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Exploring Hidden Markov Models in the Context of Genetic Disorders, and Related Conditions: A Systematic Review

Mouhamadou Djima Baranon[1, 2, *], Patrick Guge Oloo Weke[2], Judicael Alladatin[3, 4], Boni Maxime Ale[5, 6, 7, 8, 9, 10], Amos Kipkorir Langat[1]

[1]Department of Mathematics and Statistics, Pan African University Institute for Basic Sciences, Technology, and Innovation (PAUSTI), Nairobi, Kenya
[2]Ecole Nationale de Statistique, de Planification et de Demographie (ENSPD), Universite de Parakou, Parakou, Benin
[3]School of Mathematics, University of Nairobi, Nairobi, Kenya
[4]Faculte des Sciences de l'Education, Universite de Montreal, Montreal, Canada
[5]Department of Education, Consortium Siabanni Pour la Formation, la Recherche et le Developpement (Consortium SFR-D), Abomey-Calavi, Benin
[6]Institute of Tropical and Infectious Diseases, University of Nairobi, Nairobi, Kenya
[7]Strathmore University Business School, Strathmore University, Nairobi, Kenya
[8]Department of Health Research, Holo Global Health Research Institute, Nairobi, Kenya
[9]Department of Health Research, Health Data Acumen, Nairobi, Kenya
[10]College of Health Sciences, MOI University, Nairobi, Kenya

Email address:

djima.mouhamadou@students.jkuat.ac.ke (Mouhamadou Djima Baranon), pweke@uonbi.ac.ke (Patrick Guge Oloo Weke), judicael.alladatin.1@ulaval.ca (Judicael Alladatin), bonimaximeale@gmail.com (Boni Maxime Ale), moskiplangat@gmail.com (Amos Kipkorir Langat)
*Corresponding author

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Abstract: The application of Hidden Markov Models (HMMs) in the study of genetic and neurological disorders has shown significant potential in advancing our understanding and treatment of these conditions. This review assesses 77 papers selected from a pool of 1,105 records to evaluate the use of HMMs in disease research. After the exclusion of duplicate and irrelevant records, the papers were analyzed for their focus on HMM applications and regional representation. A notable deficiency was identified in research across regions such as Africa, South America, and Oceania, emphasizing the need for more diverse and inclusive studies in these areas. Additionally, many studies did not adequately address the role of genetic mutations in the onset and progression of these diseases, revealing a critical research gap that warrants further investigation. Future research efforts should prioritize the examination of mutations to deepen our understanding of how these changes impact the development and progression of genetic and neurological disorders. By addressing these gaps, the scientific community can facilitate the development of more effective and personalized treatments, ultimately enhancing health outcomes on a global scale. Overall, this review highlights the importance of HMMs in this area of research and underscores the necessity of broadening the scope of future studies to include a wider variety of geographical regions and a more comprehensive investigation of genetic mutations.

Keywords: Hidden Markov Model, Genetic Disorders, Neurological Disorders, Mutations, Healthcare

1. Introduction

Genetic, neurological, and related disorders pose significant challenges in modern healthcare, affecting a vast number of the global population and placing substantial burdens on healthcare systems worldwide [1–3]. These conditions encompass a broad number of disorders, ranging from rare genetic syndromes to common neurological diseases, each characterized by a complex interplay of genetic predispositions, environmental influences, and neurobiological mechanisms [4, 5]. Understanding the underlying molecular and phenotypic variability is crucial for achieving effective diagnosis, treatment, and management, yet the multifaceted nature of these conditions poses considerable challenges for both clinicians and researchers.

In this context, systematic reviews emerge as indispensable tools for synthesizing existing evidence, identifying gaps in knowledge, and informing clinical practice and research agendas. By systematically collating and analyzing a vast array of research studies, systematic reviews enable researchers to distill complex information, evaluate the strength of evidence, and derive meaningful conclusions to guide decision-making.

Furthermore, Hidden Markov Models (HMMs), a robust statistical framework rooted in signal processing and machine learning, have garnered growing acknowledgment within biomedical research circles. Their efficacy lies in their adeptness at modeling sequential data and elucidating concealed states within intricate systems [6]. This recognition stems from their capacity to analyze and interpret dynamic biological processes, thereby offering valuable insights into the complexities of biological phenomena [7, 8]. Moreover, a significant benefit of HMMs lies in their capacity to represent the unpredictable progression of diseases [9]. By integrating probabilistic shifts between states of illness, these models can accommodate the inherent unpredictabilities and fluctuations in disease trajectories. This feature holds particular significance in the modeling of intricate diseases characterized by various potential outcomes and diverse clinical pathways [10].

As researchers delve deeper into the realm of bioinformatics and computational biology, the application of HMMs continues to expand, showcasing their potential to revolutionize the understanding and interpretation of biomedical data. Therefore, in the area of genetics and neuroscience, HMMs offer a versatile approach for deciphering the underlying patterns and dynamics governing disease progression, treatment response, and clinical outcomes.

The aim of this systematic literature review is to investigate and assess the utilization of Hidden Markov Models (HMMs) in genetic disorders, neurological disorders, and associated condition studies. Especially, it aims to pinpoint areas where knowledge is lacking, offering insights that can steer forthcoming research endeavors and practical applications. Through this review, we answer the question: What is the current status of research regarding the use of HMMs in the study of genetic disorders, neurological disorders, and related conditions?

2. Methodology

2.1. Description of the Review Process

To validate the necessity of this systematic review, an initial search was performed on the Cochrane Database of Systematic Reviews (CDSR) and Prospero, in accordance with the guidelines of the Center for Reviews and Dissemination. No existing or ongoing systematic reviews were found on the subject of this study.

We then utilized the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) method for gathering data, which involved identifying the necessary data sources, screening, and verifying data eligibility. Using Databases such as PubMed, Scopus, Web of Science, and Google Scholar, we searched for articles related to the use of Hidden Markov Models for Genetic Disorders, Neurological Disorders, Cancer, and Tumors from 2012 to 2023. The keywords used were: “Hidden Markov Model”, “Genetic disorder”,“Cancer”, “Tumors”, “Neurological disorder”, “Mutations”, “Nerve”, “nervous system”, “Muscle”, “Alzheimer’s disease (AD)”, “Amyotrophic lateral sclerosis”, “Angelman syndrome”, “Autism spectrum disorder”, “Beta-thalassemia”, “Breast cancer”, “Cerebellar ataxia”, “Cervical cancer”, “Chronic lymphocytic leukemia”, “Cognitive impairment”, “Colon cancer”, “Congenital hypothyroidism”, “Cystic fibrosis”, “Diffuse large B-cell lymphoma”, “Down syndrome”, “Duchenne muscular dystrophy”, “Fragile X syndrome”, “Friedreich’s ataxia”, “Glaucoma”, “Glutaric acidemia type 1”, “Glioma”, “Hepatocellular carcinoma”, “Huntington’s disease”, “Hypoparathyroidism”, “Lactic acidosis”, “Leukemia”, “Lung cancer”, “Mitochondrial disease”, “Malignant lymphoma”, “Methylmalonic acidemia”, “Mitochondrial myopathy”, “Myelodysplastic syndromes”, “Niemann-Pick disease type C”, “Parkinson’s disease”, “Pancreatic cancer”, “Precancerous lesions”, “Prader-Willi syndrome”, “Prostate cancer”, “Sickle cell disease”, “Smith-Magenis syndrome”, “Spinocerebellar ataxia type 1”, “Spinocerebellar ataxia type 3”, “Syndromic form DOA ’plus”’, “Tay-Sachs disease”.

Furthermore, a standardized data extraction template was created to systematically gather pertinent information from the chosen studies. The collected data underwent analysis and synthesis to recognize prevalent themes, trends, and patterns among the chosen studies. Notable discoveries were condensed to offer an extensive overview of the existing understanding regarding the applications, constraints, and prospective avenues for additional investigation utilizing Hidden Markov Models in the examination of genetic disorders, neurological disorders, and associated conditions.

