Artificial intelligence and Machine Learning based Techniques in Analyzing the COVID-19 Gene Expression data: A Review

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REVIEW ARTICLE

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Abstract

The novel Coronavirus associated with respiratory illness has become a new threat to human health as it is spreading very rapidly among the human population. Scientists and healthcare specialists throughout the world are still looking for a breakthrough technology to help combat the Covid-19 outbreak, despite the recent worldwide urgency. The use of Machine Learning (ML) and Artificial Intelligence (AI) in earlier epidemics has encouraged researchers by providing a fresh approach to combating the latest Coronavirus pandemic. This paper aims to comprehensively review the role of AI and ML for analysis of gene expressed data of COVID-19.

Keywords: Coronavirus, Repurposing, COVID-19, Machine learning, Artificial intelligence

1. Introduction

The coronavirus (COVID-19) emerged in China is a pandemic and has become a global threat to human health by rapidly spreading its infection from human to human, transmitting to multiple countries and thus the WHO (World Health Organization) has declared it as a global health emergency [1]. The corona infection was first reported in Wuhan, China, and the patient was hospitalized on 12 December 2019 and the disease outbreak was associated with the seafood market in Wuhan, China [2]. This emerging coronavirus pathogen was characterized as a new member of beta coronaviruses which is very closely associated with bat coronaviruses causing SARS. This virus mainly affects birds and mammals by causing mild illnesses like the common cold and respiratory tract infections but in the later stages, it might also cause MERS, SARS, and COVID-19 could lead to fatal illness [3]. Six coronavirus strains are said to cause the disease among which four strains (229E, OC43, NL63, and HKU1) are prevalent and cause common cold in individuals [4]. The other two strains (SARS-CoV and MERS-CoV) have a zoonotic origin and cause lethal illness. The SARS-CoV strain was responsible to cause an outbreak of severe acute respiratory syndrome in China in the years 2002 and 2003 [5]. The MERS-CoV strain was responsible to cause a respiratory syndrome in the Middle East in the year 2012 and was capable of transmitting the infection in both humans to humans and animals to humans. It is detected that the present CoV-19 belongs to the

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beta-coronavirus genus but it is distinct from SARS-CoV and MERS-CoV [6].

The COVID-19 virus incubation period is 1−14 days and is highly diffusible that it transmits and spreads from direct contact, droplets from the infected people, through infected objects and also from asymptomatic infected people [7]. Infected individuals usually show no symptoms or might show mild to moderate respiratory symptoms. The mortality rate of COVID-19 in young generations is about 0.2% while the older individuals age 80 or more than that have the highest rate of mortality [8].

A lot of measures and strategies have been implemented worldwide to control and prevent this infection as there is no antiviral drug or vaccines available. The drugs, vaccines and immunotherapeutics available for different viral infections like Ebola, Nipah and Zika have been tested against COVID-19 to check their efficacy and potency to tackle the emerging pandemic [2]. There is a critical response in identifying a particular drug to treat against COVID-19 to its spike glycoprotein that has a key role in virus-cell receptor infection; hence treating such severe influenza is still a challenge [9]. The best way to lower the number of overall cases of the pandemic is to include non-pharmaceutical interventions such as physical/social distancing; this approach of controlling the further spread of infection is very helpful as it reduces the pressure on healthcare workers [10].

Corona Virus belongs to the Corona viridae family and subfamily of Corona virinae which infects the host in a wide range that causes SARS in the host. COVID-19 is enveloped with helical symmetry of nucleocapsid and a +ssRNA (positive-sense, single-stranded RNA) [11]. COVID-19 is known to be an RNA virus as its RNA genome is one of the largest among the viruses and consists of 29,727 nucleotides [12]. The virus diameter ranges from 70 to 120 nm. The genomic sequence analysis of CoV-19 has shown that it belongs to the Beta-coronavirus genus including the MERS and SARS. The coronavirus genome consists of 14 ORFs (open reading frames) that can code for 27 proteins [13]. The 15 non-structural proteins involved in the virus replication are encoded from the ORF1 and ORF2 at the 5′-terminal region of the virus genome [14]. The structural proteins such as nucleocapsid (N), membrane protein (M), envelope protein (E) and spike protein (S) and eight accessory proteins are encoded from the 3′-terminal region of their genome [15].

The virus is surrounded by spike-shaped proteins (glycoproteins) which is the main receptor responsible to cause the host cell infection. It was demonstrated that S of CoV-19 interacts with ACE-2 (Angiotensin Converting Enzyme 2) to enter the host's cell particularly the alveolar epithelial cells. The comparative genomic studies have shown 380 amino acid substitution between SARS and SARS-CoV, with 27 gene mutations found on the genes responsible for code S [16]. Upon the recognition of the host cell, S protein of the virus cleaves itself and forms two subunits namely S1 and S2 which are non-covalently bound to one another. During the viral entry, the S1 subunit is responsible for the host-receptor binding interaction and the S2 subunit consists of membrane fusion machinery that helps in the fusion of viral and host membranes allowing the release of the viral genome into the host cells [17].

