

Prediction of Bacterial Toxins using Machine Learning | A Review Paper

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Abstract:

Bacterial toxins also known as the soluble antigens secreted by a number of Pathogenic bacteria which have a standing notoriety of being a toxin discharged over the span of pathogenesis. These are major determinants of virulence that can modulate the cellular functions by selectively targeting a number of signaling pathways within the host cell in order to tilt the balance in bacteria favor. Two major types of bacterial toxins are present and playing their own roles according to their features and which may lead to different health hazards and also may lead to death because of these viruses, as the population in world is increasing, on the other hand different kind of bacterial toxins are emerging. This article presents a comprehensive review of such bacterial toxins, machine learning algorithms and AI techniques for the prediction of these bacterial toxins, this review article is explaining that which ML algorithm and technique is more accurate till now and is it possible to increase the existing accuracy, and improve the methodology to predict such bacterial toxins more precisely and accurately.

Keywords: Bacterial Toxins, Machine Learning

Introduction:

Bacterial toxins also known as the soluble antigens secreted by a number of Pathogenic bacterias which have a standing notoriety of being a toxin discharged over the span of pathogenesis. These are major determinants of virulence that can modulate the cellular functions by selectively targeting a number of signaling pathways within the host cell in order to tilt the balance in bacteria favor. As the population in world is increasing ,on the other hand different kind of bacterial toxins are emerging due to latest technologies and increase in industrial area or increase in radioactivity researches and experiments different bacterial toxins with different impacts are emerging (Ruas-Madiedo et al., 2010). These bacterial toxins are badly impacting human and animal health and as well as plants health, as the world population is increasing it is observed that number of bacterial toxins are also increasing, first bacterial toxin which was related to diphtheria discovered by Emile Roux and Alexandre Yersin in 1888 from the bacteria – corynebacterium diphtheriae after that different bacterial toxins have been discovered and til now there are more than 500 bacterial toxins which are producing from different sources (Zhou et al., 2020), (Kachlany et al., 2010).

There are two major types of bacterial toxins i.e. “EndoToxins” , “Exotoxins” which are also known as Gamma positive and Gamma negative and are playing their own roles in badly impacting in human health (Chowdhary, Bharagava, Mishra, & Khan, 2020),(Lucas et al., 2020),(Massey & Yang, 2020), animals health (Chmielowiec-Korzeniowska, Trawińska, Tymczyna, Bis-Wencel, & Matuszewski, 2020) and plants health (Sharifi & Ryu, 2018).

As a law of nature if there is a negative thing then there must exists a positive thing in order to take over the negative one, as in past technology was not so much fast and vast, people were not able to find or predict any thing related to a mishap or disaster and to do something necessary in order to avoid from a big loss but after discovery of 5th generation of computers when AI and ML came into being people started predicting different things on te behalf of past histories related to any situation to avoid the loss as much as it could be. It is concluded from the study that machine learning is such a promising technique that is playing it's very important role in many fields and helping the world to discover the new things and to make predictions, in the same way

machine learning is playing an important role in the field of bioinformatics and helped a lot in predicting the bacterial toxins using different AI techniques and machine learning algorithms.

This review article is explaining that how and which ML algorithm and technique is more accurate till now and is it possible to increase the existing accuracy, and improve the methodology to predict such bacterial toxins more precisely and accurately.

Biological Background:

As discussed above about the two major types of bacterial toxins (Endo & Exo toxins), here is a detailed biological background of these two major types along with their features;

EndoToxins:

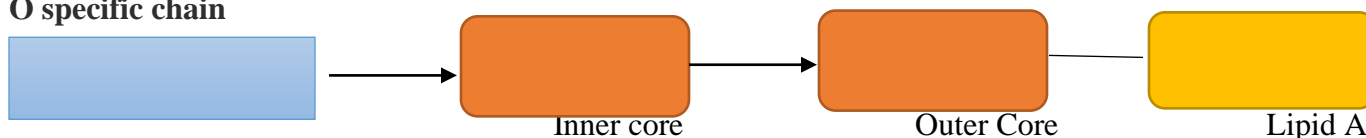
These are the integral parts of the cell walls of gram negative bacteria and are liberated when bacteria are disintegrated. Cell wall of gram negative bacteria (Boonen, Alpizar, Meseguer, & Talavera, 2018) contain lipopolysaccharides (LPS endotoxin) which further consist of:

1 Lipid A : This is endotoxin and is the core.

2 Polysaccharide form coat which is the O antigen which can include specific immunity (Dong, Tang, Zhang, & Dong, 2017).

Structure of Gram negative bacterial Endotoxin(PolySacchride):

O specific chain



EndoToxins Features:

Below are some features of Bacterial endotoxins:

- synthesis directed by chromosomal genes.
- Produce fever in the host by release of interleukin – 1
- Lipid A portion responsible for toxicity.
- Released on bacterial death and in part during growth.

