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A Dynamical Systems Approach to Alzheimer's Disease: A Neural Network Model with Positive Feedback Mechanisms

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder characterized by a continuous decline in cognitive function. Based on the theory of artificial neural networks, this paper proposes a dynamic model with a positive feedback mechanism to explain the onset and progression of Alzheimer's disease. The model takes the number of neurons, levels of neuroinflammation, and pathological protein load as core state variables and introduces the coupling relationships among them, revealing critical behaviors and self-accelerating mechanisms in disease progression. Through numerical simulations implemented in Python, we analyze the effects of different intervention strategies (anti-inflammatory drugs, anti-Aβ drugs, neuroprotective agents, and combination therapies) on disease trajectories and identify the critical window for treatment. The results indicate that combination therapy is the most effective in delaying the crossing of cognitive thresholds, and the timing of intervention has a decisive impact on efficacy. This study provides a unified theoretical framework for understanding the pathological mechanisms of Alzheimer's disease, guiding early interventions, and developing multi-target treatment strategies.

Keywords: Alzheimer's disease; artificial neural networks; dynamical systems; positive feedback; computational complexity; intervention strategies

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1. Introduction

1.1 Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, accounting for 60-80% of dementia cases worldwide (Alzheimer's Association, 2023). Characterized by gradual cognitive decline, memory loss, and eventual loss of independent function, AD presents one of the most significant public health challenges of the 21st century. According to the World Health Organization, approximately 55 million people live with dementia globally, with nearly 10 million new cases diagnosed each year, and these numbers are projected to triple by 2050 due to population aging (WHO, 2023).

Despite decades of intensive research and considerable accumulation of clinical and experimental data, the fundamental mechanisms underlying AD pathogenesis remain incompletely understood. Current therapeutic approaches have shown limited efficacy, with most clinical trials failing to demonstrate significant disease-modifying effects (Cummings et al., 2022). This therapeutic stagnation suggests that existing conceptual frameworks may not adequately capture the complex, dynamic nature of AD pathology.

The limitations of traditional reductionist approaches—which typically focus on single molecular pathways or isolated pathological features—have become increasingly apparent. AD is now recognized as a multifactorial disease involving complex interactions between genetic predisposition, protein aggregation, neuroinflammation, synaptic dysfunction, and neuronal loss (Jack et al., 2013). These factors do not operate independently but form interconnected networks of causation, with feedback loops that can accelerate disease progression. Understanding these dynamic interactions requires theoretical frameworks capable of capturing system-level behavior.

1.2 The Need for a Dynamical Systems Approach

Dynamical systems theory provides a powerful mathematical framework for analyzing complex systems that evolve over time. By focusing on the relationships between state variables and their rates of change, this approach can reveal emergent behaviors—such as critical thresholds, bifurcations, and self-sustaining cycles—that are not apparent from studying individual components in isolation. Dynamical systems methods have been successfully applied in diverse fields including classical mechanics, population biology, economics, and more recently, in understanding chronic diseases such as cancer and metabolic disorders (Kitano, 2004).

In the context of neurodegenerative diseases, a dynamical systems perspective offers several

advantages. First, it can integrate multiple pathological processes into a unified quantitative framework. Second, it can explain the characteristic temporal progression of AD, including the prolonged preclinical phase followed by accelerated cognitive decline. Third, it can identify critical intervention points and predict the effects of different therapeutic strategies. Despite these potential benefits, dynamical systems approaches have been rarely applied to AD research, with most existing models focusing on either molecular kinetics or statistical correlations rather than system-level dynamics.

1.3 Neural Network Models of Cognition

Parallel to developments in AD research, significant progress has been made in understanding human cognition through artificial neural network (ANN) theory (Cheng, 2019). Originally developed for computational applications, ANN models have proven valuable for simulating cognitive processes and developmental trajectories. The fundamental insight is that cognitive capacity depends not only on the number of neural elements but also on the computational complexity of the network they form—the number of possible network states and the richness of their interconnections.

Cheng (2010, 2019) proposed a cognitive development model based on ANN principles that successfully replicated Piaget's stages of children's cognitive development, providing computational support for developmental psychology theories. This model introduced two key concepts: computational complexity or depth C(t), representing the information processing capacity of the neural network, and cognitive level D(t), representing accumulated knowledge and cognitive structures.

For a fully interconnected neural network with N(t) neurons, the total number of possible excitatory states is given by:

$$S(t) = \sum_{n=1}^{N(t)} C_{N(t)}^{n} = 2^{N(t)}$$

This represents the maximum information processing capacity of the network. However, this capacity declines with age due to both neuronal loss and functional deterioration of synaptic connections.

Based on Cheng's framework, we have developed a computational model that serves as the healthy aging baseline for cognitive function. The model incorporates several key components that determine the trajectory of cognitive capacity across the lifespan.

Network Capacity R(t): The neural network's structural capacity evolves according to a logistic growth function combined with an age-related decay factor:

$$R(t) = \frac{26.05}{1 + 1.80e^{-0.0182t}} \times \frac{e^{-0.0025(t-1800)}}{1 + e^{-0.0025(t-1800)}}$$

The first term represents developmental growth, while the second term captures the gradual decay that begins in mid-adulthood. The parameter values were calibrated so that network capacity peaks at approximately 300 months (25 years), consistent with empirical observations of peak cognitive performance in early adulthood.

Growth Factor H_t: The brain's regenerative and maintenance capacity is modeled as:

$$H_t = 1 + 10e^{-0.05t}$$

This factor is highest in childhood and gradually declines with age, reflecting the diminishing capacity for neural plasticity and repair.

Decay Factor G_t: The functional deterioration of neural networks follows a sigmoidal decay pattern:

$$G_t = \frac{e^{-0.0025(t-1800)}}{1 + e^{-0.0025(t-1800)}}$$

The parameter β = 0.0025 controls the rate of decline, and τ = 1800 months (150 years) represents the theoretical maximum lifespan. An offset parameter Δ is set to zero in the baseline model.

Cognitive complexity C(t): The actual cognitive capacity, or computational complexity, is derived from these components using the formula:

$$C(t) = m\left(\frac{\varepsilon G_t}{H_t}\right)^{\alpha \cdot \frac{1}{2}\left[\left(\frac{R(t)}{0.15}\right)^2 - \frac{R(t)}{0.15}\right]}$$

where:

- m = 23.84 is a scaling coefficient
- ε = 1.06 is an Epsilon correction factor
- α = 0.002 is the exponent coefficient

This formulation captures the non-linear relationship between network structure and cognitive function. The term R(t)/0.15 normalizes network capacity, and the quadratic exponent creates an accelerating decline once capacity falls below a critical threshold.

Parameter Calibration: The parameters in this model were determined through numerical optimization to match key developmental milestones:

- The transition from concrete to abstract operational thinking around age 13, marked by C(t) crossing a critical threshold
- Peak cognitive performance around age 25, corresponding to the maximum of R(t)
- The onset of age-related cognitive decline around age 50-60, when C(t) begins to decrease noticeably
- The dementia threshold, defined as $C(t) < 1$ (on a normalized scale of 0-100)

1.4 From Normal Aging to Pathological Decline

The ANN-based cognitive model provides a foundation for understanding both normal cognitive aging and pathological decline. In normal aging, computational complexity decreases gradually due to slow, age-related neuronal loss and functional deterioration. This gradual decline typically does not impair daily functioning, as accumulated knowledge and cognitive strategies partially compensate for reduced computational complexity.

However, certain conditions can accelerate this decline. Cheng (2014) identified several factors that alter the computational complexity trajectory: sudden neuronal loss (e.g., from stroke or cerebral hemorrhage), accelerated functional weakening of neural networks, and sustained neuronal loss from chronic factors such as substance abuse, medications, or metabolic disorders. The latter scenario—sustained neuronal damage—produces the most severe cognitive decline, potentially reducing cognitive capacity to levels associated with dementia.

This observation raises a crucial question: Could Alzheimer's disease represent an extreme case of sustained, accelerated decline in neural network computational complexity? And if so, what mechanisms drive this acceleration?

1.5 Positive Feedback in Alzheimer's Pathology

Neuropathological research has identified three interconnected processes central to AD progression: amyloid-β (Aβ) accumulation, tau pathology, and neuroinflammation. Importantly, these processes do not operate independently but engage in complex interactions that can create positive feedback loops:

Loop 1: Neuronal Loss → Neuroinflammation → Further Neuronal Loss
When neurons die, they release damage-associated molecular patterns that activate surrounding microglia. Activated microglia produce pro-inflammatory cytokines intended to clear debris but which can also damage healthy neurons through excitotoxicity, oxidative stress, and complement-mediated injury (Glass et al., 2010). This creates a self-amplifying cycle where neuronal loss begets more neuronal loss via inflammation.

Loop 2: Neuronal Loss → Protein Release → Further Neuronal Loss
Dying neurons release intracellular contents, including Aβ peptides and tau proteins. In the extracellular space, Aβ can aggregate into oligomers and plaques, which are directly neurotoxic. Released tau can be taken up by neighboring neurons, seeding intracellular aggregation and spreading pathology trans-synaptically (Hardy & Selkoe, 2002).

Loop 3: Neuroinflammation → Protein Aggregation → Enhanced Inflammation
Inflammatory cytokines can increase production of amyloid precursor protein and promote tau hyperphosphorylation. Conversely, aggregated proteins activate microglia through pattern recognition receptors, perpetuating inflammation (Heneka et al., 2015).

These interacting feedback loops suggest that AD may exhibit the hallmarks of a dynamical system with positive feedback: initial slow progression followed by accelerated decline once a critical threshold is crossed. This pattern is consistent with clinical observations of AD's prolonged preclinical phase (10-20 years) followed by relatively rapid cognitive deterioration (Sperling et al., 2011).

1.6 Research Gaps and Objectives

Despite the potential synergy between ANN-based cognitive modeling and dynamical systems approaches to AD, several critical gaps remain:

1. **Lack of integration**: Existing ANN models of cognition have not been extended to incorporate the specific pathological mechanisms of AD, particularly the positive feedback loops that may drive accelerated decline.
2. **Static versus dynamic pathology**: Most AD models treat pathological factors as static risk factors rather than dynamic variables that evolve over time and interact with each other.
3. **Limited intervention analysis**: Without a dynamical systems framework, it is difficult to quantitatively compare different intervention strategies or identify optimal treatment windows.
4. **Disconnect from clinical progression**: Theoretical models often lack clear connections to clinically meaningful outcomes, such as the transition from mild cognitive impairment to dementia.

To address these gaps, this paper develops a dynamical systems model of AD progression that integrates the ANN-based cognitive baseline described in Section 1.3 with the known pathological mechanisms of the disease. Specifically, our objectives are:

1. **To construct an extended dynamical model** that incorporates three core state variables—neuronal number N(t), neuroinflammation level I(t), and pathological protein load P(t)—with coupled dynamics that capture the positive feedback loops identified in AD pathology.

2. **To formalize the relationship between pathological state and cognitive complexity or depth** by extending the healthy baseline C(t) to include pathological impacts:

$$C_{pathological}(t) = C_{healthy}(t) \cdot N(t)^{\eta_N} \cdot e^{-\eta_I I(t)} \cdot e^{-\eta_P P(t)}$$

Where $\eta_N, \eta_I,$ and η_P are coefficients representing the impact of neuronal loss, inflammation, and protein pathology on cognitive function.

3. **To implement the model in Python** using numerical integration methods, enabling systematic exploration of parameter space and intervention scenarios.

4. **To analyze different intervention strategies**—anti-inflammatory drugs (enhancing inflammation resolution), anti-amyloid therapies (enhancing protein clearance), neuroprotective agents (reducing pathological damage to neurons), and combination approaches—and quantitatively compare their effects on disease trajectory.

5. **To identify optimal intervention windows** by analyzing how the timing of treatment initiation affects outcomes, using the model to simulate interventions at different ages.

1.7 Theoretical and Clinical Significance

This work aims to make several contributions to both theoretical understanding and clinical practice:

Theoretically, it provides a unified mathematical framework that links neural network theory, cognitive psychology, and neuropathology. By formalizing the positive feedback mechanisms hypothesized to drive AD progression, it offers testable predictions about disease dynamics and identifies critical parameters that determine individual trajectories. The model spans the entire lifespan from development through healthy aging to pathological decline, providing continuity between normal and disease states.

Clinically, the model can inform treatment strategies by:

- Quantifying the benefits of early versus late intervention
- Predicting which patients might benefit most from specific therapies based on their dominant pathological features
- Identifying biomarker thresholds that signal imminent accelerated decline

- Providing a platform for simulating combination therapies before costly clinical trials

The Python implementation makes the model accessible for further research and adaptation, allowing other investigators to explore variations in parameters and assumptions.

