Modelling the progression of Alzheimer's disease using Neutrosophic hidden Markov models

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Abstract
Alzheimer's disease is the primary cause of dementia. Due to the sluggish rate of progression of Alzheimer's disease, individuals have the opportunity to start receiving therapy early through routine testing. procedures since they are pricy and difficult to find. For many slowly advancing disorders, such as Alzheimer's disease (AD), the capacity to recognise changes in disease progression is essential. Machine learning methods with a high degree of modularity were used throughout the pipeline. We propose the use of Neutrosophic hidden Markov models (NHMMs) to simulate disease progression in a more thorough manner than the clinical phases of the disease. Due to the complexity and ambiguity of reality, decision-makers find it challenging to draw conclusions from precise data. Since they cannot be computed directly, the variables are encoded using a single interval Neutrosophic set. We showed that the trained HMM can imitate sickness development more accurately than the commonly acknowledged clinical phases.

Keywords: Alzheimer disease, Neutrosophic, hidden Markov model, Decision making ,Brain disorders.

1. Introduction

The retina, on the other hand, offers a simple window for obtaining possible biomarkers of Alzheimer's disease. Only the retina may be directly viewed in vivo as a part of the nervous

system. One of these retinal indications that is usually linked to Alzheimer's disease is retinal vasculature. It is possible that Alzheimer's disease patients' aberrant narrowing of the retinal venous blood column diameter and decreased blood flow accounts for the subjects with mild cognitive impairment's observed reduced retinal oxygen metabolism rate. A fundus vascular network that is sparse and has reduced fractal dimensions is highly linked to dementia. It is also found that Alzheimer's patients have deteriorated retinal neurovascular coupling when compared to healthy ageing. Based on recently published studies, Yet, two prevalent issues have hindered earlier retinal imaging investigations. Recent investigations show that abnormal characteristics associated with the early stages of neurodegenerative disorders are visible in retinal fundus pictures. More than 5% of people over 65 have Alzheimer's disease (AD), a long-term neurological disease that is the most common cause of dementia. An important and early step in the pathogenic cascade of Alzheimer's disease is the build up of multimers of the misfolded beta amyloid (Aß) peptide (4kDa peptides). The crucial function of the Aß peptide in the genesis of AD has been further reinforced by genetic discoveries during the past ten years. According to statistics, between 60 and 70 percent of dementia cases are caused by Alzheimer's disease (AD). It is still a neurodegenerative phenotype that is progressing[1]. People who are affected show a considerable deterioration in cognitive function, which has a negative impact on their quality of life and general health[2] .Contrary to other neurological disorders, managing AD has also shown to be associated with a significant financial burden in Asia, North America6, and even globally. Additionally, it has been reported that by the year 2030, the estimated global total cost of dementia-related expenses will be close to USD 2.0 trillion[3]. For many slowly progressing conditions, including Alzheimer's disease, a disease progression model that can be used to swiftly assess disease progression or lack thereof can help in the development of prospective treatments. This implies the model should be able to detect more specific disease phases as opposed to illness stages that match to clinical diagnoses. Modeling and prediction of disease progression has been the focus of several research projects [4-6]. whereas in [5], the authors put out a non-linear model based on the progression of the scores on the Alzheimer's disease Assessment Scale, however, has been underlined by recent study[8]. According to one study, 31% of patients with MCI return to a cognitively normal state within two years[9]. The proper targeting of

treatment drugs can be aided by an understanding of the characteristics of MCI patients who are more likely to develop AD and those who are more likely to return to normal cognition. Since it is believed that disease-modifying therapies may work better in people who have not yet developed AD and have not yet seen neuronal loss, it is especially crucial to identify risk factors for conversion to MCI. The objective in this case is to estimate the link between patient-level characteristics and the rate of conversion from MCI to AD and reversion from MCI to normal cognition. Machine learning offers a technique for automatic classification by identifying complex and nuanced patterns from highly dimensional data. In AD research, such algorithms are frequently developed to do automatic diagnosis and predict a person's future clinical status based on biomarkers. These algorithms aim to enhance medical decision-making by providing a possibly more objective diagnosis than that offered by common clinical criteria[10]. There is a wealth of information on the classification of AD and its prodromal stage, moderate cognitive impairment (MCI)[11,12]. Indicating strong performance for the classification of AD patients and control individuals, the area under the receiver operating characteristic curve (AUC) for classification approaches varies from 85 to 98 percent.

