Systematic Review of Computational Models of Autoimmune Demyelinating Brain Diseases and Their Biological Correlates

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Abstract

Multiple Sclerosis (MS) is a chronic, neuroinflammatory disease of the central nervous system. Studying its progression presents significant hurdles. Research on human patients requires lengthy follow-up periods and necessitates stringent approval from ethics committees. Meanwhile, induced MS in animal (murine) models provides only an approximation of the human condition; their results may not translate to humans and are governed by strict ethical precautions. These limitations highlight the critical need for alternative research methodologies to accelerate understanding and therapeutic development. In this context, computational (in silico) modeling offers a powerful parallel approach. This technique uses mathematical frameworks to simulate highly complex systems, allowing months of disease progression to be analyzed in minutes, free from the ethical constraints of biological studies. However, a multitude of computational models exist, each based on specific hypotheses about the disease's mechanisms, creating a fragmented landscape. This paper addresses this gap through a systematic literature mapping. From an initial pool of 199 studies, 49 relevant articles were selected. The primary contribution is identifying mathematical models that can be integrated, aiming to build a more comprehensive simulation framework that covers a broader spectrum of the disease's developmental stages, thereby fostering a more holistic understanding of MS.

Keywords

Multiple Sclerosis (MS), Computational Modelling, Systematic Mapping Study

1 INTRODUCTION

Multiple Sclerosis (MS) is a complex disease of the central nervous system (CNS) characterized by autoimmune inflammation, demyelination, and axonal damage [1]. In 2020, approximately 2.8 million people were affected worldwide, representing a significant increase compared to 2013 [2].

In Brazil, the Brazilian Multiple Sclerosis Association (ABEM) estimates that around 40,000 people live with the disease, most of whom are young women between 18 and 30 years old [3]. This indicates that MS affects individuals during a significant stage of life. In addition to its social impact, the disease also generates economic costs, with public spending on pensions and benefits estimated at R$411 million in 2020 [4].

MS diagnosis is complex due to its heterogeneous clinical manifestations and the absence of a definitive biological marker. Common symptoms include sensory, motor, and visual impairments, as well as fatigue, while disease progression may lead to depression,

Understanding MS dynamics can be achieved through *in vivo*, *in vitro*, or *in silico* approaches. Computational mathematical models allow the study of disease progression, remission, and immune responses [5, 6]. Unlike studies involving human patients—which require long follow-up periods and strict ethical approval—or murine models that only approximate the human condition, computational modeling provides a complementary and ethically flexible research approach.

The main objective of this work is to analyze the application of computational modeling in the study of degenerative brain diseases, particularly MS, through a systematic literature mapping. The remainder of this paper is organized as follows: Section 2 presents related works; Section 3 describes the methodology; Section 4 details the study execution; Section 5 presents results and discussion; and Section 6 concludes the paper.

2 METHODOLOGY

This research followed the guidelines proposed by Kitchenham and Charters [7] for conducting a systematic mapping study aimed at identifying relationships between computational models used to investigate the progression of Multiple Sclerosis (MS). The mapping was performed with the same methodological rigor in protocol development and execution described by Travassos et al. [8].

The adopted methodology consists of three phases [9]: **Planning**, **Execution**, and **Documentation**. In the planning phase, the study objectives, research questions, and review protocol were defined and validated. In the execution phase, searches were conducted in predefined databases and the retrieved studies were filtered according to inclusion and exclusion criteria. Finally, in the documentation phase, the extracted data were organized and validated by the researchers.

2.1 Study Design and Implementation

Based on the study objective, five research questions were defined: RQ1: What computational mathematical models are used in the

studies? RQ2: How do these models relate to biological hypotheses and experimental data? RQ3: What types of differential equations are used? RQ4: What are the main challenges and limitations of these models? RQ5: What future research directions are proposed?

To support the search process, the PICO strategy [10] was applied with the following elements: **P (Population):** Multiple Sclerosis; **I (Intervention):** Computational Modeling; **C (Comparison):** Not applicable; **O (Outcome):** Prediction of disease progression.

Based on these elements and their synonyms, the following search string was defined and applied to the Scopus and IEEE Digital Library databases:

(("multiple sclerosis"**OR** "CNS demyelinating diseases"
OR "autoimmune encephalomyelitis"**OR** "neuromyelitis optica")
AND
("computational simulations"**OR** "machine learning"
OR "computational modeling"**OR** "mathematical modeling"))

The databases were selected because they support complex logical queries and are accessible through the authors' institution, in addition to covering relevant research areas.

