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A study on the application of machine learning techniques to personalized medical care in the treatment of Alzheimer's disease (AD)

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Abstract

Artificial intelligence plays a vital role in predicting and contributing much in the health care department to personalize the medicines for the patient affected by a neurological disorder. The causes for the neurological disorder may vary from infections, injury on the brain, spinal cord, or in the nerve, congenital abnormalities, and the lifestyle of an individual, environmental health problem like malnutrition, polio, or genetic disorder. Personalized medicine is a sort of customized medicine for the patients by getting the information about a person's genes, proteins to thwart, diagnose or know the form of medicine to treat the diseases. Traditional medicine may limit to cure of the disease by taking a long duration of time or might cause some side effects. This can be conquered by personalized medicine by taking care of every person's genetic information and framing the more effective drugs which help in preempting disease progression by choosing the medicine which exactly suits and works well on the patient's body condition. The advantage of this personalized medicine in health care is that it reduces the cost, the occurrence of failure rate in pharmaceuticals clinical trial, eliminate trial and error form medicine, and lastly, time-consuming. In this proposed work, we take hold of a study on one of the major neurological disorders called Alzheimer's disease (AD) that could be prevented or the risk factor can be reduced by applying the customized medicine approach by artificial intelligence techniques. Artificial intelligence helps to generate deep knowledge in finding the cause of diseases and allow the system to learn, reason, and authorize some clinical decision through augmented intelligence.

Keywords: Precision medicine, Artificial Intelligence, genetic problem, Neurological disorder, DNA sequence.

I. Introduction

Our human body is entirely built up of the nervous system. The central nervous system is most composite and responsible for orchestrating body systems. The sensory organs receive information like hearing noise and sounds, vision, touching sensation, shocks, and all sorts of sensory feelings through nerves and transmit the information to the brain through the spinal cord. The central nervous system is in charge of all internal functions like blood vessel dilation, muscle movements, and our body reactions to the world. This is carried out by passing quick signals between cells[1]. The human brain organ is large and consists of two parts. One is the central nervous system which connects the brain and spinal cord and the second one is the peripheral nervous system which carries impulses to and from the central nervous system. There are some neurological disorders that varies from common to severe such as severe headaches, Epilepsy (abnormal brain activity), Stroke (lack of blood flow to the brain), ALS (affects nerve cells in the brain and spinal cord), Parkinson's disease (affects coordination) and Alzheimer's Disease[2] and Dementia (Memory Loss in older. Since there is no permanent cure for all these neurological disorders, only therapies and medicines can help to manage symptoms.

Every individual human immunity system is different from one another. Some of the bodies can respond to the treatment very faster whereas some may take a long duration of time to respond to the prescribed medicine. This is because in general medicines can be framed or ordained by selecting a group of members in a population with similar symptoms or disease. The physician can examine all the members in the group, collect their reasons for their discomfort, difficulties and try to figure out the possible best solutions or treatment by traditionally prescribing medicines. The problem associated with this is that traditional medicine need not be exactly suited for all the body conditions of the members of the group. For example, if 50 members are there in the group. 15-25 people's body can immediately respond accordingly remaining people may be slow down in responding or not turn out by the treatment.

Alzheimer's disease is one of the neurological disorders that affect the elderly people normally at or above the age of 60. The person affected by this nervous disease problem will have confusion and increased memory loss due to a shrink in the brain[3]. The cause for this disorder is the abnormal formation of misfolded proteins (Amyloidal plaques) in and around the nerve cells in the brain. The key factors for this cause will be getting old, genetic way, and lifestyle of an individual[4]. One way of finding a solution or preventing this Alzheimer's disease is by analyzing and investigating the genetic pattern of the patient and customizing the medicine that fits the person precisely[5]. In this paper, we present how precision medicine works well in the human body by collecting the individual DNA sequence of the person and predicting the personalized medicine[6] using the algorithms of machine learning techniques which is a subset of artificial intelligence.

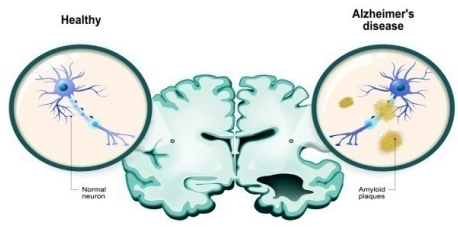

FIG.1. Formation of misfolded proteins (amyloidal plaque) in the brain nerve cell.