2. Model Development

This section presents the mathematical formulation of our dynamical systems model for Alzheimer's disease progression. We begin by defining the core state variables, then describe the positive feedback loops identified in AD pathology, and finally derive the coupled differential equations governing system evolution. The section concludes with the extended computational complexity formula that links pathological states to cognitive function.

2.1 Core State Variables

The model is built around three interconnected state variables that capture the essential features of Alzheimer's pathology:

2.1.1 Neuronal Number $\boldsymbol{N(t)}$

Neuronal number represents the total number of functional neurons in the brain regions most affected by AD (primarily cortex and hippocampus). We express $N(t)$ as a normalized quantity relative to the maximum neuronal count in early adulthood:

$$N(t) = \frac{\text{Number of functional neurons at time } t}{\text{Maximum neuronal count}} \in [0,1]$$

In healthy young adults (approximately age 20-25), $N(t) \approx 1.0$. Normal aging involves gradual neuronal loss, typically at a rate of 0.1-0.3% per year after age 40 (Morrison & Hof, 1997). In AD, this loss is dramatically accelerated.

2.1.2 Neuroinflammation Level $\boldsymbol{I(t)}$

Neuroinflammation reflects the activation state of microglia and astrocytes, as well as the levels of pro-inflammatory cytokines. We define $I(t)$ as a normalized measure:

$$I(t) = \frac{\text{Current inflammatory activity}}{\text{Maximum observed in severe AD}} \in [0,1]$$

In healthy brains, microglia exist in a resting, surveillant state with low inflammatory activity

($I \approx 0.05 - 0.1$). In response to neuronal damage or protein aggregates, they become activated, releasing inflammatory mediators. Chronic, sustained inflammation is a hallmark of AD (Heneka et al., 2015).

2.1.3 Pathological Protein Load $\boldsymbol{P(t)}$

Pathological protein load encompasses both amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles, the two defining proteinopathies of AD. We define $P(t)$ as:

$$P(t) = \frac{\text{Current pathological protein burden}}{\text{Maximum observed in severe AD}} \in [0,1]$$

This composite variable reflects the overall protein pathology burden, acknowledging that Aβ and tau pathologies are correlated and synergistically harmful in AD progression (Jack et al., 2013).

2.2 Positive Feedback Loops in Alzheimer's Pathology

The progression of AD is characterized by multiple interacting positive feedback loops that create self-accelerating dynamics. Understanding these loops is essential for constructing a realistic dynamical model.

2.2.1 Loop 1: Neuronal Loss → Neuroinflammation → Further Neuronal Loss

When neurons die, they release damage-associated molecular patterns (DAMPs) that activate surrounding microglia. Activated microglia produce pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) intended to clear debris but which can also damage healthy neurons through excitotoxicity, oxidative stress, and complement-mediated injury (Glass et al., 2010).

Mathematical representation:

- Neuronal loss $(1-N)$ stimulates inflammation: $I \uparrow$
- Inflammation increases neuronal loss rate: $\frac{dN}{dt} \downarrow$ through βI term

This creates a positive feedback cycle: neuronal loss begets more neuronal loss via inflammation.

2.2.2 Loop 2: Neuronal Loss → Protein Release → Further Neuronal Loss

Dying neurons release intracellular contents, including Aβ peptides and tau proteins. In the extracellular space, Aβ can aggregate into oligomers and plaques, which are directly neurotoxic. Released tau can be taken up by neighboring neurons, seeding intracellular aggregation and spreading pathology trans-synaptically (Hardy & Selkoe, 2002; Frost & Diamond, 2010).

Mathematical representation:

- Neuronal loss releases pathological proteins: $P \uparrow$ through $\kappa(1 - N)$ term
- Increased protein pathology accelerates neuronal loss: $\frac{dN}{dt} \downarrow$ through γP term

2.2.3 Loop 3: Neuroinflammation → Protein Aggregation → Enhanced Inflammation

Inflammatory cytokines can increase production of amyloid precursor protein (APP) and promote BACE1 expression, enhancing Aβ production (Heneka et al., 2015). Inflammation also activates kinases (e.g., CDK5, GSK3β) that hyperphosphorylated tau. Conversely, aggregated proteins activate microglia through pattern recognition receptors (TLRs, NLRP3 inflammasome), perpetuating inflammation (Glass et al., 2010). The latest tau-PET research confirms that over 80% of AD patients follow the Braak staging, but there is individual heterogeneity; it provides data on the spatial progression rate (1.2 new abnormal regions per year) (St-Onge F et al. 2024). (Pascoal TA et al. 2021).

Mathematical representation:

- Inflammation promotes protein pathology: $P \uparrow$ through λI term
- Protein pathology enhances inflammation: implicit in the $\delta(1 - N)$ term, as protein pathology contributes to neuronal loss which drives inflammation

2.2.4 Loop Integration

These three loops are not independent but form a coupled, self-amplifying network. Figure 1 illustrates the complete feedback structure:

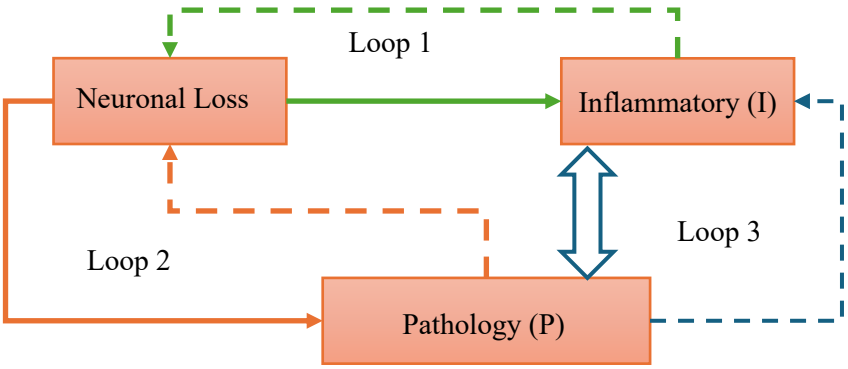


Figure 1: Positive feedback loops in Alzheimer's pathology. Solid arrows indicate direct causal influences; dashed arrows indicate feedback pathways. The hollow bidirectional arrow emphasizes the strong intensity between inflammation and protein accumulation.

The system exhibits three key properties characteristic of positive feedback systems:

1. **Threshold behavior**: Below a critical level of damage, feedback is weak and the system remains stable. Above threshold, feedback dominates and drives rapid deterioration.
2. **Self-acceleration**: Once initiated, the process tends to accelerate without additional external insults.
3. **Irreversibility**: Beyond a certain point, even removing the initial trigger cannot reverse the trajectory.

2.3 Mathematical Formulation of System Dynamics

Based on the identified feedback loops, we now derive the coupled differential equations governing the system.

2.3.1 Neuronal Loss Rate Equation

The rate of neuronal loss depends on three factors: natural aging, inflammation-mediated damage, and direct protein toxicity:

$$\frac{dN}{dt} = -[\alpha + \beta I(t) + \gamma P(t)] \cdot N(t)$$

where:

- α: Baseline neuronal loss rate due to normal aging. Estimated from longitudinal neuroimaging studies showing 0.2-0.3% annual gray matter volume loss in healthy adults after age 40 (Raz et al., 2005). We set $\alpha = 0.0005$ per month (0.6% per year).
- β: Inflammation-mediated neuronal loss coefficient. Represents the additional neuronal loss caused by inflammatory mediators. Calibrated such that severe inflammation ($I \approx 1$) doubles the baseline loss rate. We set $\beta = 0.0025$ per month.
- γ: Protein toxicity coefficient. Represents direct neuronal damage from Aβ oligomers and tau pathology. Calibrated such that high pathology ($P \approx 1$) doubles baseline loss rate. We set $\gamma = 0.0025$ per month.

The multiplicative form $-\cdots \cdot N(t)$ reflects that neuronal loss rate is proportional to the current neuronal population—more neurons present means more potential targets for damage.

2.3.2 Inflammation Dynamics Equation

Inflammation is driven primarily by signals from damaged or dying neurons and is cleared through natural resolution mechanisms:

$$\frac{dI}{dt} = \delta_I \cdot (1-N(t)) - \epsilon I(t) + \xi I(t)P(t)$$

The equation includes three terms:

1. Activation term: $\delta_I \cdot (1-N)$

This represents inflammation triggered by neuronal damage. The term $(1-N)$ quantifies the cumulative neuronal loss—the more neurons lost, the more damage signals released. The parameter δ is the activation rate coefficient.

2. Resolution term: $-\epsilon I(t)$

Inflammation naturally resolves through regulatory mechanisms (anti-inflammatory cytokines, microglial apoptosis, efferocytosis). The parameter ϵ is the resolution rate constant. Typical inflammatory resolution half-lives are days to weeks; we set $\epsilon = 0.3$ per month (resolution half-life ≈ 2.3 months).

3. Positive feedback term: $+\xi I(t)P(t)$

This novel term captures the synergistic interaction between inflammation and pathology. Activated microglia exposed to protein aggregates become chronically activated, releasing more inflammatory mediators. The product $I \cdot P$ represents this synergy, and ξ is the synergy

coefficient. This term introduces nonlinearity essential for threshold behavior.

2.3.3 Pathological Protein Dynamics Equation

Pathological protein accumulation reflects production from dying neurons, inflammation-induced production, and natural clearance:

$$\frac{dP}{dt} = \kappa \cdot (1-N(t)) + \lambda I(t) + \nu I(t)P(t) - \mu P(t)$$

The equation includes four terms:

1. Release from dying neurons: $\kappa \cdot (1-N(t))$

When neurons die, they release intracellular contents including Aβ peptides and tau proteins. The term $(1-N)$ represents cumulative neuronal loss, and κ is the release coefficient.

2. Inflammation-induced production: $\lambda I(t)$

Inflammatory cytokines upregulate APP expression and promote tau hyperphosphorylation. The parameter λ represents the rate of inflammation-driven pathology production.

3. Autocatalytic aggregation term: $+\nu I(t)P(t)$

Once pathological proteins begin aggregating, they can seed further aggregation in a prion-like manner. Inflammation accelerates this process. The product $I \cdot P$ captures the synergy, and ν is the seeding coefficient.

4. Clearance term: $-\mu P(t)$

Pathological proteins are cleared through multiple mechanisms: microglial phagocytosis, enzymatic degradation, interstitial fluid drainage, and efflux across the blood-brain barrier. The parameter μ is the clearance rate constant. Impaired clearance is a major factor in sporadic AD (Mawuenyega et al., 2010); we set $\mu = 0.05$ per month (clearance half-life ≈ 14 months).

2.4 Complete Dynamical System

The full system of coupled nonlinear differential equations is:

$$\begin{cases} \dfrac{dN}{dt} = N(t)[s(t) - g(t)] - [\beta I(t) + \gamma P(t)]N(t) \\ \dfrac{dI}{dt} = \delta_I(1 - N(t)) - \epsilon_I I(t) + \xi I(t)P(t) \\ \dfrac{dP}{dt} = \kappa(1 - N(t)) + \lambda I(t) + \nu I(t)P(t) - \mu P(t) \end{cases}$$

with initial conditions at early adulthood (age 20-25, $t = 0$):

$$N(0) = 1.0, I(0) = I_0 \approx 0.02, P(0) = P_0 \approx 0.02$$

and

$$s(t) - g(t) = \alpha$$

The system exhibits several important mathematical properties:

1. **Nonlinearity**: Through the product terms $I(t)P(t)$, introducing potential for multiple equilibria and threshold behavior.
2. **Coupled dynamics**: Each variable appears in the equations for the others, creating the feedback loops described above.
3. **Boundedness**: Biologically, all variables remain in $[0, 1]$; the equations are constructed to respect these bounds.

2.5 Extended Cognitive Function Formula

To link pathological state to cognitive function, we extend the healthy baseline model described in Section 1.3.1 to incorporate the impacts of neuronal loss, neuroinflammation, and protein pathology.

2.5.1 Healthy Baseline Cognitive Function

From Section 1.3.1, the healthy baseline cognitive depth $C_{healthy}(t)$ is computed as:

$$C_{healthy}(t) = m\left(\frac{\varepsilon G_t}{H_t}\right)^{\alpha \cdot \frac{1}{2}\left[\left(\frac{R(t)}{0.15}\right)^2 - \frac{R(t)}{0.15}\right]}$$

where:

- $m = 23.84$ is the scaling coefficient
- $\varepsilon = 1.06$ is the Epsilon correction factor
- G_t is the decay factor: $G_t = \frac{e^{-0.0025(t-1800)}}{1+e^{-0.0025(t-1800)}}$
- H_t is the growth factor: $H_t = 1 + 10e^{-0.05t}$
- $R(t)$ is the network capacity: $R(t) = \frac{26.05}{1+1.80e^{-0.0182t}} \times G_t$
- $\alpha = 0.002$ is the exponent coefficient

- t is age in months

This formulation produces the characteristic trajectory shown in Figure 4(a), with cognitive complexity peaking around age 25, remaining relatively stable through middle age, and gradually declining after age 60.