The systematic review included studies that met the following inclusion criteria: **IC1** computational models applied to autoimmune demyelinating diseases; **IC2** clear methodological description with quantitative or qualitative results; **IC3** publications in English, Portuguese, or Spanish; **IC4** studies available online; **IC5** full-text articles in electronic format.

Studies were excluded according to the following criteria: **EC1** publications in other languages; **EC2** studies focused only on clinical or epidemiological aspects; **EC3** opinion papers, editorials, book chapters, or incomplete abstracts; **EC4** studies without computational modeling, machine learning, or simulations; **EC5** duplicate publications, in which case the most recent or most complete version was retained.

The study selection process was conducted in six stages. **Stage 1:** The search string was executed in May 2025, retrieving 91 papers from Scopus and 108 from the IEEE Digital Library, of which 22 and 27 were available for full reading. **Stage 2:** The retrieved papers were merged using Zotero, resulting in 49 studies. **Stage 3:** Duplicate analysis was performed, but no duplicates were identified. **Stage 4:** Titles and abstracts were analyzed using predefined criteria, resulting in 18 studies selected for full-text review. **Stage 5:** Full-text analysis was conducted to verify alignment with the research objective, resulting in 14 selected papers. **Stage 6:** Finally, the selected studies were analyzed and the data extraction form was completed to address the research questions.

3 RESULTS AND DISCUSSION

In light of the methodological process previously described, this section presents the results obtained from the data extraction phase. A total of 15 articles were analyzed. The extraction form was completed by one researcher and validated by two others who participated in all stages of the study. The analysis performed is qualitative and conceptual, focusing on identifying relationships between computational models and biological hypotheses.

RQ1 - What computational mathematical models are used in the studies?

The analyzed studies employ diverse computational approaches, including mathematical models based on Ordinary Differential Equations (ODEs) and Partial Differential Equations (PDEs), classical neurophysiological models such as Hodgkin–Huxley and Poisson–Nernst–Planck, the Universal Immune System Simulator (UISS), machine learning techniques, stochastic processes such as high-level Stochastic Petri Nets, finite element methods (FEM), and OSEMA (Orthogonal Search Model Analysis). Some works combine multiple approaches; for instance, [11] integrates deterministic models (ODEs), PDEs, and stochastic models to represent cellular and spatial dynamics involved in demyelination.

RQ2 - How do these models relate to biological hypotheses and experimental data? Several studies ([12–15]) investigate oligodendrocyte (ODC) loss and recovery—cells responsible for myelin production [16]. Models proposed by Pappalardo et al. [12] and Pernice et al. [15] reproduce ODC loss during relapses and its relationship with lesions observed through Magnetic Resonance Imaging (MRI). Simulations also suggest partial remyelination depending on damage severity and demonstrate how drugs such as IFN-β1a, Natalizumab ([12]), and DAC ([15]) can modulate immune responses and reduce lesion load and relapse rates. Differential equation models represent processes such as Baló's concentric lesions ([17]), brain volume loss, and axonal damage ([11]).

Agent-based models combined with differential equations ([14, 15, 18]) simulate interactions between regulatory (Tregs) and effector (Teffs) T cells, incorporating factors such as viral influence (e.g., EBV) and interindividual variability through stochastic simulations. Other studies ([18, 19]) model electrophysiological mechanisms such as conduction block and hyperexcitability, explaining symptoms like Uhthoff's phenomenon and cortical hyperexcitability in MS. Machine learning approaches are also used to predict treatment response and disease progression. Study [20] predicts response to IFN-β based on gene expression data, while [11] identifies predictors of progression to secondary progressive MS (SPMS), including high EDSS scores and early disease onset. Additional studies explore speech impairments ([21]) and correlate clinical and imaging markers—such as periventricular lesions—with disease progression ([22]). Finally, Nazari-Vanani et al. [23] demonstrates that triboelectric nanogenerators (TENGs) can induce neuronal hyperexcitability, suggesting new experimental possibilities for studying neural conduction in demyelinating systems.

RQ3 - What types of differential equations are used?

Only three studies apply differential equations. These include PDEs with delay and radial symmetry, cortico-thalamic biophysical models based on reaction–diffusion–chemotaxis PDEs, and hybrid approaches combining deterministic ODE models with PDEs such as Hodgkin–Huxley, master equations, and reaction–diffusion models with chemotaxis.

RQ4 - What are the challenges and limitations of these models?

The main challenges identified include: limited datasets, which restrict model generalization; high computational cost when simulating complex CNS structures; lack of personalized biological data for calibration; structural simplifications such as 1D or 2D models and radial symmetry assumptions; difficulty in experimental validation; and limited multiscale integration across molecular, cellular,

and clinical levels.

RQ5 - What are the future directions proposed by the studies?

