



Machine learning as an artificial intelligence application in management of chronic hepatitis B virus infection

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Abstract

Let's review the role of gut microbiota in pathogenesis of chronic hepatitis B infection as addressed in by Zhu *et al*. Zhu *et al* used high-throughput technology to characterize the microbial ecosystems, which led to an explosion of various types of molecular profiling data, such as metagenomics, metatranscriptomics, and metabolomics. To analyze such data, machine learning (ML) algorithms have shown to be useful for identifying key molecular signatures, discovering potential patient stratifications, and, particularly, for generating models that can accurately predict phenotypes. Strong evidence suggests that such gut microbiome-based stratification could guide customized interventions to benefit human health. Supervised learning includes designing an algorithm to fix a pre-identified problem. To get an answer, ML software must access data that have been nominated. On the other hand, unsupervised learning does not address any pre-defined problems. Bias should be eliminated as much as possible. In unsupervised learning, an ML algorithm works to identify data patterns without any prior operator input. This can subsequently lead to elements being identified that could not be conceived by the operator. At the intersection between supervised and unsupervised learning is semi-supervised ML. Semi-supervised learning includes using a partially labeled data set. The ML algorithm utilizes unsupervised learning to label data (that has not yet been labelled) by drawing findings from the labeled data. Then, supervised techniques can be used to solve defined problems involving the labeled data. Reinforcement learning, which is similar to supervised learning in the meaning, is goal-oriented. Reinforcement learning does not need labeled data, instead, it is provided with a set of regulations on a problem. An algorithm will carry out operations to try to answer questions involving the problem. Based on obtained data of gut microbiota, various therapeutic modalities can be applied: Prebiotics, probiotics, postbiotics, engineered bacteria, bacteriophage, and novel microbe-materials therapeutic system and fecal transplantation. In conclusion, ML is an artificial intelligence application that helps in providing new perspectives on tailored therapy. Furthermore, assessing the impact of gut microbiota modification is a critical step in advanced liver disease management. These new

artificial intelligence techniques although promising, still require further analysis and validation in future studies.

Key Words: Artificial intelligence; Machine learning; Gut microbiota; Hepatitis B virus; Infection

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Core Tip: There is substantial evidence indicating that stratification based on the gut microbiome could facilitate personalized interventions aimed at enhancing human health. It became essential to characterize the microbial ecosystems, resulting in a surge of various types of molecular profiling data, including metagenomics, metatranscriptomics, and metabolomics. In the analysis of such data, machine learning algorithms have proven to be effective in identifying crucial molecular signatures, uncovering potential patient stratifications, and especially in creating models that can reliably predict phenotypes. Machine learning may be supervised, unsupervised, semi-supervised or reinforcement type. Using a method for explaining individual classifier decisions for complex microbiota analysis may help in developing personalized treatment.

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TO THE EDITOR

We are delighted to read the very interesting article by Zhu *et al*[1]. They have described the role of gut microbiota in progression of chronic hepatitis B infection. They found that the abundance of *Dorea* varies significantly across different liver fibrosis stages, suggesting it as a considerable microbial marker for diagnosing the liver fibrosis. This important finding will help in management strategy of chronic hepatitis B infection. Moreover, Zhu *et al*[1] used high-throughput technology to define the microbial ecosystems lead to a surge in various types of molecular profiling data, including metagenomics, metatranscriptomics, and metabolomics. The analysis of such data has demonstrated the significance of machine learning (ML) algorithms in identifying essential molecular markers, recognizing potential patient stratifications, and, notably, in creating models that can reliably forecast phenotypes[2,3].

Personalized medicine is increasingly leveraging the human gut microbiome[4-6]. Studies reveal distinct gut microbiota clusters, or enterotypes, primarily differentiated by the abundance of *Bacteroides*, *Ruminococcus*, and *Prevotella* [7]. These enterotypes correlate strongly with dietary habits, specifically protein and animal fat intake (*Bacteroides*) *vs* carbohydrate consumption (*Prevotella*) [8]. This strong association suggests that gut microbiome stratification can inform personalized interventions for improved health outcomes[9].

Methods of ML

ML includes two forms: Supervised and unsupervised learning. Supervised learning includes designing an algorithm to fix a pre-identified problem. Camacho *et al*[10] drew an example: “if we want to know a certain drug could be metabolized by gut microbiota or not?”. To get an answer, applying ML software must access data that have been nominated. ML algorithms can be categorized into several types, each with its own approach to learning from data. Supervised learning uses labeled data - data where the correct answers are already known - to train an algorithm to predict outcomes for new, unseen data[10]. For example, an algorithm could be trained on a dataset of drugs and their susceptibility to gut microbiota metabolism to predict whether a new drug will be metabolized similarly[11]. Unsupervised learning, in contrast, works with unlabeled data, identifying patterns and structures without pre-defined answers. This allows for the discovery of unexpected relationships within the data. Clustering and association rule mining are common unsupervised learning techniques[12]. Semi-supervised learning bridges the gap between supervised and unsupervised learning[13]. It uses a combination of labeled and unlabeled data, leveraging the unlabeled data to improve the accuracy of the supervised learning process. This is particularly useful when labeled data is scarce or expensive to obtain[14]. Finally, reinforcement learning is a goal-oriented approach where an algorithm learns through trial and error, receiving rewards or penalties based on its actions. It doesn't rely on labeled data but instead learns from interactions with an environment [15].

