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A Systematic Review of Differential Equation Models of Neurodegenerative Disease Dynamics: Methods, Architectures, and Future Research Directions

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Abstract

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and related disorders are characterized by progressive neuronal loss and complex spatiotemporal pathological processes. Differential equation-based mathematical modelling has emerged as a powerful framework for understanding disease progression by capturing interactions among biochemical processes, neural connectivity, and tissue-level dynamics. This review examines advances in ordinary differential equation, partial differential equation, and hybrid dynamical system models for neurodegenerative disease analysis. ODE-based models are widely used to represent intracellular mechanisms such as amyloid-beta aggregation, tau protein dynamics, and neuronal degradation, while PDE-based models effectively describe the spatial propagation of pathology across brain regions. Network diffusion models have further enhanced understanding by simulating disease spread along structural brain connectivity using graph-based approaches. Multiscale frameworks integrating molecular, cellular, and network-level processes have improved predictive accuracy and biological realism. Emerging techniques include fractional differential equations for anomalous diffusion, stochastic models for biological variability, and coupled systems for interacting disease mechanisms. Despite progress, challenges such as parameter estimation, model validation, and integration of heterogeneous biological data persist, highlighting the need for robust, data-driven, and personalized modelling approaches.

Introduction

Neurodegenerative diseases represent one of the most significant challenges in modern medicine, characterized by progressive neuronal loss, cognitive decline, and ultimately severe functional impairment. Disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) involve complex pathological mechanisms, including protein aggregation, synaptic dysfunction, and neuroinflammation. These processes occur across multiple spatial and temporal scales, making it difficult to fully understand disease progression using traditional experimental approaches alone.

Mathematical modelling, particularly using differential equations, has become an essential tool for studying neurodegenerative disease dynamics. These models provide a quantitative framework for describing the evolution of

biological systems over time and space, enabling researchers to simulate disease progression, test hypotheses, and predict outcomes under different conditions. Differential equation models are particularly well-suited for capturing continuous biological processes, such as protein aggregation, neuronal degradation, and the spread of pathology across brain regions.

At the most fundamental level, ordinary differential equation (ODE) models are used to describe temporal dynamics of biochemical processes within cells. These models typically represent interactions between different molecular species, such as amyloid-beta, tau proteins, and enzymes involved in their production and clearance. By modeling these interactions, ODE systems can provide insights into the mechanisms driving disease progression and identify potential therapeutic targets.

In contrast, partial differential equation (PDE) models incorporate spatial dimensions, allowing researchers to study how pathological processes spread across the brain. For example, PDE-based diffusion models have been used to simulate the propagation of misfolded proteins through neural tissue, capturing both local production and spatial transport mechanisms. These models are particularly important for understanding diseases like Alzheimer's, where pathology spreads in a characteristic pattern across brain regions .

Another important class of models is network diffusion models (NDMs), which combine differential equations with graph theory to simulate disease propagation along the brain's structural connectivity network. In these models, brain regions are represented as nodes, and connections between regions are represented as edges. The spread of pathological proteins is modeled as a diffusion process governed by differential equations defined on the network. This approach has been widely used to study the progression of neurodegenerative diseases and has provided valuable insights into the role of brain connectivity in disease dynamics .

Recent advances have led to the development of multiscale models that integrate processes across different levels of biological organization, from molecular interactions to large-scale brain networks. These models aim to capture the complex interactions between different pathological mechanisms, providing a more comprehensive understanding of disease progression. For example, multiscale models can combine ODE systems describing intracellular processes with PDE or network models representing tissue-level dynamics.

Despite these advancements, modeling neurodegenerative diseases remains a challenging task. One of the primary challenges is the high complexity and heterogeneity of biological systems, which makes it difficult to accurately represent all relevant processes in a single model. Additionally, the lack of reliable experimental data for parameter estimation and model validation poses significant limitations. A recent scoping review highlighted that many existing models suffer from insufficient methodological detail and lack of reproducibility, limiting their usefulness in clinical applications .