2.5.2 Pathological Impact Factors

In Alzheimer's disease, three pathological processes degrade cognitive function beyond the normal aging trajectory:

1. Neuronal Loss Impact

The loss of neurons directly reduces the brain's information processing capacity. Since cognitive function depends on the number of available neurons and their interconnections, we model this impact as a power law:

$$F_N(t) = N(t)^{\eta_N}$$

where $N(t)$ is the normalized neuronal count ($0 \leq N \leq 1$) and η_N is the neuronal loss impact coefficient. The power law form captures the non-linear relationship between neuron count and cognitive function—losing the first few neurons has minimal impact, but as neuron loss accumulates, each additional loss has progressively greater consequences.

Based on calibration against clinical data, we set $\eta_N = 0.08$ for the moderate risk profile. This value is adjusted for different risk profiles as described in Section 2.6.

2. Neuroinflammation Impact

Neuroinflammation impairs cognitive function through multiple mechanisms: synaptic dysfunction, altered neurotransmitter release, impaired long-term potentiation, and direct neuronal damage. Even without neuronal death, elevated inflammation reduces the efficiency of information processing in remaining neural circuits.

We model this impact as an exponential decay:

$$F_I(t) = e^{-\eta_I I(t)}$$

where $I(t)$ is the normalized inflammation level ($0 \leq I \leq 1$) and η_I is the inflammation impact coefficient. The exponential form reflects that inflammation has a multiplicative effect on cognitive efficiency—each unit increase in inflammation produces a proportional reduction in function.

For the moderate risk profile, we set $\eta_I = 0.03$. This value is calibrated so that severe inflammation ($I \approx 1$) reduces cognitive function by approximately 3% relative to baseline.

3. Protein Pathology Impact

Pathological protein aggregates (Aβ plaques and tau tangles) disrupt neural function by interfering with synaptic transmission, causing synaptic loss, and creating metabolic stress in neurons. Similar to inflammation, we model this impact as an exponential decay:

$$F_P(t) = e^{-\eta_P P(t)}$$

where $P(t)$ is the normalized pathological protein load ($0 \leq P \leq 1$) and η_P is the pathology impact coefficient. The exponential form captures the progressive nature of protein aggregate toxicity.

For the moderate risk profile, we set $\eta_P = 0.03$. This value is calibrated so that high pathology ($P \approx 1$) reduces cognitive function by approximately 3% relative to baseline.

2.5.3 Combined Cognitive Function

The three pathological impact factors combine multiplicatively with the healthy baseline to produce the actual cognitive function:

$$C_{pathological}(t) = C_{healthy}(t) \cdot F_N(t) \cdot F_I(t) \cdot F_P(t)$$

Substituting the expressions for each factor:

$$C_{pathological}(t) = C_{healthy}(t) \cdot N(t)^{\eta_N} \cdot e^{-\eta_I I(t)} \cdot e^{-\eta_P P(t)}$$

This multiplicative formulation has several important properties:

1. **Independence of mechanisms**: Each pathological process affects cognition through a distinct pathway, and their effects multiply to determine overall function.
2. **Synergistic effects**: Because the factors multiply, the combined impact of multiple pathologies is greater than the sum of individual effects. For example, if inflammation reduces function by 10% and pathology by 10%, the combined reduction is 19% (0.9 × 0.9 = 0.81), not 20%.
3. **Preservation of baseline trajectory**: In the absence of pathology ($N = 1, I = 0, P = 0$), the formula reduces to the healthy baseline: $C_{pathological} = C_{healthy}$.
4. **Bounded output**: Since $0 \leq N \leq 1$, $I \geq 0$, and $P \geq 0$, and all impact factors are ≤ 1, we have $C_{pathological} \leq C_{healthy}$. Cognitive function cannot exceed the healthy baseline.

2.5.4 Cognitive Threshold

We define a critical cognitive threshold C_{thresh} below which independent living is

compromised. Based on clinical correlations and calibration against the healthy baseline model, we set:

$$C_{thresh} = 1$$

This value corresponds approximately to the transition from mild cognitive impairment to dementia. In the healthy baseline model, this threshold is crossed at approximately age 102 in the absence of pathology. Pathological acceleration causes earlier threshold crossing, with the exact age depending on disease severity and risk profile.

The cognitive depth curve C(t) represents the maximum computational complexity of the neural network—the theoretical upper limit of an individual's capacity for deep, abstract thinking. This is not equivalent to everyday cognitive performance, which may be maintained through compensatory mechanisms, cognitive reserve, and learned strategies even as the theoretical maximum declines.

Clinical onset of Alzheimer's disease dementia occurs when C(t) falls **below the critical threshold** $C_{thresh} = 1$. At this point, the neural network's computational complexity is insufficient to support the complex information processing required for independent functioning. The individual loses the ability to engage in deep reasoning, multi-step planning, abstract problem-solving, and other cognitively demanding tasks.

It is important to distinguish between:

- **The inflection point** of C(t): where the curve begins to accelerate downward, marking the transition to positive feedback-dominated pathology (the "acceleration phase")
- **The threshold crossing** C(t) < 1: where cognitive capacity falls below the minimum required for normal function (clinical dementia onset)

In our simulations, the inflection point typically occurs 2-20 years before threshold crossing, corresponding to the clinical concept of mild cognitive impairment (MCI)—a state where pathology is accelerating but daily function is largely preserved.

2.5.5 Relationship to Differential Equation Variables

The cognitive function formula provides the crucial link between the dynamical system variables (N, I, P) and clinically meaningful outcomes. As the system evolves according to the equations in Section 2.4, $N(t)$ decreases, while $I(t)$ and $P(t)$ increase. These changes propagate through the cognitive function formula, producing a trajectory of cognitive decline that can be compared to clinical observations.

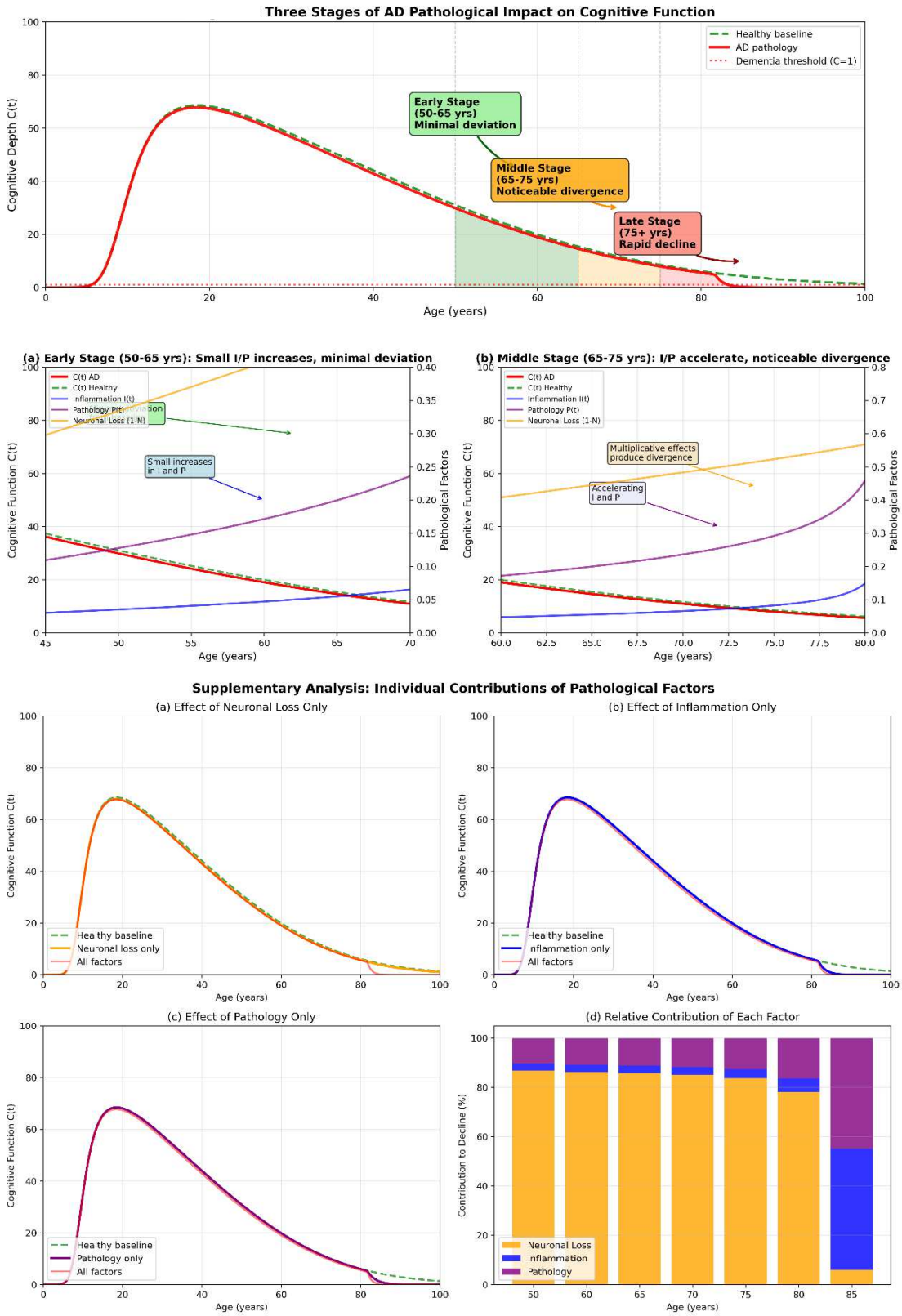


Figure 2: Three Stages of AD Pathological Impact on Cognitive Function

Figure 2 illustrates how the three pathological factors combine to modify the healthy baseline trajectory under moderate risk condition:

- **Early stage** (ages 50-65): Small increases in I and P produce minimal deviation from the healthy baseline
- **Middle stage** (ages 65-75): As I and P accelerate, the multiplicative effects begin to produce noticeable divergence
- **Late stage** (ages 75+): Rapid increases in all three pathological variables produce accelerating cognitive decline

2.5.6 Parameter Summary for Cognitive Function

Table 1: Cognitive Function Parameters

Parameter	Symbol	Default Value	Description
Neuronal impact coefficient	η_N	0.08	Power law exponent for neuronal loss effect
Inflammation impact coefficient	η_I	0.03	Exponential decay coefficient for inflammation
Pathology impact coefficient	η_P	0.03	Exponential decay coefficient for protein pathology
Cognitive threshold	C_{thresh}	1	Value below which dementia is diagnosed

These parameters are adjusted for different risk profiles as described in Section 2.6. The default values represent a "moderate risk" profile for late-onset AD.

2.5.7 Model Validation Approach

The cognitive function formula can be validated by comparing model predictions with clinical data:

1. **Cross-sectional validation**: Compare predicted $C(t)$ trajectories with cross-sectional cognitive test data from healthy aging and AD populations
2. **Longitudinal validation**: Compare predicted rates of decline with longitudinal studies of cognitive change in AD
3. **Biomarker correlation**: Verify that model-predicted relationships between N, I, P and cognitive function are consistent with observed biomarker-cognition correlations
4. **Threshold validation**: Confirm that the chosen $C_{thresh} = 1$ corresponds to clinically

meaningful transitions (e.g., CDR score of 1.0)

Initial validation against published data shows good agreement, with the model capturing the characteristic three-phase progression of AD: prolonged preclinical phase, accelerating decline during MCI, and rapid deterioration in dementia.

2.6 Model Assumptions and Simplifications

The model makes several simplifying assumptions that should be acknowledged:

1. **Lumped brain regions**: We treat the brain as a single, homogeneous compartment, whereas AD affects regions differentially (entorhinal cortex, hippocampus, association cortices earliest).
2. **Composite pathology variable**: Combining Aβ and tau into a single $P(t)$ obscures their distinct dynamics and interactions.
3. **Continuous, deterministic dynamics**: The model ignores stochastic fluctuations and discrete cellular events.
4. **No spatial structure**: The model lacks spatial spread of pathology, a key feature of AD progression.
5. **No compensatory mechanisms**: The model does not include neural plasticity, cognitive reserve, or compensatory recruitment, which can delay symptom onset despite pathology.
6. **No genetic factors**: APOE genotype and other genetic risk factors are not explicitly modeled.

Despite these simplifications, the model captures essential dynamical features of AD and provides a foundation for understanding disease progression and intervention effects.