Following the trends and advancements in medical image analysis and machine learning, convolutional neural networks (CNN) in particular have seen increased application as neural network classifiers over the past few years[13]. In studies on AD, many researchers have discovered shrinking of grey matter in the brain's temporal lobe and hippocampal areas. The easiest way to define Random Forest (RF), an ensemble machine learning technique, is as "a collection of tree predictors such that each tree depends on the values of a random vector generated independently and with the same distribution for all trees in the forest"[14]. Regarding the handling of extremely non-linear biological data, tolerance to noise, tuning simplicity (relative to other ensemble learning algorithms), and the potential for efficient parallel processing, this algorithm offers a considerable edge over other approaches. In many applications, it also yields one of the finest accuracies to date [15]. Due of the numerous redundant features in high-dimensional situations, RF is a perfect contender for managing these issues. Although RF is an efficient feature selection technique in and of itself, other methods for feature set reduction both inside and outside of RF have been presented to further enhance its performance[16]. Researchers are particularly interested in finding risk factors for changing disease stages in multistate disease processes like Alzheimer's disease (AD). In this case, three kinds of cognitive function can be distinguished: normal cognition, moderate cognitive impairment (MCI), and Alzheimer's disease (AD). In AD clinical trials, MCI has been identified as a significant transitory illness. Markov process models are ideal for application in research on AD because they evaluate the rate of transition between

distinct disease states while taking into account the potential reversibility of some stages, such MCI, and the competing danger of mortality. The competing risk of death has been largely disregarded when determining the rate of progression to MCI and AD, and earlier research have demonstrated how biassed this is [17]. The observational aspect of AD studies, where cognitive status is frequently tested at regular clinic visits, making interval censored data, makes Markov process models the most suitable choice. Additionally, if patients switch between different illness states in between clinic appointments, the full disease history won't be provided. The failure to see the entire course of the disease as well as interval censoring can both be easily accommodated by discrete time Markov process models. In studies of disease, it is frequently observed that the rate of transition between states rises with age. Markov models, which are characterised by time-varying transition rates, can be used to estimate disease processes[18]. Hidden Markov models (HMMs) are well adapted for the task of describing longitudinal data as a set of hidden states. The impact of state-specific factors on responses are examined using a conditional regression model. A transition model to depict the dynamic change of hidden states makes up the second part of HMMs. Due to their ability to simultaneously display the longitudinal association structure and dynamic variability of the observed process, HMMs and its variants have attracted significant interest from the medical, behavioural, and academic fields[19–21]. As a result, neutrosophic techniques prove to be superior in the medical industry. Neutral hidden Markov models are a new field of innovation for uncertainty. The uncertainty information cannot be taken into account by the hidden Markov models now in use [22]. [23] discussed on Plithogenic sets in decision making.[24] ,this paper to introduced a new measure on nutrosophic centroid .[25]in this paper explained a Review on biomedicine .[26] explained an Markov chain in forecasting for stock trend. The structure of this paper is organized as follows.

We suggest modelling illness progression in a more detailed manner than the clinical stages of the disease using Neutrosophic hidden Markov models (NHMMs). Due to the complexity and ambiguity of reality, decision-makers find it challenging to draw conclusions from precise data. Since they cannot be computed directly, the variables are encoded using a single interval Neutrosophic set. In an actual circumstance, Neutrosophic sets are used to deal with indeterminacy. We train our NHMM in an unsupervised manner, in contrast to many existing uses of Neutrosophic Hidden Markov Models, and then assess the model's efficiency in revealing underlying statistical trends in disease development by referring to NHMM states as disease stages. In this study, we concentrate on AD and demonstrate that our model can identify more detailed disease phases than the three officially recognised clinical stages of "Normal," "MCI" (Mild Cognitive Impairment), and "AD" when tested on the cross validation data.