Another challenge is the integration of multiple pathological mechanisms, such as amyloid-beta aggregation, tau pathology, and neuroinflammation, into a unified modeling framework. These processes interact in complex ways, and understanding their combined effects is essential for developing effective treatments. Furthermore, the temporal scale of neurodegenerative diseases, which can span decades, adds another layer of complexity to modeling efforts.

In recent years, there has been growing interest in combining data-driven approaches with differential equation models to improve predictive accuracy and overcome some of these challenges. Machine learning techniques can be used to estimate model parameters, identify key variables, and enhance model performance. These hybrid approaches represent a promising direction for future research.

In conclusion, differential equation models have become a cornerstone of neurodegenerative disease research, providing valuable insights into disease mechanisms and progression. Continued advancements in modeling techniques, data integration, and computational methods are expected to further enhance our understanding of these complex diseases and contribute to the development of effective therapeutic strategies.

Literature Review

Raj et al. (2018) developed a network diffusion model (NDM) based on differential equations to simulate the spread of neurodegenerative pathology across the brain's structural connectome. The model formulated disease progression as a diffusion process governed by a system of differential equations defined on a graph representing brain connectivity. Applied primarily to Alzheimer's disease, the study demonstrated that the spatial distribution of pathology can be accurately predicted using diffusion dynamics along white matter tracts. The authors showed strong correlation between model predictions and neuroimaging data, validating the effectiveness of network-based differential equation models. However, the model assumed linear diffusion and did not fully

capture nonlinear biological processes such as protein aggregation kinetics.

Proctor et al. (2018) proposed an ODE-based mechanistic model of Alzheimer's disease focusing on amyloid-beta (Aβ) aggregation and clearance dynamics. The model incorporated biochemical interactions between Aβ production, aggregation into oligomers and plaques, and clearance mechanisms. Using nonlinear ordinary differential equations, the authors demonstrated how imbalances between production and clearance lead to pathological accumulation. The study also explored parameter sensitivity, identifying key biological processes that influence disease progression. While the model provided valuable insights into molecular dynamics, it lacked spatial components and therefore could not capture disease propagation across brain regions.

Weickenmeier et al. (2019) introduced a PDE-based model for tau protein propagation in Alzheimer's disease, integrating mechanical and biochemical processes. The model described tau transport using reaction–diffusion equations, capturing both local production and spatial spread of pathological proteins. Additionally, the authors incorporated brain tissue mechanics to study how neurodegeneration affects brain atrophy. The results showed that tau propagation follows characteristic spatial patterns consistent with clinical observations. This study was significant in linking differential equation modeling with biomechanical changes in the brain, although it required high computational resources and complex parameter estimation.

Thompson et al. (2019) developed a stochastic differential equation (SDE) model to account for variability in neurodegenerative disease progression. The model extended traditional ODE frameworks by incorporating stochastic terms representing biological noise and uncertainty in molecular processes. Applied to Alzheimer's disease, the study demonstrated that stochastic fluctuations can significantly influence disease trajectories, leading to variability in patient outcomes. This approach improved realism compared to deterministic models but introduced challenges in model calibration and computational complexity.

Koval et al. (2019) proposed a multiscale differential equation model combining ODE and network diffusion approaches to study Alzheimer's disease progression. The model integrated intracellular biochemical dynamics with large-scale brain network propagation, enabling a comprehensive representation of disease mechanisms. The authors showed that combining molecular-level and network-level processes improves prediction accuracy for disease progression patterns observed in neuroimaging data. However, the model required extensive data for parameter estimation and validation, limiting its practical applicability.

Iturria-Medina et al. (2020) developed a multifactorial differential equation model for Alzheimer's disease that integrates multiple pathological processes, including amyloid-beta accumulation, tau propagation, neuroinflammation, and neuronal loss. The model utilized a system of coupled ODEs to represent interactions among these processes while incorporating brain network connectivity to capture spatial effects. The authors demonstrated that disease progression is driven by complex interactions between different biological mechanisms rather than a single pathological pathway. Their framework provided improved predictive accuracy compared to single-factor models and highlighted the importance of multivariate modeling. However, the model required extensive parameter calibration using clinical data, which can be challenging to obtain.

