1:

1) The vascular compartment (V): This represents the capillary lumen, acting as the source for peripheral immune infiltration. It acts as a reservoir for leukocytes (T-cells, monocytes) and serum proteins, which are "exogenous" variables that enter the system only when barrier integrity is compromised [34].

2) The blood-brain barrier (BBB) interface (B): The BBB is not merely a static wall but a dynamic control parameter. Biologically composed of endothelial cells, pericytes, and astrocytic end-feet, mathematically it is represented as a variable permeability coefficient (P_{BBB}). In healthy states, $P_{BBB} \approx 0$ for cells, during inflammation, it functions as a non-linear gate modulated by local cytokine concentrations, permitting flux [35].

3) The parenchymal compartment (P): The spatial domain containing the neural circuitry. This is the primary "reaction volume" for neuroinflammation models, housing resident glial populations (microglia and astrocytes) and neurons [36].

The abstraction of this anatomical structure into a compartmental mathematical model is depicted in Figure 1. The right panel illustrates the ODE framework, where the compartments (V, B, P) interact via flux rates (k_{in}, k_{out}) of immune mediators, governed by the barrier permeability κ.

Left panel (biological architecture): A schematic representation of the physiological NVU, illustrating the physical interaction between the capillary endothelium,

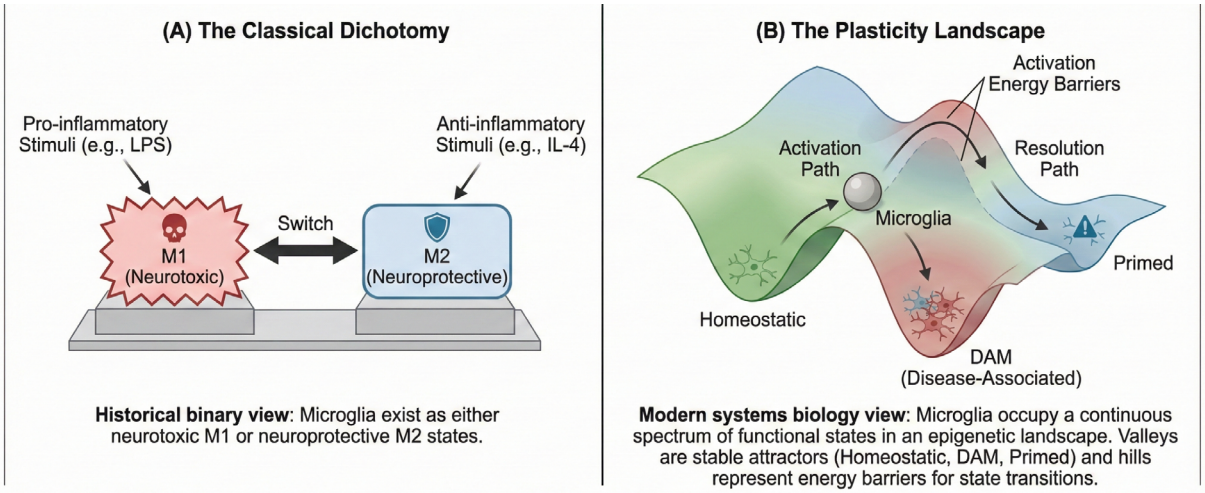

Figure 2. The shift from binary switches to epigenetic landscapes

pericytes, astrocytic end-feet, and surveillance microglia within the neural parenchyma.

Right panel (mathematical abstraction): The corresponding compartmental model used in ODE frameworks. The system is defined by three distinct compartments: the Vascular space (V), the Blood-Brain Barrier interface (B), and the Parenchymal volume (P). Arrows represent the flux rates (k_{in}, k_{out}) of immune mediators, where the barrier permeability (P_{BBB}) functions as a variable gate modulated by local cytokine concentrations.

As noted in the comprehensive analysis by Lecrux & Hamel (2011), the coordinated activity of all cells within this unit is essential for regulating the inflammatory environment [36]. The breakdown of the NVU—specifically the decoupling of neurovascular coupling—is a critical "system failure" mode in diseases like Alzheimer's and Ischemic Stroke [37]. Similarly, emerging evidence underscores the critical role of these neuroimmune interactions in the pathophysiology of Huntington's disease [38].

Cellular players in the network

The accuracy of any in silico model depends on the definition of its state variables. While early models treated glial cells as simple binary switches, modern systems biology demands a more nuanced representation of cellular plasticity and crosstalk.

Microglial plasticity: Beyond the M1/M2 dichotomy

Microglia, the resident macrophages of the CNS, are the primary state variable in neuroinflammation models [39]. Historically, mathematical models categorized microglial activation into two distinct, opposing phenotypes, mirroring the peripheral macrophage classification:

1) M1 (classical activation): A pro-inflammatory, cytotoxic state induced by stimuli, such as lipopolysaccharide (LPS) or interferon-gamma. It is characterized by the secretion of TNF-α and ROS [40].

2) M2 (alternative activation): An anti-inflammatory, reparative state associated with tissue repair and the secretion of IL-10 and brainderived neurotrophic factor (BDNF) [41].

However, recent single-cell RNA sequencing (scRNA-seq) studies cited by Weathered et al. (2024) have revealed that this binary paradigm is an oversimplification [23, 42]. Microglia in vivo exist in a continuous multidimensional spectrum of activation [43].

Mathematical implication: Modern models, such as ABMs and advanced ODE systems, now represent microglial polarization not as a switch (0→1) but as a continuous variable or probability distribution. This allows for the simulation of "hybrid" phenotypes (e.g. M2b, M2c) and specific disease-associated states like the "disease-associated microglia" (DAM) observed in Alzheimer's, which simultaneously express specific markers, such as triggering receptor expressed on myeloid cells 2 (TREM2), while downregulating homeostatic genes [44-46]. Figure 2 contrasts the historical binary classification with the modern 'epigenetic landscape' view, where microglia occupy a continuous spectrum of functional states.

