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Machine learning model for analysis of critically important antimicrobials for human medicine

Abstract

With the development of antimicrobials, microbes have adapted and become resistant to previous antimicrobial agents. Hence WHO recommended complete list of critically important antimicrobials, highly important and important antimicrobials. So there is a need to classify critically important antimicrobials for human medicine so these can be used only for humans. Therefore machine learning model is developed in this paper to classify critically important antimicrobials based on their amino acid composition with great accuracy.

Keywords: antimicrobials, WHO, machine learning, amino acid composition

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Introduction

The science and practice of the diagnosis, treatment, and prevention of disease is called medicine. Properties of medicine are maintenance and restoration of health by the preventing and treating the ill effects. They are responsible for killing or slow down the microbial growth. Any kind of bacteria, viruses etc that are not visible to naked eyes are called micro-organisms or microbes. Some category of microbe is available in Table 1.

Table 1 Variety of microbes with example and their infection

Microbe	Example	Type of infection caused
Bacteria	*Staphylococcus aureus,* etc	Some staph infections
Virus	Influenza	Flu
Fungi	*Candida albicans,* etc	Yeast infections
Parasites	*Plasmodium falciparum,* etc	Malaria

For treating human diseases different variety of antimicrobial classes are used. These antimicrobials if used regularly develop resistance called antimicrobial resistance. And the genes responsible for resistance are called anti microbial resistance. For example, the ndm-1 gene encodes resistance to the carbapenem family was first discovered in *Klebsiella pneumonia* that was isolated from an infected person.[1] Most of the AMR are hazardous to human health. Characteristics by which antimicrobials are classified are as follows:

Characteristic 1 (C1): The class that treat serious ill effects caused by bacteria in people.

Characteristic 2 (C2): The action of antimicrobials include:(a) Bacteria that transmitted to humans from nonhuman sources, (b) Bacteria that may acquire genes for resistance from sources other than humans.

Antimicrobials vs antibiotics

The preventive measure in form of medicine are called antibiotics which work against bacteria and treat bacterial infections. When bacteria change their forms in response to the repeated use of antibiotics develops antibiotic resistance. Broadly antimicrobial resistance to drugs to treat infections caused by other microbes such as parasites (e.g. malaria), viruses (e.g. HIV) and fungi (e.g. Candida). Hence Antimicrobials are one of few alternatives for the treatment of serious bacterial infections in humans that occupies an important place in human medicine. Serious infections are likely to result in significant morbidity or mortality if left untreated. Multidrug resistance is also the outcomes of disease which relate to the site of infection e.g. pneumonia, meningitis or the host e.g. infant, immunosuppressant. The use of such antibacterial agents is preserved, as loss of efficacy in these drugs due to the emergence of resistance leads to significant impact on human health, especially for people with life-threatening infections. These are the alternatives for the treatment of serious bacterial infections in human that play an important role in human medicine. If infections left untreated there would be significant morbidity or mortality. Sometimes multidrug resistance would also occur like pneumonia, meningitis etc. The antimicrobial agents that used to treat diseases caused by bacteria are transmitted to humans from non-human sources i.e. water, food, environment or animal. These are considered as highly important antimicrobials because such infections are most amenable to risk management. Nonhuman sources and the bacteria causing human diseases are linked. Such example includes non-typhoidal salmonella, campylobacter spp. *E. coli* etc. This is called commensalism. The commensalisms themselves may also be pathogenic in immuno suppressed hosts. The transfer of their genes shows the transmission of AMR. Interpretation of categorization of antimicrobial class:

Critically important: Antimicrobial classes which meet both C1 and C2 are termed critically important for human medicine.

Highly important: Antimicrobial classes which meet either C1 or C2 are termed highly important for human medicine.

Important: Antimicrobial classes used in humans which meet neither C1 nor C2 are termed important for human medicine. The list below is meant to show examples of members of each class of drugs. All drugs that are listed in a given class have not necessarily been proven safe and effective for the diseases.[2]

There are many antimicrobials like Aminoglycocides, ansamycins, carbapenems and other penems, Cephalosporins, Glycopeptides, Glycylcyclines, lipopeptides, Macrolids and ketolids, monobactrum, Oxazolidinones, Penicillins, Phosphonic acid derivatives, Polymyxins, Quinolones, sulfones, Tetracyclines, Nitrofuratoins, etc are classified according to their mode of action and above explained three categories. All the details of these antimicrobials are explained in Table 2 which also describes their significance of treating disease and their causative organism respectively.