2.2. Inclusion and Exclusion Criteria

Table 1. Inclusion and Exclusion Criteria.

Feature	Inclusion Criteria	Exclusion Criteria
Model used	Research related to the application, development, or extinction of Hidden Markov Models	Research not related to Hidden Markov Models
Area of the study	Studies within genetic disorders, neurological conditions, Cancer, and Tumors	Studies not related to genetic disorders, neurological conditions, Cancer, or Tumors
Quality of the study	Research disseminated through peer-reviewed academic journals, conference presentations, or credible scientific outlets	Studies lacking peer-reviewed validation, credible sourcing, methodological robustness, transparent dissemination, or affiliation with reputable scientific channels
Period	Studies published between 2012 and 2023	Research published prior to 2012 or subsequent to 2023

3. Results and Discussions

The PRISMA Diagram is:

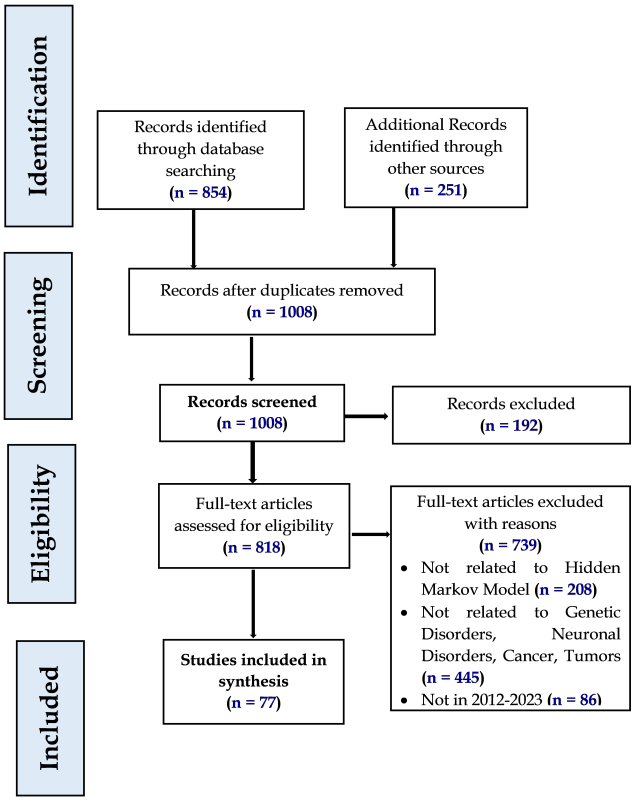

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram.

3.1. HHM-related Papers by Disease Category over Time

Figure 2 below presents the number of Hidden Markov Model (HMM)-related papers published annually across different disease categories (genetic disorders, neurological disorders, cancer, and tumors), providing insights into the utilization of HMMs over twelve years.

A total of 77 papers were published over the specified period, suggesting a significant body of research focused on applying HMMs to those conditions. There appears to be variability in the number of HMM-related papers published each year. For example, there's a noticeable increase in the total number of papers from 2018 to 2020, with a peak of 14 papers in 2020. Moreover, Neurological disorders seem to be the most extensively studied, with 31 papers dedicated to this category. This could be attributed to the complexity and diversity of neurological conditions, which present rich opportunities for applying HMMs to model disease progression, patient trajectories, and treatment outcomes.

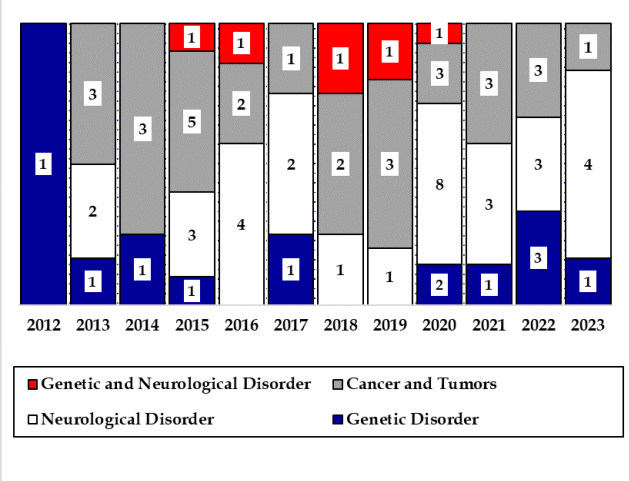

Figure 2. *Number of Hidden Markov Model-related papers by year and disease category.*

The relatively lower number of papers in certain disease categories, such as genetic disorders and genetic and neurological disorders, suggests potential research gaps or areas with less explored applications of HMMs. Identifying and addressing these gaps could lead to novel insights and advancements in understanding the underlying mechanisms of these diseases and improving diagnostic and therapeutic approaches.

3.2. HMM-related Papers by Geographic Location

The distribution of Hidden Markov Model (HMM) related papers across various countries highlights the global interest and engagement in this field of study. The following map (Figure 3) presents the number of HMM-related papers by country around the world.