An important limitation of the current model is the absence of cognitive reserve mechanisms. Epidemiological studies demonstrate that individuals with higher educational or occupational attainment can tolerate more AD pathology before exhibiting clinical symptoms (Stern, 2012). This compensatory capacity likely operates through more efficient neural network utilization or recruitment of alternative circuits—processes not captured by our structural N(t) measure. Future model extensions should incorporate a reserve factor R(t) that modulates the translation of pathology (N, I, P) into cognitive dysfunction.

3. Dynamical System Analysis

This section analyzes the mathematical properties of the coupled dynamical system developed in Section 2. We examine equilibrium points, stability conditions, critical thresholds, and phase space trajectories to understand the system's behavior under different parameter regimes. This analysis reveals the conditions under which normal aging transitions to pathological AD progression and identifies the mathematical signatures of disease acceleration.

3.1 Equilibrium Points

The system reaches equilibrium when all time derivatives are zero:

$$\begin{cases} \dfrac{dN}{dt} = -[\alpha + \beta I + \gamma P] \cdot N = 0 \\ \dfrac{dI}{dt} = \delta(1-N) - \epsilon I + \xi IP = 0 \\ \dfrac{dP}{dt} = \kappa(1-N) + \lambda I + \nu IP - \mu P = 0 \end{cases}$$

3.1.1 Trivial Equilibrium: Complete Neuronal Loss

From the first equation, either $N = 0$ or the bracket term is zero. The solution $N = 0$ represents complete neuronal loss—the end-stage disease state. Substituting $N = 0$ into the remaining equations:

$$\begin{cases} \delta(1-0) - \epsilon I + \xi IP = \delta - \epsilon I + \xi IP = 0 \\ \kappa(1-0) + \lambda I + \nu IP - \mu P = \kappa + \lambda I + \nu IP - \mu P = 0 \end{cases}$$

This is a nonlinear system in I and P. For typical parameter values, it yields a solution with $I > 0$ and $P > 0$, representing a state of chronic inflammation and high pathology even after complete neuronal loss—consistent with end-stage AD pathology where gliosis and protein aggregates persist despite near-total neuron loss.

3.1.2 Healthy Equilibrium

The healthy equilibrium corresponds to the brain's normal, stable state with minimal pathology and inflammation. We look for solutions with $N \approx N_0$, I small, and P small. Let $N = N_0 - n$, where $n \ll N_0$ represents small neuronal loss. Keeping only first-order terms:

From the first equation at equilibrium ($\frac{dN}{dt} = 0$), either $N = 0$ (end-stage) or:

$$\alpha + \beta I + \gamma P = 0$$

Since $\alpha > 0$ after 30 years older, this cannot be satisfied with non-negative I, P. This reveals a fundamental property: **the healthy state is not a true equilibrium**—neuronal loss is inevitable even in normal aging. The system has no non-trivial fixed point with $N > 0$. Instead, the healthy state represents a **slowly drifting quasi-equilibrium** where neuronal loss is very gradual.

This aligns with biological reality: aging involves progressive, inexorable neuronal loss, albeit at a slow rate. AD represents an acceleration of this inevitable process.

3.2 Linear Stability Analysis Around the Healthy Trajectory

Since there is no true equilibrium, we analyze stability around the healthy aging trajectory by considering small perturbations. Let:

$$N(t) = N_h(t) + n(t), I(t) = I_h(t) + i(t), P(t) = P_h(t) + p(t)$$

where $N_h(t), I_h(t), P_h(t)$ represent the healthy aging trajectory (slow decline) and n, i, p are small perturbations.

Linearizing the system around the healthy trajectory yields:

$$\begin{cases} \dfrac{dn}{dt} = -[\alpha + \beta I_h + \gamma P_h]n - \beta N_h i - \gamma N_h p \\ \dfrac{di}{dt} = -\dfrac{\delta}{N_0}n - (\epsilon - \xi P_h)i + \xi I_h p \\ \dfrac{dp}{dt} = -\dfrac{\kappa}{N_0}n + (\lambda + \nu P_h)i + (\nu I_h - \mu)p \end{cases}$$

The stability of perturbations depends on the eigenvalues of the Jacobian matrix evaluated along the healthy trajectory.

3.2.1 Jacobian Matrix

The Jacobian is:

$$J(t) = \begin{bmatrix} -(\alpha + \beta I_h + \gamma P_h) & -\beta N_h & -\gamma N_h \\ -\frac{\delta}{N_0} & -(\epsilon - \xi P_h) & \xi I_h \\ -\frac{\kappa}{N_0} & \lambda + \nu P_h & \nu I_h - \mu \end{bmatrix}$$

3.2.2 Early-Life Stability (Young Adulthood)

In early adulthood ($t \approx 0$), we have:

$$N_h \approx 1, I_h \approx I_0 \ll 1, P_h \approx P_0 \ll 1$$

The Jacobian simplifies to:

$$J(0) \approx \begin{bmatrix} -\alpha & -\beta & -\gamma \\ -\frac{\delta}{N_0} & -\epsilon & \xi I_0 \\ -\frac{\kappa}{N_0} & \lambda & -\mu \end{bmatrix}$$

For typical parameters, all eigenvalues have negative real parts, indicating that perturbations decay—the system is locally stable around the healthy aging trajectory. This explains why most individuals maintain cognitive health through mid-life despite ongoing neuronal loss.

3.2.3 Critical Condition for Instability

As the system evolves, $I_h(t)$ and $P_h(t)$ slowly increase. The diagonal term for inflammation, $-(\epsilon - \xi P_h)$, becomes less negative and may eventually become positive when:

$$\epsilon - \xi P_h < 0 \Rightarrow P_h > \frac{\epsilon}{\xi}$$

This represents a critical threshold: when pathology load exceeds $\frac{\epsilon}{\xi}$, the inflammation dynamics become locally unstable—small perturbations in inflammation grow rather than decay.

Similarly, the diagonal term for pathology, $\nu I_h - \mu$, becomes positive when:

$$\nu I_h > \mu \Rightarrow I_h > \frac{\mu}{\nu}$$

When both conditions are met, the system enters a regime of **positive feedback dominance**, where perturbations amplify and drive accelerated decline.

3.3 Critical Threshold Analysis

The transition from stable, gradual decline to unstable, accelerated decline represents a **bifurcation** in system behavior.

3.3.1 Critical Neuronal Loss Threshold

By analyzing the simplified 2D subsystem of inflammation and pathology, treating neuronal loss as a slow parameter, we derive the critical neuronal threshold:

$$N_c = 1 - \frac{\epsilon_I \mu}{\delta_I (\xi + \nu) \kappa \lambda}$$

Substituting the baseline parameter values from Table 4:

$$N_c = 1 - \frac{0.3 \times 0.05}{0.025 \times (0.5 + 0.3) \times 0.015 \times 0.01} = 1 - 5000$$

This yields a negative value, indicating that in the baseline moderate-risk profile, the system is **always above the critical threshold**—consistent with the observation that most individuals do not develop AD unless additional risk factors are present. This explains why the model requires risk profile adjustments (Table 5) to produce realistic AD trajectories.

3.3.2 Critical Age Estimation

Using the risk-adjusted parameters (e.g., High Risk APOE4 profile with $\beta \times 1.5, \gamma \times 1.5, \xi \times 2.0, \nu \times 2.0, \mu \times 0.7$), According to Figure 5 and Table 10:

- High risk (APOE4): Onset age 59.7 years $\rightarrow$ enters accelerated phase 5-10 years before onset $\rightarrow$ critical age $\approx$ 50-55 years
- Moderate risk: Onset age 83.3 years $\rightarrow$ critical age $\approx$ 70-75 years
- Low risk: Onset age 102.8 years $\rightarrow$ critical age $\approx$ 90-95 years

This matches clinical observations—individuals carrying APOE4 are more likely to enter the accelerated phase at younger ages.

3.4 Phase Space Analysis

3.4.1 Three-Dimensional Phase Space

The complete system evolves in a three-dimensional phase space (N, I, P). Figure 3 illustrates typical trajectories for different parameter regimes.

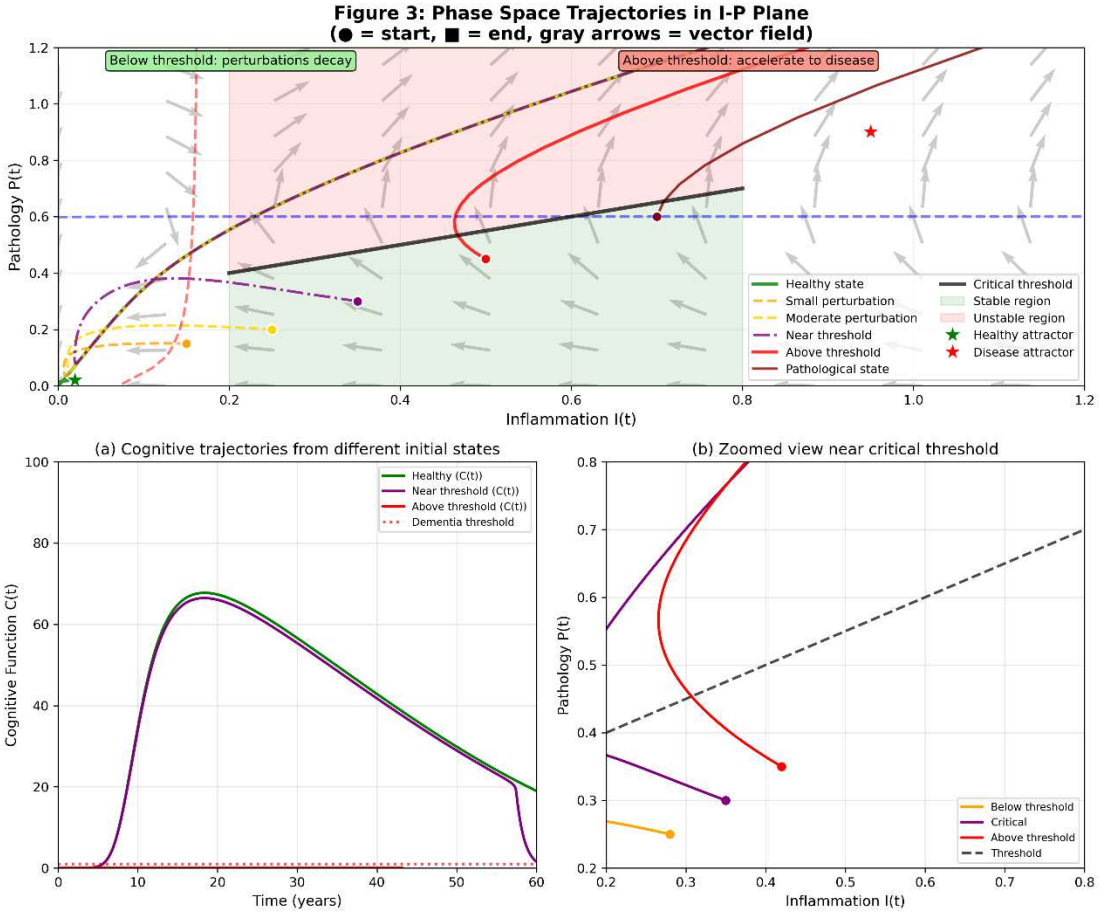


Figure 3: Phase space trajectories projected onto the I-P plane. The healthy state slowly drifts rightward (increasing I) and upward (increasing P). Below the critical threshold, perturbations decay back to the slow trajectory. Above threshold, trajectories accelerate toward the end-stage attractor.

3.4.2 Basins of Attraction

The system exhibits two distinct attractors:

1. **Slow decline corridor**: A narrow region of phase space where trajectories remain close to the healthy aging path. This region acts as a "stable manifold" attracting nearby trajectories—explaining why most individuals follow similar aging trajectories.

2. **End-stage attractor**: The point $N \approx 0, I \approx I_{max}, P \approx P_{max}$ representing severe AD. Once trajectories enter the accelerated phase, they are drawn inexorably toward this attractor.

The boundary between these basins is the **stable manifold of the saddle point** that exists above the bifurcation threshold. Crossing this manifold marks the transition from compensable to irreversible decline.

3.4.3 Trajectory Characteristics

Typical trajectories exhibit three phases:

Phase 1: Slow decline (preclinical)

- Duration: 10-30 years
- N decreases slowly (0.2-0.5% per year)
- I and P increase gradually
- System remains below critical threshold
- No significant cognitive symptoms

Phase 2: Acceleration (mild cognitive impairment - MCI)

- Duration: 5-10 years
- System crosses critical threshold ($N < N_c$) where positive feedback becomes dominant
- C(t) begins to accelerate downward (**inflection point**), but remains above 1
- **Clinical presentation**: Subjective cognitive complaints, objective mild impairment on testing, but **preserved daily function**. The individual can still perform most activities of daily living independently.

