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A Multiscale Coupled Reaction-Diffusion Model of Amyloid-Beta and Tau Pathology in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFTs), as well as by chronic neuroinflammation and blood-brain barrier (BBB) dysfunction. Although these pathological features are well known, their complex interactions remain poorly understood. This study proposes a comprehensive multiscale coupled reaction-diffusion model composed of 13 partial differential equations to simulate the spatio-temporal dynamics of Aβ and tau pathology, neuroinflammatory responses, BBB integrity, and neuronal degeneration. The model captures biochemical reaction kinetics, diffusion-driven propagation, and regulatory feedback among key cellular components, including microglia, astrocytes, and cytokines. Furthermore, the effects of therapeutic interventions, such as anti-amyloid drugs and dietary modifications, are incorporated to assess their influence on disease progression. Numerical simulations using finite difference methods provide insights into how these factors contribute to or mitigate AD pathogenesis. The results support the potential of mathematical modeling as a tool to understand disease mechanisms and evaluate treatment strategies.

Keywords Alzheimer's disease, amyloid-beta, tau pathology, reaction-diffusion models, neurodegeneration, mathematical modeling

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1. Introduction

Alzheimer's disease (AD) is the most prevalent progressive neurodegenerative disorder characterized by cognitive impairment, neuronal degeneration, and synaptic failure. Alzheimer's disease (AD) pathogenic hallmarks consist primarily of extracellular deposition of amyloid-beta (Aβ) plaques and intracellular accumulation of tau neurofibrillary tangles (NFTs), resulting in diffuse neuronal damage and synaptic loss [1–4]. Despite decades of research, AD remains an incurable disease even today, which emphasizes the importance of mathematical modeling as an instrumental asset towards understanding disease progression and evaluating pharmacologic

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intervention capable of delaying disease progression [5–8].

2. History and development of mathematical modeling in Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder first described by Alois Alzheimer in 1906 [9–12]. Characteristic features of AD pathology include amyloid-beta (Aβ) plaques, tau neurofibrillary tangles (NFTs), neuronal death, and synaptic dysfunction. Although clinical and biological research has improved in elucidating the disease, mathematical modeling has been critical in offering a quantitative and predictive foundation for the study of the disease's evolution and potential treatment approaches [13].

2.1. Early theoretical approaches (1970s–1990s)

Mathematical models in neuroscience were dominated by neuronal networks and electrophysiology in the early years (Hodgkin & Huxley, 1952) [14]. However, at least as early as the 1980s and 1990s, researchers began developing compartmental models of neurodegeneration processes.

Linear Compartmental Models: Previous models of AD employed compartmental kinetics to depict amyloid-beta production, clearance, and aggregation [15]. Despite their simplicity, these models were critical for measuring the protein turnover rates occurring in the brain [16, 17].

Population-Based Models: Such epidemiological models were built to understand the incidence and progression of AD across diverse populations. Using these models helped estimate risk factors of disease and effectiveness of public health interventions [18].

2.2. Expansion into biochemical and cellular models (2000s–2020s)

With advances in molecular biology and imaging, mathematical models became more mechanistic, incorporating biochemical pathways of protein aggregation and neuronal damage.

Reaction-Kinetics Models (2000s): These models described Aβ and tau aggregation using reaction-diffusion equations, modeling how monomers transition into oligomers and fibrils [19–21].

Neuronal Network-Based Models: Computational neuroscience methods used graph theory to characterize the loss of connectivity in neuronal networks, modeling how synaptic damage spreads in time [22].

Inflammation and Immune Response Models: Researchers incorporated the role of microglia and cytokines, demonstrating how neuroinflammation contributes to AD pathology [23].

2.3. Modern reaction-diffusion and multi-scale models

Recent research has mostly focused on spatially explicit reaction-diffusion models, which also aim to simulate the spread of pathology (both amyloid-beta and tau)