Table 2 Following is the list of microbes important for human medicine

Antimicrobial class	Example of drugs	Mode of action	Causative organism	Treating disease	References
Critically important antimicrobials					
Aminoglycosides	Gentamicin	Irreversibly bind 30S ribosomal proteins (bactericidal)	*P. aeruginosa* Gram negative bacteria	Bone infections, endocarditis, pelvic inflammatory disease, meningitis, pneumonia, urinary tract infections	22
Ansamycins	Rifampicin	DNA directed RNA polymerase	*Mycobacterium tuberculosis*, *Mycobactterium Kansasii*	Tuberculosis, *mycobacterium* avium complex, leprosy, and Legionnaire's disease	23
Carbapenems and other penems	Meropenem	Inhibition of peptidoglycan synthesis (bactericidal)	Many Gram-positive and Gram-negative bacteria (including Pseudomonas) and *anaerobic bacteria*.	Meningitis, intra-abdominal infection, pneumonia, sepsis, and anthrax.	24
Cephalosporins (3rd,4th and 5th generation)	Ceftriaxone, cefepime, ceftaroline	Cell wall synthesis	Gram positive and gram negative bacteria i.e. , *H. influenzae*, and susceptible *E. coli*, Klebsiella, and penicillin-resistant N. gonorrhoeae	Typhoid fever	25
Glycopeptides	Vancomycin	Disrupts peptidoglycan cross-linkage	Gram-negative bacteria *Enterococci*, Clostridium difficile	Skin infections, bloodstream infections, endocarditis, bone and joint infections, and meningitis caused by methicillin-resistant *Staphylococcus aureus*	26
Glycylcyclines	Tigecycline		Gram positive bacteria penicillin-resistant *Streptococcus pneumoniae*, *methicillinresistant Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), and *vancomycin-resistant Enterococcus* (VRE)	Neusea, vomiting,diarrhoea	27
Lipopeptides	Daptomycin	Cytoplasmic membrane structure	*S. aureus*	Skin and skin structure infections	28
Macrolides and ketolides	Erythromycin, Telethromycin	Protein synthesis (50 s inhibitor)	Erm encoded methylases in *S. aureus*	Respiratory tract infections.	29
Monobactrum	Aztreonam	Cell wall synthesis	Gram-negative bacteria such as *Pseudomonas aeruginosa*	Bone infections, endometritis, intra abdominal infections, pneumonia, urinary tract infections, and sepsis.	30
Oxazolidinones	Linezolid	Protein synthesis inhibitor	*E. facium* and *S. aureus*	Infection of skin and pneumonia	31
Penicillins (natural, aminopenicillins, antipseudomonal	Ampicillin	Cell wall synthesis	Group B streptococcal infection in newborn	respiratory tract infections, urinary tract infections, meningitis, salmonellosis, and endocarditis	32
Phosphonic acid derivatives	Fosfomycin	Bacterial cell wall biogenesis	*Proteus spp*., *Enterobacter spp*., *Citrobacter spp*., *Serratiamarcescens* and *Salmonella enterica E. faecalis, E. coli*	Sepsis, urinary tract infections	33
Polymyxins	Colistin	cytoplasmic membrane structure	*Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter*.	Kidney infections	34

Table Continued...