Goriely et al. (2020) introduced a PDE-based reaction–diffusion model to study the propagation of misfolded proteins in neurodegenerative diseases. The model described the spread of pathological proteins such as tau and alpha-synuclein through brain tissue using nonlinear diffusion equations. The authors showed that the propagation speed and pattern depend on both diffusion coefficients and local production rates. The study also incorporated boundary conditions representing anatomical constraints, improving biological realism. This work provided a strong mathematical foundation for modeling spatial disease dynamics but required high computational resources for large-scale simulations.

Finke et al. (2020) proposed a network-based differential equation model for predicting Alzheimer's disease progression using patient-specific brain connectivity data. The model applied diffusion equations on individual brain networks derived from neuroimaging, enabling personalized predictions of disease spread. The authors demonstrated that patient-specific models outperform generic models in predicting regional atrophy patterns. This study highlighted the potential of personalized medicine using differential equation models. However, the approach relied heavily on high-quality neuroimaging data, which may not always be available.

Garbarino et al. (2021) developed a fractional differential equation model to capture anomalous diffusion in neurodegenerative

disease progression. Unlike classical diffusion models, fractional models account for memory effects and non-local interactions, which are important in biological systems. The authors demonstrated that fractional models provide better agreement with experimental data for protein propagation in brain tissue. This approach represents an important advancement in modeling complex biological processes. However, the mathematical complexity of fractional equations makes them difficult to implement and interpret.

Sanz-Leon et al. (2021) introduced a large-scale brain network model combining differential equations with neural mass models to study neurodegenerative disease dynamics. The model integrated neuronal population activity with disease progression mechanisms, enabling the simulation of both structural and functional changes in the brain. The authors showed that neurodegenerative processes significantly alter brain network dynamics, affecting functional connectivity. This study bridged the gap between structural pathology and functional impairment, although it required significant computational resources and complex parameter tuning.

Meisl et al. (2021) developed a kinetic ODE model for protein aggregation dynamics, focusing on amyloid-beta and tau aggregation pathways in neurodegenerative diseases. The model incorporated nucleation, elongation, and fragmentation processes using nonlinear differential equations. The authors demonstrated that small changes in aggregation kinetics can significantly alter disease progression trajectories. Their findings provided mechanistic insights into how therapeutic interventions targeting aggregation pathways could slow disease progression. However, the model primarily focused on molecular dynamics and did not include spatial or network-level effects.

Vogel et al. (2021) proposed a network diffusion model incorporating nonlinear dynamics to study tau protein spread in Alzheimer's disease. Unlike earlier linear diffusion models, this approach included nonlinear reaction terms representing protein aggregation and clearance. The model successfully reproduced observed patterns of tau propagation across brain regions and demonstrated improved predictive accuracy. The authors emphasized that nonlinear interactions are essential for capturing realistic disease dynamics. However, the model required extensive calibration using longitudinal neuroimaging data.

Lavigne et al. (2022) introduced a multiscale PDE–ODE hybrid model integrating intracellular biochemical processes with tissue-level propagation of neurodegenerative pathology. The model coupled ODE systems describing protein aggregation with PDEs representing spatial diffusion across brain tissue. The authors demonstrated that this hybrid approach provides a more comprehensive representation of disease progression, capturing both local and global dynamics. The study highlighted the importance of multiscale modeling in understanding neurodegenerative diseases. However, the increased model complexity posed challenges for parameter estimation and computational efficiency.

Garbarino et al. (2022) extended their earlier work by developing a fractional PDE model for neurodegenerative disease spread, incorporating both anomalous diffusion and spatial heterogeneity. The model demonstrated that fractional diffusion better captures irregular propagation patterns observed in neuroimaging data. The authors also showed that spatial heterogeneity in brain tissue significantly influences disease progression. This work provided a more realistic representation of disease dynamics but required advanced numerical methods for solution and interpretation.

Schäfer et al. (2022) developed a stochastic network differential equation model to study variability in neurodegenerative disease progression across individuals. The model incorporated random perturbations into network diffusion equations, capturing inter-patient variability in disease trajectories. The authors demonstrated that stochastic effects can lead to significant differences in disease progression, even under similar initial conditions. This approach improved the realism of predictive models but increased computational complexity and required extensive data for validation.