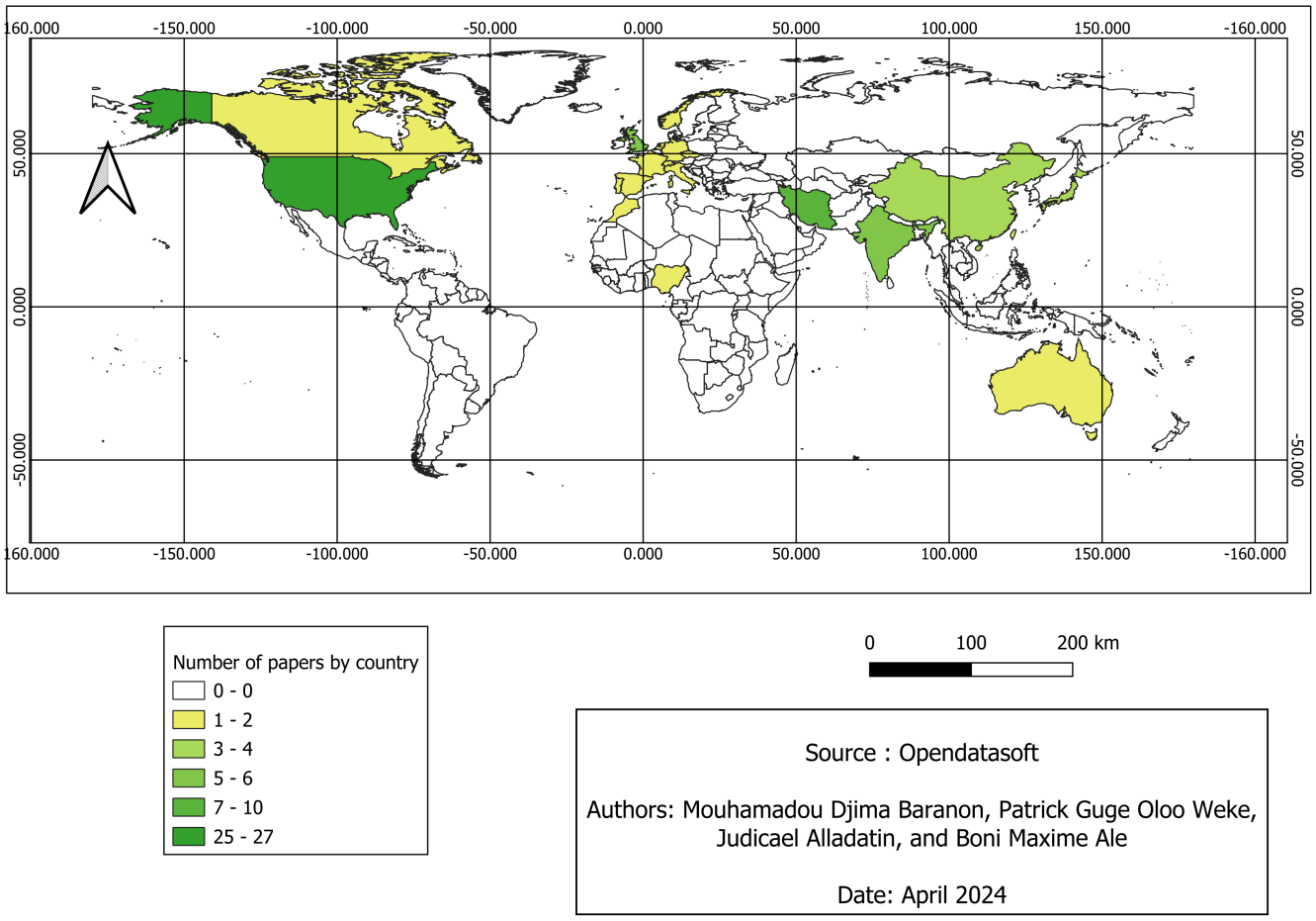

Figure 3. *Number of Hidden Markov Model-related papers by country.*

Leading the pack, the United States emerges as the dominant contributor with 27 papers, showcasing its strong research infrastructure and expertise in HMM applications. Following closely behind, Iran demonstrates significant activity with 7 papers, indicating a burgeoning interest and investment in this area. India also makes a notable contribution with 6 papers, underscoring its growing prominence in scientific research. Other countries such as China, Japan, and the United Kingdom display substantial engagement with 4, 3, and 5 papers respectively, reflecting diverse geographical centers

of HMM-related research. While some nations like Canada, Italy, France, and Taiwan demonstrate moderate involvement with 2 papers each, several countries register a single paper, indicating a smaller but still present level of interest. Overall, this data underscores the global nature of HMM research, with various countries actively contributing to advancements in this statistical modeling technique across a range of disciplines.

3.3. Synthesis of the Use of HMM in Genetic Disorders Studies

The complete designations for the abbreviated terms are provided within the Appendix, specifically referenced in Abbreviations.

The following table (Table 2) provides an overview of studies that employed HMM to investigate genetic disorders.

Table 2. *Hidden Markov Model used for Genetic Disorders.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)	Related to mutation	Type of mutation
Emerson A. C. et al. [11]	2020	Portugal	1,500 families	3-state HMM	ASD	No	
Knudson K., Gupta A. [12]	2022	United States	60 people	AR-HMM	SCA1, SCA3, and FRDA	No	
Sukkar R., Katz E. et al. [9]	2012	United States	120 patients with AD	Unsupervised HMM	AD	Yes	Amyloid beta (Aβ)
Nayarisseri A., et al. [13]	2013	India	100 patients	eXome HMM	CF, HD, SCD	Yes	Amino acid seq.
Chenna R. G. et al. [14]	2014		20 tissues	HMM	PWS and AS	Yes	CNV
Safca et al. [15]	2017	Morocco	100 patients	HMM	SCD	Yes	Hemoglobin S
Li Y., et al. [16]	2015	China	8 families	HMM	DMD	Yes	DMD exons
Chen D., et al. [17]	2020	China	13 families	HMM	DMD	Yes	DMD exons
Simona K. Z. et al. [18]	2021	United Kingdom	24 PWS-cr m+/p-, 31 wild mice	HMM	PWS	Yes	PWS-cr region
Narita K., et al. [19]	2022	Japan	177 patients	HMM	AS, CH, DMD, FXS, GAT1, MMA, MPC, PWS, SMS	Yes	SNVs and CNVs
Frohlich J., et al. [20]	2022	United States	105 AS, 30 Dup15q, 40 NT	Time Delay Embedded HMM	AS and Dup15q	Yes	Deletions of 15q11.2-q13.1 in AS and Dup15q
Fechner R., et al. [8]	2023			Multivariate HMM	SCA3	Yes	TNR

The table underlines the collective efforts of researchers worldwide, showcasing the versatility and applicability of HMMs in genetic research. For instance, studies such as those by Emerson A. C. et al. [11] in Portugal, Knudson K., Gupta A. [12] in the United States of America, Nayarisseri A., et al. [13] in India, and Li Y., et al. [16] in China, among others, highlight the global reach of HMM-based genetic analysis. These studies delve into diverse genetic disorders, including Autism Spectrum Disorder (ASD), Alzheimer's Disease (AD), Cystic Fibrosis (CF), Huntington's Disease (HD), and others, underscoring the broad spectrum of diseases that can be studied using HMMs. Moreover, Studies such as Sukkar R., Katz E., et al. [9] in the United States of America, Safca, et al. [15] in Morocco, Chenna R. G., et al. [14] investigating Prader-Willi Syndrome (PWS) and Angelman Syndrome (AS), and Narita K., et al. [19] in Japan, explore mutations such as Amyloid beta (Aβ), Hemoglobin S, Copy Number Variants (CNVs), Single Nucleotide Variants (SNVs), and trinucleotide repeats (TNR).

3.4. Synthesis of the Use of HMM in Neurological Disorders Studies

3.4.1. Papers Not Directly Related to Mutations in Neurological Disorders Studies

The table below offers a comprehensive overview of studies not directly related to mutations, focusing on neurological disorders, employing Hidden Markov Models (HMM) across different geographic regions and populations.

These studies represent a diverse range of research efforts aimed at understanding and diagnosing various neurological conditions. For example, Chen Y., Pham T. [21] in the United States, Houmani N., et al. [22] in France, and Martinez-Murcia F., et al. [27] in the United States investigated Alzheimer's Disease (AD) utilizing HMMs with different methodologies and study populations. Similarly, studies by Severson K. A., et al. [33] in the United States focused on Parkinson's Disease (PD), while Abed Khorasani M. et al. [26] in Iran explored Amyotrophic Lateral Sclerosis (ALS) using Factorial HMMs (FHMM). Furthermore, the table encompasses studies examining other neurological conditions such as Glaucoma, Mild Cognitive Impairment (MCI), and Cerebellar Ataxias (CAs). Furthermore, the utilization of various HMM variants,

including Continuous-Time HMMs (CT-HMMs), Factorial HMMs, Semiparametric mixed HMMs, and Hierarchical Bayesian multistate HMMs, reflects the adaptability of HMMs in modeling complex neurological processes. The table also highlights the importance of large-scale data analysis, with studies like Williams J., Storlie C., et al. [36] in the United States and Ceritli T., et al. [41] in the United Kingdom involving thousands of AD and PD patients, respectively.

Table 3. *Synthesis of papers not related to mutations in neurological disorders studies.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)
Chen Y., Pham T. [21]	2013	United States	100 individuals	HMM	AD
Houmani N., et al. [22]	2013	France	50 AD patients and 50 healthy	HMM	AD
Liu Y., et al. [23]	2015	United States		Continuous-Time HMM (CT-HMM)	Glaucoma and AD
Houmani N., Dreyfus G., Vialatte F. B. [24]	2015	France	112 AD patients and 112 healthy	HMM	AD
Wang W., Wu H., and Chung P. [25]	2015	Taiwan	42 AD patients and 64 healthy	HMM	AD
Abed Khorasani M. et al. [26]	2016	Iran	16 healthy and 13 ALS subjects	Factorial HMM (FHMM)	ALS
Martinez-Murcia F., et al. [27]	2016	United States	261 AD patients	HMM	AD
Seltman H., Mitchell S., Sweet R. [28]	2016	United States	434 AD patients	HMM	AD
Benoit J., Chan W., Luo S., Yeh H., and Yang Y. [29]	2016	United States	100 AD patients	CT-HMM	AD
Liu Y., Moreno A., Li, S., Li F., and Song L. [30]	2017	Multiple countries		CT-HMM AD	Glaucoma and
Sitnikova T. A, et al. [31]	2018	United Kingdom	26 AD patients and 26 healthy	HMM	AD
Kang K., Cai J., Song X., Zhu H. [32]	2019	United States	1,988 AD patients	Semiparametric mixed HMM (BSMHM2)	AD, MCI
Severson K. A., et al. [33]	2020	United States	2,462 PD patients	Personalized Input-Output HMM	PD
Mancy K. M. et al. [34]	2020	India	200 PD patients	HMM	PD
Jamaloo F., Mikaeili F., Noroozian M. [35]	2020	Iran	7 MCI patients and 7 healthy	Continuous HMM (CHMM)	AD
Williams J., Storlie C.et al. [36]	2020	United States	4,742 AD patients	Hierarchical Bayesian multistate HMM	AD
Naranjo L., et al. [37]	2020	Spain	100 PD patients	Inhomogeneous HMM with continuous state-space	PD
Baucum M., Khojandi A., and Papamarkou T. [38]	2021	United States	1,000 AD patients	HH recurrent neural network (HMRNN)	AD
Roth N., KÃ¼derle A. et al. [39]	2021	Erlangen, Germany	28 PD patients	HMM	PD
VyÅ¡ata O. Et al. [40]	2021	Czech Republic	23 ataxic, 20 healthy	HMM	CAs
Ceritli T., et al. [41]	2022	United Kingdom	1,500 PD patients	Mixture of input-output HMM (mIOHMMs)	PD
Shankar V., Sisodia D., Chandrakar P. [42]	2023	United States	1,514 AD patients	CT-HMM	AD
Li C., Li Y., Tao Y., et al. [43]	2023		23 AD patients, 54 MCI patients, and 217 healthy	HMM	AD, MCI