Antimicrobial class	Example of drugs	Mode of action	Causative organism	Treating disease	References
Quinolones	Ciprofloxacin	DNA gyrase	Kill growth of bacteria	chest infections, urine infections, prostatitis, infections of the digestive system, bone and joint infections, and some sexually transmitted infections.	35
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Isoniazid	Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme in *Mycobacterium tuberculosis* called KatG. it inhibits the cytochrome P450 system and hence acts as a source of free radicals.	or atypical types of *mycobacteria*, such as *M. avium*, *M. kansasii*, and *M. xenopi*.	Tuberculosis	36
Highly important antimicrobials					
Amidinopenicillins	Mecillinam	Cell wall synthesis	*Escherichia coli*. most pathogenic Gram-negative bacteria, except *Pseudomonas*, k; paeruginosa and some species of Proteus. *Staphylococcus saprophyticus*	Urinary tract infections, and has also been used to treat typhoid and paratyphoid fever.	37
Amphenicols	Chloramphenicol	Cytoplasmic membrane structure	*Lactobacilli* and leuconostoc CAT in *S. pneumoniae*	Conjunctivitis, meningitis, plague, cholera, and typhoid fever	38
Cephalosporins (1st and 2nd generation) and cephamycins	Cefazolin	Cell wall biosyntesis	Gram-positive aerobes: *Staphylococcus aureus* (including beta-lactamase producing strains) *Staphylococcus* Gram-Negative Aerobes: *Escherichia coli*, *Proteus mirabilisepidermidis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae* and other strains of *streptococci*	Cellulitis, urinary tract infections, pneumonia, endocarditis, joint infection, and biliary tract infections	39
Lincosamides	Clindamycin	Binds 50S ribosome, blocks peptide elongation; Inhibits peptidyl transferase by interfering with binding of amino acid-acyl-tRNA complex	*Staphylococcus aureus*, *Bacteroides*, *Fusobacterium* and *Prevotella*, although resistance is increasing in *Bacteroides fragilis*.	Dental infections and infections of the respiratory tract, skin, and soft tissue, and peritonitis	40
Penicillins (anti-staphylococcal)	Oxacillin	Cell wall synthesis	Methicillin and oxacillin resistant *staphylococcus*	Respiratory or urinary tract infections	41
Pseudomonic acids	Mupirocin	Inhibition of protein synthesis	Methicillin-resistant *S. aureus* (MRSA)	Superficial skin infections	42
Riminofenazines	Clofazimine	guanine bases of bacterial DNA, thereby blocking the template function of the DNA and inhibiting bacterial proliferation	Different species of *Mycobacterium*.	Leprosy	43

Table Continued...

Antimicrobial class	Example of drugs	Mode of action	Causative organism	Treating disease	References
Steroid antibacterials	Fusidic acid	Protein synthesis	*Staphylococcus aureus*, most coagulase-positive *staphylococci*, *Beta-hemolytic streptococci*, *Corynebacterium* species and most *clostridium* species.	Acne vulgaris	44
Streptogramins	quinupristin/ dalfopristin	Protein synthesis inhibitors	*staphylococci* and vancomycin-resistant *Enterococcus faecium*.	Infection caused by *staphylococcus* and *enterococcus faecium*	45
Sulfonamides, dihydrofolate reductase inhibitors and combinations	Sulfamethoxazole, trimethoprim	Compete with p-aminobenzoic acid (PABA) preventing synthesis of folic acid	Most of the bacteria.	Bacterial infections (such as middle ear, urine, respiratory, and intestinal infections). It is also used to prevent and treat a certain type of pneumonia (pneumocystis-type).	46
Sulfones	Dapsone	bacterial synthesis of dihydrofolic acid,		Leprosy, acne, dermatitis herpetiformis, and various other skin conditions	47
Tetracycline	Coretetracycline	Block tRNA binding to 30S ribosome-mRNA complex (b-static)	Aerobic and anaerobic bacterial genera, both Gram-positive and Gram-negative, with a few exceptions, such as *Pseudomonas aeruginosa* and Proteus spp.,	Acne, cholera, brucellosis, plague, malaria, and syphilis	48
Important antimicrobials					
Aminocyclitols	*Spectinomycin*	Inhibits protein synthesis	Bacteria	Gonorrhoea infections, used by those who are allergic to penicillin or cephalosporins	49
Cyclic polypeptides	*Bacitracin*	Inhibits RNA transcription	*Staphylococcus aureus* – *Staphylococcus epidermidis*, *Streptococcus pyogenes*	Skin, eye and wound infections.	50
Nitrofurantoins	*Nitrofurantoin*		Nitrofurantoin has been shown to have good activity against: *E. coli*, *Staphylococcus saprophyticus*, *Coagulase negative staphylococci*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Citrobacter species*, *Klebsiella species*, *Bacillus subtilis species*	Bladder infections, uncomplicated urinary tract infections (UTIs	51
Nitroimidazoles	*Metronidazole*	Disrupts nucleic acid synthesis	*Aerobic bacteria*	Vaginal infection in women	52
Pleuromutilins	*Retapamulin*	Protein synthesis inhibitor	*Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*	Impetigo	53

All the details of microbes, their antibiotic with mode of action and disease are taken from Wikipedia and corresponding drug bank.[3] Different antimicrobials have different mode of action which can be diagrammatically as discussed and described in Figure 1 as:

Here in this paper an effort is made to classify Critically Important Antimicrobials according to the amino acid composition of responsible microbes. Because amino acids are the building blocks of proteins. And the effect of antimicrobials directly or indirectly affects proteins of microbes.