II. Literature Survey

Tran Quoc Bao Tran, Clea du Toit, Sandosh Padmanabhan, "Artificial intelligence in healthcare - the road to precision medicine", Journal of Hospital Management and Health Policy, 2021,http://dx.doi.org/10.21037/jhmhp-20-132.

To obtain customized medicine requires a huge number of data collected from clinical, genetic information of the patients like DNA sequence, genomics, and environmental details. To handle this numerous data or datasets we should know how to use and train the model to learn or predict the output by using machine learning (ML) techniques.

Machine Learning can be categorized into three sub-divisions.

1. **Supervised learning** – Train the models by labeling the context. The machine learns the models and predicts the output. For every breed of disease, we have effective prediction algorithms as follows.
   - **Boosting Algorithm:** Predicting adverse events in patients undergoing major cardiovascular procedures, Predicting urinary tract infections in the emergency department, Classifying lung nodules.
   - **Decision Tree:** Diabetic foot amputation risk analysis, Identifying diffusion lesions in acute ischemic stroke, Performance surveillance of infant incubators.
   - **Random forest:** Predicting risk of suicide attempts over time, Assessing risk of fibrosis and other liver-related outcomes in chronic Hepatitis C patients, Predicting readmission rate in heart failure patients.
   - **Support Vector Machine:** Differentiating responders and non-responders to depression treatment, Detecting structural imaging signature of schizophrenia, and Automatic detection of seizures in single-channel intra-cranial electroencephalograph recording.
   - **Naive Bayes:** Detecting clinically important colorectal surgical site infection, Improving detection and diagnosis of bone tumor, Microprocessor-based device for real-time prediction of acute cardiovascular events.
   - **Logistic Regression:** Early identification of patients with acute decompensated heart failure, Predicting early- and long-term mortality in hospitalized patients at risk of malnutrition, Predicting autism spectrum disorder diagnosis.
   - **K-Nearest Neighbors (KNN):** Analyzing and identifying kidney stones, Classifying venomous and non-venomous snake bites, Classifying lower back pain.
2. **Unsupervised Learning** – In this learning algorithm no labeling for the context or models is performed. The machine automatically acquires knowledge or learns the model by implementation. Some examples of these algorithms are as follows.
   - **Expectation-maximization:**MER and ECG signals through Gaussian's mixtures with the Expectation-Maximization algorithm, Automated segmentation and classification of brain stroke.
   - **Hierarchical clustering:**Detecting thyroid diseases, Classifying prognostic phenotypes in heart failure

patients, Clustering blood results in pediatric inflammatory bowel disease.

- **Affinity propagation:**Using affinity propagation for identifying subspecies among clonal organisms, Clustering Protein Sequences Using Affinity PropagationBased on an Improved Similarity Measure.

3. **Reinforcement Learning –** Machine can adopt the situations and self learns the environment and takes actions accordingly.

In this survey paper, they incorporated the data collected from the patients such as clinical information, Demographic, Laboratory test, Images (ECG, MRI), Metabolomics Proteomics, and Genomics and then stored the data as an electronic health record (EHRs) called biobanks[7]. On applying the machine learning models like clustering, classification, and regression we can validate the cost-effectiveness, regulatory approval, and then finally lay into the clinical implementation.

Murugan Subramanian, Anne Wojtusciszyn, Lucie Favre, Sabri Boughorbel, Jingxuan Shan,Khaled B. Letaief, Nelly Pitteloud and LotfiChouchane, "Precision medicine in the era of artificialintelligence: implications in chronic diseasemanagement",Journal ofTranslational Medicine, https://doi.org/10.1186/s12967-020-02658-5.

The life span of humans today is comparatively less when we compared to our ancestors. This is due to the change in environment, lifestyle, and modern medicine while in taken for a long time which leads to some side effects. The main reasons for chronic (continuous for a long time) diseases are diet, consumption of alcohol, smoke, stress, food containment, pollution, pesticides, global warming, dense pollution, etc.