What Endotoxins can produce?

Endotoxins can produce the following diseases:

- Fever
- Chills
- Tissue Damage
- Organ Damage
- Miscarriage during pregnancy.

Organisms that can produce endotoxins:

1 Salmonella Typhi:

These are the bacterias that can infect intestine system and can produce infection in blood and also responsible in typhoid fever specially this kind of infection attack children between age of 5 to 15 years and also in adults but ratio in adults is very less (Luo et al., 2020).



Figure 1: Salmonella typhi (agent of typhoid)

2 Proteus Spp

A gram negative bacteria that is responsible for swarming motility and urease activity. It is 90% responsible for all uterus and vaginal infections in a human body and as well as in animals (Aziz, Albukhaty, & Abbood, 2017).

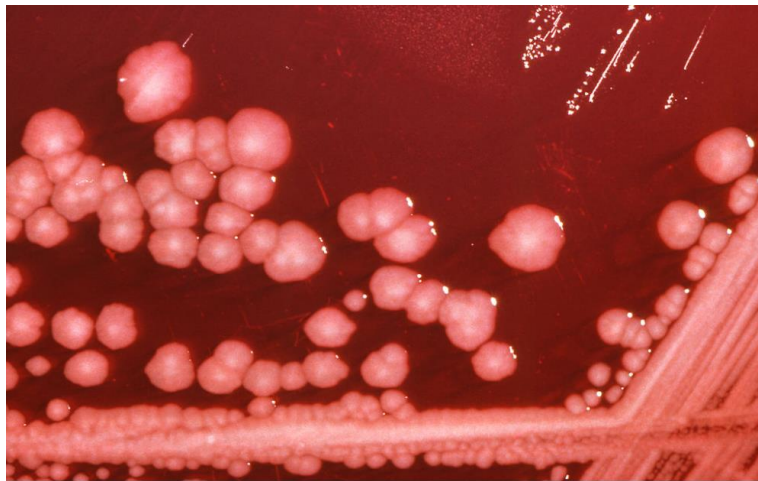


Figure 2 : Proteus Spp bacteria in human body

3 Pseudomonas Spp:

A gram negative bacteria that may badly impact on human, animals and as well as on plants health. In human this bacteria can cause lungs related issues i.e. lungs inflammation, pneumonia, blood cancer respectively (Bisht, Baishya, & Wakeman, 2020).

Here we can see that how this bacteria is infecting healthy lungs;