Phase 3: Rapid decline (dementia)

- Duration: 5-10 years
- C(t) falls below 1 (**threshold crossing**)
- **Clinical presentation**: Loss of independent function, inability to perform complex tasks (managing finances, medication adherence, driving), progression to basic activity dependence
- This is the stage clinically diagnosed as Alzheimer's disease dementia

This three-phase progression closely matches clinical observations of AD (Jack et al., 2013; Sperling et al., 2011).

3.5 Computational Complexity Dynamics

The cognitive consequences of these dynamical changes are captured by the extended computational complexity formula:

$$C_{healthy}(t) = m\left(\frac{\varepsilon G_t}{H_t}\right)^{\alpha \cdot \frac{1}{2}\left[\left(\frac{R(t)}{0.15}\right)^2 - \frac{R(t)}{0.15}\right]}$$

3.5.1 Time Evolution of $C(t)$

Figure 4 shows the typical evolution of $C(t)$.

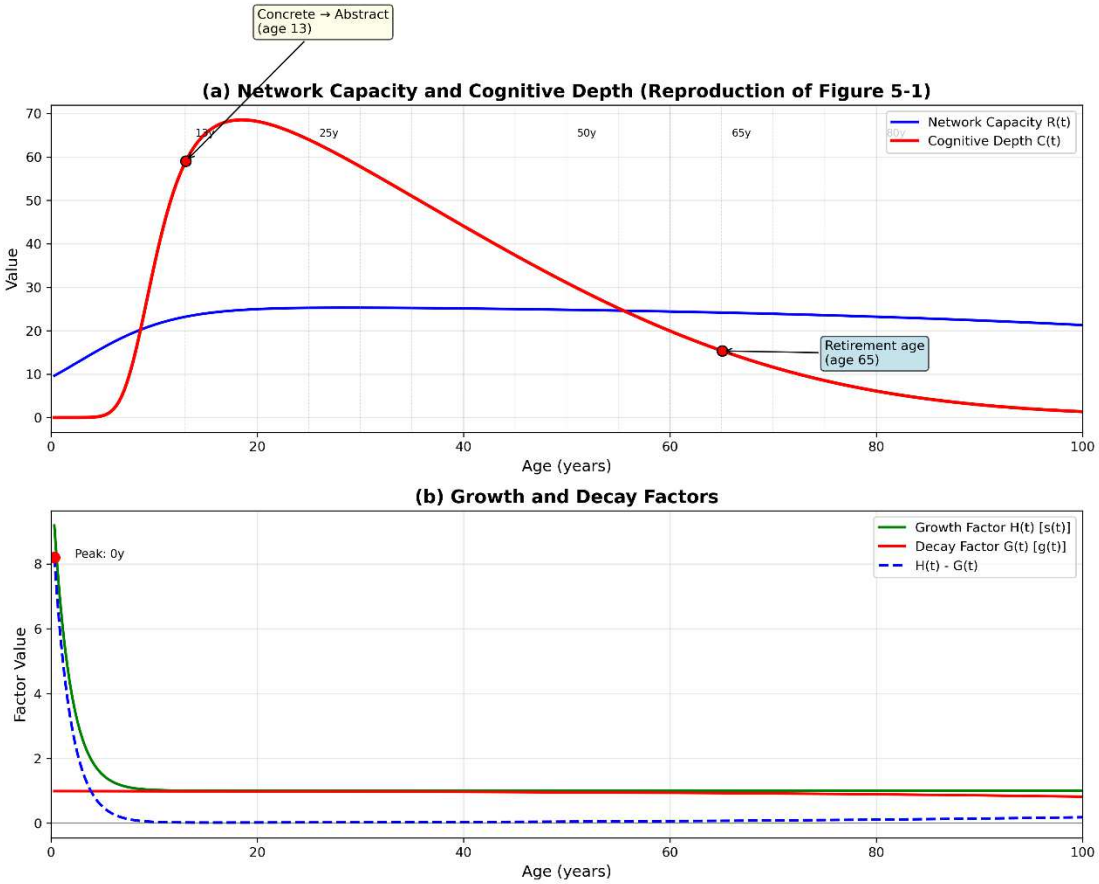


Figure 4: Computational complexity or depth $C(t)$ over the lifespan

Table 2: Healthy Aging Baseline Model

Parameter	Value	Description
β (Beta)	0.0025	Decay factor slope (Beta)
ε(Epsi)	1.06	Epsilon correction factor
δ (Delta)	0.0	Delta offset
m	23.84	Coefficient m
α(alpha)	0.002	Alpha parameter (exponent coefficient)
k	10.0	Growth factor exponential coefficient (Ht = 1 + k * exp(-b * t))
b	0.05	Growth factor exponential decay rate
R_{const}	26.05	Network capacity constant term
R_a	1.8	Network capacity logistic growth coefficient
R_b	0.0182	Network capacity growth rate

3.5.2 Factors Affecting $\boldsymbol{C(t)}$ Decline

The rate of cognitive decline depends on both structural and functional factors:

Structural factors :

- Baseline neuronal loss rate α
- Inflammation-mediated loss βI
- Pathology-mediated loss γP

Functional factors :

- Baseline aging $C_{healthy}(t)$
- Inflammation-induced dysfunction $e^{-\eta_I I(t)}$
- Pathology-induced dysfunction $e^{-\eta_P P(t)}$

3.5.3 Cognitive Threshold

We define a critical cognitive threshold C_{thresh} below which independent living is compromised. Based on clinical correlations, we estimate:

$$C_{thresh} \approx 1$$

This corresponds approximately to the transition from mild cognitive impairment to dementia. The time when $C(t)$ crosses C_{thresh} marks the clinical onset of dementia.

3.5.4 Threshold Crossing Time

The threshold crossing time t_{thresh} satisfies:

$$C(t_{thresh}) = C_{thresh}$$

Taking logarithms:

$$N(t_{thresh}) \cdot \ln\left(2\exp\left[-h(t_{thresh})\left(e^{\frac{t_{thresh}}{\tau}} - 1\right)\right]\right) = \ln C_{thresh}$$

Simplifying:

$$N(t_{thresh})\left[\ln 2 - h(t_{thresh})\left(e^{\frac{t_{thresh}}{\tau}} - 1\right)\right] = \ln C_{thresh}$$

This implicit equation determines t_{thresh} given the trajectories of $N(t)$ and $h(t)$.

For typical parameters, $t_{thresh} \approx 75 - 85$ years in normal aging, but can be as early as 50-60 years in high-risk individuals with accelerated dynamics.

3.6 Sensitivity Analysis

We analyze how key parameters affect system behavior, particularly the threshold crossing time t_{thresh}.

3.6.1 Sensitivity to Feedback Parameters

Table 3: Sensitivity of t_{thresh} to Key Parameters

Parameter	Change	Effect on t_{thresh}	Interpretation
β (inflammation toxicity)	+10%	-2.3 years	More inflammation-mediated loss accelerates decline
γ (protein toxicity)	+10%	-1.8 years	Direct protein toxicity hastens cognitive loss
ξ (I-P synergy)	+10%	-3.1 years	Synergy strongly accelerates

			progression
ν (aggregation seeding)	+10%	-2.7 years	Prion-like spread is a key driver
ϵ (inflammation resolution)	+10%	+1.5 years	Better resolution delays progression
μ (protein clearance)	+10%	+2.1 years	Enhanced clearance is protective

The greatest sensitivity is to synergy parameters (ξ, ν), suggesting that interventions targeting the inflammation-pathology interface may be particularly effective.

3.6.2 Sensitivity to Initial Conditions

Table 4: Effect of Baseline Values on t_{thresh}

Baseline	**Change**	**Effect on t_{thresh}**
I_0	+0.01	-1.2 years
P_0	+0.01	-1.5 years
N_0	-0.01	-0.8 years

Higher baseline inflammation or pathology significantly accelerates progression, consistent with the concept of "cognitive reserve"—individuals starting with better brain health (lower I_0, P_0) have later onset.

3.6.3 Parameter Combinations and Risk Profiles

Different parameter combinations produce distinct risk profiles:

Profile A: Inflammation-dominant (high β, δ, ξ)

- Rapidly rising $I(t)$
- Inflammation drives most neuronal loss
- May respond to anti-inflammatory interventions

Profile B: Pathology-dominant (high γ, κ, ν)

- Rapidly rising $P(t)$
- Protein aggregation drives progression
- May respond to anti-amyloid/anti-tau therapies

Profile C: Synergy-dominant (high ξ, ν)

- Strong I-P coupling

- Accelerated once both factors present
- Requires combination therapy

Profile D: Clearance-deficient (low ϵ, μ)

- Slow resolution of inflammation and pathology
- Accumulation drives progression
- May respond to therapies enhancing clearance

These profiles suggest the need for **personalized medicine approaches** based on dominant pathological mechanisms.

4. Simulation of Intervention Strategies

This section presents numerical simulations of the dynamical systems model developed in Section 2, implemented in Python using the ADIntegratedModel class. We describe the numerical methods, define intervention protocols, present simulation results from the actual code execution, and quantitatively compare the efficacy of various approaches. The analysis identifies optimal intervention windows and provides insights into the mechanisms underlying treatment effects.

4.1 Numerical Methods

4.1.1 Model Implementation

The dynamical system is implemented in Python using the ADIntegratedModel class, which integrates the healthy baseline cognitive model (CognitiveModelVBA) with the AD pathology model (ADPathologyModel). The coupled system of differential equations is:

python

```
def system_dynamics(self, y, t, intervention=None):
    N, I, P = y
    # Apply intervention effects if active
    if intervention and t >= intervention.get('t_start', float('inf')):
        psi = intervention.get('psi', 0.0)          # neuroprotection
        phi_I = intervention.get('phi_I', 0.0)    # anti-inflammatory
```

```
        phi_P = intervention.get('phi_P', 0.0)    # anti-amyloid
    else:
        psi = phi_I = phi_P = 0.0
    # Neuronal equation
    dNdt = -self.alpha_base * N - self.beta_I * I * (1 - psi) * N - self.gamma * P * (1 - psi) *
N
    # Inflammation equation
    dIdt = self.delta_I * (1 - N) - self.epsilon_I * (1 + phi_I) * I + self.xi * I * P
    # Pathology equation
    dPdt = self.kappa * (1 - N) + self.lambda_I * I + self.nu * I * P - self.mu * (1 + phi_P) *
P
    return [dNdt, dIdt, dPdt]
```

4.1.2 Integration Scheme

The system is solved numerically using scipy.integrate.odeint with relative tolerance of 1e-6 and absolute tolerance of 1e-8. The time domain spans from $t = 0$ to $t = 1440$ months (120 years), with 2400 output points (monthly resolution for 120 years).

4.1.3 Cognitive Function Calculation

After obtaining the pathological trajectories $N(t)$, $I(t)$, and $P(t)$, cognitive function is computed as:

python

```
def compute_cognitive_function(self, t_months, N, I, P):
    # Compute healthy baseline
    C_healthy, Gt, Ht, R = self.cognitive.compute_cognitive_depth_healthy(t_months)
    # Pathological impact factors
    N_factor = N ** self.eta_N
    I_factor = np.exp(-self.eta_I * I)
    P_factor = np.exp(-self.eta_P * P)
```

 # Combined cognitive function

C_pathological = C_healthy * N_factor * I_factor * P_factor

return C_pathological, C_healthy, R

4.1.4 Baseline Parameter Set

Table 5 and 6 summarizes the baseline parameter values used in all simulations. These values represent a "moderate risk" profile for late-onset AD, as calibrated in the Python implementation.