Table 1. The evolving definition of microglial states in computational models

Phenotype Classification	Biological Function	Key Molecular Markers	Mathematical Representation (Old)	Mathematical Representation (New)
M1 (classical)	Pro-inflammatory; pathogen defense; neurotoxicity via ROS/TNF-α.	CD86, iNOS, TNF-α, IL-1	Binary variable (or)	High value in a continuous probability distribution (P_{act}>0.8)
M2 (alternative)	Anti-inflammatory; tissue repair; phagocytosis; neurotrophic support	CD206, Arginase-1, IL-10, BDNF	Binary variable (or)	Low value in a continuous probability distribution; often split into sub-states (M2a, M2b, M2c)
DAM	Response to neurodegeneration; barriers around plaques; "sensing" mode	TREM2, APOE, Clec7a	Not represented	Distinct state vector or agent rule-set triggered by specific DAMP thresholds.
Primed/Dark	Hypersensitive state; exaggerated response to secondary insults (e.g. aging/stress)	MHC-II (high), P2RY12 (low)	Not represented	"Hysteresis" state: Lower activation threshold ($K_{0.5}$) with standard decay rates.

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Abbreviations: TREM2: Triggering receptor expressed on myeloid cells 2; DAMPs: Damage-associated molecular patterns; IL: Interleukin; TGF: Transforming growth factor; iNOS: Inducible nitric oxide synthase; BDNF: Brainderived neurotrophic factor; APOE: Apolipoprotein E; MHC-II: Major histocompatibility complex class II; ROS: Reactive oxygen species; P2RY12: Purinergic receptor P2Y12.

A) The classical dichotomy: The historical view of microglial activation as a simple binary switch between the neurotoxic "M1" phenotype and the neuroprotective "M2" phenotype.

B) The plasticity landscape: The modern systems biology perspective, visualized as a Waddington epigenetic landscape. Microglia (represented as a ball) traverse a continuous 3D terrain of gene expression.

"Valleys" represent stable attractors, such as the Homeostatic state, the DAM state, and the Primed state. The height of the "hills" represents the activation energy required to switch phenotypes, illustrating that intermediate or hybrid states are possible and that phenotypic transitions are continuous rather than discrete.

Despite these advances, a critical gap remains between high-dimensional experimental data and their incorporation into dynamical models. While scRNA-seq and single-nucleus RNA sequencing (snRNA-seq) have revolutionized our understanding of microglial heterogeneity—revealing a continuum of activation states rather than a strict M1/M2 dichotomy [47, 48]—translating these high-dimensional, yet inherently static, transcriptomic snapshots into continuous dynamical models remains a significant challenge [49].

In particular, scRNA-seq data are obtained from dissociated cells and therefore lack temporal resolution, obscuring the kinetics of activation and the rates of transitions between microglial states. Although computational approaches, such as pseudotime analysis, can infer relative progression, they do not provide the absolute kinetic parameters required to parameterize dynamical systems models [49]. Moreover, transcriptomic profiles do not always correlate directly with functional phenotypes or protein-level activity, and single-nucleus approaches may fail to capture key activation markers [50].

An additional limitation lies in the loss of spatial context. Neuroinflammatory processes are inherently spatial—shaped by gradients of signaling molecules and localized cell–cell interactions—yet scRNA-seq disrupts this organization through tissue dissociation. While emerging spatial transcriptomics techniques partially address this issue, they currently involve trade-offs in gene coverage and sensitivity, creating a fundamental data bottleneck for model construction.

From a modeling perspective, treating experimentally identified microglial clusters as discrete, fixed states risks neglecting the continuous transitions and plasticity that define microglial dynamics. Consequently, parameterizing differential equation models directly from such data introduces substantial uncertainty, particularly when the timescales of gene expression changes do not align with physiological processes such as cytokine secretion or clearance [49].

Addressing these limitations will require next-generation modeling frameworks that integrate multi-omic data with time-resolved functional assays and explicitly account for parameter uncertainty, thereby bridging the gap between static transcriptomic measurements and continuous dynamical representations of neuroinflammation. Table 1 summarizes the shift from binary classification to continuous spectrum modeling.

The astrocyte-microglia crosstalk

Astrocytes are not passive bystanders but active regulators of the inflammatory response. Farina et al. (2023) emphasize that effective models must capture the bidirectional communication between these glial types [51, 52].

1) Forward signaling (microglia astrocyte): Activated microglia release factors, such as C1q and TNF-α, which induce a reactive "A1" phenotype in astrocytes, stripping them of their ability to support synapses [52].

2) Feedback signaling (astrocyte microglia): Conversely, astrocytes release regulatory cytokines (TGF-β, IL-10) that can dampen microglial activation, acting as a "buffer" to prevent runaway inflammation [53].

Neuronal feedback and DAMPs

Neurons are the ultimate "victim" in neurodegenerative models, but they are also active participants. When stressed or injured, neurons release DAMPs—such as ATP or misfolded proteins (e.g. alpha-synuclein, Amyloid-) [54]. These pathways are central to the genetic risk and phenotypic progression observed in PD [55].

In mathematical terms, DAMPs function as the forcing function or input signal that drives the system away from equilibrium [56]. The release of DAMPs creates a positive feedback loop: inflammation triggers neuronal death, which in turn releases more DAMPs, which further inflames [57].

The cytokine network topology

Cytokines serve as the molecular "edges" connecting the cellular "nodes" in the neuroimmune graph. The topology of this network—specifically the arrangement of positive and negative feedback loops—determines the system's stability [58].

Key signaling hubs

1) TNF-α-(the accelerator): Identified via network analysis as a highly connected "hub," TNF-α acts as an early responder. It induces its own expression (autoamplification) and triggers downstream cascades (IL-1, IL-6) [59].

2) IL-10 (the brake): A potent anti-inflammatory cytokine that inhibits pro-inflammatory production. Crucially, its expression is often delayed relative to TNF-α, creating a temporal window where inflammation can occur before resolution kicks in [60].

3) TGF-β (the stabilizer): Unlike IL-10, TGF-β is often constitutively expressed, providing a baseline inhibitory tone that prevents spontaneous microglial activation [6, 61].

Feedback timing and adaptation

A critical insight derived from computational modeling, highlighted by Anderson et al. (2015), is that the timing of feedback is as important as its strength [62].

1) Adaptation: When exposed to a constant stimulus, the system does not maintain peak output; instead, it adapts (desensitizes) to a lower steady state to prevent tissue damage [63].

2) Mechanism: In silico knockout experiments revealed that TGF-β provides early, rapid damping, while IL-10 handles late-phase resolution. Removing TGF-β in simulations eliminates adaptation (leading to a sustained cytokine storm), whereas removing IL-10 paradoxically enhances early adaptation due to compensatory dynamics before failing to resolve the chronic phase [62].

This specific kinetic "fingerprint"—where rapid positive feedback is followed by delayed negative feedback—is the hallmark of an excitable system. This property forms the basis for the mathematical frameworks discussed in the next section.