The primary function of N protein is to protect the viral genome from extracellular agents by forming of viral capsid called nucleocapsids which are flexible, long helical ribonucleoprotein (RNP). The fragments of N protein with its dimerization domain will bind to the RNA-binding site in the region between 248 and 280 residues within the viral RNA genome [18]. The nucleocapsid plays a major role in protecting the genome by ensuring reliable replication and transmission of it. The main core component is the M protein where its 16 amino acid domain binds with the N protein through ionic interactions leading in the encapsidation of the budding virus. Studies suggest that the complex of M protein and the nucleocapsid is stabilized due to the interaction that associates M with N protein [19].

The formation of the viral envelope is associated with the E protein as it binds to the BRD2 and BRD4 (bromodomain-containing proteins). BRD2 helps in regulating the gene transcription by binding with acetylated histones that share a similar sequence of 15 residues over E protein. E is very beneficial to the virus as it disrupts its interaction with BRD2 by mimicking its histones, and thus induces the change in the expression of the host's protein [20].

2. Treatment

COVID-19 is now global pathogen with no antiviral drugs, interventions, or vaccines available. Well to design targeted therapeutics against COVID-19, there is a need to understand the virus molecular mechanism involved in its replication and pathogenesis [21]. The scientists have discovered several methods that could lead to the discovery of a potential antiviral drug for the treatment of present COVID-19 human pathogen. The first method is to select the antiviral drugs used to treat other viral infections [22]. The drugs selected under this method include interferon I and interferon II which are good at their pharmacodynamic and

pharmacokinetic activities. Whereas there is no specific evidence of how these drugs act on the coronavirus [23]. In the second method, screening of the existing compounds from the database or library has been carried out. After screening, the selected compounds are further evaluated for their antiviral activities. This method is also termed as drug repurposing as the compounds selected from the screening process are used to treat a particular disease [24]. The third method is to redevelop a new medication to treat the coronavirus based on their genomic sequence.

3. Prevention of infection

The current strategy to prevent and limit the infection from spreading is to follow certain measures. The measures to control the infection include social distancing, isolation of patients, appropriate steps adopted in the diagnosis (precautions taken during specimen collection), and giving proper clinical care to an infected patient [25]. The most common and important measure undertaken to control the spread of infection is to frequent hand wash, usage of hand sanitizers, and face masks. The transmission of pathogens must be prevented in the healthcare workers in the hospitals caring for the infected individuals and the usage PPE kits that include N95 or FFP3 face masks, gloves, gowns, and eye protection has made compulsory [26].

To combat this global novel pandemic, WHO, scientists, and clinicians in the medical industry are looking for new technology to screen infected patients at various stages, find the best clinical trials, control the virus's spread, develop a vaccine to cure infected patients, and track infected patients' contacts [27]. Machine Learning and Artificial Intelligence, according to recent studies, are promising technologies used by various healthcare providers because they provide better scale-up, faster processing power, and even outperform humans in specific healthcare jobs [28]. As a result, healthcare companies and physicians around the world used a variety of machine learning and artificial intelligence (AI) technologies to combat the COVID-19 epidemic and address the issues that arose during the outbreak. This work seeks to provide an artificial intelligence-based system for genome sequence analysis of COVID-19, which is inspired by the previous debate and the advancement of artificial intelligence in genome sequence analysis.

4. Genomics of COVID-19

The virus's initial genome sequence was made available on January 10, 2020, 9 days after the first probable COVID-19 patient was found. Thousands more samples have been sequenced worldwide since then [29]. One of the most promising fields of research for COVID-19 is genomics, which is concerned with an organism's genetic content. Genome sequence analysis uses information from an organism's genome to help clinical specialists make more tailored therapy or diagnostic decisions. Experts want to better inform public health, make smarter judgments, and identify effective treatments by unlocking the virus's genetic code and the most severely impacted hosts (patients). The nucleic acids of an organism are made up of four nucleotide bases (Adenine-A, Guanine-G, Cytosine-C, and Thymine-T) stored as an encoded sequence in the genome. The unique COVID-19 genome sequence is an enclosed single-stranded positive-sense RNA (Ribonucleic acid) from the Coronavirus family, which is around 30 kB long and divided into three groups, two of which cause infections in mammals, such as bat SARSCoV-like diseases (MERS-CoV) [30].