3.4.2. Papers Related to Mutations in Neurological Disorders Studies

The table presents a collection of papers (related to mutations) exploring various aspects of neurological disorders through the lens of Hidden Markov Models (HMMs). These studies offer insights into the complex dynamics of neurological diseases and their underlying mechanisms, providing valuable contributions to the field.

Table 4. *Synthesis of papers related to mutations in neurological disorders studies.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)	Type of mutation
Li A., Wang. M., et al. [44]	2017	China	100 healthy individuals	HMM	CNV	Gain or loss of genetic material
Zhou X., Kang K., Song X. [45]	2020	United States	1,088 patients	Two-part HMM	AD	APOE $\epsilon 4$ mutation, SNP
Wijeratne P., Alexander D. [46]	2020	United States	1,037 AD patients	Event-Based HMM (EBMM)	AD	Amyloid-beta plaques and tau tangles
Baucum M., Khojandi A., Papamarkou T. [47]	2020	United States	1,500 AD patients	HM recurrent neural network (HMRNN)	AD	Single point mutation
Lin Y., Song X. [48]	2022	N/A	N/A	Regression-based HMM (RHMM)	AD	SNPs
Liu H., Song X., Zhang B. [49]	2022	United States	685 AD patients	Varying-coefficient HMM (VC-HMM)	AD	APOE $\epsilon 4$ allele
Nagarajan D., et al. [50]	2023	United States	100 AD patients	Neutrosophic HMM (NHMM)	AD and MCI	APP gene
Zou Y., Lin Y., Song X. [51]	2023	United States	1,117 patients	Heterogeneous HMM (HMM)	AD	SNP

Li A., Wang. M., et al. [44] conducted a study in China involving 100 healthy individuals, utilizing HMM to analyze Copy Number Variations (CNVs) and their potential implications, such as gain or loss of genetic material. Similarly, Zhou X., Kang K., Song X. [45] in the United States employed a Two-part HMM to investigate Alzheimer's Disease (AD), focusing on mutations like the APOE $\epsilon 4$ allele and Single Nucleotide Polymorphisms (SNPs) in a sample of 1,088 patients. Other studies, such as Wijeratne P., Alexander D. [46] and Baucum M., Khojandi A., Papamarkou T. [47], delved into AD using Event-Based HMM (EBMM) and HM recurrent neural network (HMRNN), respectively, to explore factors like amyloid-beta plaques, tau tangles, and single point mutations. Furthermore, the table includes investigations utilizing innovative HMM variants, such as Regression-based HMM (RHMM) by Lin Y., Song X. [48], Varying-coefficient HMM (VC-HMM) by Liu H., Song X., Zhang B. [49], Neutrosophic HMM (NHMM) by Nagarajan D., et al. [50], and Heterogeneous HMM (HMM) by Zou Y., Lin Y., Song X. [51], to study AD and Mild Cognitive Impairment (MCI) through various perspectives.

3.5. Synthesis of the Use of HMM in Conditions both Genetic and Neurological

Table 5. *Synthesis of papers related to conditions both genetic and neurological.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)	Related to mutation	Type of mutation
Mannini A., et al. [52]	2015	Italy	60 patients	HMM	HD	No	
Mannini A., et al. [53]	2016	Italy	100 patients	HMM	HD, Post-stroke	No	
Olson D., Wheeler W. [54]	2018	N/A	N/A	HMM	HD, FXS	No	
Kwon B. C., et al. [55]	2020	United States	N/A	HMM	HD, PD, T1D	No	
Sun Z., Ghosh S., et al. [56]	2019	United States	1,890 HD patients	Continuous-Time HMM (CT-HMM)	HD	Yes	HTT gene mutation

The table presents a synthesis of studies utilizing Hidden Markov Models (HMMs) in conditions that are both genetic and neurological. The study of Mannini A., et al. [52] and Mannini A., et al. [53] conducted in Italy focused on HD and post-stroke patients, respectively, utilizing HMMs. These studies aimed to uncover patterns and dynamics within patient data, despite not explicitly focusing on genetic mutations. Similarly, the research conducted by Olson D., and Wheeler W. [54] included HD and FXS, employing HMMs to analyze data related to these conditions. This study explored temporal patterns or disease progression dynamics using HMMs, although genetic mutations were not explicitly addressed. Furthermore, the study of Kwon B. C., et al. [55] in the United States of America involved HD, PD, and T1D, utilizing HMMs. While these studies explored temporal dynamics or patient trajectories, genetic mutations were not explicitly studied or addressed in the context of HMM analysis. On the other hand, the study conducted by Sun Z., Ghosh S., et al. [56] in the United States of America focused on HD patients and utilized Continuous-Time HMM (CT-HMM). This study explicitly addressed genetic mutations by focusing on the HTT gene mutation, which is implicated in HD.

3.6. Synthesis of the Use of HMM in Cancer and Tumors Studies

3.6.1. Papers Not Directly Related to Mutations in Cancer and Tumor Studies

Table 6. *Synthesis of papers not related to mutations in cancer and tumor studies.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)
Madadizadeh F., et al. [57]	2015	Iran	900 breast cancer patients	HMM	Breast cancer
Hosaini S. S., Emadi M. [58]	2015	Iran	150 mammogram images	HMM	Breast Cancer
Mahmoudzadeh E. et al. [59]	2015	Iran	200 images	Extended HMM	Breast cancer
Mukhopadhyay S., et al. [60]	2016	India	100 cervical tissue samples	HMM	Cervical cancer
Amoros, R. et al. [61]	2019	Japan	1,524 patients	Continuous-Time HMM (CT-HMM)	HCC
Li W., Denton B. T. et al. [62]	2020	United States, Canada	9,021 patients	HMM	Pca
Wolfs J. et al. [63]	2020	Canada and The Netherlands	483 fractions from 24 patients treated with 3D-CRT or IMRT, and 263 fractions from 30 patients treated with VMAT or hybrid plans	HMM	Lung cancer
Ludwig R., et al. [64]	2021	Switzerland	1,000 HNSCC patients	HMM	HNSCC
Meng R., et al. [65]	2022	Norway	41 women with cervical cancer	Hierarchical continuous-time inhomogeneous HMM(HCT-iHMM)	Cervical cancer
Nuka N., Ofor D. [66]	2022	Nigeria	200 images (100 benign and 100 malignant)	HMM	Cancer

The table presents papers that explore various aspects of cancer and tumor studies utilizing Hidden Markov Models (HMMs), and not taking into account the mutation aspect. These studies analyzed different aspects of cancer pathology, diagnosis, and treatment across diverse geographic locations and populations. For instance, Madadizadeh F., et al. [57] and Hosaini S. S., Emadi M. [58] conducted studies in Iran focusing on breast cancer. Madadizadeh et al. utilized HMM to predict outcomes in 900 breast cancer patients, while Hosaini and Emadi employed HMM to analyze mammogram images for breast cancer diagnosis. Similarly, Mahmoudzadeh E. et al. [59] utilized Extended HMM to analyze images in the context of breast cancer diagnosis. Mukhopadhyay S., et al. [60] in India explored cervical cancer using HMMs to analyze cervical tissue samples. Furthermore, studies such as Amoros, R. et al. [61] in Japan focused on Hepatocellular Carcinoma (HCC) using Continuous-Time HMM (CT-HMM), while Li W., Denton B. T. et al. [62] in the United States and Canada investigated Prostate Cancer (Pca) utilizing HMM. Other studies in the table include research on lung cancer by Wolfs J. et al. [63] in Canada and The Netherlands, Head and Neck Squamous Cell Carcinoma (HNSCC) by Ludwig R., et al. [64] in Switzerland, and cervical cancer by Meng R., et al. [65] in Norway, all employing HMMs to analyze different aspects of cancer pathology and treatment. Additionally, Nuka N., Ofor D. [66] in Nigeria explored cancer diagnosis using HMM to analyze images for distinguishing between benign and malignant tumors.