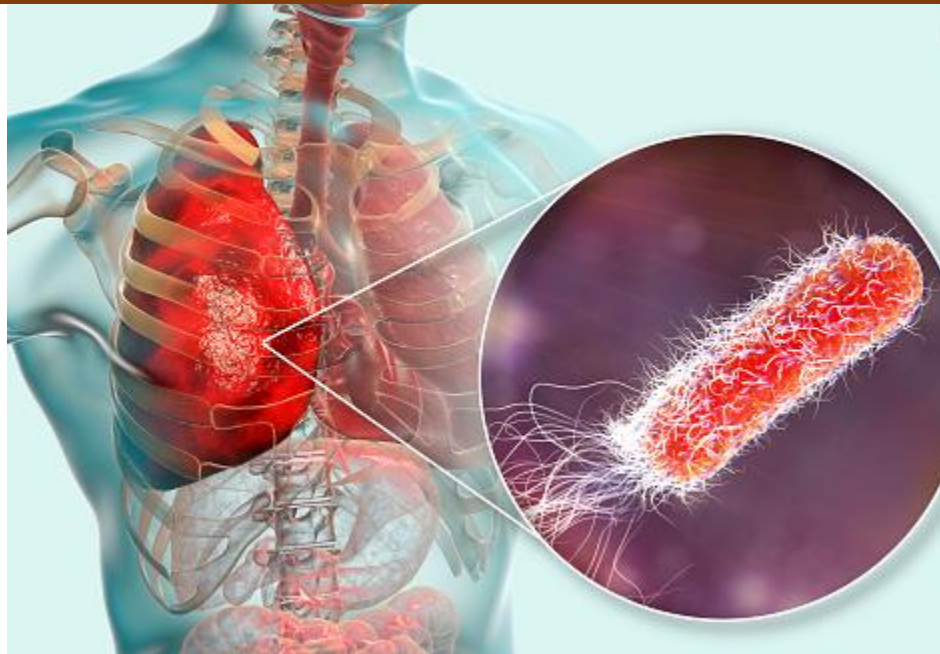


Figure 3; Attack of Pseudomonas Spp on lungs

Below mentioned DICOM images are showing that how this toxin is causing damage to healthy human lung;