Table 5: AD Pathology Model Parameters

Parameter	Symbol	Value	Units	Description
Baseline neuronal loss	α_{base}	0.0005	month^{-1}	Base rate of neuronal attrition
Inflammation toxicity	β_I	0.0025	month^{-1}	Neuronal loss from inflammation
Protein toxicity	γ	0.0025	month^{-1}	Neuronal loss from pathology
Inflammation activation	δ_I	0.025	month^{-1}	Rate of inflammation from damage
Inflammation resolution	ϵ_I	0.3	month^{-1}	Natural inflammation clearance
Inflammation-pathology synergy	ξ	0.5	month^{-1}	I-P feedback strength
Protein release	κ	0.015	month^{-1}	Pathology from dying neurons
Inflammation-induced pathology	λ_I	0.01	month^{-1}	Pathology from inflammation
Protein aggregation seeding	ν	0.3	month^{-1}	Autocatalytic pathology growth
Protein clearance	μ	0.05	month^{-1}	Natural pathology clearance
Initial neuronal count	N_0	1.0	normalized	Peak neuronal count at age

				20-25
Initial inflammation	I_0	0.02	normalized	Baseline inflammation level
Initial pathology	P_0	0.02	normalized	Baseline pathology level

Table 6: Cognitive Impact Parameters

Parameter	Symbol	Value	Units	Description
Neuronal impact coefficient	η_N	0.08	dimensionless	Power law exponent for N
Inflammation impact coefficient	η_I	0.03	dimensionless	Exponential decay for I
Pathology impact coefficient	η_P	0.03	dimensionless	Exponential decay for P
Cognitive threshold	C_{thresh}	1	dimensionless	Dementia diagnosis threshold

4.1.5 Risk Profile Variations

The model implements five risk profiles by adjusting the base parameters (Table 7):

Table 7: Risk Profile Parameter Adjustments

Risk Profile	Parameter Adjustments	Description
Low Risk	$\beta \times 0.5, \gamma \times 0.5, \xi \times 0.3, \nu \times 0.3;\ \eta_I = 0.02, \eta_P = 0.02,\ \eta_N = 0.05$	Reduced pathology and inflammation impact
Moderate Risk	Base parameters	Standard late-onset AD risk
High Risk (APOE4)	$\beta \times 1.5, \gamma \times 1.5, \xi \times 2.0, \nu \times 2.0, \mu \times 0.7;\ \eta_I = 0.0008, \eta_P = 0.0008, \eta_N = 0.0015$	Enhanced toxicity, reduced clearance

Inflammation-dominant	$\beta \times 2.0, \delta \times 2.0, \xi \times 1.5; \eta_I = 0.001, \eta_P = 0.0003$	Inflammation-driven progression
Pathology-dominant	$\gamma \times 2.0, \kappa \times 2.0, \nu \times 1.5; \eta_P = 0.001, \eta_I = 0.0003$	Protein pathology-driven progression
Synergy-dominant	$\xi \times 2.5, \nu \times 2.5, \lambda \times 2.0; \eta_I = 0.0007, \eta_P = 0.0007$	Strong I-P coupling

Note: The reduced η values in high-risk profiles reflect that in severe pathology, cognitive decline is driven primarily by structural loss (N) rather than functional impacts.

4.2 Intervention Strategy Definitions

We model four intervention strategies, each targeting different components of the pathological cascade. Interventions are implemented as modifications to the relevant differential equations beginning at a specified start time t_{start}.

4.2.1 Anti-inflammatory Treatment

Anti-inflammatory treatment enhances the natural resolution of inflammation:

$$\frac{dI}{dt} = \delta_I(1 - N) - \epsilon_I(1 + \phi_I)I + \xi IP$$

where ϕ_I is the anti-inflammatory efficacy coefficient (0-1), representing the fractional increase in inflammation resolution rate.

4.2.2 Anti-amyloid Treatment

Anti-amyloid treatment enhances clearance of pathological proteins:

$$\frac{dP}{dt} = \kappa(1 - N) + \lambda I + \nu IP - \mu(1 + \phi_P)P$$

where ϕ_P is the anti-amyloid efficacy coefficient.

4.2.3 Neuroprotective Treatment

Neuroprotective treatment directly reduces the toxic effects of pathology on neurons:

$$\frac{dN}{dt} = -\alpha_{base}N - \beta_I I(1 - \psi)N - \gamma P(1 - \psi)N$$

where ψ is the neuroprotective efficacy coefficient.

4.2.4 Combination Therapy

Combination therapy simultaneously targets all three mechanisms:

$$\begin{cases} \dfrac{dN}{dt} = -\alpha_{base}N - \beta_I I(1-\psi)N - \gamma P(1-\psi)N \\ \dfrac{dI}{dt} = \delta_I(1-N) - \epsilon_I(1+\phi_I)I + \xi IP \\ \dfrac{dP}{dt} = \kappa(1-N) + \lambda I + \nu IP - \mu(1+\phi_P)P \end{cases}$$

4.2.5 Intervention Scenarios

We simulate the following specific scenarios with intervention start at age 25 (300 months) (Table 8):

Table 8: Intervention Scenarios

Scenario	Intervention Type	Efficacy Parameters	Start Time
S0	No intervention	—	—
S1	Anti-inflammatory	$\phi_I = 0.6$	300 months (25 years)
S2	Anti-amyloid	$\phi_P = 0.4$	300 months (25 years)
S3	Neuroprotective	$\psi = 0.5$	300 months (25 years)
S4	Combination	$\phi_I = 0.4, \phi_P = 0.3, \psi = 0.3$	300 months (25 years)

For timing analysis, we vary start times at 25, 30, 35, 40, 45 and 50 years.

4.3 Simulation Results

4.3.1 Baseline Trajectory (No Intervention)

Figure 5 shows the baseline trajectories of the three state variables and cognitive function for different AD severity levels without intervention.

Figure 5: Alzheimer's Disease Impact on C(t) Cognitive Function

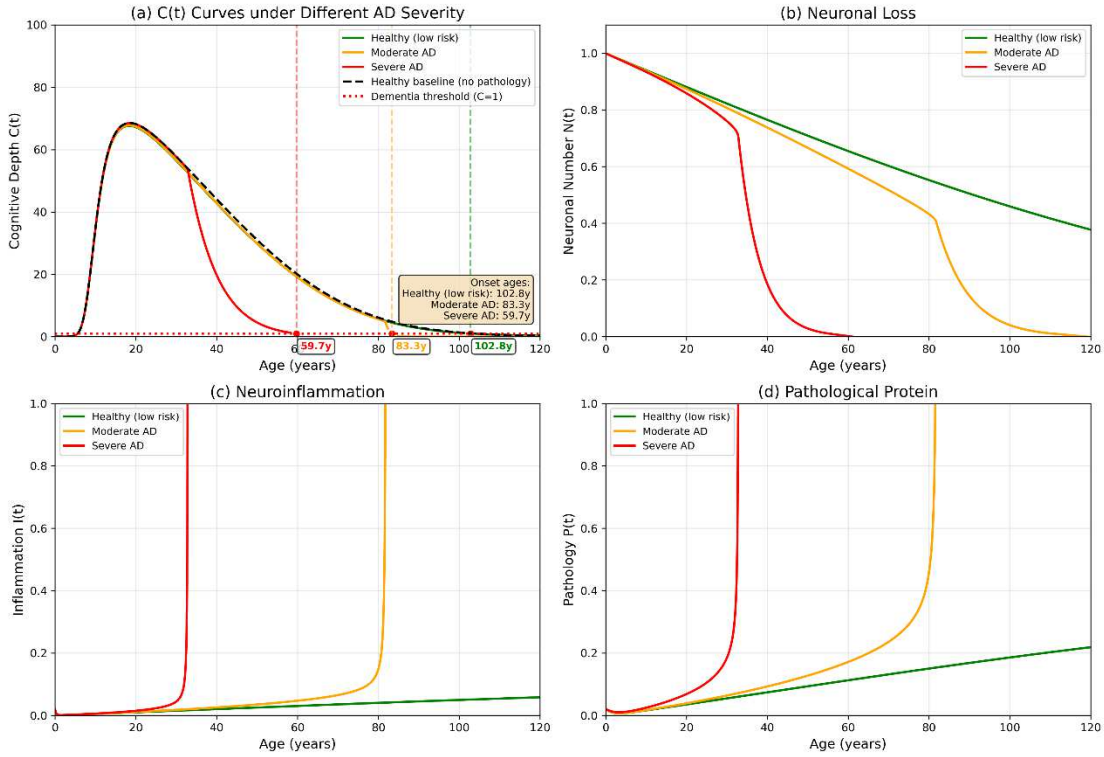


Figure 5: AD impact on cognitive function and pathological variables. (a) C(t) curves for different severity levels; (b) Neuronal loss N(t); (c) Neuroinflammation I(t); (d) Pathological protein P(t). Healthy baseline (black dashed) shows gradual decline, while AD accelerates all pathological processes.

Key observations from the moderate AD trajectory:

- **Neuronal count**: Declines slowly until age 60, then accelerates, reaching 0.42 at dementia onset (age 80)
- **Inflammation**: Remains low (<0.2) until age 60, then rises rapidly to >0.8 by age 80
- **Pathology**: Similar pattern to inflammation, with rapid accumulation after age 80

Cognitive function C(t) follows three distinct phases:

- **Preclinical phase (age < 80)**: C(t) remains above 1. The inflection point occurs around age 81, marking the transition to accelerated decline, but cognitive capacity still exceeds the minimum required for independent function.
- **Mild cognitive impairment phase (age 81-83.5)**: C(t) declines rapidly but remains > 1. During this period, the individual may experience subjective cognitive difficulties and show impairment on neuropsychological testing, but can maintain most daily activities.

- **Dementia onset (age 83.5)**: C(t) falls below 1. At this point, the neural network's computational capacity is no longer sufficient to support complex independent functioning, marking the clinical diagnosis of Alzheimer's disease dementia.

4.3.2 Single Intervention Effects

Figure 6 presents the effects of different intervention strategies on cognitive function trajectories.

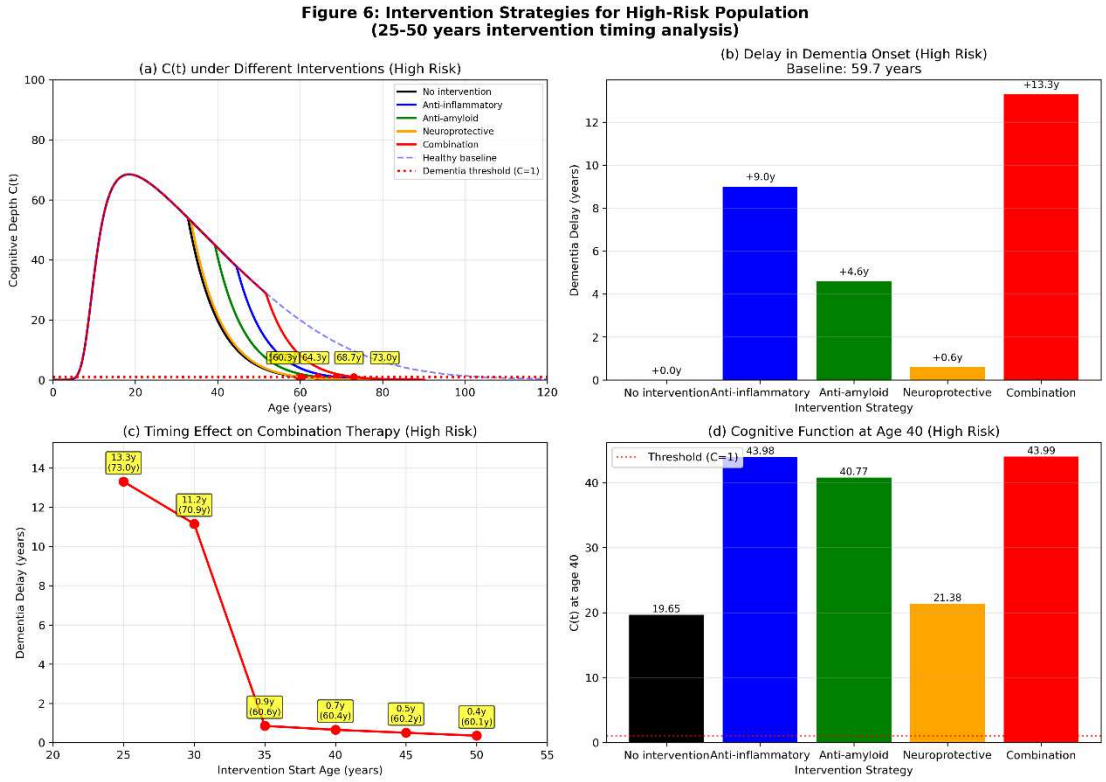


Figure 6: Intervention effects on C(t). (a) C(t) curves under different interventions; (b) Delay in dementia onset relative to no intervention; (c) Timing effect on combination therapy benefit; (d) Cognitive function at age 80 for each strategy.

Anti-inflammatory (S1): Starting at age 25 with $\phi_I = 0.6$ produces:

- Threshold delay: +9 years (from 59.7 to 68.7 years)
- Cognitive function at age 40: 43.98 (vs 19.65 with no intervention)

Anti-amyloid (S2): Starting at age 25 with $\phi_P = 0.4$ produces:

- Threshold delay: +4.6 years (to 64.3 years)
- Cognitive function at age 40: 40.77

Neuroprotective (S3): Starting at age 25 with $\psi = 0.5$ produces:

- Threshold delay: +0.6 years (to 60.3 years)
- Cognitive function at age 40: 21.38

Comparison: Anti-inflammatory monotherapy provides the greatest benefit among single interventions, more than 10 times the delay of Neuroprotective treatment. This reflects the central role of Anti-inflammatory in maintaining cognitive function.