Mathematical frameworks: The theoretical core

The translation of neuroimmunological phenomena into computational models requires selecting an appropriate mathematical formalism. This choice is not merely technical but philosophical, reflecting a hypothesis about which biological scales—molecular, cellular, or tissue—are the primary drivers of the disease process [5]. The field relies heavily on two divergent yet complementary approaches: continuous equation-based modeling (ODEs and PDEs), which assumes large, smooth populations, and discrete ABMs, which focus on individual stochastic behaviors. Table 2 presents a comparative overview of these modeling approaches, highlighting their respective strengths and limitations.

ODEs: Temporal dynamics and deterministic kinetics

ODEs represent the most established formalism in systems biology. They are employed when the primary

research question concerns the temporal evolution of a system—"When will the cytokine storm peak?" or "How fast will neurons degenerate?"—under the assumption that the biological compartment is "well-mixed" (spatial homogeneity) [28].

Theoretical basis: Mass action and saturation kinetics

The foundation of ODE modeling in neuroinflammation is the Law of Mass Action, which states that the rate of a reaction is proportional to the product of the reactants' concentrations. However, biological interactions rarely scale linearly indefinitely. Therefore, modern neuroimmune models typically incorporate saturation kinetics (michaelis-menten or hill functions) to represent the limited availability of cellular receptors or enzymes [64]. These models are underpinned by the intricate intercellular signaling loops that form the foundation of these ODE representations [38].

A generalized canonical equation for the activation of a resting glial population (G_R) into a reactive phenotype (G_A) by a pathological stimulus (P) often includes a Hill coefficient (n). A high Hill coefficient (n>2) creates a "switch-like" behavior, which is critical for bistability [65]. Such mathematical formulations must also accurately describe the dynamic activation rates and metabolic shifts of microglial cells [66].

Case study: The Puri and Li Alzheimer's model

A seminal application of ODEs to neurodegeneration is the model developed by Puri and Li (2010), which mathematically formalizes the "Inflammation Hypothesis" of AD [67]. Parallel modeling frameworks are now being developed to better understand and parameterize disease-associated states in other neurodegenerative conditions, such as PD [68]. This model distills the complex AD microenvironment into a system of seven coupled differential equations tracking neurons (N_s, N_d), astrocytes (A_q, A_p), microglia (M_1, M_2), and Aβ.

The model structure explicitly couples neuronal survival to the ratio of pro-inflammatory (M_1) to anti-inflammatory (M_2) microglia. The governing equation for surviving neurons (N_s) illustrates this dependency (Equation 3):

$$3.\ \frac{dN_s}{dt} = \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1$$

The model structure explicitly couples neuronal survival to the ratio of pro-inflammatory (M_1) to anti-inflammatory (M_2) microglia. The governing equation for surviving neurons (N_s) illustrates this dependency:

Here, α_1, α_2, and α_3 represent the "pathway weights" for neurotrophic support (from quiescent astrocytes) and neurotoxicity (from reactive astrocytes and M1 microglia).

Key finding: Through a sensitivity analysis (SA), the authors found that the system is most sensitive to cross-inhibitory interactions between M1 and M2 phenotypes. The model predicts that therapeutic interventions enhancing the M2→M1 inhibition pathway are significantly more effective than those merely suppressing M1 production, identifying a specific "control node" for drug development [67].

Modeling clinical heterogeneity in traumatic brain injury (TBI)

ODE models have also been pivotal in TBI. Vaughan et al. (2018) developed a model parameterizing the cytokine network (IL-1, IL-10, IL-6) using clinical cerebrospinal fluid (CSF) data [18]. By fitting the model to individual patient trajectories, they identified distinct "inflammatory phenotypes." The analysis revealed that unfavorable outcomes were not solely due to excessive inflammation but could also result from a "blunted" or "sub-physiological" response, suggesting that broad anti-inflammatory treatment could be harmful to specific patient subgroups [18].

PDEs: Spatiotemporal propagation

While ODEs capture when events happen, they are blind to where they happen. In conditions like MS or ischemic stroke, the spatial propagation of pathology—the expansion of a demyelinating lesion or the spread of the ischemic penumbra—is the defining clinical feature. PDEs extend the ODE framework by introducing spatial derivatives (∇^2) to model diffusion and transport [69].

Theory: Reaction-diffusion and chemotaxis

The standard mathematical description for the spread of neuroinflammatory mediators is the reaction-diffusion equation. However, cells do not move randomly; they migrate actively toward chemical signals. This requires the Keller-Segel model for chemotaxis [70] (Equation 4):

$$4.\ \frac{\partial M}{\partial t} = \underbrace{D_M \nabla^2 M}_{\text{Random Motility}} - \underbrace{\nabla \cdot (\chi M \nabla C)}_{\text{Directed Chemotaxis}} + \underbrace{f(M,C)}_{\text{Proliferation/Death}}$$

Here, χ (Chi) represents the chemotactic sensitivity coefficient. A high χ leads to rapid cellular aggregation [71].

Instability: Mathematical analysis shows that if exceeds a critical value relative to diffusion (D), the uniform steady state becomes unstable, leading to the spontaneous formation of cellular aggregates or "patterns" (turing instability) [72]. Furthermore, these cellular migration and interaction dynamics are inherently multiscale, with microglia and astrocytes structurally remodeling and communicating across these boundaries [73].

Case study: Pattern formation in MS

The power of PDEs is exemplified in models of Baló's concentric sclerosis, a rare variant of MS characterized by concentric rings of demyelination. Lombardo et al. (2017) utilized a Reaction-Diffusion-Chemotaxis system to simulate macrophage recruitment (m), cytokine diffusion (c), and oligodendrocyte death (d) [74].

The model demonstrated that these complex anatomical rings are not pre-programmed but are emergent structures resulting from a specific dynamic instability. The "wave" of demyelination travels outward, driven by macrophage chemotaxis. As macrophages destroy myelin, they exhaust the local attractant or enter a refractory state, causing the wave to stall and form a ring. Recovery allows a new wave to initiate, creating the concentric pattern [75]. This provides a mechanistic explanation of how molecular transport rates link to macroscopic tissue pathology.

Modeling anisotropy in the brain

A critical limitation of basic PDE models is the assumption of isotropic (uniform) diffusion. In the brain, white matter tracts create "highways" for molecular transport. Advanced models incorporate Diffusion Tensor Imaging data to define an anisotropic diffusion tensor, allowing simulations to predict how inflammation spreads preferentially along neural pathways, a key feature in neurodegenerative progression [76].