Lifestyle factors like lack of regular physical activities, sleep, and consumption of alcohol and tobacco leads to chronic inflammation[8]. Variation or differences in the genetic DNA sequences causes epigenetic which consists of insertion, deletion, silent, and missense in Mutation. Another aspect of human health affecting factor is micro-biome which vary from person to person is the cause for gaining weight, developing depression and stress. By collecting all this deep knowledge about the patient's phenotype, the data can be stored and analyzed by the big data analysis and incorporated with artificial intelligence techniques to make the powerful decision. For example, patients are asked to wear a smart watch that is connected to the health care system used to monitor their physical activities, heart rate, blood oxygen, blood pressure, and calories burnt. The system automatically alerts the patient to take medicine on time, alerts to drink water at some intervals, alerts if he or she sitting idle for a long time without any physical activities. Considering and designing medicine by the personal intervention of phenotype of the patient helps us to cure the diseases and early prevention.

III. Personalized Precision Medicine

Precision medicine[9] is one of the emerging techniques for leading the individual patient to get the correct treatment or diagnosis by tailoring the medicines by analysis their phenotype (physical attributes of an organism including the development, appearance, and its behavior), biological

information, and all kind of clinical information or history. Every human body is different from one another. Same medicine can react diversely in different bodies. For example, we can take COVID'19 respiratory affected disease[10], the national and globe wide suggested and prescribed vaccine is covaxin or covidshield. The same medicine reacts in different ways for all. Somebody got mild to severe fever, headaches, the person already affect by heart diseases or taking medicines for other species of disease got side effects and complications by the same one-size-fit-for-all medicine (Traditional Medicine). Genetics plays a significant role in inheritance, mutation and enables us to find a person's health and diseases. Thus studying and analyzing the evolutionary algorithm[11], DNA sequence and patterns, genetics, and genomics will help to launch precision or customized medicine accurately[12].

IV. Evolutionary Algorithm

The genetic algorithm[13] is the direct search optimized algorithm based on the mechanics of biological evolution. It helps to understand the adaptive process of the natural system and to model artificial intelligence systems that sustain the robustness of the natural system. The foundation of genetic algorithms is as follows.

Step 1: Each chromosome represents a possible solution. Thus the population is a set of chromosomes.

Step 2: The Solution from one population is taken to form the new population with the hope that the new one will be better than the old one.

Step3: Out of the available individuals in the population, the best individuals (with high fitness usually called ad offspring) are used to reproduce the next generation offspring's.

Step4: The offspring generated will have features of both the parents and is a result of mutation. A mutation is a small modification or change in the gene structure.

To represent the scheme of genetic algorithm uses the finite length of the binary value of zeros and ones. The fitness function defines how well the solution obtained will solve the problem objectively. The evolution of survival of fitness is performed by genetically breeding the population of individuals over several generations.

The figures showing the genetic algorithm and generation cycle are as follows.

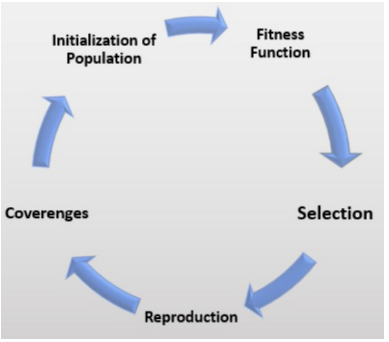

FIG.2: Genetic Algorithm

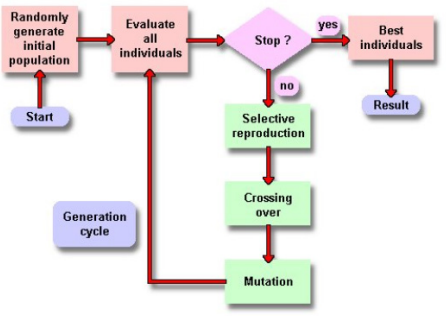

FIG.3: Genetic Algorithm Presenting Generation Cycle.

In the randomly generated initial population evaluate every individual; select

the best-fit one to generate a new one. Generation can be performed by crossover and mutation and finally, we get the best new inherited output.

Crossover: One of the genetic operators[14] is crossover which is also called recombination. It helps us to combine the genetic information of two parents (Mother and Father) to produce new offspring.

The example of the crossover operator in the genetic algorithm is shown below.

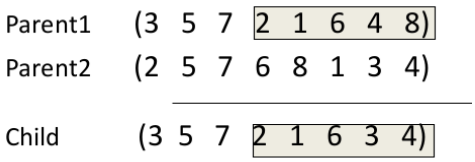

FIG.4: Crossover operator in Genetic Algorithm

Mutation: Mutation operators in genetic algorithms will alter a certain percentage of the gene in the chromosomes. This is used to generate diversity in genetics from one generation to the newly produced population. It changes the values of some genetic information by that we can obtain or increase the quality of the newly generated chromosomes or population.