An algorithm performs operations to answer questions related to a given problem. The closer an action brings the system to a solution, the greater the reward it receives. Conversely, if an action leads away from the solution, the system is penalized. Over time, the algorithm learns which types of actions are rewarding. In this way, a solution-oriented pathway begins to emerge. This process contributes to building an optimal approach to solving the problem. Reinforcement learning algorithms face the challenge of exploring new methods while simultaneously striving to maximize rewards; this is referred to as the exploration *vs* exploitation trade-off[16]. Reinforcement learning has notably demonstrated its prowess in mastering complex games, such as the ancient game of “Go”. A significant milestone was achieved in 2017 when a reinforcement learning algorithm reached superhuman performance in “Go” without any human intervention, effectively learning through self-teaching. Prominent examples of reinforcement learning algorithms

encompass temporal-difference learning, Q-learning, and state-action-reward-state-action learning[17].

Microbiota as a target of therapeutic modalities in chronic hepatitis B virus infection

Accruing evidence suggests interdependence between chronic hepatitis B virus (HBV) infections and alterations in the gut flora. Prior research indicated potential strategies for modulating the gut microbiome to treat chronic hepatitis B or to slow the progression of the disease[18].

Probiotics

An effective method to treat gut microbiota issues is the use of probiotics, which are specific live microorganisms intended to alter a person's microflora. Though probiotics are safe and supportive for a person's well-being, there needs to be an optimal concentration to promote growth of healthy bacteria. *Lactobacillus* and *Bifidobacterium* represent two types of bacteria used as probiotics. The genus *Lactobacillus* has about 300 species of bacteria[19]. Xia *et al*[20] studied probiotics in patients with HBV. Patients suffering from HBV-related cirrhosis and diagnosed with minimal hepatic encephalopathy were randomly assigned to receive probiotics ($n = 30$) consisting of *Clostridium butyricum* and *Bifidobacterium infantis*, or to receive local standard treatment alone ($n = 30$) as a control group. The group receiving probiotics demonstrated significantly improved changes of alanine aminotransferase, aspartate aminotransferase, total bilirubin and albumin levels compared to the control. There was also an increase in absolute faecal bacterial load of *Clostridium* and *Bifidobacterium*, while *Enterococcus* and *Enterobacteriaceae* decreased. Improvement in psychometric tests and significant reduction of venous ammonia, lipopolysaccharide, D-lactate and diamine oxidase was also noted for the probiotic group [20].

Prebiotics

Prebiotics are microbial ingredients derived from food that encourage specific probiotic activities through fermentation. These prebiotics includes conjugated linoleic acid, polyunsaturated fatty acids, some oligosaccharides like inulin, fructooligosaccharides, galacto-oligosaccharides, mannan oligosaccharides, and even xylan oligosaccharides as well as human milk oligosaccharides. Compared to dietary fibers such as pectin, cellulose and xylans, prebiotics tend to be metabolized only by beneficial microbes in the host[21]. Fermentation by these prebiotics alters gut microbes and thus construct the gut microbial flora as well as provide energy for host cells[22]. Among the fermentative products of prebiotics, short-chain fatty acids are essential factors for extensive well-being. Short-chain fatty acids exert anti-inflammatory effects by shaping the immune community and its bio-functioning[23].

Postbiotics

The phrase "postbiotics" denotes the application of non-viable microorganisms and/or their components (such as metabolites or cells) to achieve beneficial effects on the host[24,25]. In the same context, heat-killed bacteria and microbial metabolites can be used as postbiotics to improve host health. Postbiotics effects are shown through by five mechanisms include: Adjusting resident microbiota, enhancing epithelial barrier function, modifying host immune responses, influencing host metabolic responses, and generating signals through the nervous system[26].

Engineered bacteria

Certain bacteria present in the human body can be safely altered to perform designated roles as live diagnostic and therapeutic agents, potentially offering novel solutions for a range of diseases[27]. There have been previous attempts at managing liver disease with the help of modified bacteria. The use of engineered *Limosilactobacillus reuteri* in mice with ethanol-induced liver disease resulted in the disease being alleviated due to interleukin-22 production and stimulation of the expression of regenerating islet-derived 3 gamma in the intestine[20]. A reduction in the activity of fumarylacetoacetate hydrolase leads to hereditary tyrosinemia type 1, which may result in severe liver disease that poses a risk to life. Genetically modifying *Escherichia coli* Nissle 1917 to incorporate genes linked to tyrosine metabolism facilitated the breakdown of tyrosine and alleviated the severe liver damage observed in the hereditary tyrosinemia type 1 mouse model[28]. Moreover, non-alcoholic fatty liver disease progression might be modified by the release of glucagon-like peptide-1 engineered bacteria affecting the production of insulin, its levels in circulation as well as its secretion in the body[29].