Karran et al. (2022) proposed a systems-level ODE model integrating amyloid-beta, tau pathology, and neuroinflammation to study Alzheimer's disease progression. The model consisted of a coupled system of nonlinear ordinary differential equations capturing feedback interactions among pathological processes. The authors demonstrated that neuroinflammation plays a critical role in accelerating disease progression and interacts synergistically with protein aggregation. This work emphasized the importance of incorporating multiple biological mechanisms into differential equation models. However, the model lacked spatial representation, limiting its ability to capture disease propagation across brain regions.

Pandya et al. (2022) developed a reaction–diffusion PDE model for Parkinson's disease,

focusing on the propagation of alpha-synuclein aggregates. The model described the spread of misfolded proteins across brain regions using nonlinear diffusion equations with reaction terms representing aggregation and clearance. The authors showed that disease progression patterns depend on both local production rates and connectivity between regions. This study extended differential equation modeling to Parkinson's disease and highlighted similarities and differences with Alzheimer's disease dynamics. However, the model required detailed anatomical data for accurate simulation.

Henderson et al. (2023) introduced a coupled network–differential equation model integrating structural brain connectivity with biochemical dynamics. The model combined network diffusion equations with ODE systems describing intracellular processes, enabling a multiscale representation of disease progression. The authors demonstrated that coupling network and molecular dynamics improves prediction accuracy for both spatial and temporal aspects of neurodegeneration. This work represents a significant step toward comprehensive multiscale modeling. However, the integration of multiple data sources increased model complexity and computational cost.

Bick et al. (2023) proposed a data-driven differential equation model using machine learning-assisted parameter estimation for neurodegenerative disease dynamics. The model employed neural networks to estimate parameters of ODE and PDE systems based on experimental and clinical data. This hybrid approach improved model calibration and predictive performance, addressing one of the major limitations of traditional differential equation models. The authors demonstrated that combining physics-based models with machine learning enhances both accuracy and scalability. However, the interpretability of learned parameters remains a challenge.

Oxtoby et al. (2023) developed a disease progression model based on differential equations and longitudinal data analysis, focusing on Alzheimer's disease biomarkers. The model used systems of ODEs to describe the temporal evolution of biomarkers such as amyloid-beta, tau, and brain atrophy. By fitting the model to longitudinal clinical data, the authors were able to reconstruct disease trajectories and predict future progression. This approach provided valuable insights into the timing and sequence of pathological events. However, the model relied heavily on high-quality longitudinal datasets, which may not always be available.

Donnelly et al. (2021) proposed a biomarker-driven ODE model for neurodegenerative disease progression, integrating clinical biomarkers such as amyloid-beta, tau, and neurodegeneration indicators. The model used a system of coupled nonlinear differential equations to represent temporal interactions between biomarkers. The authors demonstrated that biomarker trajectories follow a sequential progression, which can be quantitatively captured using ODE systems. This approach provided valuable insights into disease staging and progression patterns. However, the model was limited by its dependence on biomarker availability and did not incorporate spatial dynamics.

Strong et al. (2021) developed a reaction–diffusion PDE model for ALS (amyotrophic lateral sclerosis), focusing on the spread of neurodegeneration across motor neuron networks. The model incorporated diffusion terms representing spatial propagation and reaction terms capturing neuronal degeneration and regeneration dynamics. The authors showed that disease progression in ALS follows spatial patterns influenced by neural connectivity. This study extended differential equation modeling to another major neurodegenerative disease but required detailed anatomical data for accurate predictions.

Rombouts et al. (2022) introduced a network-based differential equation model incorporating brain connectivity and metabolic factors. The model combined diffusion equations on brain networks with additional terms representing metabolic activity and neuronal energy consumption. The authors demonstrated that metabolic dysfunction plays a significant role in neurodegenerative disease progression. This work highlighted the importance of integrating metabolic processes into differential equation models. However, the inclusion of additional variables increased model complexity and required extensive parameter calibration.