ABMs: Stochastic emergence and spatial heterogeneity

While continuous frameworks (ODEs/PDEs) excel at modeling "mean field" behavior in well-mixed populations, they often fail to capture the granular complexity of neuroinflammation. Biological systems are inherently stochastic (governed by random probability) and heterogeneous (no two cells are identical). Furthermore, the brain is not a continuous gel but a structured network of connected nodes. To address these realities, in silico neuroimmunology increasingly relies on discrete modeling architectures.

ABMs represent a "bottom-up" paradigm shift. Instead of describing the system using aggregate variables (e.g. "concentration of microglia"), ABMs simulate the individual behavior of autonomous entities, or "agents," within a virtual environment [81, 82]. These bottom-up frameworks have been reviewed to show how individual rules can accurately simulate complex interactions and emergent behaviors in immunology [83].

Theoretical basis: Rules, states, and emergence

In an ABM, each agent corresponds to a distinct biological component—such as a single microglial cell, a neuron, or even a discrete A plaque. The behavior of each agent is governed by a predefined set of probabilistic rules (a "state chart") that dictate how it interacts with its local environment and other agents.

The defining power of ABMs is emergence: Complex macroscopic phenomena—such as the formation of a glial scar or the concentric patterning of a lesion—are not explicitly programmed into the model but arise spontaneously from the collective interactions of thousands of individual agents [84].

Case study: Microglial dynamics in AD

A landmark application of ABM technology is the 3D simulation of Alzheimer's pathology developed by Weathered et al. (2024) using the Repast Simphony platform [77]. This model was designed to elucidate the spatiotemporal dynamics of microglia interacting with Aβ in a simulated hippocampal section.

1) Model structure: The simulation initializes with "inactive" microglial agents and diffusing A monomers. Upon sensing A above a specific threshold, microglia transition to an "activated" state, enabling chemotaxis, phagocytosis, and proliferation. These microenvironmental feedbacks—where Aβ or tau pathology induces new microglial expression profiles—are central to increasing subsequent neuronal toxicity [85].

2) Emergent behavior: The model successfully reproduced the formation of plaque barriers—structures where activated microglia physically wall off amyloid deposits to prevent further growth [86].

Table 2. Comparative analysis of mathematical frameworks in neuroimmunology

Framework	Core Assumption	Best Application	Primary Limitation	Seminal Ref.
ODEs	"Well-mixed": Spatial homogeneity; concentration depends only on time (t)	Temporal dynamics; feedback loops; dose-response curves; clinical phenotyping	Cannot model lesions, plaques, or cell migration; assumes infinite population size	[18, 67]
PDEs	Continuum mechanics: variables depend on time and space (x, y, z, t)	Spatiotemporal spread; lesion expansion (MS); gradient formation; edema	Computational cost scales poorly with complexity; difficult to model single-cell heterogeneity	[70, 74]
ABMs	Stochastic autonomy: Individual "agents" follow probabilistic rule sets.	Emergent behavior (swarming); spatial heterogeneity (plaques); stochastic noise	Computationally expensive; "black box" nature makes mathematical analysis (e.g. bifurcation) difficult	[77, 78]
Network/graph theory	Connectivity: Interactions defined by structural edges (axons) between nodes (regions)	Prion-like spread of misfolded proteins (Tau, α-syn) across the connectome	Lacks molecular detail; abstracts away cellular interactions within the node	[79, 80]

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3) Therapeutic simulation: The study used "in silico knockout" experiments to selectively disable specific microglial functions (e.g. chemotaxis vs phagocytosis). The results quantified that microglial activation sensitivity was the single most critical parameter determining final plaque size and coverage, suggesting that therapies modulating surveillance thresholds may be more effective than those merely increasing phagocytic rate [77]. Accounting for such critical control parameters is essential, as microglial dysfunction and parameter uncertainty remain major challenges in validating these models against clinical Alzheimer's progression [87].

Case study: Microglia-neuron crosstalk

Complementary work by Ty et al. (2025) utilized ABMs to explore the "Find-Me" and "Eat-Me" signals between damaged neurons and microglia [78]. This model specifically focuses on the consequences of microglial deficiency. By simulating microglial failure to chemotactically locate and clear damaged neurons, the model demonstrates how the accumulation of uncleared neuronal debris acts as a secondary inflammatory trigger, establishing a mechanistic link between senescent microglial function and accelerated neurodegeneration.

Network and graph-theoretic models: Connectome-based pathology

Moving from the cellular scale to the whole-brain scale, neuroinflammation must be understood in the context of the connectome—the comprehensive map of neural connections in the brain.

Theory: The network degeneration hypothesis

Emerging evidence suggests that neurodegenerative pathology (e.g. misfolded tau or α-synuclein) spreads through the brain in a "prion-like" manner, traversing anatomical axonal pathways [80]. Network models formalize this by treating the brain as a graph G=(V, E), where nodes V represent brain regions and edges E represent white matter tracts.

The network diffusion model (NDM)

The seminal NDM, described by Raj et al. (2012), utilizes the graph Laplacian (L) to predict the trajectory of disease progression [79]. The governing equation is a graph-based heat equation (Equation 5):

$$\frac{d\mathbf{x}}{dt} = -\beta L\mathbf{B} \quad (5)$$

Key Finding: This elegant, low-parameter model demonstrated that the pattern of atrophy in Alzheimer's and Frontotemporal Dementia is mathematically predictable from the brain's connectivity alone. Pathology does not spread by proximity (such as an oil spill) but by connectivity (such as a virus in an airport network), flowing from "seed" regions to their connected neighbors [88]. This framework is now being adapted to model the spread of neuroinflammation, tracking how cytokine signals propagate along functional networks. Recent evidence demonstrates that this microglia-driven network diffusion plays a pivotal role in spreading progressive tauopathies and synucleinopathies throughout the brain [89].

Logic-based and boolean networks: managing intracellular complexity

At the intracellular level, the signaling networks governing glial activation (e.g. TLR4, nuclear factor kappa B [NF-κB], Janus Kinase/signal transducer and activator of transcription) involve dozens of proteins with unknown kinetic parameters. To bypass the "parameter

scarcity" problem of ODEs, researchers employ Logic-Based Models.

Theory: Qualitative topology

These models abstract biological states into binary variables: a gene is either ON (1) or OFF (0). Interactions are defined by Boolean logic gates (AND, OR, NOT) rather than rate constants [90].