These studies collectively highlight the versatility of HMMs in cancer research, showcasing their utility in analyzing various data types, including patient outcomes, medical images, and treatment plans. By employing HMMs, researchers can gain valuable insights into cancer pathology and develop more effective diagnostic and therapeutic strategies, ultimately contributing to improved patient outcomes and personalized cancer care.

3.6.2. Papers Related to Mutations in Cancer and Tumor Studies

The table provides an overview of papers related to mutations in cancer and tumor studies, showcasing the application of Hidden Markov Models (HMMs).For instance, Shihab H. et al. [67] conducted a study in the United Kingdom focusing on predicting mutations in 1,000 human genes associated with cancer, heart disease, and diabetes using HMM with Dirichlet mixtures. Similarly, Bonneville R., Jin X. V. [68] in the United States utilized HMM to analyze mutations in breast cancer, particularly focusing on the ERα gene. Furthermore, several studies like Mayilvaganan M., et al. [70] in India and Seifert A., et al. [71] in the United States investigated mutations in liver cancer and breast cancer/glioma, respectively, using HMMs. These studies targeted mutations such as Single Nucleotide Polymorphisms (SNPs) and gene Copy Number Alterations (CNAs) to elucidate their role in cancer development and progression. Moreover, the table includes studies employing innovative HMM variants, such as Bayesian HMM with Gaussian Mixture Clustering by Manogaran G., et al. [77] in Taiwan and HMM with Multinomial Mixture Model by Emdadi A. and Eslahchi C. [81], aiming to identify mutations in cancer cells and understand their implications. Additionally, studies like Wojtowicz D., et al. [78] in the United States and Momenzadeh M., et al. [79] in Iran explored mutations in breast cancer, pancreatic cancer, and leukemia using HMMs, shedding light on the genetic factors underlying these malignancies.

Table 7. *Synthesis of papers related to mutations in cancer and tumor studies.*

Author(s)	Year	Geographic location	Population or sample	Model used	Disease(s)	Type of mutation
Shihab H. et al. [67]	2013	United Kingdom	1,000 human genes	HMM with Dirichlet mixtures	Cancer, heart disease, and diabetes	MM
Bonneville R., Jin X. V. [68]	2013	United States		HMM	Breast cancer	ERα
Shihab H., et al. [67]	2013	Worldwide	318,476 genomes	HMM	Cancer	MM
Eric L. Seiser [69]	2014	United States	100 samples	HMM	DLBCL, breast cancer	SCNA
Mayilvaganan M., et al. [70]	2014	India	100 patients	HMM	Liver cancer	SNP
Seifert A., et al. [71]	2014	United States	296 breast cancer patients and 104 glioma patients	Autoregressive higher-order HMM	Breast cancer and glioma	Gene CNA
Nguyen T., et al. [72]	2015	Australia	62 breast cancer patients and 62 colon cancer patients	HMM	Cancer	SNP
Sasikumar R., Kalpana V. [73]	2015	N/A	50 cancer seq.	Profile HMM	Cancer	RIP
Yu X., Sun S. [74]	2016	China	100 breast cancer patients and 100 healthy	HMM	Breast cancer	CGM, SNP
Cosma G., et al. [75]	2017	UK	11,806 patients	HMM	PCa	Gene
Mukhopadhyay S. et al. [76]	2018	India	100 cervical tissue samples	HMM	Cervical cancer and precancerous lesions	p53 gene
Manogaran G., et al. [77]	2018	Taiwan	1,000 breast cancer patients	Bayesian HMM with Gaussian Mixture Clustering	Cancer	DNA
Wojtowicz D., et al. [78]	2019	United States	1,000 breast cancer tumors	HMM	Breast cancer, pancreatic cancer, CLL, malignant lymphoma	RIP
Momenzadeh M., et al. [79]	2019	Iran	323 patients	HMM	Leukemia cancer, DLBCL and Pca	SNP
Momenzadeh M., et al. [80]	2020	US, Iran	332 genes (breast cancer)	HMM	Breast cancer	SNP
Emdadi A. and Eslahchi C. [81]	2021	N/A	12,397 cancer cell	HMM with Multinomial Mixture Model	Cancer	SPG
Laxmi V. [82]	2021	India	800 patients	HMM with Gaussian Mixture clustering	Breast cancer, lung cancer, and colon cancer.	DNA
Ikesu R., et al. [83]	2022	Japan	729 CIN patients	HMM	CIN and cervical cancer.	HPV
Shokoohi F., Khaniki S. H. [84]	2023	United States	1,000 cancer samples	HMM	Cancer	HPV

4. Conclusion

The analysis carried out via the systematic review of the application of Hidden Markov Models in modeling genetic diseases, neurological disorders, and associated conditions has unveiled a significant research gap, particularly concerning the African continent. Among the 77 studies meeting the criteria for inclusion, only two focused on investigating these diseases within an African context (Morocco and Nigeria), showing a clear lack. Similar limitations in research representation were found for South America and Oceania. This emphasizes the need for increased research endeavors in these regions, acknowledging the crucial role of robust health research in addressing prevalent health disparities and enhancing healthcare outcomes. Furthermore, although certain continents exhibit relatively higher publication rates, the overall quantity of publications remains low, over the entire 11-year period covered by this review. This underscores the persistent requirement for sustained investment and dedication to research globally, ensuring a more equitable dissemination of scientific knowledge and advancements in the realm of genetic and neurological disorders, and related conditions.

Additionally, a crucial aspect highlighted by the review is that more than half of the studies are not related to mutations. Out of the 77 studies analyzed, a significant 39 were conducted without an exploration of the role and implications of mutations in these diseases. Even among the remaining 38 studies that acknowledged mutations, the analysis depth was shallow. This underscores a significant gap in current research efforts, as mutations are fundamental to the pathophysiology and etiology of genetic disorders, neurological conditions, and related conditions. Therefore, there is a need for future research initiatives to prioritize integrating mutation modeling into their investigative frameworks. Such efforts hold great promise in advancing understanding the intricate interplay between genetic variations and disease manifestations, as well as in informing the development of targeted intervention strategies and personalized treatment approaches. By addressing this critical research gap, the scientific community can significantly enhance its ability to tackle the multifaceted challenges posed by genetic diseases, neurological disorders, and related conditions, ultimately leading to improved health outcomes and a better quality of life for individuals globally.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursor protein
AS	Angelman syndrome
ASD	Autism spectrum disorder
CAs	Cerebellar ataxia
CF	Cystic fibrosis
CGM	CG methylation
CH	Congenital hypothyroidism
CIN	Cervical intraepithelial neoplasia
CLL	Chronic lymphocytic leukemia
CNV	Copy number variation
MM	Missense mutations
MPC	Niemann-Pick disease type C
Pca	Prostate cancer
RIP	Repeat induced point mutation
SMS	Smith-Magenis syndrome
SCA3	Spinocerebellar ataxia type 3
SNP	Single nucleotide polymorphism
SPG	Signaling pathways genes
TNR	Trinucleotide repeat expansion
DLBCL	Diffuse large B cell lymphoma
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
Dup15q	Duplication 15q11.2-13.1 syndrome
FRDA	Friedreich's ataxia
FXS	Fragile X syndrome
GAT1	Glutaric acidemia type 1
HCC	Hepatocellular carcinoma
HD	Huntington's disease
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human papillomavirus
MCI	Mild Cognitive Impairment
MMA	Methylmalonic acidemia
NT	neurotypical
PWS	Prader-Willi Syndrome
SCD	Sickle Cell Disease
SCA1	Spinocerebellar ataxia type 1
SCNA	Somatic copy number alterations
SNVs	Single-nucleotide variants
T1D	Type 1 diabetes

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We affirm that this paper is original and is not currently under consideration by any other publication.