The example of the mutation operator in genetic algorithm is shown below.

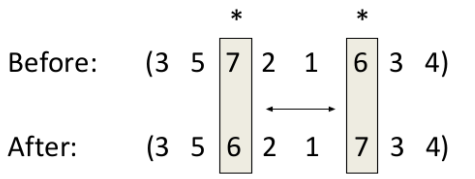

FIG.5: Mutation operator in Genetic Algorithm

By understanding the evolutionary algorithm and its operations like how genetic reproduction and recombination is done through crossover, mutation, and selection it is easier to identify whether the patient is affected by the disease through gene, or is there any damage in the gene by analyzing all those genetic information we can provide or tailored a customized medicine effectively.

V. DNA Sequencing Technology

DNA sequencing[15] means it governs the formation of the four building blocks chemical named Adenine (A), thymine (T), cytosine (C), guanine (G) that are made up of DNA molecules called bases. In molecular biology to learn genomics and the proteins to make a decision for that sequencing is used. Information gathered from the sequence is helpful to handle the disease and the phenotype, to identify the modification that happens in genes or damages that happened in DNA, and allow us to predict the customized medicine that best suits the target patient. DNA is capable of transforming the properties of the cell. It could change one form of bacteria into another. DNA sequencing is used in evolution to know how various organisms are evolved and related to each other. Sequencing is one of the important tools in the virology department to identify and learn about the virus. Diagnosis and drugs can also test based on DNA sequence. Physicians can analyze sequences from patient genes to decide the risk factor of the disease or to treat the rare genetic disease. DNA pattern is responsible for unique fingerprints (ridges), hair follicles, saliva, and determining the eye color of the living organism.

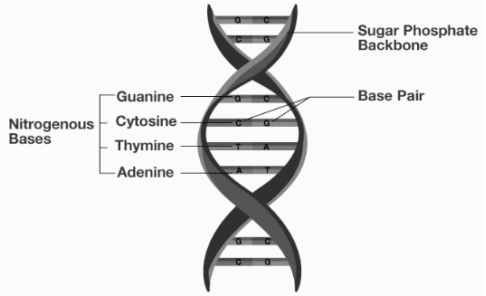

FIG.6: Structure of the DNA Sequence

The persistent change in the DNA sequence leads the way to replication or recombination of genetic formation which is called a mutation. DNA mutation[16] can be categorized into three types.

1) **Base Substitutions:** also called a point mutation. It was categorized into two types.
   - i) **Transition:** this occurs a pyrimidine is replaced with another pyrimidine or purine is replaced with another purine.
   - ii) **Transversion:** when pyrimidine is replaced for a purine or a purine replaced for a pyrimidine.

Point mutations that happen in DNA sequences encoding proteins will produce output by any one of the following - silent, missense, or nonsense.

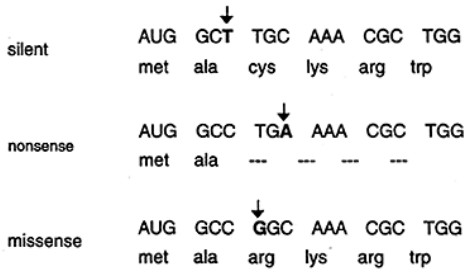

FIG.7: Point mutation (Single base substitution) in the DNA Sequence

Codon is the sequence of three nucleotides that together continuously form a unit of genetic code called DNA (Deoxyribonucleic acid) or RNA Molecules. For example, in the above figure, AUG is codon 1, GCT is codon 2, TGC is codon 3 likewise it goes on. Each codon represents and specifies the order of the amino acid in encoded proteins.

Silent: If the substitution occurs in the third position then the amino acid sequence is not changed and so mutation is silent.

Missense: It can be either conservative or non-conservative depending upon the nature of the amino acid substitution. In conservative mutation, the substituted amino acid properties and structures are similar to the original amino acid which results in little effect on the protein structure. The non-conservative mutation leads to different properties and structures of amino acids will result in bad protein structure.