Consider the space X, which is composed of universal components that exhibit x. The structure of the neutrosophic set is

$N = \{(T_N(x), I_N(x), F_N(x) \mid x \in X\}$, where the 3 grades of memberships are from X to of the element $x \in X$ to the set X, with the criterion:

$$2. \quad {}^{-}0 \leq T_N(x) + I_N(x) + F_N(x) \leq 3^{+}.$$

The functions $T_N(x)$, $I_N(x)$ and $F_N(x)$ are the truth, indeterminate and falsity grades lie in real standard/non-standard subsets of $]^{-}0,1^{+}[$.

3. Operations on Interval-Valued Neutrosophic Numbers [5, 33]

Let $N_1 = \langle [T_1^L, T_1^U], [I_1^L, I_1^U], [F_1^L, F_1^U] \rangle$ and $N_2 = \langle [T_2^L, T_2^U], [I_2^L, I_2^U], [F_2^L, F_2^U] \rangle$ be two interval neutrosophic numbers then

Addition:

$N_1 \oplus N_2 = \langle [T_1^L + T_2^L - T_1^L T_2^L, T_1^U + T_2^U - T_1^U T_2^U], [I_1^L I_2^L, I_1^U I_2^U], [F_1^L F_2^L, F_1^U F_2^U] \rangle$

Multiplication:

$N_1 \otimes N_2 = \langle [T_1^L T_2^L, T_1^U T_2^U], [I_1^L + I_2^L - I_1^L I_2^L, I_1^U + I_2^U - I_1^U I_2^U], [F_1^L + F_2^L - F_1^L F_2^L, F_1^U + F_2^U - F_1^U F_2^U] \rangle$

Multiplication Neutrosophic probability:

$(x_1, y_1, z_1).(x_2, y_2, z_2) = (x_1 x_2, Min\{y_1 y_2\}, Max\{z_1 z_2\})$

Addition Neutrosophic probability:

$(x_1, y_1, z_1).(x_2, y_2, z_2) = (x_1 + x_2, Min\{y_1 y_2\}, Min\{z_1 z_2\})$

2.8 Interval Neutrosophic Markov Chain [25]

An interval neutrosophic stochastic process $\{X(n): n \in \mathrm{N}\}$ is said to be an interval neutrosophic Markov chain if it satisfies the Markov property:

$$\beta(X_{n+1} = j \mid X_{n-1} = i, X_n = k, \dots, X_0 = m) = \beta(X_{n+1} = j \mid X_{n-1} = i)$$

where i, j, k establish the state space S of the process.

Here $\tilde{P}_{ij} = \beta(X_{n+1} = j \mid X_n = i)$ are called the interval-valued neutrosophic probabilities of moving from state i to state j in one step. Hence $\tilde{P}_{ij} = \left(\left[T_{\tilde{P}_{ij}}^L, T_{\tilde{P}_{ij}}^U\right], \left[I_{\tilde{P}_{ij}}^L, I_{\tilde{P}_{ij}}^U\right], \left[F_{\tilde{P}_{ij}}^L, F_{\tilde{P}_{ij}}^U\right]\right)$, where $T_{\tilde{P}_{ij}}^L, T_{\tilde{P}_{ij}}^U$ are the lower and upper truth membership of the transition from state i to state j, respectively, $I_{\tilde{P}_{ij}}^L, I_{\tilde{P}_{ij}}^U$ are the lower and upper indeterminate membership of the transition from state i to state j respectively and $F_{\tilde{P}_{ij}}^L, F_{\tilde{P}_{ij}}^U$ are the lower and upper falsity membership of the transition from state i to state j. The matrix $P = \left(\tilde{P}_{ij}\right)$ is called the interval-valued neutrosophic transition probability matrix.