ORCID

0009-0005-7783-653X (Mouhamadou Djima Baranon)
0000-0002-6283-4567 (Patrick Guge Oloo Weke)
0000-0001-7230-9953 (Judicael Alladatin)
0000-0002-8449-3310 (Boni Maxime Ale)
0000-0002-7813-6835 (Amos Kipkorir Langat)

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Ethics Statement

This research does not require ethical approval.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Valery L Feigin et al. "Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019". In: *The Lancet Neurology* 20.10 (2021), pp. 795-820. https://doi.org/10.1016/S1474-4422(21)00252-0

[2] Dina Nur Anggraini Ningrum and Woon-Man Kung. "Challenges and Perspectives of Neurological Disorders". In: *Brain Sciences* 13.4 (2023), p. 676. https://doi.org/10.3390/brainsci13040676

[3] Swetha Ramadesikan, Jennifer Lee, and Ruben Claudio Aguilar. "The Future of Genetic Disease Studies: Assembling an Updated Multidisciplinary Toolbox". In: *Frontiers in Cell and Developmental Biology* 10 (2022), p. 886448. https://doi.org/10.3389/fcell.2022.886448

[4] Sridhar Sivasubbu and Vinod Scaria. "Genomics of rare genetic diseases-experiences from India". In: *Human genomics* 13.1 (2019), p. 52. https://doi.org/10.1186/s40246-019-0215-5

[5] Roscoe O Brady. "Inherited Metabolic Diseases of the Nervous System: The pathogenesis and strategies for the control of heritable neurological disorders are examined." In: *Science* 193.4255 (1976), pp. 733-739. https://doi.org/10.1126/science.822514

[6] Mouhamadou Djima Baranon et al. "Modeling the progression of genetic disorders and infectious diseases with mutations by extended Markov processes on dynamic state-space: a probabilistic perspective". In: *Commun. Math. Biol. Neurosci.* 2024 (2024), Article-ID. https://doi.org/10.28919/cmbn/8497

[7] Gary Xie and Jeanne M Fair. "Hidden Markov Model: a shortest unique representative approach to detect the protein toxins, virulence factors and antibiotic resistance genes". In: *BMC Research Notes* 14 (2021), pp. 1-5. https://doi.org/10.1186/s13104-021-05531-w

[8] Richard Fechner et al. "A Generic Framework for Hidden Markov Models on Biomedical Data". In: *arXiv preprint arXiv:2307.13288* (2023). https://doi.org/10.48550/arXiv.2307.13288

[9] Rafid Sukkar et al. "Disease progression modeling using hidden Markov models". In: *2012 annual international conference of the IEEE engineering in medicine and biology society*. IEEE. 2012, pp. 2845-2848. https://doi.org/10.1109/EMBC.2012.6346556

[10] Ahmed T Salawudeen et al. "Optimal determination of hidden Markov model parameters for fuzzy time series forecasting". In: *Scientific African* 16 (2022), e01174. https://doi.org/10.1016/j.sciaf.2022.e01174

[11] Emerson A Carvalho et al. "Hidden Markov models to estimate the probability of having autistic children". In: IEEE Access 8 (2020), pp. 99540-99551. https://doi.org/10.1109/ACCESS.2020.2997334

[12] Karin C Knudson and Anoopum S Gupta. "Assessing cerebellar disorders with wearable inertial sensor data using time-frequency and autoregressive hidden Markov model approaches". In: *Sensors* 22.23 (2022), p. 9454. https://doi.org/10.3390/s22239454

[13] Anuraj Nayarisseri et al. "Impact of Next-Generation Whole-Exome sequencing in molecular diagnostics". In: *Drug Invention Today* 5.4 (2013), pp. 327-334. https://doi.org/10.1016/j.dit.2013.07.005

[14] Chenna R Galiveti et al. "Differential regulation of non-protein coding RNAs from Prader-Willi Syndrome locus". In: *Scientific reports* 4.1 (2014), p. 6445. https://doi.org/10.1038/srep06445

[15] Wilkie Delgado-Font et al. "Erythrocytes morphological classification through HMM for sickle cell detection". In: *Articulated Motion and Deformable Objects: 9th International Conference, AMDO 2016, Palma de Mallorca, Spain, July 13-15, 2016, Proceedings 9*. Springer. 2016, pp. 88-97. https://doi.org/10.1007/978-3-319-41778-3_9

[16] Yan Xu et al. "Haplotype-based approach for noninvasive prenatal tests of Duchenne muscular dystrophy using cell-free fetal DNA in maternal plasma". In: *Genetics in Medicine* 17.11 (2015), pp. 889-896. https://doi.org/10.1038/gim.2014.207

[17] Min Chen et al. "Noninvasive prenatal diagnosis for Duchenne muscular dystrophy based on the direct haplotype phasing". In: *Prenatal Diagnosis* 40.8 (2020), pp. 918-924. https://doi.org/10.1002/pd.5641

[18] Simona K Zahova et al. "Comparison of mouse models reveals a molecular distinction between psychotic illness in PWS and schizophrenia". In: *Translational Psychiatry* 11.1 (2021), p. 433. https://doi.org/10.1038/s41398-021-01561-x

[19] Kotaro Narita et al. "Whole-exome analysis of 177 pediatric patients with undiagnosed diseases". In: *Scientific reports* 12.1 (2022), p. 14589. https://doi.org/10.1038/s41598-022-14161-6

[20] Joel Frohlich et al. "Neural complexity is a common denominator of human consciousness across diverse regimes of cortical dynamics". In: *Communications Biology* 5.1 (2022), p. 1374. https://doi.org/10.1038/s42003-022-04331-7

[21] Ying Chen and Tuan D Pham. "Development of a brain MRI-based hidden Markov model for dementia recognition". In: *Biomedical engineering online* 12.1 (2013), pp. 1-16. https://doi.org/10.1186/1475-925X-12-S1-S2

[22] Nesma Houmani et al. "Stationary epoch-based entropy estimation for early diagnosis of Alzheimer's disease". In: *2013 IEEE Faible Tension Faible Consommation*. IEEE. 2013, pp. 1-4. https://doi.org/10.1109/FTFC.2013.6577776

[23] Yu-Ying Liu et al. "Efficient learning of continuous-time hidden markov models for disease progression". In: *Advances in neural information processing systems* 28 (2015).