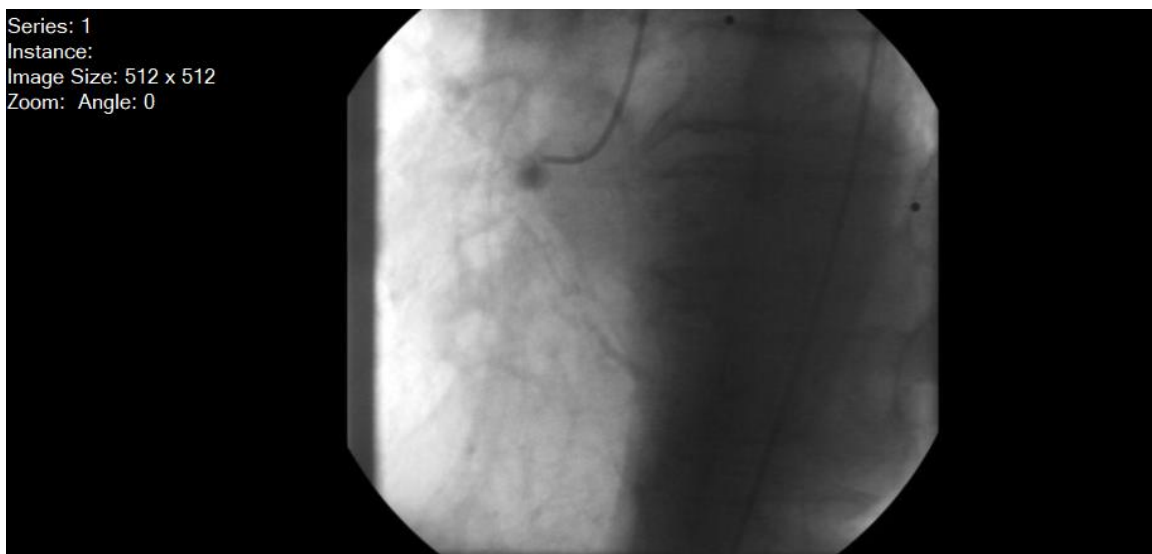


Figure 4 : healthy lung

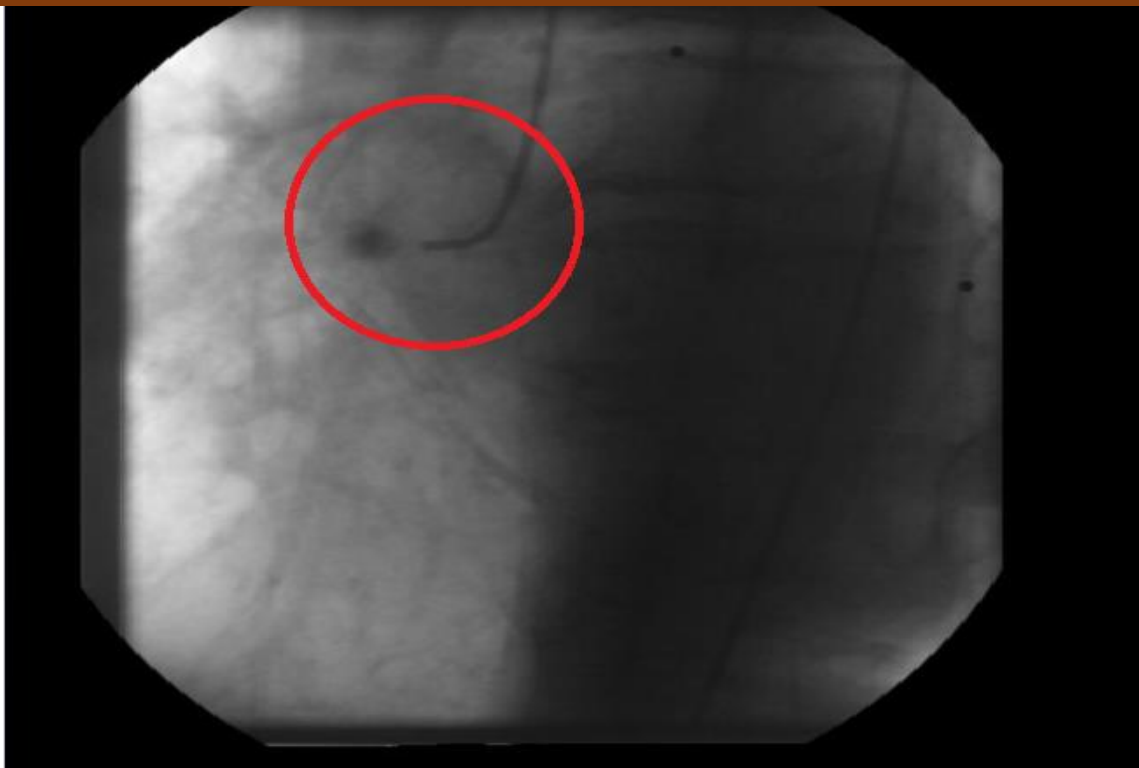


Figure 5 : Entry of Bacterial toxin in lung.



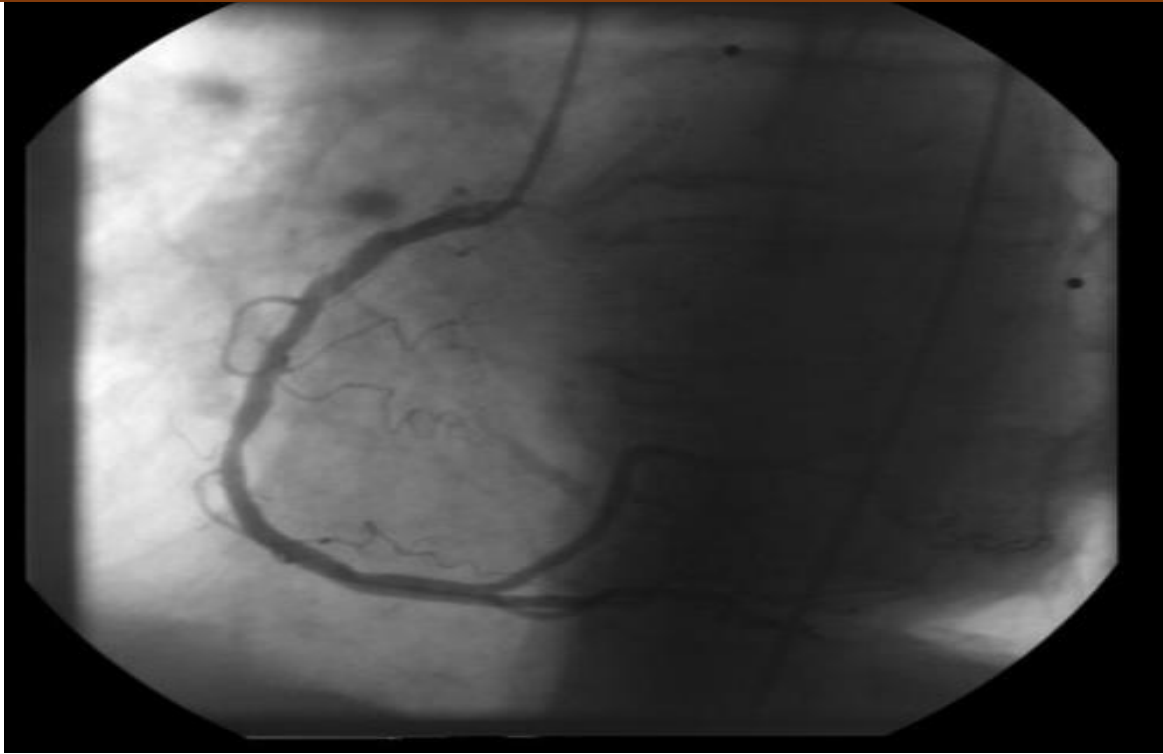


Figure 6 and 7 are showing that how the bacteria infected lungs and we can see the lungs inflammation and bleeding inside the lungs which may lead to death.