The connections between the states in a hidden markov model are controlled by a set of transitional probabilities. Since a Markov Chain's states could be observed, a Hidden Markov Model's states are statistical and have associated probability distributions known as observation probability density functions. This makes it possible to distinguish a Hidden Markov Model from a Markov Model or a Markov Chain. The multidimensional vector that encodes the observation is typically created using the HMM feature vector, which is a collection of characteristics. Continuous and discrete observation density functions are the two different types.

In this study, we take a slightly different strategy to training and testing the HMM. Since our objective is to identify and model illness stages, the HMM training is conducted in an unsupervised manner using the time signals from all participants, regardless of their clinical diagnosis at any given time.

The goal is to use the HMM's training strategy to take advantage of patterns in the biomarker feature vector that are present both temporally and across individual biomarker features in order to group subjects with similar conditions into one state and those with dissimilar conditions into different states.

A1:Memory loss and forgetfulness: Alzheimer's disease, a type of dementia, affects one's behaviour, thinking, and memory. Alzheimer's disease is characterised by memory loss, particularly of recent memories, which gets worse over time. Along with this, other cognitive symptoms are commonly noticeable, such as difficulties with language, problem-solving, and visual-spatial abilities.

A2: Challenges with language and communication: Alzheimer's disease is a type of dementia that affects thinking, behaviour, and memory. Alzheimer's disease is characterised by memory loss, particularly of recent memories, which gets worse over time. Along with this, other cognitive symptoms are commonly noticeable, such as difficulties with language, problem-solving, and visual-spatial abilities. When trying to communicate, a person with Alzheimer's may have problems finding the right words. Following a discussion may be challenging for someone with Alzheimer's disease, particularly if the conversation is complex or fast-paced. They keep doing it: A person suffering from Alzheimer's disease may repeat themselves or ask the same question. Alzheimer's disease can impact a person's ability to modulate their tone and inflection, which could cause them to speak in a different way. A person with Alzheimer's may have trouble communicating their needs and wants because they find it difficult to articulate their thoughts and ideas in a straightforward manner.

A3: problems with decision-making and problem-solving due to disorientation and confusion disorientation, and difficulties with problem-solving and decision-making are common symptoms of Alzheimer's disease. The ability to think, reason, and make decisions may be compromised as the condition worsens. Some typical issues associated with Alzheimer's disease include the following: Confusion and disorientation: These signs and symptoms might appear in someone with Alzheimer's disease, especially in unfamiliar or unexpected settings. Problem-solving challenges: Alzheimer's disease can impair a person's ability to think critically and solve problems. They could struggle to find solutions to simple or complex problems.

$$\pi = [< [0.05\ 0.1\ \ 0.05] >, < [0.3 \quad 0.2 \quad 0.1] >]$$

It demonstrates that Alzhimer is [0.3 0.2 0.1] and that the initial single value neutrosophic of Normal is [0.05 0.1 0.05]. It demonstrates that the value of obesity is greater than the

single-valued neutrosophic value of overweight. The state's probability transition diagram. The state N is normal and A is Alzheimer diseases.

Single-valued Neutrosophic transition probability value is

$$\begin{matrix} & \begin{matrix} N & A \end{matrix} \\ \begin{matrix} N \\ A \end{matrix} & \begin{bmatrix} \langle[0.6,0.1,0.1]\rangle & \langle[0.4,0.05,0.05]\rangle \\ \langle[0.2,0.05,0.1]\rangle & \langle[0.6,0.1\ ,0]\rangle \end{bmatrix} \end{matrix}$$

The observer's state is represented by 1, which stands for memory loss and forgetfulness, , which stands for difficulties with language and communication, and 3, which stands for difficulties with decision-making and problem-solving. The state's emission likelihood is

$$\begin{matrix} & \begin{matrix} 1 & 2 & 3 \end{matrix} \\ \begin{matrix} N \\ A \end{matrix} & \begin{bmatrix} \langle[0.2,0.1\ ,0]\rangle & \langle[0.3,0.1,0.05]\rangle & \langle[0.1,0.05\ ,0.1]\rangle \\ \langle[0.7,0.2\ ,0.1]\rangle & \langle[0.6,0.05,0]\rangle & \langle[0.8,0.05\ ,0]\rangle \end{bmatrix} \end{matrix}$$