[24] Nesma Houmani, G'erard Dreyfus, and Franc, ois B Vialatte. "Epoch-based entropy for early screening of Alzheimer's disease". In: *International journal of neural systems* 25.08 (2015), p. 1550032. https://doi.org/10.1142/S012906571550032X

[25] Wei-Hsin Wang et al. "An HMM-based gait comparison: using Alzheimer's disease patients as examples". In: *2015 International Joint Conference on Neural Networks (IJCNN)*. IEEE. 2015, pp. 1-6. https://doi.org/10.1109/IJCNN.2015.7280795

[26] Abed Khorasani, Mohammad Reza Daliri, and Mohammad Pooyan. "Recognition of amyotrophic lateral sclerosis disease using factorial hidden Markov model". In: *Biomedical Engineering/Biomedizinische Technik* 61.1 (2016), pp. 119-126. https://doi.org/10.1515/bmt-2014-0089

[27] Francisco J Martinez-Murcia et al. "A structural parametrization of the brain using hidden Markov models-based paths in Alzheimer's disease". In: *International journal of neural systems* 26.07 (2016), p. 1650024. https://doi.org/10.1142/S0129065716500246

[28] Howard J Seltman, Shaina Mitchell, and Robert A Sweet. "A Bayesian model of psychosis symptom trajectory in Alzheimer's disease". In: *International journal of geriatric psychiatry* 31.2 (2016), pp. 204-210. https://doi.org/10.1002/gps.4326

[29] Julia S Benoit et al. "A hidden Markov model approach to analyze longitudinal ternary outcomes when some observed states are possibly misclassified". In: *Statistics in medicine* 35.9 (2016), pp. 1549-1557. https://doi.org/10.1002/sim.6861

[30] Yu-Ying Liu et al. "Learning continuous-time hidden markov models for event data". In: *Mobile Health: Sensors, Analytic Methods, and Applications* (2017), pp. 361-387. https://doi.org/10.1007/978-3-319-51394-2_19

[31] Tatiana A Sitnikova et al. "Short timescale abnormalities in the states of spontaneous synchrony in the functional neural networks in Alzheimer's disease". In: *NeuroImage: Clinical* 20 (2018), pp. 128-152. https://doi.org/10.1016/j.nicl.2018.05.028

[32] Kai Kang et al. "Bayesian hidden Markov models for delineating the pathology of Alzheimer's disease". In: *Statistical methods in medical research* 28.7 (2019), pp. 2112-2124. https://doi.org/10.1177/0962280217748675

[33] Kristen A Severson et al. "Personalized input-output hidden markov models for disease progression modeling". In: *Machine learning for healthcare conference*. PMLR. 2020, pp. 309-330.

[34] KM Mancy, G Suresh, and C Vijayalakshmi. "Implementation of a Markov Model for the Analysis of Parkinson's Disease". In: *First International Conference on Sustainable Technologies for Computational Intelligence: Proceedings of ICTSCI 2019*. Springer. 2020, pp. 481-493. https://doi.org/10.1007/978-981-15-0029-9_38

[35] Fatemeh Jamaloo, Mohammad Mikaeili, and Maryam Noroozian. "Multi metric functional connectivity analysis based on continuous hidden Markov model with application in early diagnosis of Alzheimer's disease". In: *Biomedical Signal Processing and Control* 61 (2020), p. 102056. https://doi.org/10.1016/j.bspc.2020.102056

[36] Jonathan P Williams et al. "A Bayesian approach to multistate hidden Markov models: application to dementia progression". In: *Journal of the American Statistical Association* 115.529 (2020), pp. 16-31. https://doi.org/10.1080/01621459.2019.1594831

[37] Lizbeth Naranjo et al. "A hidden Markov model addressing measurement errors in the response and replicated covariates for continuous nondecreasing processes". In: *Biostatistics* 21.4 (2020), pp. 743-757. https://doi.org/10.1093/biostatistics/kxz004

[38] Matt Baucum, Anahita Khojandi, and Theodore Papamarkou. "Hidden Markov models as recurrent neural networks: An application to Alzheimer's disease". In: *2021 IEEE 21st International Conference on Bioinformatics and Bioengineering (BIBE)*. IEEE. 2021, pp. 1-6. https://doi.org/10.1109/BIBE52308.2021.9635256

[39] Nils Roth et al. "Hidden Markov Model based stride segmentation on unsupervised free-living gait data in Parkinson's disease patients". In: *Journal of neuroengineering and rehabilitation* 18.1 (2021), pp. 1-15. https://doi.org/10.1186/s12984-021-00883-7

[40] Oldřich Vyšata et al. "Classification of ataxic gait". In: *Sensors* 21.16 (2021), p. 5576. https://doi.org/10.3390/s21165576

[41] Taha Ceritli, Andrew P Creagh, and David A Clifton. "Mixture of input-output hidden Markov models for heterogeneous disease progression modeling". In: *Workshop on Healthcare AI and COVID-19*. PMLR. 2022, pp. 41-53. URL: https://proceedings.mlr.press/v184/ceritli22a

[42] Venkatesh Gauri Shankar, Dilip Singh Sisodia, and Preeti Chandrakar. "A Novel Continuous-time Hidden Markov Model Based on a Bag of Features Extracted from MR Brain Images for Alzheimer's Stage Progression and Detection". In: *Current Medical Imaging* (2023). https://doi.org/10.2174/1573405619666230213111047

[43] Chaofan Li et al. "Prolonged latent 'baseline' state of large-scale resting state networks in Alzheimer's disease as revealed by hidden Markov modelling". In: (2023). https://doi.org/10.21203/rs.3.rs-2417116/v1

[44] Ao Li et al. "ExomeHMM: a hidden Markov model for detecting copy number variation using whole-exome sequencing data". In: *Current Bioinformatics* 12.2 (2017), pp. 147-155.

[45] Xiaoxiao Zhou, Kai Kang, and Xinyuan Song. "Two-part hidden Markov models for semicontinuous longitudinal data with nonignorable missing covariates". In: *Statistics in Medicine* 39.13 (2020), pp. 1801-1816. https://doi.org/10.1002/sim.8513

[46] Peter A Wijeratne and Daniel C Alexander. "Learning transition times in event sequences: the Event-Based Hidden Markov Model of disease progression". In: *arXiv preprint arXiv:2011.01023* (2020). https://doi.org//10.48550/arXiv.2011.01023

[47] Matthew Baucum, Anahita Khojandi, and Theodore Papamarkou. "Hidden Markov models are recurrent neural networks: A disease progression modeling application". In: (2020). URL: https://openreview.net/forum?id=xcd5iTC6JW

[48] Yiqi Lin and Xinyuan Song. "Order selection for regression-based hidden Markov model". In: *Journal of Multivariate Analysis* 192 (2022), p. 105061. https://doi.org/10.1016/j.jmva.2022.105061

[49] Hefei Liu, Xinyuan Song, and Baoxue Zhang. "Varying-coefficient hidden Markov models with zero-effect regions". In: *Computational Statistics & Data Analysis* 173 (2022), p. 107482. https://doi.org/10.1016/j.csda.2022.107482

[50] D Nagarajan et al. "Modelling the progression of Alzheimer's disease using Neutrosophic hidden Markov models". In: *Neutrosophic Sets and Systems* 56.1 (2023), p. 4. URL: https://digitalrepository.unm.edu/nss_journal/vol56/iss1/4

[51] Yudan Zou, Yiqi Lin, and Xinyuan Song. "Bayesian heterogeneous hidden Markov models with an unknown number of states". In: *Journal of Computational and Graphical Statistics* (2023), pp. 1-10. https://doi.org/10.1080/10618600.2023.2231055

[52] Andrea Mannini et al. "Hidden Markov model-based strategy for gait segmentation using inertial sensors: application to elderly, hemiparetic patients and Huntington's disease patients". In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE. 2015, pp. 5179-5182. https://doi.org/10.1109/EMBC.2015.7319558

[53] Andrea Mannini et al. "A machine learning framework for gait classification using inertial sensors: Application to elderly, post-stroke and huntington's disease patients". In: *Sensors* 16.1 (2016), p. 134. https://doi.org/10.3390/s16010134

[54] Daniel R Olson and Travis J Wheeler. "TRUCE: A Hidden Markov Model for Annotation of Tandem Repeats". In: (2018). URL: https://scholarworks.umt.edu/gsrc/2018/pod2/2/.