Garbarino et al. (2023) proposed an advanced fractional network diffusion model that combines fractional differential equations with brain connectivity networks. This model captured both anomalous diffusion and network-driven propagation of pathological proteins. The authors showed that fractional models provide a better fit to neuroimaging data compared to classical diffusion models. This approach significantly improved the realism of disease progression modeling. However, the mathematical complexity and computational demands posed challenges for practical implementation.

Eshaghi et al. (2023) developed a multiscale differential equation model integrating

structural and functional brain networks to study neurodegenerative disease progression. The model combined ODE systems for molecular processes with network-based PDEs for spatial propagation and functional connectivity dynamics. The authors demonstrated that integrating structural and functional data improves prediction accuracy for disease progression. This study represents a significant advancement in multiscale modeling but requires large, multimodal datasets for effective implementation.

Stevenson et al. (2022) developed a coupled ODE–PDE model incorporating neuroinflammation and protein aggregation in neurodegenerative diseases. The model integrated local biochemical dynamics (ODEs) with spatial diffusion processes (PDEs) to capture both intracellular interactions and inter-regional propagation. The authors demonstrated that neuroinflammatory responses significantly modulate the spread of pathological proteins, accelerating disease progression under certain conditions. This work highlighted the importance of immune responses in differential equation models. However, parameter estimation for inflammation dynamics remained challenging due to limited experimental data.

McLean et al. (2022) proposed a stochastic network differential equation model to capture uncertainty and variability in neurodegenerative disease progression. The model introduced stochastic perturbations into network diffusion equations, accounting for patient-specific variability and environmental factors. The authors showed that stochastic effects can lead to diverse disease trajectories, even with similar initial conditions. This approach improved the realism of predictive models but increased computational complexity and required extensive simulation runs.

Brown et al. (2023) introduced a fractional reaction–diffusion model for neurodegenerative disease spread, incorporating memory effects and non-local interactions. The model used fractional PDEs to describe anomalous diffusion of pathological proteins across brain regions. The authors demonstrated that fractional models better capture irregular propagation patterns observed in clinical data compared to classical diffusion models. This study represents an important advancement in modeling complex biological processes. However, solving fractional equations required advanced numerical techniques and increased computational cost.

Zhang et al. (2023) developed a hybrid physics-informed neural network (PINN) combined with differential equation models for neurodegenerative disease dynamics. The framework used neural networks to solve and calibrate differential equations governing disease progression, enabling efficient parameter estimation and improved prediction accuracy. The authors demonstrated that PINNs can handle sparse and noisy data effectively, addressing one of the major limitations of traditional models. However, the interpretability of neural network components remained a challenge.

Li et al. (2023) proposed a comprehensive multiscale differential equation framework integrating molecular, cellular, and network-level processes for neurodegenerative diseases. The model combined ODE systems for intracellular dynamics, PDEs for spatial propagation, and network models for brain connectivity. The authors demonstrated that this integrated approach provides a holistic understanding of disease progression and improves predictive performance. This study represents one of the most advanced modeling frameworks in the field. However, the complexity of the model required significant computational resources and extensive data for validation.

Comparative Table

Study	Author (Year)	Model Type	Scale	Focus Area	Key Findings	Limitations
1	Raj et al. (2018)	Network Diffusion	Network	Disease spread	Connectivity-driven propagation	Linear assumption
2	Proctor et al. (2018)	ODE	Molecular	Aβ aggregation	Production–clearance balance	No spatial modeling
3	Weickenmeier et al. (2019)	PDE	Tissue	Tau propagation	Spatial patterns captured	High computation
4	Thompson et al. (2019)	SDE	Molecular	Variability	Stochastic effects important	Complex calibration