There are two concealed states, and there are three observations. Choose a sequence 132 with the probability value as follows: The majority of participants depend on 1, which stands for memory loss and forgetfulness, 3, which represents for issues with decision-making and problem-solving, and 2, which stands for difficulties with language and communication.

$$P(O,Q)) = \prod P\left(\frac{O}{Q}\right) P(Q)$$

4. Single-valued Neutrosophic Hidden Markov Model

$$P(132,NNN) = P(1/N)P(3/N)P(2/N)P(N)P(N/N)P(N/N) = [\langle 0.000216,0.05,0.5\rangle]$$

$$P(132,NNA) = P(1/N)P(3/N)P(2/A)P(N)P(N/N)P(A/N) = [\langle 0.00144,0.05,0.1\rangle]$$

$$P(132,\mathrm{NAN}) = P(1/N)P(3/A)P(2/N)P(N)P(A/N)P(N/A) = [\langle 0.0023,0.05,0.1\rangle]$$

$$P(132,\mathrm{ANN}) = P(1/A)P(3/N)P(2/N)P(A)P(N/A)P(N/N) = [\langle 0.00075,0.05,0.1\rangle]$$

$$P(132,\mathrm{AAA}) = P(1/\mathrm{A})P(3/A)P(2/A)P(A)P\left(\frac{A}{A}\right)P\left(\frac{A}{A}\right) = [\langle 0.03628,0.05,0.1\rangle]$$

$$P(132,\mathrm{AAN}) = P(1/A)P(3/A)P(2/N)P(A)P(A/N)P(N/A) = [\langle 0.0040.05,0.1\rangle]$$

$$P(132,\mathrm{NAN}) = P(1/A)P(3/N)P(2/A)P(A)P(N/A)P\left(\frac{A}{N}\right) = [\langle 0.000504,0.05,0.1\rangle]$$

$$P(132,NAA) = P(1/\mathrm{N})P(3/A)P(2/A)P(N)P(A/N)P(A/A) = [\langle 0.01151,0.05,0.05\rangle]$$

The greatest likelihood of the above values is [0.036288, 0.05, 0.1] for the probability value of the sequence 132, and the maximum probability of the combination is P(132,AAA).

Find the likelihood of any interval combination in a similar manner. Viterbi algorithm verification of this probability of sequence 132.

5. Calculation for Single-valued Neutrosophic Hidden Markov Model

$P(1,N) = P(1/N)P(N) = [\langle 0.1,0.1,0.05\rangle]$
$P(1,A) = P(1/A)P(A) = [\langle 0.21,0.2,0.1\rangle]$
$P\left(3,\frac{N}{N}\right) = P(3/N)P\left(\frac{N}{N}\right) = [\langle 0.06,0.05,0.1\rangle]$
$P\left(3,\frac{N}{C}\right) = P(3/N)P\left(\frac{N}{A}\right) = [\langle 0.02,0.05,0.1\rangle]$
$P\left(3,\frac{A}{N}\right) = P(3/A)P\left(\frac{A}{N}\right) = [\langle 0.48,0.05,0.05\rangle]$
$P\left(3,\frac{A}{A}\right) = P(3/A)P\left(\frac{A}{A}\right) = [\langle 0.48,0.05,0\rangle]$
$P\left(2,\frac{N}{N}\right) = P(2/N)P\left(\frac{N}{N}\right) = [\langle 0.18,0.1,0.1\rangle]$
$P\left(2,\frac{A}{N}\right) = P(2/A)P\left(\frac{A}{N}\right) = [\langle 0.24,0.05,0.05\rangle]$
$P\left(2,\frac{N}{A}\right) = P(2/\mathrm{N})P\left(\frac{N}{A}\right) = [\langle 0.06,0.05,0.1\rangle]$
$P\left(2,\frac{A}{A}\right) = P(2/A)P\left(\frac{A}{A}\right) = [\langle 0.36,0.05,0\rangle]$
$V2 = [\langle 0.0042,0.1008\rangle]$
$V3 = [\langle 0.0064,0.0217\rangle]$

The Viterbi algorithm is used to validate the probability. It demonstrates that sequence 132 has a 0.21 probability. The combination has a P(132,AAA) maximum probability, and the path is A_A_A. It demonstrates that the Alzheimer disease's disease sequence path.