Future directions include the integration of multi-omics data (genomic, transcriptomic, and epigenetic) for personalized simulations; development of clinical platforms for *in silico* therapy testing and AI-supported decision making; validation using larger cohorts and longitudinal data; structural improvements with 3D geometries and more complex neural networks; testing new algorithms such as quantum approaches, τ-leaping, and attention mechanisms; and modeling individualized treatment responses based on clinical and biological data.

4 CONCLUSIONS

This work presents and analyzes several computational modeling approaches applied to neurodegenerative diseases, with a particular focus on Multiple Sclerosis. A systematic survey of the methods used to model these diseases can support researchers in identifying challenges and developing new strategies to address them. However, some threats to validity and limitations must be considered. Among the internal threats, the filtering process was conducted by only two researchers; in cases of disagreement, the studies were retained for the next stage. Additionally, the search string may not have included all relevant keywords, which could have led to the exclusion of some studies. The selection of databases was also limited, potentially resulting in the omission of relevant research. Despite these limitations, the chosen approach was sufficient to provide an overview of the main computational models and challenges related to the study of degenerative diseases. Future work includes conducting a quality assessment of the selected studies, performing a snowballing process by analyzing the references of the selected papers, expanding the number of databases considered, and developing a more robust computational model based on the evidence identified in this study.

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Referências

[1] Lucas Mainardo Rodrigues Bezerra, Fernando Akio Yamashita, Júlia Lorena Lacerda Ferreira Pinho, Jucimar Milhomem Coêlho Sobrinho, Caio César Silva Rocha, Caio Breno Reis Pires, Gabriel Osaki Queiroz Urzedo, and Cleidson De Morais Silva. ESCLEROSE MÚLTIPLA - ABORDAGENS DIAGNÓSTICAS E TERAPÊUTICAS: UMA revisão BIBLIOGRÁFICA. *RECIMA21 - Revista Científica Multidisciplinar - ISSN 2675-6218*, 5(2):e524950, 2024.

[2] Clare Walton, Rachel King, Lindsay Rechtman, Wendy Kaye, Emmanuelle Leray, Ruth Ann Marrie, Neil Robertson, Nicholas La Rocca, Bernard Uitdehaag, Ingrid van der Mei, Mitchell Wallin, Anne Helme, Ceri Angood Napier, Nick Rijke, and Peer Baneke. Rising prevalence of multiple sclerosis worldwide: Insights from the atlas of MS, third edition. *Mult. Scler.*, 26(14):1816–1821, 2020.

[3] Santa Casa BH. Esclerose múltipla afeta 40 mil pessoas no brasil: diagnóstico precoce aumenta a eficiência do tratamento. https://santacasabh.org.br/esclerose-multipla-afeta-40-mil-pessoas-no-brasil-diagnostico-precoce-aumenta-a-eficiencia-do-tratamento/, 2024. Accessed: 2025-7-22.

[4] Roche Farma Brasil / Centro de Inovação SESI Higiene Ocupacional. Novo estudo aponta que 40% das pessoas com esclerose múltipla estão fora do mercado de trabalho no brasil. https://www.roche.com.br/imprensa/novo-estudo-aponta-que-40-das-pessoas-com-esclerose-multipla-estao-fora-do-mercado-de-trabalho-no-brasil, 2019. Accessed: 2025-7-22.

[5] Alberto Montolío, José Cegoñino, Elvira Orduna, Berta Sebastian, Elena Garcia-Martin, and Amaya Pérez Del Palomar. A mathematical model to predict the evolution of retinal nerve fiber layer thinning in multiple sclerosis patients. *Comput. Biol. Med.*, 111(103357):103357, 2019.

[6] Bárbara de M Quintela, Rodrigo Weber dos Santos, and Marcelo Lobosco. On the coupling of two models of the human immune response to an antigen. *Biomed Res. Int.*, 2014:410457, 2014.

[7] Barbara Kitchenham and Stuart Charters. Guidelines for performing systematic literature reviews in software engineering. 2, 01 2007.

[8] Guilherme Travassos, Paulo Sérgio Dos Santos, Paula Mian, Arilo Neto, and Jorge Biolchini. An environment to support large scale experimentation in software engineering. pages 193–202, 03 2008. doi: 10.1109/ICECCS.2008.30.

[9] Pearl Brereton, Barbara A. Kitchenham, David Budgen, Mark Turner, and Mohamed Khalil. Lessons from applying the systematic literature review process within the software engineering domain. *Journal of Systems and Software*, 80(4): 571–583, 2007. ISSN 0164-1212. doi: https://doi.org/10.1016/j.jss.2006.07.009. URL https://www.sciencedirect.com/science/article/pii/S016412120600197X. Software Performance.