4 Neisseria SPP

Gram negative bacteria that is causing HIV AIDS and Tb in human bodies , and as well as responsible in the human upper respiratory and female urogenital tracts this is also icnlude in rabbies (dog bite) (Crew et al., 2019), (Cobiella, Gram, & Santoro, 2019).

Exotoxins:

These are secreted by bacteria and are more dangerous as compared to endotoxins, they are highly potent and cause damage to host cell directly and can disturb whole cell metabolism. They can be denatured by heat, acid , protteolytic enzymes. They act as catalyst in milk products and can cause damage at high speed.

Effects of Exotoxins (Peterson & Schlievert, 2006), (Ayllon, Hutchinson, Velasquez, Alex, & Fologea, 2020):

They have following effects.

- Entrotoxic
- Cytotoxic
- Hemolytic
- Neurotoxic

What Exotoxins can cause?

Exotoxins can produce the following:

- Food poisoning – they produce when a person contaminanted food and they ususally occurred over the milk products (Mourenza, Gil, Mateos, & Letek, 2021) , (Duport, Rousset, & Armengaud, 2020)
- Nausea – vomit like condition in which a person may loose his stomach and digestion power (G Abril et al., 2020)

- Diarrhea – Happened normally after 2 to 6 hrs after consuming food which may cause disturbance to the supply of oxygen to brain and the blood pressure becomes very low where a human can lose its senses and may lead to coma stage due to brain damage (Yinadsawaphan, Ngamskulrungraj, Chalermwai, Dhitanmuang, & Angkasekwini, 2020), (Colaco, Basile, Draper, & Ferguson, 2021).

Here is the biological background related to bacterial toxins let's have a review on technical background that how people contribute in order to predict these bacterial toxins using computer science and machine learning algorithms that how they perform and what was the accuracy and which one was best accuracy.

Literature Review Table:

| Researcher Name | Year | Technique | Remarks |
|--|------|--|--|
| (Saha & Raghava) | 2007 | Support vector machine Researchers used SVM techniques tested and trained 150 non redundant dataset and then they two modules composition and discrimination and they achieved total accuracy of 92% | Good methodology adopted by researchers but accuracy was not enough good, it can be improved more. |
| (Chakraborty, Ghosh, Chowdhary, Maulik, & Chakrabarti) | 2012 | Researchers worked on human exotoxins databases and implemented them over the CGI-PERL web based platform where one can predict the types of possible existing exotoxins in order to find out the desired properties. | It was a good step to develop such a system where one can get exact properties of existing exotoxins and provided insights towards the molecular interactions leading to the discovery of important pathways in cell biology. |
| (Sperschneider) | 2016 | Researchers used first proposed machine learning method EFFECTORP that was the first trained method to predict bacterial toxins and divided them in parts as subsets to predict them using trained data for increased and verified bacterial toxins. They used SIGNALP v 4.1 with default parameters to detect secretomes. Then by using python scripts and weka tool feature vectors calculated and then divided into frequencies using naïveBayes, logistic regression due to which it gave +ve and –ve series and they got the required result with accuracy of 93% | A good technique used i.e effort scaling a vast and helpful and easiest technique of machine learning to get the results in accurate form and the robust algorithms naïveBayes and logistical regression to achieve the good results and played important role as bacterial effector prediction and they used effectorP as naïveBayes which is a robust approach without any doubt but still it could be improved and can be classified in more accurate and reliable way. |
| (Lupolova, Dallman, Holden, & Gally) | 2017 | Two life threatening infection causing bacterial toxins Salmonella enterica and Escherichia coli were predicted using machine learning via support vector machine classifiers the accuracy was only 83% | Machine learning is a good way to be applied in order to investigate source attribution of bacterial toxins, but the accuracy here was not good enough which can be improved more. |