[55] Bum Chul Kwon et al. "DPVis: Visual analytics with hidden markov models for disease progression pathways". In: *IEEE transactions on visualization and computer graphics* 27.9 (2020), pp. 3685-3700. https://doi.org/10.1109/TVCG.2020.2985689

[56] Zhaonan Sun et al. "A probabilistic disease progression modeling approach and its application to integrated Huntington's disease observational data". In: *JAMIA open* 2.1 (2019), pp. 123-130. https://doi.org/10.1093/jamiaopen/ooy060

[57] Farzan Madadizadeh, Mitra Montazeri, and Abbas Bahrampour. "Predicting the survival in breast cancer using Hidden Markov Model". In: *10th International Breast Cancer Congress*. 2015, pp. 25-27. URL: https://www.sid.ir/paper/934263/en.

[58] Sayedeh Somayeh Hosaini and Mehran Emadi. "Breast Cancer Tumor Diagnosis from Mammography Images Using Wavelet Transform and Hidden Markov Model". In: *International Journal of Advanced Research in Electrical, Electronics and Instrumentation Engineering* 4.8 (2015). https://doi.org/10.15662/ijareeie.2015.0408002

[59] E Mahmoudzadeh et al. "Extended hidden Markov model for optimized segmentation of breast thermography images". In: *Infrared Physics & Technology* 72 (2015), pp. 19-28. https://doi.org/10.1016/j.infrared.2015.06.012

[60] Sabyasachi Mukhopadhyay, Sanket Nandan, and Indrajit Kurmi. "Multiclass Classification of Cervical Cancer Tissues by Hidden Markov Model". In: *arXiv preprint arXiv:1512.06014* (2015). https://doi.org/10.48550/arXiv.1512.06014

[61] Ruben Amoros et al. "A continuous-time hidden Markov model for cancer surveillance using serum biomarkers with application to hepatocellular carcinoma". In: *Metron* 77 (2019), pp. 67-86. https://doi.org/10.1007/s40300-019-00151-8

[62] Weiyu Li et al. "Comparison of biopsy under-sampling and annual progression using hidden markov models to learn from prostate cancer active surveillance studies". In: *Cancer medicine* 9.24 (2020), pp. 9611-9619. https://doi.org/10.1002/cam4.3549

[63] Cecile JA Wolfs et al. "External validation of a hidden Markov model for gamma-based classification of anatomical changes in lung cancer patients using EPID dosimetry". In: *Medical Physics* 47.10 (2020), pp. 4675-4682. https://doi.org/10.1002/mp.14385

[64] Roman Ludwig et al. "A hidden Markov model for lymphatic tumor progression in the head and neck". In: *Scientific Reports* 11.1 (2021), p. 12261. https://doi.org/10.1038/s41598-021-91544-1

[65] Rui Meng et al. "Hierarchical continuous-time inhomogeneous hidden Markov model for cancer screening with extensive followup data". In: *Statistical Methods in Medical Research* 31.12 (2022), pp. 2383-2399.

[66] Nanwin Domaka Nuka Nuka and Williams Daniel Ofor. "Hidden markov model classification scheme for cancer detection in image processing". In: *Asian Journal of Multidimensional Research* 11.7 (2022), pp. 72-83. https://doi.org/10.5958/2278-4853.2022.00170.7

[67] Hashem A Shihab et al. "Predicting the functional consequences of cancer-associated amino acid substitutions". In: *Bioinformatics* 29.12 (2013), pp. 1504-1510. https://doi.org/10.1093/bioinformatics/btt182

[68] Russell Bonneville and Victor X Jin. "A hidden Markov model to identify combinatorial epigenetic regulation patterns for estrogen receptor α target genes". In: *Bioinformatics* 29.1 (2013), pp. 22-28. https://doi.org/10.1093/bioinformatics/bts639

[69] Eric L Seiser and Federico Innocenti. "Hidden markov model-based CNV detection algorithms for illumina genotyping microarrays". In: *Cancer informatics* 13 (2014), CIN-S16345. https://doi.org/10.4137/CIN.S16345

[70] M Mayilvaganan and R Rajamani. "Analysis of nucleotide sequence with normal and affected cancer liver cells using Hidden Markov model". In: *2014 IEEE International Conference on Computational Intelligence and Computing Research*. IEEE. 2014, pp. 1-4. https://doi.org/10.1109/ICCIC.2014.7238349

[71] Michael Seifert et al. "Autoregressive higher-order hidden Markov models: exploiting local chromosomal dependencies in the analysis of tumor expression profiles". In: *PloS one* 9.6 (2014), e100295. https://doi.org/10.1371/journal.pone.0100295

[72] Thanh Nguyen et al. "Hidden Markov models for cancer classification using gene expression profiles". In: *Information Sciences* 316 (2015), pp. 293-307. https://doi.org/10.1016/j.ins.2015.04.012

[73] R Sasikumar and V Kalpana. "Profile hidden markov model for sequence alignment to cancer sequence". In: *Global Journal of Pure and Applied Mathematics* 11.5 (2015), pp. 3665-3675. https://doi.org/10.1016/j.ins.2015.04.012

[74] Xiaoqing Yu and Shuying Sun. "HMM-DM: identifying differentially methylated regions using a hidden Markov model". In: *Statistical applications in genetics and molecular biology* 15.1 (2016), pp. 69-81. https://doi.org/10.1515/sagmb-2015-0077

[75] Georgina Cosma et al. "A survey on computational intelligence approaches for predictive modeling in prostate cancer". In: *Expert systems with applications* 70 (2017), pp. 1-19. https://doi.org/10.1016/j.eswa.2016.11.006

[76] Sabyasachi Mukhopadhyay et al. "Efficacy of hidden markov model over support vector machine on multiclass classification of healthy and cancerous cervical tissues". In: *Optical Diagnostics and Sensing XVIII: Toward Point-of-Care Diagnostics*. Vol. 10501. SPIE. 2018, pp. 324-327. https://doi.org/10.1117/12.2291485

[77] Gunasekaran Manogaran et al. "Machine learning based big data processing framework for cancer diagnosis using hidden Markov model and GM clustering". In: *Wireless personal communications* 102 (2018), pp. 2099-2116. https://doi.org/10.1007/s11277-017-5044-z

[78] Damian Wojtowicz et al. "Hidden Markov models lead to higher resolution maps of mutation signature activity in cancer". In: *Genome medicine* 11 (2019), pp. 1-12. https://doi.org/10.1186/s13073-019-0659-1

[79] Mohammadreza Momenzadeh, Mohammadreza Sehhati, and Hossein Rabbani. "A novel feature selection method for microarray data classification based on hidden Markov model". In: *Journal of biomedical informatics* 95 (2019), p. 103213. https://doi.org/10.1016/j.jbi.2019.103213

[80] Mohammadreza Momenzadeh, Mohammadreza Sehhati, and Hossein Rabbani. "Using hidden Markov model to predict recurrence of breast cancer based on sequential patterns in gene expression profiles". In: *Journal of Biomedical Informatics* 111 (2020), p. 103570. https://doi.org/10.1016/j.jbi.2020.103570

[81] Akram Emdadi and Changiz Eslahchi. "Auto-HMM-LMF: feature selection based method for prediction of drug response via autoencoder and hidden Markov model". In: *BMC bioinformatics* 22.1 (2021), pp. 1-22. https://doi.org/10.1186/s12859-021-03974-3

[82] Vijay Laxmi et al. "Cancer Diagnosis through Hidden Markov Model and Gaussian Mixture based Novel DNA Sequencing Approach". In: *2021 8th International Conference on Computing for Sustainable Global Development (INDIACom)*. IEEE. 2021, pp. 626-632. URL: https://ieeexplore.ieee.org/abstract/document/9441090.

[83] Ryo Ikesu et al. "Prognosis of high-risk human papillomavirus-related cervical lesions: A hidden Markov model analysis of a single-center cohort in Japan". In: *Cancer medicine* 11.3 (2022), pp. 664-675. https://doi.org/10.1002/cam4.4470

[84] Farhad Shokoohi and Saeedeh Hajebi Khaniki. "Uncovering Alterations in Cancer Epigenetics via Trans-Dimensional Markov Chain Monte Carlo and Hidden Markov Models". In: *bioRxiv* (2023), pp. 2023-06. https://doi.org/10.1101/2023.06.15.545168