1) **Nonsense (Stop):** To stop or truncate the codon. (Nonfunctioning protein)
2) **Deletion:** In deletion when one or more base pairs are missed or lost in the codon from the DNA structure then it results in a frameshift.
3) **Insertion:** Insertion may also make a way to frameshift but to ensure that whether or not three pairs are inserted.

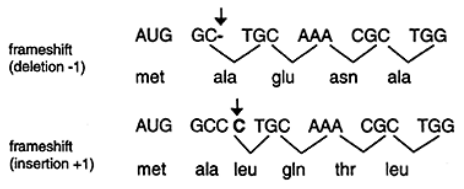

FIG.8: Insertion and deletion in the DNA Sequence

The main cause for this mutation is that by DNA damage, repair, radiation, recombination and replications.

VI. Genetic and Alzheimer's Disease

Alzheimer's disease is the type of neurological disorder [17]that affects the people on two phases.

i) Early phase

Alzheimer's disease affected people in the early stages is in very rare cases. The mutation in three chromosomes is the major cause for early phase detection or developing of symptoms which are as follows.

1) **Chromosome 21 with Amyloid precursor protein (APP),**
2) **Chromosome 14 with Presenilin 1 (PSEN1),**
3) **Chromosome 1 with Presenilin 2 (PSEN2).**

This mutation is resulting in the abnormal generation of proteins that are allied with the disease. In the mutation process, the breakdown of APP is responsible for generating or producing the amyloidal plaque, which is a core reason for this Alzheimer's disease.

ii) Late phase

In the late phase, the symptoms of the disease appear at or above the age of 60's. The main cause for this disease is that by a genetic variant. The genetic variant in chromosome 19 that is on the apolipoprotein E (APOE) gene happens will increase the risk of severe in disease. This APOE gene is the one responsible for controlling the cholesterol and fat that passed into the bloodstream. APOE gene comes from various forms. APOE ε2 is rare, the person having chromosomes 19 with APOE ε3 is at moderate risk that is neither decreasing nor increasing. The patient with APOE ε4 is at high risk of developing the symptoms and disease further. This doesn't mean that all people who are having chromosome 19 with APOE ε4 will have the possibility of developing this disease and someone who is already suffered from this Alzheimer's disorder does not have APOE ε4.

VII. Artificial Intelligence Technology

Today the availability of technology is high, the computational power like Graphics Processing Unit (GPU) and Tensor Processing Units (TPUs) which are offered by Google technology helps us to process and analyze a large number of data[18] and balance the workload effectively. With the sustenance of machine learning algorithms which is an application and subset of artificial intelligence, the medical record or history of the patient such as MRI, X-Rays, CT scan reports, and DNA structures[19] will be given as the dataset or as input data. This is possible through long-term medical health monitoring of the patient through wearable smart devices like a wristwatch, or by the injected microchip the condition of the patient is transferred now and then to the health care systems. The first step is to convert the unstructured data to a structured format so that it can be easily analyzed. Next to diagnose and predict the treatment for the diseases we have to train the machine with the possible symptoms, genetic characteristics which are responsible for the development of the disease, and the structural change in the DNA pattern.

Using the algorithms like i) Naive Bayes – helps in risk prediction of the disease and decision making, ii) SVM(Support Vector Machine)–helps in analyze and classifying the better diagnosis system, iii) LDA (linear discriminant analysis) – helps in detecting the protein-coded region of the affected patient, iv) deep learning – to analyze the CT scan, MRI scan, X-Rays in effective way, and v) ensemble learning[20] random forest – This is used in wide area of the medical department for analyzing the non-medical factors related to health, medical wireless sensors, diagnosing mental illness and in predicting the condition of the ICU patients. By the advancement of these types of algorithms the machine can able to predict the disease and customized medicine can be provided according to the natural cause of the disease.

VIII. Conclusion

The application developed by artificial intelligence already has a high impact on the health care department. It has been achieving more successes in accurately predicting the method for diagnosing and treating the disease. By integrating the biological-driven data with a machine learning algorithm, we can able to produce a more effective diagnosis system and drug discovery[21] than that in the existing traditional way. Most of the available treatments are high in cost and cannot be afforded by the normal population. This customized medicine helps all sorts of people to get the proper treatment on time with cost savings and affordability. This technology highly supports the development of the health department as well as the well-being of the population. Still, there are many challenges to getting perfection in predicting accuracy. But by precision medicine with the help of machine learning techniques, one size fit for all medicine is possible.

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