Application: Phenotypic attractors

Boolean networks allow for the computation of Attractors—stable states that the system naturally evolves toward. In neuroimmunology, these attractors correspond to distinct microglial phenotypes [91].

Insight: Boolean modeling has revealed that the "M1" and "M2" states are not transient fluctuations but deep basins of attraction. Furthermore, analysis of these networks suggests that "cyclic attractors" (oscillatory states) may represent a "primed" microglial phenotype, allowing for rapid responses without the metabolic cost of full activation [92]. To capture this complexity across systems, recent multiscale models have integrated network diffusion with ODE and Boolean modeling to better represent inflammatory modulation of network-driven spread [93]. This formalism is particularly advocated by Foster-Powell and Krishnan (2024) as a necessary tool for deciphering the dense signaling webs that underpin neuroinflammatory switches [9].

Critical evaluation of mathematical frameworks

To guide the selection and application of in silico models, it is essential to understand the trade-offs inherent in each modeling paradigm. The primary frameworks used in neuroimmunology differ significantly in their mathematical assumptions, computational costs, and validation challenges. ODEs represent the most established formalism for analyzing temporal dynamics under the assumption that the system is well-mixed and spatially homogeneous. While ODEs have very low computational cost, allowing rapid bifurcation analysis and robust parameter sweeping, they completely neglect localized tissue heterogeneity and complex spatial cell-to-cell interactions. Furthermore, parameter estimation in ODE models often suffers from identifiability issues and the phenomenon of "sloppiness," where the system's output is sensitive to only a few linear combinations of parameters while remaining functionally insensitive to others.

To address these spatial limitations, reaction-diffusion PDEs incorporate spatial derivatives to model the transport and chemotactic movement of cells and cytokines. While PDEs introduce essential spatial dynamics, they operate under the continuum assumption, treating cell populations as continuous densities rather than discrete entities. This approximation breaks down at low cell densities or when individual stochastic cell behaviors (e.g. a single microglial cell initiating a response) drive the system [69]. Additionally, PDEs suffer from significant parameterization challenges; measuring in vivo diffusion coefficients and chemotactic sensitivities within the complex, anisotropic extracellular matrix of the brain is exceptionally difficult, and small errors in these parameters can drastically alter pattern formation dynamics (e.g. Turing instabilities) [71].

ABMs bypass the constraints of continuum assumptions by treating biological components, such as microglia and astrocytes, as discrete and autonomous entities. These models can capture emergent phenomena, such as the formation of microglial plaque barriers around amyloid-beta, without requiring a priori assumptions of spatial homogeneity. However, while ABMs excel at generating complex, emergent macroscopic phenomena from simple microscopic rules, their application in neuroimmunology is constrained by several critical limitations. First, simulating thousands of autonomous agents interacting within a 3D virtual tissue requires immense computational power, often limiting the feasible temporal or spatial scales of the simulation [81]. Second, ABMs require the specification of numerous probabilistic rules and thresholds, leading to severe parameter uncertainty and the 'curse of dimensionality' that complicates exhaustive SA [94]. Finally, ABMs function as 'black boxes' that resist traditional mathematical analysis (e.g. bifurcation analysis). Without rigorous pattern-oriented validation against spatially resolved quantitative data, there is a significant risk of constructing biologically plausible but mechanistically incorrect models [84]."

To address these limitations, the field is moving toward Surrogate modeling and model order reduction. Techniques, such as physics-informed neural networks (PINNs) or dynamic mode decomposition, are used to train fast, continuous surrogate models that approximate the input-output map of the slow ABM, thereby bypassing computational cost while retaining the emergent dynamics.

Finally, NDMs describe the whole-brain propagation of pathological agents along axonal tracts. While computationally efficient and valuable for mapping large-

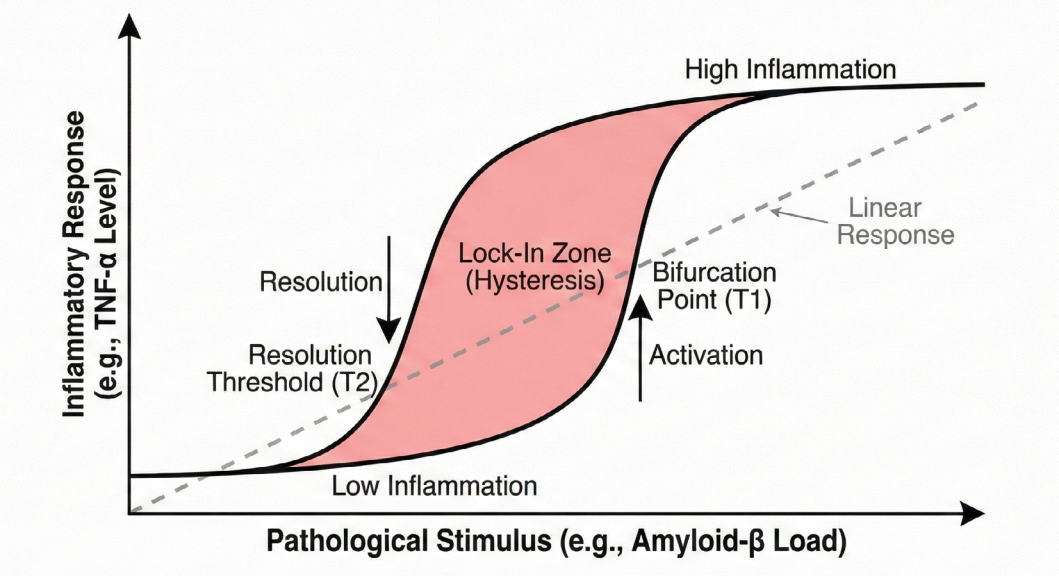

Figure 3. The dynamics of neuroinflammatory hysteresis and the "lock-in" effect IMMUNOREGULATION

scale connectome topology, NDMs lack molecular and cellular resolution, abstracting away local microglial and astrocytic interactions within each node. To address these discrepancies, future approaches will require hybrid multiscale platforms that couple network-level connectome diffusion operators with local parenchymal ODEs or ABMs, thereby capturing both macro-scale spreading and micro-scale cellular dynamics.

Quantitative analysis and model behavior

The true utility of mathematical modeling in neuroimmunology lies not merely in reproducing observed data but in revealing the underlying dynamic principles—the "quantitative logic"—that govern the system. This section explores three critical quantitative concepts that have emerged from in silico studies: Bistability (and the associated phenomenon of hysteresis), stability analysis, and parameter sensitivity.