Novel microbe-materials therapeutic system

The use of engineered microorganisms has raised questions concerning the "fate of the administered microorganisms" due to low bioavailability, as well as potential infectious clinical complications of ectopic migration of bacteria from the intestines to other parts of the body. In developing new treatment modalities, emerging materials were combined with engineered microbes to enhance bio-functional specificity, therapeutic targetability, and spatiotemporal controllability[30, 31]. Also, a technology for surface nanocoating was developed to increase the stability of living therapies to improve their resilience to difficult host environmental conditions[32]. This work demonstrates the need to advance microbial therapy for many liver diseases toward new avenues to tackle human diseases.

Bacteriophages

Bacteriophages are viruses that occur naturally and are associated with bacterial cells. They play a significant role in the colonization of intestinal bacteria and the regulation of bacterial metabolism. Due to their remarkable genetic adaptability, bacteriophages can be influenced by a variety of surface modifications, which can be applied for preventive, diagnostic, and therapeutic purposes in liver disease[33]. Bacteriophages have been employed to display hepatitis B core

antigen on their surface for the production of anti-hepatitis B core antigen monoclonal antibodies, which are utilized to identify and neutralize HBV infections[34]. In addition, bacteriophages could serve as a treatment option for infections in patients with weakened immune systems, like those suffering from cirrhosis or after a liver transplant[35].

Fecal transplantation

There is a scarcity of information regarding the efficacy of fecal microbiota transplantation (FMT) in the treatment of chronic viral B hepatitis. Ren *et al*[36] carried out a pilot study to assess the effectiveness of FMT in five patients suffering from chronic hepatitis B, all of whom were undergoing long-term antiviral therapy and had not achieved hepatitis B virus e-antigen (HBeAg) clearance or seroconversion. They compared these individuals to a control group of thirteen other chronic hepatitis B patients who were in similar circumstances but did not receive FMT. In the group that received FMT, a significant reduction in HBeAg levels was observed, although none of the patients attained seroconversion. Conversely, none of the patients in the control group exhibited any reduction in HBeAg levels[36]. Another pilot study looked at how effective FMT was in achieving HBeAg and hepatitis B surface antigen (HBsAg) clearance, along with a reduction in serum HBV DNA in patients chronically infected with HBV and HBeAg positive on long-term antiviral treatment[37]. Of the 12 patients who were given FMT, 2 achieved HBeAg clearance while none in the control group did. Also, none of the patients from either group were able to achieve HBsAg clearance. After 6 months, reduced levels of HBV DNA serum were observed in the FMT group among patients who had positive DNA at baseline, and the controls showed no change [38].

After all, the study of Zhu *et al*[1] is a promising one. Chronic HBV infection is serious health problem. About 254 million people are chronic carriers of the HBsAg, making HBV infection a public health concern[39]. The prevalence of HBsAg-positive individuals is between 3.6% and 4.1% worldwide, however, estimates and disease-related burdens vary greatly throughout time and geography, ranging from low (< 2%) to high (> 8%) endemicity levels[40]. The infection caused by the HBV represents a significant health concern that may result in liver cirrhosis, decompensation, and the development of hepatocellular carcinoma, according to Abdelhamed and El-Kassas[41]. HBV is responsible for one-third of liver cancer deaths globally. The most notable influence on the decrease in HBV prevalence was the implementation of the standard birth-dose vaccination. The incidence of hepatocellular carcinoma varies from 0.9% to 5.4% per year in people with liver cirrhosis and from 0.01% to 1.40% in patients without the disease. So, applying an artificial intelligence tool like ML to detect gut microbiota and its impact on progression of chronic HBV infection will pave the way for development of personalized therapy. Towards evidence-based medicine, ML technique will convert theoretical research into application.

There is no doubt that the “ecosystem” microbiome has been involved in health and disease development. The human microbiome consists of promising biomarkers for various diseases as proved by enormous metagenomics results. Translating this information into diagnostic and therapeutic modalities. The near future presents a significant challenge. Microorganisms and host cells collaboratively create and exchange metabolites, leading to the development of metabolic networks that can be leveraged to construct meta-metabolic network models. The exploration of network biology through ML provides an excellent opportunity for investigating the “human health condition”.

However, such a huge amount of information needs to be reported in a logical manner. Each expectation allows for broader investigation, which help clinicians to make evidence-based decisions. Employing a technique to elucidate the choices made by individual classifiers in the context of complex microbiota analysis could assist in the formulation of personalized treatment. This approach can also assist physicians in enhancing the clinical experience, thus, opening new perspectives on tailored therapy. Furthermore, assessing the impact of gut microbiota modification accounts a critical step in advancing liver disease management. These new artificial intelligence techniques are promising but require further analysis and validation in future studies. After all, limitations of Zhu *et al*[1] includes small sample size. It is recommended to apply ML algorithm on more population or to carry out multicenter study to receive more significant and reliable results. In the same context, to reach optimum eubiosis of gut microbiota, we must validate other natural therapies like healthy diet and change of life style.

FOOTNOTES

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