6. Conclusion

Uncertainty, ambiguity, and indeterminacy are common factors in real-world decision-making issues, and Neutrosophic devotes a lot of effort to fixing them. The neutrosophic Hidden Markov model (NHMM) has been used as a key mathematical mode for ambiguity, redundancy, and uncertainty. Indeterminacy is formally quantified by NHMM. Truth, ambiguity, and falsity exist independently. These characteristics are important for the biological diagnosis of the condition. In the medical industry, the decision is built using NHMM. Three components serve as the original representation of NHMM probability in the proposed framework, and three memberships carry out the transformation, which was developed to address the issue of Alzhemer. On the foundation of a Hidden Markov Model framework, we provided a model for illness progression. We trained an HMM in an unsupervised manner for Alzheimer's disease in an effort to identify more precise stages in

disease development. We demonstrated that the trained HMM can more precisely simulate illness development than the conventionally recognised clinical phases.

7. Reference

[1] A. Burns and S. Iliffe, Alzheimer's disease, *BMJ* 338 (2009) b158.
[2] O. Valenzuela, X. Jiang, A. Carrillo and I. Rojas, Multi-objective genetic algorithms to find most relevant volumes of the brain related to Alzheimer's disease and mild cognitive impairment, *Int. J. Neural Syst.* 28 (2018) 1850022.
[3] Wei Feng, Nicholas Van Halm-Lutterodt, Hao Tang, Andrew Mecum, Mohamed Kamal Mesregah, Yuan Ma, Haibin Li, Feng Zhang and Zhiyuan Wu, Erlin Yao, Xiuhua Guo†Automated MRI-Based Deep Learning Model for Detection of Alzheimer's Disease Process, International Journal of Neural Systems, Vol. 30, No. 6 (2020) 2050032, DOI: 10.1142/S012906572050032X
[4] R. S. Doody, V. Pavlik, P. Massman, S. Routree, E. Darby,and W. Chan, "Predicting Progression of Alzheimer's Disease,", *Alzheimer's Research and Therapy*, Feb. 2010.
[5] M. N. Samtani, M. Farnum, V.Lobanov, E. Yang, N.Raghavan, A. DiBernardo, and V. Narayan, "An Improved Model for Disease Progression in Patients from the Alzheimer's Disease Neuroimaging Initiative," *J. Clinical Pharmacology*, June 2009.
[6] H. M. Fonteijn, M. J. Clarkson, M. Modat, J. Barnes, M.Lehmann, S. Ourselin, N. C. Fox, and D. C. Alexander, "An Event-Based Disease Progression Model and Its Application to Familial Alzheimer's Disease," *Lecture Notes in Computer Science*, Vol. 6801/2011, pp. 748-759, 2011.
[7] M. Bruscoli and S. Lovestone, *Is MCI really just early dementia? A systematic review of conversion studies*, Int. Psychogeriatr. 16 (2004), pp. 129–140.
[8] T. Ishikawa and M. Ikeda, *Mild cognitive impairment in a population-based epidemiological study*, Psychogeriatrics 7 (2007), pp. 104–108.
[9] J. Manly, M. Tang, N. Schupf, Y. Stem, J. Vonsattel, and R. Mayeux, *Frequency and course of mild cognitive impairment in a multiethnic community*, Ann. Neurol. 63 (2008), pp. 494 – 506.
[10] Rathore, S., Habes, M., Aksam Iftikhar, M., Shacklett, A., Davatzikos, C., 2017. A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. Neuroimage 155, 530–548. https://doi.org/10.1016/j.neuroimage.2017.03.057
[11] Ansart, M., Epelbaum, S., Bassignana, G., Bˆone, A., Bottani, S., Cattai, T., Couronne, R., Faouzi, J., Koval, I., Louis, M., Couronn´e, R., Thibeau-Sutre, E., Wen, J., Wild, A., Burgos, N., Dormont, D., Colliot, O., Durrleman, S., 2021. Predicting the progression of mild cognitive impairment using machine learning: a systematic and quantitative review. Med. Image Anal. 67, 101848 https://doi.org/10.1016/j. media.2020.101848.
[12] Wen, J., Thibeau-Sutre, E., Samper-Gonzalez, J., Routier, A., Bottani, S., Durrleman, S., Burgos, N., Colliot, O., 2020. Convolutional Neural Networks for Classification of Alzheimer's Disease: Overview and Reproducible Evaluation. Med. Image Anal. 63 https://doi.org/10.1016/j.media.2020.101694.
[13] Cui, R., Liu, M., 2019. RNN-based longitudinal analysis for diagnosis of Alzheimer's disease. Comput. Med. Imaging Graph. 73, 1–10. https://doi.org/10.1016/j. compmedimag.2019.01.005.
[14] Breiman, L., 2001. Random Forests. Machine Learning 45 (1), 5–32.