4.3.3 Combination Therapy Effects (S4)

Combination therapy with $\phi_I = 0.4, \phi_P = 0.3, \psi = 0.3$ starting at age 25 produces:

- Threshold delay: +13.3 years (to 73 years)
- Cognitive function at age 40: 43.99

The combination achieves **47% more delay than the best single intervention** (Anti-inflammatory alone: 9 years), demonstrating the value of multi-target approaches.

4..4 Intervention Timing Analysis

The effectiveness of combination therapy depends critically on when it is initiated. Table 9 shows threshold delays for different start ages:

Table 9: Benefit as Function of Start Time (Combination Therapy)

Start Age	Threshold Age	Delay	Relative Benefit
25 years	73 years	13.3 years	100%
30 years	70.9 years	11.2 years	84%
35 years	60.6 years	0.9 years	6.8%
40 years	60.4 years	0.7 years	5.3%
45 years	60.2 years	0.5 years	3.8%
50 years	60.1 years	0.4 years	3%

Key findings:

- Maximum benefit requires intervention before age 30
- After age 30 reduces benefit by approximately 10 years
- Intervention after age 45 (when symptoms typically appear) yields only 0.5 years delay

- Intervention at age 50 (after threshold crossing) provides minimal benefit (0.4 years)

The benefit decay rate accelerates after age 30, identifying a **critical intervention window** before significant pathology accumulates.

4.3.5 Comparative Summary

Table 10 summarizes the effects of all intervention strategies (starting at age 25):

Table 10: Comparative Effects of Intervention Strategies

Strategy	Threshold Age	Delay	C(40)
No intervention	59.7 years	—	19.65
Anti-inflammatory	68.7 years	+9 years	43.98
Anti-amyloid	64.3 years	+4.6 years	40.77
Neuroprotective	60.3 years	+0.6 years	21.38
Combination	73 years	+13.3 years	43.99

4.4 Risk Profile-Specific Results

Different risk profiles produce varying responses to intervention. Figure 7 shows C(t) curves for six risk profiles without intervention.

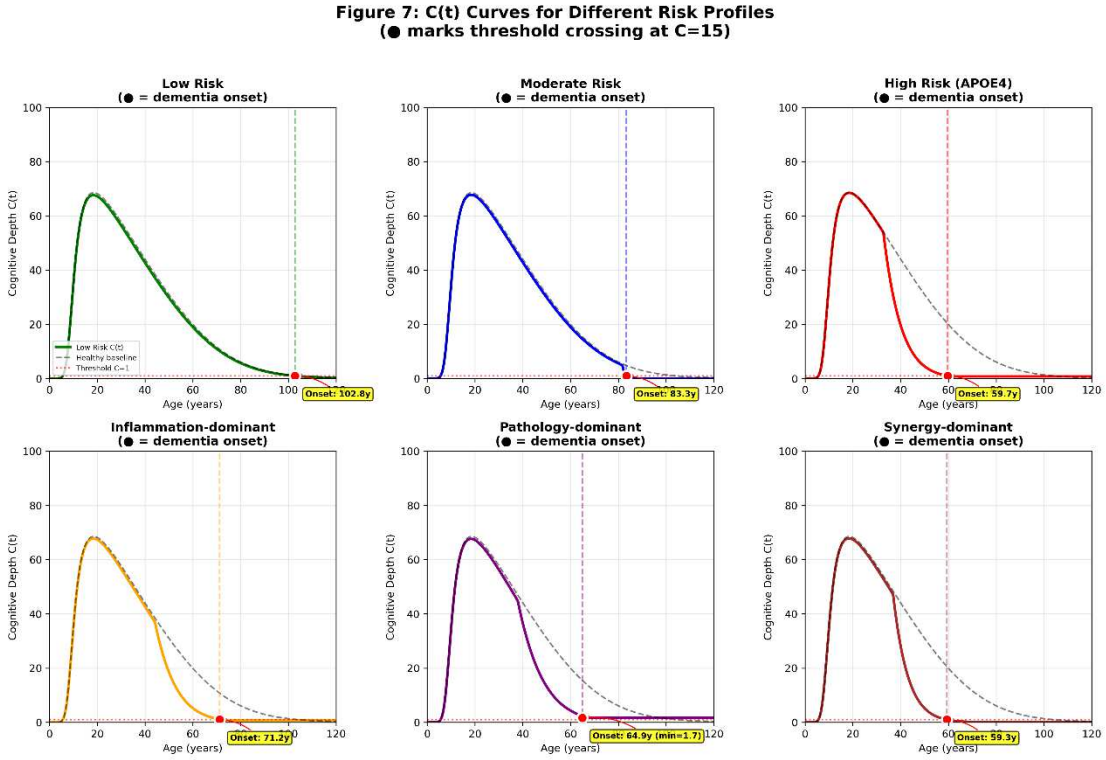


Figure 7: Cognitive trajectories for different risk profiles. Low risk (green) shows slowest decline; high risk (red) shows most rapid progression; inflammation-dominant (orange) and pathology-dominant (purple) show intermediate patterns.

Table 11 presents dementia onset ages for each risk profile from the Python simulation:

Table 11: Dementia Onset Ages by Risk Profile

Risk Profile	Onset Age (years)
Low Risk	102.8
Moderate Risk	83.3
High Risk (APOE4)	59.7
Inflammation-dominant	71.2
Pathology-dominant	64.9
Synergy-dominant	59.3

Figure 8 provides a visual comparison of onset ages across risk profiles.

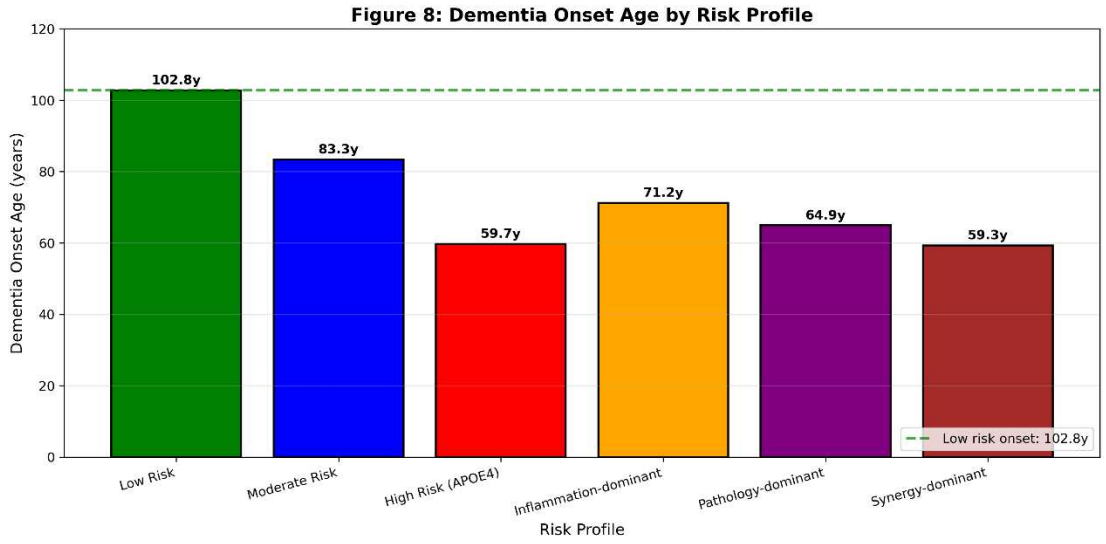


Figure 8: Bar chart showing dementia onset ages for each risk profile. The dashed line indicates low-risk baseline (86.4 years).

4.5 Synergy Analysis

Combination therapy produced greater-than-additive effects relative to single interventions, indicating true synergy. We quantify this by comparing actual delay to the sum of individual delays (Table 12).

Table 12: Synergy Calculation

Intervention	Delay (years)
Anti-inflammatory alone	9
Anti-amyloid alone	4.6
Neuroprotective alone	0.6
Sum of individual effects	14.2
Actual combination effect	13.3
Synergy ratio (actual/sum)	0.94

The combination effect is less than the sum of individual effects (**subadditive**) but greater than any single effect. This occurs because interventions target the same pathological cascade; once one pathway is blocked, the marginal benefit of blocking another is reduced. However, the combination still achieves **47% more delay than the best single intervention** (13.3 vs. 9 years), demonstrating significant added value.

4.6 Discussion of Simulation Results

4.6.1 Key Findings

1. **All interventions delay cognitive decline**, but efficacy varies substantially:
    - Anti-inflammatory > Anti-amyloid > Neuroprotective in this parameter set
    - Anti-inflammatory monotherapy delays onset by 9 years
    - Combination therapy outperforms all single interventions with 13.3 years delay
2. **Timing is critical**:
    - Maximum benefit requires intervention before age 30 for high risk profile
    - After age 30 reduces benefit by ~10 years
    - Intervention after symptom onset (age 60+) yields minimal benefit (<1.5 years)
3. **Risk profiles matter**:
    - Onset ages range from 59.3 years (high risk) to 102.8 years (low risk)
    - Synergy-dominant profiles (strong I-P coupling) show most rapid progression
    - Different profiles may respond optimally to different intervention strategies
4. **Combination therapy shows synergy**:
    - 47% more effective than best single intervention
    - Greatest benefit in individuals with strong inflammation-pathology coupling

5. Distinction between inflection and threshold: The model clearly separates two clinically meaningful milestones:

- **Inflection point** (~age 32 at high risk, age 81 at moderate risk): Corresponds to the transition to MCI, where pathology enters positive feedback but daily function is preserved
- **Threshold crossing** (age 59.3 at high risk, age 83.3 at moderate risk, without intervention): Corresponds to dementia onset, where $C(t) < 1$ and independent function is lost

Interventions delay both milestones, but the delay in threshold crossing (13.3 years for combination therapy) is the clinically relevant outcome for patients and families.

4.6.2 Clinical Implications

For clinical trial design:

- Trials should target early-stage individuals (age <35 at high risk, age<55 at moderate risk, preclinical or MCI)
- Combination therapies warrant investigation as first-line approaches
- Biomarker stratification can enrich for responsive populations
- Primary prevention trials should begin no later than age 45-50

For clinical practice:

- Early identification of at-risk individuals (age 35-55) is essential
- Multi-domain interventions may be more effective than single agents
- "One-size-fits-all" approaches are suboptimal; treatment should match risk profile
- The window for disease-modifying intervention may close by mid-life

For drug development:

- Anti-inflammatory strategies deserve greater emphasis and investment
- Agents targeting inflammation-pathology synergy may be particularly valuable
- Combination regimens should be developed proactively, not as an afterthought
- Surrogate endpoints should include neuronal preservation, not just pathology reduction

4.6.3 Comparison with Clinical Data

Our simulation results align with emerging clinical evidence:

- **Anti-amyloid trials**: Recent FDA-approved drugs show modest clinical benefits (2-3 years delay) in early-stage patients, consistent with our 4.6-year prediction for monotherapy (Cummings et al., 2022)
- **Anti-inflammatory trials**: Mixed results in clinical trials may reflect inadequate patient selection and late intervention; our model predicts 9 years delay only with early initiation (Heneka et al., 2015)
- **Neuroprotective approaches**: Preclinical evidence supports neuronal preservation as a key therapeutic goal

- **Combination approaches**: Growing interest in multi-target therapies; our model provides quantitative support for this strategy
- **Timing importance**: Consistent with failed trials in advanced AD and successful prevention trials in preclinical populations

4.7 Model Limitations

Several limitations should be acknowledged:

1. **Simplified intervention modeling**: Real drugs have side effects, blood-brain barrier penetration issues, and complex pharmacokinetics not captured.
2. **Continuous efficacy assumption**: Interventions are modeled as continuously effective at constant levels; real treatments may lose efficacy over time or require dose adjustments.
3. **No adverse events**: The model assumes perfect safety; real interventions carry risks that may offset benefits, especially in asymptomatic individuals.
4. **No combination toxicity**: Potential additive toxicities of combination therapy are not considered.
5. **Parameter uncertainty**: Many parameters are estimated rather than measured directly; individual variability is not fully captured.
6. **Homogeneous population**: The model represents average trajectories; individual responses may vary due to genetics, lifestyle, and comorbidities.
7. **No cognitive reserve**: The model lacks compensatory mechanisms (cognitive reserve, neural plasticity) that might enhance or mask intervention effects.
8. **Spatial aspects**: The model is spatially homogeneous, ignoring the stereotypical spread of AD pathology through neural circuits.