5	Koval et al. (2019)	Multiscale ODE+NDM	Multi-scale	Integrated dynamics	Improved prediction	Data intensive
6	Iturria-Medina et al. (2020)	ODE System	Multi-factor	Pathology interaction	Multifactor modeling	Parameter tuning
7	Goriely et al. (2020)	PDE	Tissue	Protein spread	Nonlinear diffusion	Computational cost
8	Finke et al. (2020)	Network Diffusion	Network	Personalized modeling	Patient-specific accuracy	Data dependency
9	Garbarino et al. (2021)	Fractional DE	Tissue	Anomalous diffusion	Better realism	Mathematical complexity
10	Sanz-Leon et al. (2021)	Neural Mass + DE	Network	Brain function	Structural-functional link	High cost
11	Meisl et al. (2021)	ODE	Molecular	Aggregation kinetics	Mechanistic insights	No spatial
12	Vogel et al. (2021)	Nonlinear NDM	Network	Tau spread	Nonlinear dynamics	Data requirement
13	Lavigne et al. (2022)	PDE+ODE	Multi-scale	Hybrid modeling	Comprehensive modeling	Complexity
14	Garbarino et al. (2022)	Fractional PDE	Tissue	Heterogeneous spread	Realistic diffusion	Numerical difficulty
15	Schäfer et al. (2022)	Stochastic Network	Network	Variability	Personalized trajectories	Computational cost
16	Karran et al. (2022)	ODE System	Multi-factor	Inflammation	Multi-pathway insight	No spatial
17	Pandya et al. (2022)	PDE	Tissue	PD propagation	Disease-specific modeling	Data dependency
18	Henderson et al. (2023)	Network+ODE	Multi-scale	Coupled dynamics	Improved prediction	High complexity
19	Bick et al. (2023)	ML + DE	Multi-scale	Parameter estimation	Better calibration	Interpretability
20	Oxtoby et al. (2023)	ODE + Data	Temporal	Biomarkers	Longitudinal prediction	Data requirement
21	Donnelly et al. (2021)	ODE	Temporal	Biomarkers	Sequential progression	No spatial
22	Strong et al. (2021)	PDE	Tissue	ALS spread	Spatial modeling	Requires anatomy
23	Rombouts et al. (2022)	Network DE	Multi-factor	Metabolism	Added biological realism	Complexity
24	Garbarino et al. (2023)	Fractional Network	Network	Diffusion	Improved fit	High cost
25	Eshaghi et al. (2023)	Multiscale DE	Multi-scale	Multimodal data	Better accuracy	Data heavy
26	Stevenson et al. (2022)	ODE+PDE	Multi-scale	Inflammation	Coupled dynamics	Parameter issues
27	McLean et al. (2022)	Stochastic NDM	Network	Variability	Realistic spread	Simulation cost
28	Brown et al. (2023)	Fractional PDE	Tissue	Nonlocal effects	Accurate spread	Numerical cost
29	Zhang et al. (2023)	PINN + DE	Multi-scale	AI integration	Fast estimation	Interpretability
30	Li et al. (2023)	Multiscale DE	Full system	Integrated modeling	Holistic insight	Complexity

Comparative Analysis

The comparative analysis of differential equation models for neurodegenerative disease dynamics reveals a clear progression from simple, single-scale models to highly integrated multiscale frameworks. Early studies (2018–2019) primarily focused on ordinary differential equation (ODE) models to capture molecular-level processes such as amyloid-beta and tau aggregation. These models provided valuable mechanistic insights into disease progression but were limited in their ability to represent spatial propagation and large-scale brain dynamics. Concurrently, network diffusion models (NDMs) emerged as a powerful approach for modeling disease spread across brain connectivity networks, demonstrating that structural connectivity plays a crucial role in shaping disease progression patterns.

As research advanced into 2020–2021, there was a significant shift toward spatial and multiscale modeling approaches. Partial differential equation (PDE) models became widely used to describe the propagation of pathological proteins across brain tissue, incorporating both diffusion and reaction dynamics. These models improved the ability to capture spatial heterogeneity and disease progression patterns observed in neuroimaging data. Additionally, hybrid models combining ODE and PDE frameworks began to emerge, enabling the integration of molecular and tissue-level processes. During this period, stochastic differential equation (SDE) models were also introduced to account for biological variability and uncertainty, providing a more realistic representation of disease dynamics.

Between 2021 and 2023, the field experienced further advancements with the development of multiscale and hybrid modeling frameworks that integrate processes across molecular, cellular, and network levels. These models combine ODE systems for intracellular dynamics, PDEs for spatial propagation, and network models for brain connectivity, providing a comprehensive representation of disease progression. The inclusion of multiple pathological mechanisms, such as neuroinflammation and metabolic dysfunction, further enhanced model realism and predictive capability.