The identification of nucleotides in a genome sequence is known as genome sequence analysis. Until now, the COVID-19 or SARS-CoV-2 genome had been sequenced by multiple organisations across the world, providing information on the virus's various strains [31]. The identification of genome features aids biomedical specialists in making predictions regarding these features' impact on disease implications in the population. Despite the fact that it is usually a time-consuming and resource-intensive technique that relies heavily on field experience. Various strains of COVID-19's first genome sequencing failed to produce timely actionable conclusions, and many aspects of disease behaviour remain unexplained [32].

5. Machine learning employed for genome sequence analysis of COVID-19

Artificial intelligence and related technologies, such as data analysis [33], machine learning [34], and deep learning [35], can help speed up the process of identifying actionable insights while also improving global response. Computational approaches that enable the study of massive, complex, and high-dimensional genomic data sets are in high demand [36]. Artificial intelligence can help to stimulate new discoveries in large data sets without requiring explicit rules or interests at various stages of the genomic data pipeline as shown in Fig. 1. The analysis and perception stage has seen the most developed work in artificial intelligence using genomic data sets [37]. Artificial intelligence has made tremendous progress in clinical genome analysis, including phenotyping in
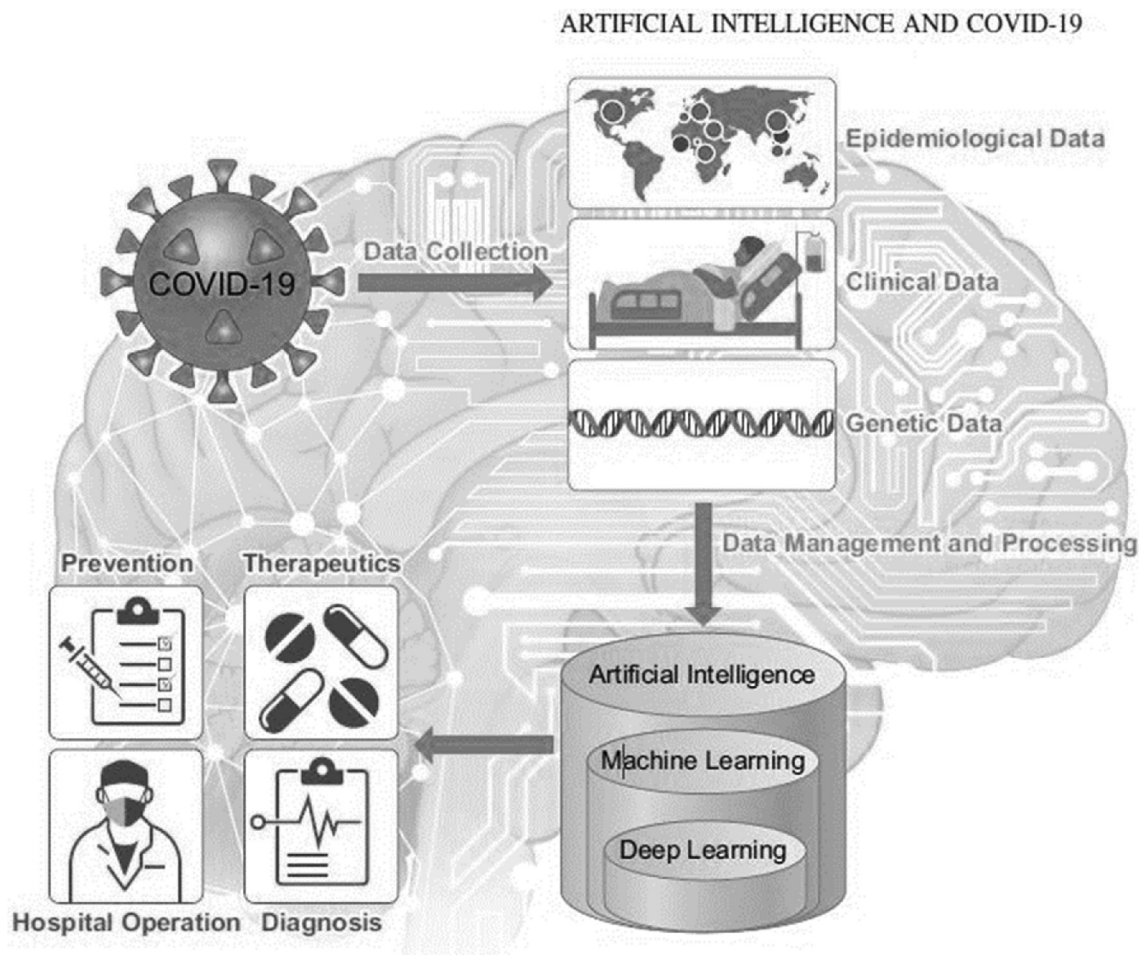
Fig. 1. Figure depicting how artificial intelligence and machine learning can help in preventing the COVID-19 infection.