Dynamics of state transitions: Bistability and hysteresis

One of the most profound insights provided by mathematical modeling is the characterization of neuroinflammation as a bistable system. In dynamical systems theory, a bistable system is one that possesses two distinct stable equilibrium states (attractors) for the same set of parameters.

The concept of "lock-in" (hysteresis)

In a linear biological system, the response is proportional to the stimulus: if the stimulus is removed, the response returns to baseline. However, neuroinflammation models, particularly those involving positive feedback loops (e.g. TNF-α auto-induction or the α-synuclein/ROS loop), exhibit hysteresis [27].

1) The healthy state: At low levels of stimulus (e.g. minimal amyloid load), the system resides in a "basal" state where anti-inflammatory mechanisms (TGF-β, IL-10) dominate.

2) The tipping point: As the stimulus increases, the system resists change until it crosses a critical threshold (the bifurcation point). Once crossed, the system rapidly transitions to a "high-inflammation" state.

3) The chronic state: Crucially, if the stimulus is subsequently reduced, the system does not immediately return to the healthy state. Instead, it remains "locked in" to the high-inflammation attractor due to self-sustaining internal feedback [95].

Figure 3 shows this dynamic irreversibility, illustrating how the 'lock-in' zone prevents the system from returning to homeostasis despite a reduction in the initial stimulus.

In a linear system (dashed grey line), the inflammatory response is proportional to the pathological stimulus; removing the stimulus returns the system to baseline. In

Table 3. The systems logic of neurodegenerative diseases

Disease Context	Primary Driver (Input)	Key Feedback Loop Topology	Resulting System Behavior (Dynamical Feature)
AD	Amyloid- accumulation (plaques)	Bistable switch: Microglial failure to clear A leads to chronic inflammation, which suppresses clearance.	"Lock-in"/hysteresis: Once A exceeds a threshold, the system is trapped in a disease basin even if A production slows.
PD	α-synuclein/ROS aggregation	Double negative: α-syn induces ROS; ROS promotes α-syn aggregation and kills neurons.	Irreversible transition: A tipping point separates healthy homeostasis from runaway degeneration.
MS	Autoimmune demyelination	Delayed negative feedback: Immune attack destroys myelin delayed repair signals recovery.	Limit cycles (oscillations): The system oscillates between relapse (high inflammation) and remission (repair) before eventual collapse.
Ischemic stroke	Acute hypoxia/Flow cessation	Biphasic response: Early microglial activation (protective) vs Late activation (toxic).	Critical transitions: The fate of the penumbra depends on the timing of the inflammatory switch relative to reperfusion.

ROS: Reactive oxygen species.

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a bistable neuroimmune system (solid black line), the response follows a hysteresis loop. As the pathological load (e.g. Aβ) increases, the system resists activation until it crosses a critical "bifurcation point" (T1), triggering a rapid transition to a chronic high-inflammation state. Crucially, reducing the stimulus back to original levels is insufficient to resolve inflammation. The system remains trapped in the "lock-in zone" (shaded red area) due to self-perpetuating feedback loops. Homeostasis can only be restored if the stimulus is reduced below a much lower "resolution threshold" (T2).

Biological Implication: This mathematical property explains the clinical observation in Alzheimer's and MS that therapeutic interventions often fail if administered too late. Once the "lock-in" point is passed, the disease becomes self-perpetuating, independent of the original trigger [10].

Stability analysis: Defining the landscape

To understand these transitions, modelers perform Stability Analysis. This involves calculating the eigenvalues of the Jacobian matrix of the system's differential equations at steady states.

1) Stable node: If all eigenvalues have negative real parts, the state is stable (such as a ball in a valley). Small perturbations dampen out, returning the system to health.

2) Unstable saddle point: If eigenvalues are mixed, the state is unstable (like a ball on a hill). This often represents the "separatrix"—the boundary between health and disease.

3) Limit cycles (oscillations): In some conditions, such as the relapsing-remitting phase of MS, the system enters a "Hopf Bifurcation," where stability is lost to sustained oscillations. The Jenner et al. (2025) model mathematically demonstrates that high inflammatory strength (ϕ) drives the system into this oscillatory regime, providing a rigorous explanation for the cyclic clinical course of MS [26].

Parameter sensitivity and uncertainty

Complex neuroimmune models often contain dozens of parameters (rate constants, binding affinities, diffusion coefficients). SA is the quantitative method used to determine which of these parameters truly matter.

Critical vs sloppy parameters

Global SA techniques (e.g. Sobol indices or Partial Rank Correlation Coefficients) consistently reveal that biological models are "sloppy"—meaning the system's output is highly sensitive to a few "stiff" parameters but largely indifferent to many others [94, 96].

Critical parameters: In neuroinflammation models, the parameters with the highest sensitivity scores are frequently decay rates (e.g. the half-life of cytokines) and activation thresholds ($K_{0.5}$), rather than production rates [62]. For instance, in the Puri & Li AD model, the "cross-inhibition" parameters (M2 inhibiting M1) were identified as the most potent control levers.

Implication for Therapy: This finding suggests that drugs designed to accelerate the clearance of inflammatory mediators or modulate receptor sensitivity may be more effective than those simply blocking cytokine production [67].

Addressing data scarcity

A major challenge, noted as the "Parameter Identification Problem," is the lack of precise human kinetic data.

Most parameters are derived from murine in vitro studies. Advanced modeling addresses this through ensemble modeling, where simulations are run thousands of times with randomized parameter values within biologically plausible ranges. This generates a "probability cloud" of outcomes rather than a single prediction, allowing researchers to assess the robustness of their conclusions despite data uncertainty [28].

Disease-specific modeling paradigms

While the fundamental machinery of neuroinflammation is conserved across the CNS, the specific driving forces and temporal dynamics differ vastly among pathologies. Mathematical modeling allows researchers to customize "generic" neuroimmune models to specific disease states by adjusting initial conditions, boundary conditions, and feedback topology. Despite their biological differences, these pathologies share common dynamical features, such as bistability and feedback loops, as detailed in Table 3.

AD: Amyloid kinetics and the inflammatory feedback loop

AD is characterized by the accumulation of extracellular Aβ plaques and intracellular Tau tangles, accompanied by chronic neuroinflammation. The "Inflammatory Hypothesis" of AD suggests that microglia, unable to effectively clear Aβ, become chronically activated, causing collateral damage to neurons [97].