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| (Dao et al) | 2017 | Researchers worked on conotoxins which is an important part of neurobiological sciences, they use general ability prediction model i.e binomial distribution model, relief algorithm, and F-score algorithm and then finally they applied diffusion map reduction, and then they use support vector k-local hyperplane nearest neighbor algorithm. | It was a good methodology as conotoxins has wide applications in the development of neuroscience research this method helped a lot of researchers to discover new drugs for different neurological issues specially chronic pain epilepsy, spasticity issues. Machine learning played an important role in these inventions and in discovery of clinical medicine. |
| (Wang, Guo, Pu, & Li.) | 2017 | Reserachers worked on type IV secretion systems (T4SS) that causes problems in host cells and cause different diseases. They use machine learning and defined method of predicting for T4SE by integrating N terminal and C terminal sequence information. And then applied support vector machine model and 125 distinct positions residues were signed out with an accuracy of 85.29% on actual set and 87% on training set. | A good work in developing a novel inter species prediction tool for type IV bacterial toxins which was based on SVM which was helpful in finding significant difference between type 4 and non type 4 bacterial toxins and helped in utilizing different sequences. |
| (Yoshida et al) | 2018 | A closed loop artificial evolution system applied to discover microbial peptides and then antimicrobial peptides using machine learning with an improved potency using a genetic algorithm and as a result got 160 fold potency increase observed. | A new approach developed in order to design the AMPs by combining an evolutionary algorithm, machine-learning-based prediction and <i>in vitro</i> bacterial assays. This robust method helped in rapid improvement of antimicrobial activity. It achieved 162-fold more than the original peptide within three generations. It was a good invention. |
| (Her & Wu) | 2018 | A pan genome based approach proposed to characterize antibiotic resistant for microbial strains in order to test this approach on the bacterial model organism escherichia coil. Researchers selected subset of AMR genes within the necessary part of pan – genome using machine learning genetic algorithm. | A good work in order to discover drugs for different chronic diseases which is a major issue now a days in both developed and under developed countries. |
| (Baskin) | 2018 | Researcher worked on applications of unsupervised machine learning methods i.e. graph mining and graph kernel, kohonen’s self organizing | Good work in predicting and combining different ML approaches with data analysis and visualization in order to predict bacterial |

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| | | maps. Researcher focused on naïve bayse classifier and k nearest algorithm in order to predict toxins. | toxins and brought eveloution in computational toxicology. |
| (Ramesh et al) | 2018 | Worked on plant diseases that what bacterial toxins are causing issue to plants using SVM and Random forest algorithm and histogram oriented gradient. | Good method in order to protect plants and growth from bacterial toxins and which is definitely helpful in growth of plants and crops and can increase production of any country and also helpful in increasing GDP of any country. |
| (Roux-Dalvai et al) | 2019 | Researchers worked on urine specimens in order to find out the bacterial toxins that are causing issues to urethra, they used MALDI TOF MS technology a ML model and obtained pure bacterial colonies they used Naïve Byse , BayesNet and Hoeffding tree and defined a peptide signature and predict 190 toxins that cause urethra issues with an accuracy of 84% | Good work in detecting the urethra issues due to bacterial toxins (endotoxins). |
| (Cipullo, Snapir, Prpich, Campo, & Coulon) | 2019 | Researchers used artificial neural network and random forest ML models in order to predict temporal bioavailability changes of complex chemical mixtures that are cause of bacterial toxins and also they perfrom experiments on soil that what toxins are producing from this and causes diseases. They used incubation time of the ML models and classical liner regression used in order to understand rate limiting process and what toxins are affecting soil and recovery methods. | As researchers focused on soil that what kind of toxins are causing issues to soil and due to which diseases are living things getting they predicted and also suggest drugs for it, although it’s a good work in order to protect plants animals and as well as human from such diseases such as lungs inflammation. |
| (Barman, Mukhopadhyay, Maulik, & Das,) | 2019 | New machine learning based techniques were developed to identify disease associated host genes by integrating sequences and protien interaction. They used deep neural network model with 16 features for pseudo amino acid composition (PAAC)and network properties acieved with the highest accuracy of 86% The DNN classifier achieved the accuracy of 83.33% as well on blind dataset and 83% on independent dataset. | A good work in order to predict unknown infectious diseases that are associated to host genes and it was very robust appraoch as 76 out of 100 ifectious diseases were predicted and then a highly predicted infectious disease was analysed. Which is helpful for drugs discovery. |