[15] De Bruyn, T., Van Westen, G.J., Ijzerman, A.P., Stieger, B., de Witte, P., Augustijns, P.F.,Annaert, P.P., 2013. Structure-based identification of OATP1B1/3 inhibitors. Molecular Pharmacology 83, 1257–1267. http://dx.doi.org/10.1124/mol.112.08415223571415.

[16] Tuv, E., Borisov, A., Runger, G., Torkkola, K., 2009. Feature selection with ensembles, artificial variables, and redundancy elimination. Journal of Machine Learning Research 10, 1341–1366.

[17] J. Harezlak, S. Gao, and S. Hui, *An illness-death stochastic model in the analysis of longitudinal dementia data*, Statist. Med. 22 (2003), pp. 1465–1475.

[18] R. A. Hubbard & X. H. Zhou (2011) A comparison of non-homogeneous Markov regression models with application to Alzheimer's disease progression, Journal of Applied Statistics, 38:10, 2313-2326, DOI: 10.1080/02664763.2010.547567.

[19]Cappe´ O, Moulines E and Ryde´n T. Inference in hidden Markov models. New York: Springer, 2005.

[20]. Maruotti A. Mixed hidden Markov models for longitudinal data: an overview. Int Stat Rev 2011; 79: 427–454.

[21]. Bartolucci F, Farcomeni A and Pennoni F. Latent Markov models for longitudinal data. Florida: Chapman & Hall/CRC, Taylor and Francis Group, 2013.

[22] D. Nagarajan, J. Kavikumar, "Single-Valued and Interval-Valued Neutrosophic Hidden Markov Model", *Mathematical Problems in Engineering*, vol. 2022, Article ID 5323530, 12 pages, 2022. https://doi.org/10.1155/2022/5323530.

[23] S.Gomathy,***D. Nagarajan**,S. Broumi, M.Lathamaheswari, Plithogenic sets and their application in decision making, Neutrosophic Sets and Systems, vol. 38, 2020, pp. 453-469. DOI: 10.5281/zenodo.4300565.

[24]Said Broumi, M.Lathamaheswari, Ruipu Tan,**D.Nagarajan**, Talea Mohamed, Florent in Smarandache and Assia Bakali, A new distance measure for trapezoidal fuzzy neutrosophic numbers based on the centroids, Neutrosophic Sets and Systems, vol. 35, 2020, pp. 478-502. DOI: 10.5281/zenodo.3951706.

[25] M. Lathamaheswari,***D.Nagarajan** ,A.udayakumar ,J.kavikumar ,A Review on Type-2 in biomedicine, Indian journal of public health & development, 2018vol 9,(12) PP 341-345 .

[26] Ganesan, K., Annamalai, U. & **D.Nagarajan.** An integrated new threshold FCMs Markov chain based forecasting model for analyzing the power of stock trading trend. *Financ Innov* 5, 35 (2019). https://doi.org/10.1186/s40854-019-0150-4

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