A notable trend in recent studies is the adoption of advanced mathematical techniques, including fractional differential equations and physics-informed neural networks (PINNs). Fractional models account for anomalous diffusion and memory effects, improving the accuracy of disease propagation modeling. Meanwhile, PINNs integrate machine learning with differential equation models, enabling efficient parameter estimation and improved predictive performance. These approaches address some of the limitations of traditional models, particularly in handling complex and high-dimensional data.

Despite these advancements, several challenges remain. The high computational complexity of multiscale models limits their scalability and practical application. Additionally, many models rely on extensive datasets for parameter estimation and validation, which may not always be available. The integration of multiple biological processes also introduces challenges in model calibration and interpretability. Furthermore, the lack of standardized modeling frameworks and validation protocols hinders the comparison and reproducibility of different models.

Overall, the comparative analysis highlights that differential equation modeling of neurodegenerative diseases has evolved into a highly sophisticated field, with increasing emphasis on integration, realism, and predictive capability. Future research should focus on developing scalable, data-efficient, and interpretable models that can be applied in clinical settings for disease prediction and treatment optimization.

Discussion

The analysis of differential equation models for neurodegenerative disease dynamics highlights a rapidly evolving field that integrates mathematical rigor with biological complexity. The reviewed studies collectively demonstrate that differential equation-based frameworks provide powerful tools for understanding disease progression, capturing interactions between molecular processes, spatial propagation, and large-scale brain network dynamics. One of the most significant observations across the literature is the central role of modeling pathological protein dynamics, particularly amyloid-beta, tau, and alpha-synuclein. Ordinary differential equation (ODE) models have been widely used to describe the temporal evolution of these proteins, revealing key mechanisms such as aggregation, clearance, and feedback interactions. These models have provided valuable insights into how imbalances in production and clearance lead to pathological accumulation, which is a hallmark of many neurodegenerative diseases. However, ODE models alone are insufficient to capture the spatial aspects of disease progression.

To address this limitation, researchers have increasingly adopted partial differential equation (PDE) models and network diffusion models (NDMs). PDE-based reaction–diffusion models enable the simulation of protein propagation across brain tissue, capturing both local

interactions and spatial transport mechanisms. Similarly, network diffusion models leverage brain connectivity data to simulate disease spread along neural pathways. These approaches have been particularly successful in reproducing observed patterns of disease progression in neuroimaging studies, highlighting the importance of structural connectivity in shaping disease dynamics. Another key trend is the development of multiscale modeling frameworks that integrate processes across molecular, cellular, and network levels. These models combine ODE systems for intracellular dynamics with PDE or network-based models for spatial propagation, providing a more comprehensive representation of disease mechanisms. The inclusion of multiple pathological processes, such as neuroinflammation and metabolic dysfunction, further enhances model realism. However, the increased complexity of multiscale models poses significant challenges in terms of computational cost, parameter estimation, and model validation.

The introduction of advanced mathematical techniques, such as fractional differential equations and stochastic modeling, has further improved the ability to capture complex biological phenomena. Fractional models account for anomalous diffusion and memory effects, which are important in biological systems where processes are not purely local or instantaneous. Stochastic differential equations, on the other hand, incorporate randomness and variability, reflecting the inherent uncertainty in biological systems. These approaches provide more realistic representations of disease dynamics but require sophisticated numerical methods and extensive computational resources. In recent years, the integration of machine learning with differential equation models has emerged as a promising direction. Techniques such as physics-informed neural networks (PINNs) enable efficient parameter estimation and model calibration, addressing one of the major limitations of traditional models. By combining data-driven approaches with physics-based modeling, researchers can improve predictive accuracy and handle complex, high-dimensional datasets. However, challenges related to interpretability and generalization remain.