uncommon syndromes, cancer, and its variations research and explanation [38]. Although, in the field of genomics, most artificial intelligence-based work is still in the research phase. Machine and deep learning approaches are in high demand for functional genomics analysis. These techniques have been used to track most elements of genome analysis, including genome sequencing, phenotyping, and variation detection, as well as downstream analysis [39]. Improvements in computation, artificial intelligence, and the growth of biological data sets now allow for advancements in existing service domains. Simultaneously, advances in open access research and open-source tools enable the application and success of artificial intelligence in a variety of genetic investigations [40]. Furthermore, good software distributors include machine learning algorithms into their genomic analysis tools and services, using publicly available resources.

Researchers can use artificial intelligence and data analytics approaches to better comprehend factors, behaviors, and data trends in a variety of scenarios,

issues, and diseases. Statistical, data mining, and machine learning approaches were used in early research and studies for many types of investigations such as predicting and risk assessments [41] of various diseases.

6. Machine learning algorithms

This section gives a quick rundown of the machine learning algorithms that can be used to analyze of gene expression data for COVID-19. The use of machine learning to combat COVID-19 is critical in the current circumstances.

6.1. K nearest neighbours (KNN)

The classification in this case is based on the data points' location. The number of neighbours is used to group similar objects together. Non-parametric categorization is used. There are no assumptions made regarding the data. It's also known as a lazy learner algorithm because the learning process is

delayed and the action is only performed after the data is classified [42]. The minimum number of neighbours necessary is set to k by the user. In general, the predictions are more reliable when the value of k is larger. To improve classification accuracy, weights are attached to the neighbours [43].

6.2. Support vector machine (SVM)

The data is divided into separate groups using a hyperplane. To locate the smallest gap between data points, SVM calculates the maximum marginal distance. Hyperplanes serve as borders, dividing data points into categories. When there are just two attributes, a single line exists. When the input size is increased to three, a 2D plane is created [44]. It becomes increasingly harder to see the hyperplane as the number of characteristics grows.

6.3. Logistic regression

It uses a sigmoid curve as a cost function to predict a categorical variable (dependent variable) based on one or more independent factors. The Sigmoid function (Logistic function) is an S-shaped curve that divides data into classes. Binomial, multinomial, and ordinal classifications can all benefit from logistic regression [45].

6.4. Decision trees

The outcome is predicted by the leaf nodes, decisions are made by the branches, and characteristics are internal nodes in a decision tree. Decision trees distribute instances by assembling them down the tree from the root to the leaf nodes, resulting in the instance's classification [46].

6.5. Random forests

When the data is big, classification using a decision tree might lead to overfitting. Random forests can help us overcome these restrictions. To boost accuracy, different decision trees are categorized and then combined together. "Bagging" is the term for this process. The spatial−temporal distribution of COVID-19 daily cases around the world was estimated using a random forest machine learning approach [47].

6.6. Artificial neural network (ANN)

They are a multi-layered network that is entirely connected. An input layer, an output layer, and numerous hidden layers are among the layers. The nodes in one layer are connected to the nodes in the preceding and subsequent layers. The inputs are processed by an activation function. One layer's output becomes the input for the following layer. The location of the user was determined using ANN and IoT. Although the data was restricted, the accuracy was great [48].

7. Discussion and conclusion

Since the outbreak of the novel SARS-CoV-2 virus, scientists and medical industries all over the world have been urging people to fight the pandemic by looking for alternative methods of rapid screening and prediction, contact tracing, forecasting, and vaccine or drug development that is more accurate and reliable [49]. Machine Learning and Artificial Intelligence are two promising technologies that are being used by a variety of healthcare providers [50]. This study examines recent studies that use advanced technology to assist researchers in a variety of ways, addressing the difficulties and obstacles that arise when utilizing such algorithms to assist medical experts in real-world problems. The application of modern technology with AI and ML increases screening, prediction, contact tracing, forecasting, and drug/vaccine development with extraordinary dependability, according to this review. Deep learning algorithms were used in the majority of the papers and were determined to have greater potential, robustness, and advancement than other learning algorithms. However, given the current urgency, an improved model with high-end performance accuracy in screening and predicting SARS-CoV-2 with a different type of linked disease by assessing clinical, mammographic, and demographic data of suspects and infected patients is required. Finally, it is clear that AI and machine learning may dramatically improve Covid-19 pandemic therapy, medication, screening and prediction, forecasting, contact tracking, and drug/vaccine research while reducing human engagement in medical practice. The majority of the models, however, have not been deployed enough to demonstrate their real-world functionality, but they are still capable of combating the epidemic.

Conflict of interest

There is no conflict of interest.

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