Modeling the cycle of chronicity (the Puri and Li model)

The model by Puri and Li (2010) demonstrates that the system exhibits bistability: Below a certain A threshold, the brain maintains a healthy state dominated by M2 microglia; however, once A exceeds a critical level, the system crosses a separatrix into a self-sustaining disease state characterized by M1 dominance and progressive neuronal loss [67].

Amyloid aggregation kinetics

The accumulation of A is modeled as a nucleation-polymerization process. Mathematical analysis of global kinetic data has revealed that secondary nucleation—where existing fibrils catalyze the formation of new nuclei on their surface—is the dominant driver of the "explosive" phase of plaque growth [98, 99]. This insight implies that therapeutic antibodies targeting fibril surfaces (to prevent secondary nucleation) may be more effective than those sequestering soluble monomers.

Agent-based simulations of "frustrated phagocytosis"

To capture spatial dynamics, Weathered et al. (2024) developed a 3D ABM simulating microglial responses to amyloid plaques [77]. The model reproduces the phenomenon of "frustrated phagocytosis," where microglia swarm plaques but fail to clear them, instead forming a physical barrier. In silico knockout experiments within this framework quantified that the activation threshold (sensitivity to A) significantly impacts plaque size and coverage, validating the role of TREM2-mediated signaling in regulating the plaque boundary.

PD: The "double negative" and oxidative stress

In PD, the pathology is centered on the loss of dopaminergic neurons in the substantia nigra, driven by the aggregation of alpha-synuclein (α-syn) [21].

The α-synuclein/ROS feedback loop

Mathematical models of PD pathogenesis emphasize a destructive "Double Negative" feedback loop involving ROS.

1) The loop: Aggregated α-syn activates microglia via TLR2/TLR4 receptors, causing them to release ROS.

2) The feedback: ROS promotes further α-syn aggregation (by damaging protein structure) and simultaneously inhibits mitochondrial function in neurons [100].

3) Systems behavior: This mutual reinforcement creates a bistable system. The brain can tolerate a certain level of α-syn and ROS (healthy equilibrium), but once a critical threshold is exceeded, the system irreversibly shifts toward neurodegeneration.

Modeling prion-like spread

The "network degeneration hypothesis" in PD posits that α-syn pathology propagates along neural connections. NDMs utilizing the Graph Laplacian of the human connectome have successfully predicted the patterns of atrophy observed in PD patients, supporting the theory that pathology starts in the brainstem (or gut) and diffuses via axonal transport to the cortex [79, 101].

MS: Spatiotemporal lesion dynamics

MS is unique among these disorders due to its highly focal pathology (plaques) and the prominent role of peripheral immune infiltration.

Modeling relapse and remission (oscillatory dynamics)

The clinical course of relapsing-remitting MS begs for a dynamic explanation. A minimal ODE model by Jenner et al. (2025) captures this behavior using two variables: healthy myelin (M) and inflammation (I). The model reveals that high inflammatory strength (ϕ) drives the system through a Hopf bifurcation, where a stable steady state loses stability and enters a limit cycle [26]. These mathematical oscillations correspond directly to the clinical cycles of relapse (high inflammation, low myelin) and remission (low inflammation, recovering myelin).

Reaction-diffusion and pattern formation

To explain the spatial structure of lesions, such as the concentric rings seen in Baló's sclerosis, researchers use PDEs that incorporate chemotaxis [74]. The model demonstrates that these "Turing patterns" emerge from the interplay between macrophage chemotaxis (towards cytokines) and differential diffusion rates. The "travelling wave" of demyelination expands outward until local resources are exhausted or refractory periods set in, creating stationary rings of destruction [75].

TBI: Temporal phenotyping

In TBI, the insult is acute, but the sequelae can be chronic. The models here focus on predicting long-term outcomes from acute cytokine profiles. Vaughan et al. (2018) developed an ODE model calibrated with CSF data from TBI patients [18]. By analyzing the kinetic parameters of cytokines (IL-1β, IL-6, IL-10), the study identified distinct patient subgroups.

1) Resolving profile: Patients with a transient inflammatory spike that resolves quickly (good outcome).

2) Chronic/blunted profiles: Patients with either prolonged, non-resolving inflammation or a "blunted," subphysiological response (poor outcome). Implication: This modeling suggests that "anti-inflammatory" treatment might actually harm the "blunted" group by deepening their immune paralysis, necessitating personalized modeling for clinical decision support [18].

Ischemic stroke: The penumbra and edema

Stroke models are characteristically "multi-physics," coupling fluid dynamics (blood flow/edema) with reaction-diffusion (inflammation). The critical target in stroke modeling is the penumbra—the tissue surrounding the infarct core that is functionally impaired but still viable. Differential equation models track oxygen supply versus metabolic consumption. A key insight from these models is the dual role of microglia: early activation (<24 hours) is modeled as potentially protective (sealing the core), while late activation (>3 days) drives secondary neurodegeneration and edema formation [102].

Tools, implementation, and standardization

The translation of mathematical frameworks into actionable scientific results relies heavily on the computational infrastructure employed. As the complexity of neuroimmune models increases—moving from simple two-equation systems to multiscale simulations involving thousands of agents—the choice of software platform and adherence to standardization protocols becomes critical for reproducibility and collaboration.

Simulation platforms: A comparative review

No single software solution addresses the diverse needs of in silico neuroimmunology. Consequently, the field utilizes a stratified ecosystem of tools, ranging from general-purpose mathematical solvers to specialized biological simulators. Table 4 presents the capabilities and specific applications of the most prominent software platforms.

Deterministic and equation-based solvers

For systems modeled via ODEs, MATLAB (SimBiology) remains the industry standard. It offers robust "stiff" solvers (e.g. ode15s) essential for handling the multiple timescales of neuroinflammation, as well as sophisticated toolboxes for global SA and parameter estimation. However, its proprietary nature can limit accessibility.

Complex pathway simulator (COPASI) serves as a powerful open-source alternative. Designed specifically for biochemical networks, it excels at analyzing steady states and metabolic control, though it lacks the spatial capabilities required for tissue-level modeling.