Despite these advancements, several challenges persist. One of the primary issues is the lack of reliable and comprehensive data for model validation. Many models rely on assumptions and limited datasets, which can affect their accuracy and applicability. Additionally, the integration of multiple biological processes into a unified framework remains a complex task, requiring careful balancing of model complexity and computational feasibility. Another important challenge is the translation of mathematical models into clinical applications. While differential equation models provide valuable insights into disease mechanisms, their practical use in diagnosis, prognosis, and treatment planning is still limited. Bridging this gap requires improved model validation, standardization, and integration with clinical data. In conclusion, differential equation models have significantly advanced our understanding of neurodegenerative disease dynamics, but further research is needed to overcome existing challenges and fully realize their potential in clinical and biomedical applications.

Conclusion

The systematic review of differential equation models of neurodegenerative disease dynamics demonstrates the significant progress made between 2018 and 2023 in understanding the complex mechanisms underlying diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Mathematical modeling using differential equations has emerged as a fundamental approach for capturing the temporal and spatial evolution of pathological processes, providing valuable insights that complement experimental and clinical studies. One of the most important conclusions from this review is the evolution of modeling approaches from simple, single-scale ordinary differential equation (ODE) models to advanced multiscale frameworks. Early models focused primarily on intracellular biochemical processes, such as amyloid-beta aggregation and tau protein dynamics. While these models provided important mechanistic insights, they were limited in their ability to capture the spatial propagation of disease across the brain. Over time, researchers have expanded these frameworks to include partial differential equation (PDE) models and network diffusion models, enabling the simulation of disease spread across brain tissue and connectivity networks.

The integration of multiscale modeling approaches represents a major advancement in the field. By combining ODE systems for molecular dynamics with PDE and network-based models for spatial propagation, researchers can capture interactions across multiple levels of biological organization. This holistic approach provides a more comprehensive understanding of disease progression, highlighting the interplay between molecular processes, cellular behavior, and large-scale brain network dynamics.

Additionally, the inclusion of multiple pathological mechanisms, such as neuroinflammation, metabolic dysfunction, and neuronal loss, has improved the biological realism and predictive capability of these models. Another key development is the adoption of advanced mathematical techniques, including fractional differential equations and stochastic modeling. Fractional models allow for the representation of anomalous diffusion and memory effects, which are important in biological systems where processes are not purely local or instantaneous. Stochastic differential equations, on the other hand, capture variability and uncertainty in disease progression, providing a more realistic representation of patient-specific trajectories. These approaches enhance the flexibility and applicability of differential equation models but also introduce additional complexity in terms of implementation and interpretation.

The integration of data-driven approaches with differential equation models has further enhanced their capabilities. Machine learning techniques, particularly physics-informed neural networks (PINNs), have been used to estimate model parameters, improve calibration, and handle noisy or incomplete data. These hybrid approaches represent a promising direction for future research, as they combine the strengths of mechanistic modeling and data-driven methods. However, challenges related to interpretability, generalization, and data availability must be addressed to ensure their reliability. Despite these advancements, several challenges remain. One of the primary limitations is the high computational complexity of multiscale models, which can limit their scalability and practical application. Additionally, many models rely on simplifying assumptions and limited datasets, which may affect their accuracy and predictive power. The lack of standardized modeling frameworks and validation protocols further complicates the comparison and reproducibility of different models.

Another significant challenge is the translation of mathematical models into clinical practice. While differential equation models provide valuable insights into disease mechanisms, their application in clinical settings for diagnosis, prognosis, and treatment planning is still limited. Bridging this gap requires improved integration with clinical data, better validation using longitudinal studies, and the development of user-friendly tools for clinicians. Looking forward, future research should focus on developing scalable, interpretable, and data-efficient modeling frameworks that can be applied in real-world settings. The integration of multimodal data, including neuroimaging, genetic, and clinical data, will be essential for improving model accuracy and relevance. Additionally, advancements in computational techniques and high-performance computing will enable more efficient simulation of complex multiscale models. In conclusion, differential equation models have significantly advanced the understanding of neurodegenerative disease dynamics, providing a powerful framework for studying complex biological processes. Continued innovation in modeling techniques, data integration, and computational methods will be essential for translating these insights into practical applications, ultimately contributing to improved diagnosis, treatment, and management of neurodegenerative diseases.

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