[10] Madhukar Pai, Michael McCulloch, Jennifer D Gorman, Nitika Pai, Wayne Enanoria, Gail Kennedy, Prathap Tharyan, and John M Colford, Jr. Systematic reviews and meta-analyses: an illustrated, step-by-step guide. *Natl. Med. J. India*, 17(2): 86–95, 2004.

[11] Mauro F Pinto, Hugo Oliveira, Sónia Batista, Luís Cruz, Mafalda Pinto, Inês Correia, Pedro Martins, and César Teixeira. Prediction of disease progression and outcomes in multiple sclerosis with machine learning. *Sci. Rep.*, 10(1):21038, 2020.

[12] Francesco Pappalardo, Giulia Russo, Marzio Pennisi, Giuseppe Alessandro Parasiliti Palumbo, Giuseppe Sgroi, Santo Motta, and Davide Maimone. The potential of computational modeling to predict disease course and treatment response in patients with relapsing multiple sclerosis. *Cells*, 9(3):586, 2020.

[13] Simone Pernice, Greta Romano, Giulia Russo, Marco Beccuti, Marzio Pennisi, and Francesco Pappalardo. Exploiting stochastic petri net formalism to capture the relapsing remitting multiple sclerosis variability under daclizumab administration. In *2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. IEEE, 2019.

[14] Giulia Russo, Giuseppe Alessandro Parasiliti Palumbo, Valentina Di Salvatore, Davide Maimone, and Francesco Pappalardo. Computational models to predict disease course and treatment response in multiple sclerosis. In *2021 International Conference on Electrical, Computer and Energy Technologies (ICECET)*. IEEE, 2021.

[15] Simone Pernice, Laura Follia, Alessandro Maglione, Marzio Pennisi, Francesco Pappalardo, Francesco Novelli, Marinella Clerico, Marco Beccuti, Francesca Cordero, and Simona Rolla. Computational modeling of the immune response in multiple sclerosis using epimod framework. *BMC Bioinformatics*, 21(Suppl 17):550, 2020.

[16] Oligodendrócitos. https://www.kenhub.com/pt/library/fisiologia-pt/oligodendrocitos-pt, March 2025. Accessed: 2025-6-19.

[17] Marijn Huiskamp, Svenja Kiljan, Shanna Kulik, Maarteen E Witte, Laura E Jonkman, John Gjm Bol, Geert J Schenk, Hanneke E Hulst, Prejaas Tewarie, Menno M Schoonheim, and Jeroen Jg Geurts. Inhibitory synaptic loss drives network changes in multiple sclerosis: An ex vivo to in silico translational study. *Mult. Scler.*, 28(13):2010–2019, 2022.

[18] Jay S Coggan, Stefan Bittner, Klaus M Stiefel, Sven G Meuth, and Steven A Prescott. Physiological dynamics in demyelinating diseases: Unraveling complex relationships through computer modeling. *Int. J. Mol. Sci.*, 16(9):21215–21236, 2015.

[19] Zoltan Gerevich, Richard Kovács, Agustin Liotta, Luisa A Hasam-Henderson, Ludwig Weh, Iwona Wallach, and Nikolaus Berndt. Metabolic implications of axonal demyelination and its consequences for synchronized network activity: An in silico and in vitro study. *J. Cereb. Blood Flow Metab.*, 43(9):1571–1587, 2023.

[20] S Mostafavi, S Baranzini, J Oksenberg, and P Mousavi. A fast multivariate feature-selection/classification approach for prediction of therapy response in multiple sclerosis. In *2006 IEEE Symposium on Computational Intelligence and Bioinformatics and Computational Biology*. IEEE, 2006.

[21] Gábor Gosztolya and Jose Egas-López. Speech-based screening of multiple sclerosis by features derived from self-supervised models. pages 1–5, 11 2023. doi: 10.1109/ICECET58911.2023.10389218.

[22] Jyoti Garg, Vaishali Mehta Wadhwa, Harminder Kaur, Rohak Tiwari, Vasu Mittal, and Avinash Sharma. Diagnosis, prediction, and risk factor analysis of multiple sclerosis disease using quantum machine learning classifier. In *2025 International Conference on Pervasive Computational Technologies (ICPCT)*, pages 714–718. IEEE, 2025.

[23] Razieh Nazari-Vanani, Raheleh Mohammadpour, Elham Asadian, Hashem Rafii-Tabar, and Pezhman Sasanpour. A computational modelling study of excitation of neuronal cells with triboelectric nanogenerators. *Sci. Rep.*, 12(1):13411, 2022.