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| (Vilne, Meistere, Grantiņa-Ieviņa, & Ķibilds) | 2019 | Machine learning approaches used in order to predict the toxins that were causing issue to food and causing different diseases after consuming food. They worked on gastrointestinal tract. They worked on some fungi samples and then using artificial intelligence and sub discipline machine learning in order to interrogate FDB (foodborne diseases) outbreaks by using a whole genome sequence as it was more accesible and affordable. They divided the work into four steps as de novo genome assembly , genome chracterization, comparitive genomics , and then finally inference of phnylogenomics. | A good work in predicting exotoxins that are producing issues to food and causing different diseases food poisoning etc. |
| (Martínez-Agüero, Mora-Jiménez, Lérída-García, Álvarez-Rodríguez, & Soguero-Ruiz) | 2019 | Researchers worked using different machine learning techniques in order to predict and detect bacterial toxins in any intensive care unit(ICU). They used clinical and demographic features from patients and as well as data from different cultures and antibiograms considered, Machine learning techniques evidence non linear relationships to helping to identifying the bacterial toxins at the ICU. | A good approach in order to predict toxins in ICU of any hospital which will help doctors to protect patients from different infectious diseases and will cure them more properly. |
| (Ong et al) | 2020 | Vaxign – ML a supervised ML classification used to predict protective antigens in order to identify the best ML method to predict the bacterial toxins and rational vaccine design applied to enhance the accuracy of RV prediction. They used five ML methods nested 5 fold cross.validation and leave one pathogene , extreme gradiant boosting vaxign, vaxijen, and antigenic based on SVM based methodology. Which showed a superior perfromance in predicting Bpags and dicoverly of drugs against the bacterial toxins that are causing malaria, HIV. | Good contribution in order to predict the toxins that are causing issues related to malaria and HIV and hepatitis which is very helpful in drug discovery of such diseases due to these toxins. |
| (Rentzsch, Deneke, Nitsche, & Renard) | 2020 | Dimer based SVM methodology adopted to predict virulence factors and bacterial toxins within dimer | Good contriubution in the field microbiology in order to sampling the families of different toxins by |

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| | | hybrid classifiers. In order to predict the bacterial toxins at first they worked on datasets that were considerably diverse one then they move on real world data and observed strikingly low correlations between different features and classifiers while ranking proteins by VF and achieved accuracy of 80% | combining ML approached and then finding the best one to achieve and predict better results in which the highest accuracy obtained was 80% among the real world. |
| (Altaner et al) | 2020 | Naïve byse and random forest techniques used to predict and group the families of microcystins and then defined them in classes of toxins which resulted 80 -90 % correct predictions. | Fair contribution in order to predict and group the families of toxins in one place and i.e microcystins (exotoxins). |
| (Mohabatkar, Ebrahimi, & Moradi) | 2020 | Used different machine learning algorithms using chou’s five rule step to predict the bacterial toxins, research focused on glutathione s along with different machine learning approaches that how bacterial toxins can act over glutathione which is the important part of any living organism weather it is plant, animal or human. They used SVM, evidence theoretic K nearest neighbour , random forests which were the most robust machine learning approaches in order to predict bacterial toxins and they achieved the accuracy of 93.39% , 89.90% and 96.55% for plants, animals, and human respectively. | Good contribution in the research area of bioinformatics in order to predict the toxins which are direct harmful to glutathione s an important part of all living organisms. |
| (Jamal et al.) | 2020 | Artificial intelligence and machine learning based research conducted in order to predict the toxins that are causing Tuberculosis(TB) using machine learning they predicted resistance genes rPob, inhA. They used naïve byse, k nearest, SVM and artificial neural networks approaches to build a model that predicted bacterial toxins causing TB issues among human and they achieved the accuracy of 85% | Good contribution in order to predict toxins that are causing TB issues and which is really helpful in order to discover the drugs of TB. |

Conclusion:

After a deep study it is found that there should be need of more improvement in order to predict the bacterial toxins, as the world is making progress day by day there are a lot of countries that are developed and under developed in both countries people are suffering from different diseases and no doubt that technology is also getting advance day by day with respect to time but as technology is making progress on the other hand diseases due to bacterial toxins are also increasing recent example is COVID – 19. After a deep study it is concluded that that machine learning and artificial intelligence brought evolution in the world of microbiology and prediction of toxins has become easy which was difficult in previous era. ML algorithms which are in use now a days in prediction of bacterial toxins, there is a need to work more in this field to improve it more as possible as a time is coming where it is very important to protect the world from different diseases as It is observed that most of the researchers are only using SVM method due to which accuracy is not increasing much better and normally lies between 80 to 90 % on some it is 95% but failed over the real world data. There is a need of work in order to increase the efficiency over the real world data and maybe it is possible if we combine two or more ML algorithms with highest accuracy to get the much better efficiency on the real world data is still a challenge and needs more work to do in this field.

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