Agent-based and spatial simulators

For spatially explicit ABMs, different platforms offer varying balances of ease-of-use versus computational power:

1) NetLogo: Widely used for rapid prototyping and educational models due to its intuitive "turtle-patch" logic. It is effective for visualizing emergent phenomena, such

Table 4. Ecosystem of computational tools for in silico neuroimmunology

Software Platform	Mathematical Focus	Key Features for Neuroimmunology	Open Source?	Best For...
MATLAB (simbiology)	ODEs/systems biology	Rigid/stiff solvers (ode15s) for multi-scale time problems; parameter estimation toolboxes	No (proprietary)	Precise kinetic modeling; clinical QSP models; sensitivity analysis.
COPASI	ODEs/stochastic	User-friendly GUI; specialized for biochemical pathways; SBML compatible	Yes	Studying intracellular signaling networks (e.g. NF-B pathway).
CompuCell3D	PDEs/GGH (potts)	Models cell shape, adhesion, and tissue mechanics (e.g. glial scarring)	Yes	Tissue engineering simulations; barrier formation models.
Repast Simphony	ABM	High-performance Java base; supports massive numbers of agents in 3D space	Yes	Large-scale simulations of plaque formation or viral spread.
NetLogo	ABM	Highly intuitive "Turtle/Patch" language; rapid prototyping	Yes	Educational demos; simple visualizations of chemotaxis/swarming.

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Abbreviations: ODEs: Ordinary differential equations; PDEs: Partial differential equations; GGH: Glazier-graner-hogeweg; SBML: Systems biology markup language; NF-B: Nuclear factor kappalightchainenhancer of activated B cells; COPASI: Complex pathway simulator; QSP: Quantitative systems pharmacology; ABM: Agent-based models.

as chemotactic swarming, but may struggle with the computational demands of massive cell populations.

2) Repast simphony: A high-performance, Java-based platform utilized in advanced studies, such as the Alzheimer's amyloid model by Weathered et al. (2024). It supports complex 3D environments and rigorous data collection, making it suitable for large-scale "in silico knockout" experiments [77].

3) CompuCell3D: Based on the Glazier-Graner-Hogeweg (GGH) or cellular potts model, this platform models cells as deformable objects with energy constraints. It is the gold standard for simulating tissue mechanics, such as how microglia physically squeeze through the neuropil or how an astrocytic scar compacts over time.

Standardization and reproducibility: The crisis of "black box" models

A significant hurdle in the maturation of systems neuroimmunology is the "reproducibility crisis." Foster-Powell and Krishnan (2024) highlight a concerning statistic: less than 20% of published quantitative systems pharmacology (QSP) models in neuroscience have publicly available, executable code. This opacity renders many models "black boxes," preventing independent validation.

To combat this, the community is increasingly adopting systems biology markup language (SBML). SBML is a machine-readable, XML-based standard that describes biological models (species, reactions, parameters) independently of the software used to run them. This interoperability allows a model built in MATLAB to be validated in COPASI. Furthermore, adherence to the minimum information requested in the annotation of biochemical models (MIRIAM) guidelines ensures that model components are annotated with unique biological identifiers (e.g. UniProt IDs for proteins), facilitating the integration of disparate models into larger supermodels.

Future frontiers: From explanation to control

The next generation of neuroimmune modeling is transitioning from explanatory (reproducing past data) to predictive and interventional (controlling future states).

Digital twins and patient-specific modeling

The ultimate application of these mathematical frameworks is the realization of "digital twins," which serve as high-fidelity virtual replicas of individual patients. By integrating structural data, such as MRI-derived connectomics, with functional immune profiles—including CSF cytokines and APOE genotypes—into a unified multiscale model, clinicians can simulate a patient's specific disease trajectory with unprecedented accuracy. This synthesis enables the transition from generalized medical observations to predictive, personalized simulations that account for the unique biological nuances of an individual.

The "Virtual Brain Twin" project represents a significant leap in this direction by effectively linking microscopic molecular changes to macroscale brain activity patterns. This approach is already yielding practical results in TBI research; for instance, Vaughan et al. (2018) demonstrate that patient-specific ODE models can classify individuals into distinct immune subtypes, such as "resolving" versus "chronic" [18]. These models provide a definitive roadmap for precision immunomodu-

lation, allowing clinicians to time specific therapies to coincide with the patient's unique inflammatory phase.

Machine learning integration: PINNs

To address the "Parameter Scarcity" problem, the field is increasingly integrating machine learning with classical differential equations. PINNs represent a sophisticated hybrid approach to this challenge. Rather than treating biological systems as "black boxes" that ignore underlying mechanics, PINNs use neural networks to approximate unknown parts of an equation, such as the exact shape of a reaction curve, while simultaneously enforcing strict adherence to fundamental physical laws, such asthe conservation of mass and energy.

By embedding these physical constraints directly into the neural network's loss function, this framework ensures the resulting model remains biologically and physically plausible. This integration is particularly transformative for clinical research, as it allows robust models to be trained on sparse clinical data that would otherwise be insufficient for traditional parameter estimation methods. Consequently, PINNs bridge the gap between data-driven discovery and mechanistic understanding, offering a more reliable path toward modeling complex neuro-immune interactions.

From explanation to control: In silico trials

Finally, the field is moving toward engineering control. QSP models are now being used to conduct "in silico clinical trials". By generating virtual populations with realistic biological variability, researchers can test drug candidates to identify "tipping points"—the specific dosage and timing required to push the neuroimmune system out of a chronic disease basin and back toward homeostasis. This capability promises to de-risk drug development and rescue promising anti-inflammatory therapies that failed in broad trials by identifying the specific patient subgroups in which they would be effective.

Conclusion

Neuroinflammation is a fundamental pillar of CNS function, acting as both a guardian of homeostasis and an executioner in neurodegeneration. The complexity of this system—characterized by non-linear feedback loops, paradoxical cytokine functions, and interactions spanning milliseconds to decades—often exceeds the intuitive grasp of the unaided human mind.

This review has demonstrated that in silico neuroimmunology is no longer a niche abstraction but an indispensable engine of discovery. Through the rigorous application of ODEs, PDEs, and ABMs, researchers have quantitatively defined the "logic" of the system. We now understand that glial phenotypes are continuous spectra rather than binary switches; that the timing of feedback (e.g. TGF-β vs IL-10) determines the success of resolution; and that stochastic noise is a feature, not a bug, of immune decision-making.

As high-resolution data from single-cell sequencing and connectomics continue to grow, the fidelity of these models will only increase. The future of combating AD, Parkinson's disease, and MS lies not just in the wet lab, but in the equations and simulations that allow us to understand, predict, and ultimately control the complex dynamic system we call the brain.

Ethical Considerations

Compliance with ethical guidelines

This article is a review paper with no human or animal sample.

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Conflicts of interest

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