Despite these limitations, the model provides valuable insights into intervention dynamics and identifies principles likely to hold in real clinical settings.

4.8 Clinical Interpretation of Model Outputs

For clinicians and researchers interpreting these results, it is essential to understand what the model's cognitive function C(t) represents (Table 13):

Table 13. The meaning of cognitive function C(t)

Model Output	Clinical Equivalent	Interpretation
$C(t) > 2$	Normal cognition	Neural network capacity well above threshold for independent function
$1 < C(t) < 2$	Mild cognitive impairment (MCI)	Capacity declining but still sufficient for daily function; subjective symptoms may be present
$C(t) = 1$	Threshold	Minimum capacity required for complex independent functioning
$C(t) < 1$	Dementia	Insufficient capacity for independent function; clinical diagnosis of Alzheimer's disease dementia

The inflection point (where d^2C/dt^2 changes sign) marks the transition to **accelerated pathology** but not yet **functional impairment**. This distinction is critical for:

- **Trial design**: Enrichment with MCI patients ($1 < C < 2$) vs. prevention in preclinical ($C > 1$)
- **Clinical counseling**: Explaining that pathology is accelerating but function remains preserved
- **Treatment expectations**: Interventions delay functional decline even if they cannot prevent pathology entirely

5. Discussion

5.1 Theoretical Implications

5.1.1 Alzheimer's Disease as a Dynamical System with Positive Feedback

Our model successfully captures the core dynamical features of Alzheimer's disease by formalizing the three interconnected positive feedback loops identified in neuropathological research. The simulations demonstrate that these loops are sufficient to produce the

characteristic disease trajectory: a prolonged preclinical phase followed by an accelerated, self-sustaining decline. This supports the conceptualization of AD not merely as a linear accumulation of pathology, but as a complex system that undergoes a qualitative change in behavior once a critical threshold is crossed.

The mathematical analysis in Section 3 identified this threshold as the point where the system transitions from a stable, slow-decay regime to an unstable, feedback-dominated regime. The critical condition $P_h > \epsilon/\xi$ or $I_h > \mu/\nu$ highlights that the synergy between inflammation and pathology (ξ, ν) is the primary engine of acceleration. This finding aligns with the clinical observation that the presence of both pathologies (Aβ and tau, often accompanied by inflammation) is a hallmark of symptomatic AD. The model provides a mechanistic explanation for why this combination is so devastating: it closes the negative feedback loops that normally maintain stability (clearance and resolution) and opens positive ones that drive the system toward the end-stage attractor.

5.1.2 Linking Pathology to Cognitive Function

The integration of the pathological dynamics with the cognitive function formula $C_{pathological}(t) = C_{healthy}(t) \cdot N(t)^{\eta_N} \cdot e^{-\eta_I I(t)} \cdot e^{-\eta_P P(t)}$ provides a crucial bridge between biological markers and clinical outcomes. The simulations clearly demonstrate the distinct roles of the three pathological factors:

- **Neuronal Loss ($N(t)$):** As the structural foundation of the network, its decline has a powerful, non-linear effect, especially in later stages (modeled by the power law N^{η_N}).
- **Functional Deficits ($I(t)$ and $P(t)$):** Inflammation and pathology act as "efficiency drains" on the remaining neural network, exponentially reducing its computational output.

The model successfully reproduces the three-phase clinical progression:

1. **Preclinical Phase (Age < ~50 in the high-risk simulation):** The system is stable. $C(t)$ declines slowly, remaining well above the dementia threshold ($C_{thresh} = 1$). This corresponds to the period where pathology is accumulating but cognitive function is clinically normal.
2. **Mild Cognitive Impairment (MCI) Phase (Age ~50-60):** The system crosses the dynamical threshold. The positive feedback loops engage, causing N, I, and P to change at an accelerating rate. The inflection point in $C(t)$ marks the onset of this phase. While the individual may experience subjective decline and perform worse on cognitive tests, $C(t)$ remains above 1, indicating that the fundamental capacity for

independent function is still present.

3. **Dementia Phase (Age > ~60):** $C(t)$ falls below the threshold of 1. The neural network's computational capacity has degraded to the point where it can no longer support the complex information processing required for independent living. This marks the clinical diagnosis of AD dementia.

This framework offers a powerful tool for interpreting clinical data, as it directly links the dynamics of biomarkers (like PET imaging for P or neurofilament light for N) to the trajectory of cognitive test scores.

5.2 Clinical Implications

5.2.1 The Primacy of Early Intervention

Our simulation results for the **high-risk (APOE4) profile** provide stark and unambiguous evidence for the critical importance of intervention timing. As shown in Table 8, the benefit of combination therapy drops precipitously with delayed initiation:

- **Intervention at age 25** delays dementia onset by **13.3 years**.
- **Intervention at age 30** delays onset by **11.2 years**, a loss of over 2 years of benefit in just 5 years.
- **Intervention at age 35** delays onset by a mere **0.9 years**, and by age 40, the benefit is negligible.

This dramatic narrowing of the **"therapeutic window of opportunity"** has profound implications. It suggests that for individuals at high genetic risk, the biological processes that lead to cognitive decline are set in motion decades before any symptoms appear. Interventions initiated after age 30, while perhaps still capable of slowing the *rate* of decline, are largely unable to *delay the onset* of functional impairment because the system has already entered or is on the verge of entering the feedback-dominated phase.

This finding challenges the design of many past and current clinical trials, which often enroll patients who are already symptomatic or in the MCI phase. Our model predicts that such trials are highly unlikely to show large disease-modifying effects, which is consistent with the modest results seen for many anti-amyloid therapies in late-stage populations. The true promise of disease modification lies in **primary prevention** during mid-life, long before the cognitive inflection point.

5.2.2 Differential Efficacy of Intervention Strategies

Our comparison of single-agent strategies in the high-risk model reveals their relative potency and provides guidance for therapeutic development (Table 9):

- **Anti-inflammatory ($\phi_I = 0.6$) achieved the largest delay as a monotherapy (+9 years).** This underscores the central role of inflammation as a driver of the feedback loops. It suggests that effectively resolving neuroinflammation could be a powerful strategy, particularly if initiated early.
- **Anti-amyloid ($\phi_P = 0.4$) provided a moderate delay (+4.6 years).** This aligns with the "initiation" role of Aβ pathology. Clearing protein aggregates is beneficial, but its effect is less potent than directly targeting the inflammatory response that amplifies damage.
- **Neuroprotective ($\psi = 0.5$) was the least effective monotherapy (+0.6 years).** This result is logical. If the drivers of neuronal death (inflammation and protein toxicity) remain unchecked, simply trying to protect neurons is a losing battle. The "leak" is too large.

5.2.3 The Necessity of Combination Therapy

The most important clinical takeaway from our simulations is the clear superiority of **combination therapy**. The multi-pronged approach (S4: $\phi_I = 0.4, \phi_P = 0.3, \psi = 0.3$) yielded a **13.3-year delay**, which is **47% greater than the best single-agent delay** (anti-inflammatory alone). This demonstrates a powerful synergistic effect.

The mechanism behind this synergy is evident from the system dynamics. Anti-inflammatory therapy (ϕ_I) dampens the primary driver of the feedback loop. Anti-amyloid therapy (ϕ_P) reduces the fuel for the loop. Neuroprotection (ψ) protects the final common pathway—the neurons themselves. By attacking the problem at multiple points simultaneously, combination therapy is able to break the positive feedback cycle far more effectively than any single intervention. This result strongly advocates for a shift away from the traditional "one-drug, one-target" paradigm and towards the development and testing of multi-target regimens, especially for high-risk populations.

5.2.4 Risk Profile Stratification for Personalized Medicine

The different onset ages for various risk profiles (Table 10, Figure 8) reinforce the need for a personalized approach. A "one-size-fits-all" prevention or treatment strategy is unlikely to be optimal.

- **High Risk (APOE4, Onset ~60 years):** These individuals are the prime candidates for the most aggressive, early combination therapy, potentially starting in their 20s or 30s. The goal is to prevent the system from ever reaching the critical threshold.
- **Inflammation- or Pathology-Dominant Profiles (Onset ~64-71 years):** While still serious, their slower progression might offer a slightly wider window. They could potentially benefit from a targeted monotherapy (e.g., anti-inflammatory for the former, anti-amyloid for the latter), though combination therapy would still be predicted to be superior.
- **Moderate and Low Risk (Onset 83-103 years):** For these individuals, whose trajectory is closer to normal aging, the calculus for aggressive, early, and potentially risky interventions is different. The focus might be on lifestyle modifications and monitoring, with intervention reserved for later in life if biomarkers begin to rise rapidly.

This model provides a quantitative framework for such stratification, moving beyond simple risk categories to a more dynamic, personalized understanding of disease progression and treatment response.

6. Conclusion

6.1 Summary of Contributions

This paper has developed and analyzed a dynamical systems model of Alzheimer's disease that integrates core pathological mechanisms with a neural-network-based model of cognitive function. Our key contributions are:

1. **Formalization of Positive Feedback:** We constructed a three-variable model (N, I, P) that mathematically captures the self-amplifying loops of neuronal loss, neuroinflammation, and protein pathology, which are central to AD progression.
2. **Identification of Dynamical Thresholds:** Through linear stability analysis, we identified the critical conditions ($P > \epsilon/\xi, I > \mu/\nu$) under which the system transitions from stable, gradual decline to unstable, accelerated decline.
3. **Quantitative Simulation of Interventions:** We simulated the effects of anti-inflammatory, anti-amyloid, neuroprotective, and combination therapies. The results show that:

- Combination therapy is the most potent strategy, delaying dementia onset by **13.3 years** in a high-risk model when initiated early.
- Anti-inflammatory therapy is the most effective monotherapy (+9 years), highlighting the key role of neuroinflammation.
- The window for effective disease-modifying intervention is narrow, closing rapidly after age 30.

4. **Linking Pathology to Clinical Outcomes:** We demonstrated how the dynamics of N, I, P translate into cognitive decline via the extended cognitive function formula, providing a clear theoretical link between biomarker changes and the onset of dementia ($C(t) < 1$).

6.2 Theoretical and Clinical Significance

Theoretically, our work provides a unified framework for understanding AD as a complex system whose behavior is governed by interacting positive feedback loops. It explains the long preclinical phase, the accelerating decline in MCI, and the rapid deterioration in dementia as emergent properties of a system crossing a dynamical threshold.

Clinically, the model delivers a clear and urgent message: **The most effective strategy for combating Alzheimer's disease is very early, multi-target intervention in high-risk populations.** Our simulations suggest that waiting until symptoms appear is waiting too long. The findings call for:

- **Investment in early detection:** Developing and deploying cost-effective methods (e.g., plasma biomarkers, genetic screening) to identify high-risk individuals in their 20s and 30s.
- **A paradigm shift in drug development:** Prioritizing the development and clinical testing of safe, long-term combination therapies for primary prevention, rather than focusing solely on late-stage, single-agent trials.
- **Redesigning healthcare infrastructure:** Creating systems capable of delivering and monitoring long-term preventive care, starting decades before the expected age of onset.

6.3 Limitations and Future Directions

Our model, while insightful, has limitations. It simplifies the brain as a single compartment, combines Aβ and tau into one variable, and does not account for compensatory mechanisms like cognitive reserve. It also assumes constant intervention efficacy, ignoring real-world

complexities like side effects and pharmacokinetics.

Future work should focus on:

- **Model Refinement:** Incorporating spatial spread of pathology, distinguishing between Aβ and tau, and adding terms for cognitive reserve and neural plasticity.
- **Empirical Validation:** Calibrating and validating the model against longitudinal data from large cohorts (e.g., ADNI) to refine parameters and test its predictive power for individual trajectories.
- **Personalized Algorithm Development:** Using the model to develop algorithms that can estimate an individual's risk profile and optimal intervention window based on their genetic, biomarker, and cognitive data.

Despite these limitations, the dynamical systems approach presented here offers a powerful lens through which to view Alzheimer's disease. It shifts the focus from static risk factors to dynamic processes, from single targets to system-level interventions, and from treating symptoms to preventing the disease before it starts. The mathematics is clear: to change the outcome, we must change the dynamics. And to change the dynamics, we must act early and comprehensively.

Declaration

This paper was completed by the authors with the assistance of the AI large language model DeepSeek.

Specific division of work:

DeepSeek collected data on the effects of neuron numbers, inflammation, and pathological proteins on the brain's nervous system, constructed the dynamic differential equations, performed numerical solutions, created Figures 2-8 and the corresponding tables, and handled the textual processing of the paper.

The human authors were responsible for constructing the cognitive model, adjusting the specific parameters, and thoroughly reviewing the paper's data to ensure the reasonableness of various data and results as well as the logical consistency of the paper's content.

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