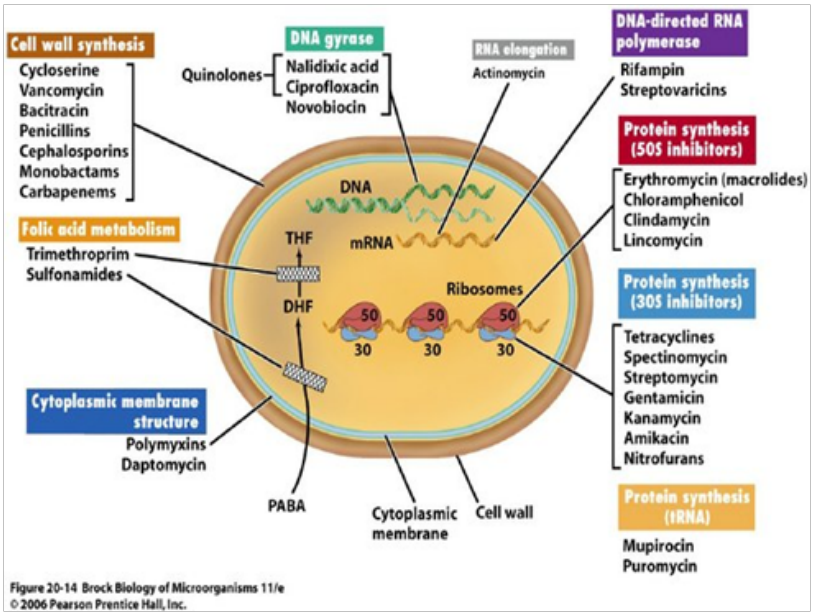

Figure 1 Mode of action of antibiotics in humans.[22]

Materials & methods

For classification of antimicrobials, machine learning (ML) techniques are employed. Because it is good in data analysis and model building. ML is a branch of artificial intelligence[3–9] it makes system learn from data, identify patterns and make great decisions without human interference. As there is huge amount of variety of data computational processing are a need to understand huge data in a better way for further use. These ML computational techniques are cheaper and powerful tools to apply. Here in this paper author tries to classify and develop model for critically important antimicrobials for human medicine by support vector machines (SVM). It can be defined as a discriminative classifier means two objects or set of objects are classified by a separating hyperplane. It could be said that, as labelled training data (*supervised learning*) is given, the algorithm outputs an optimal hyperplane which categorizes new examples. Hence hyperplane is a line dividing a plane in two parts where in each class lay in either side in a two dimensional space.[10–16]

Data

In this section, preparation of training and testing dataset is described. The amino acid composition of all the protein sequences are taken from PROCOS (Protein composition server).[17] It is very time consuming and accurate. Predictions of sub cellular localization of proteins are also used amino acid composition as described in [4] But due to importance of amino acids, related work was also done. It is said that the fraction of each type of amino acid type within a protein is called as amino acid composition.

$$\text{Amino acid composition} = \frac{\text{total number of amino acid i}}{\text{total number of amino acid in a protein}} \quad \text{equation1}$$

After gathering all the protein sequence data which are called peptides are divided into different groups called datasets. There are three different datasets according to importance of antimicrobials.[18]

Datasets

Dataset 1: Critically important antimicrobials: The microbes' protein data which is available in Uniprot database is taken. And there amino acid composition is taken by PROCOS software as input for SVM. These are called training set and are positive samples needed to be classified. For testing we took negative samples of other enzymatic group.

Dataset 2: Highly important antimicrobials: Same as dataset 1 dataset 2 is prepared.

Dataset 3: Important antimicrobials: similarly dataset 3 for important antimicrobials are also prepared.

Negative samples examples: With respect to positive samples, it requires negative interaction examples to process the positive samples accurately, as the SVM is a discriminative approach. When experimental methods do not report an interaction between two proteins, it means there positive signal does not imply a negative signal. Hence no interaction between amino acids. It is required that real negative examples are of important part for providing better results.

Feature selection with SVD: (SVD) is a method to reduce the dimensions and select the most relevant and informative features. Principal component analysis[19,20] is also used for feature selection and dimensionality reduction. The higher the value of linear combination of attributes, the more important it is. For any feature corresponding eigen-value for PCA or singular value for SVD is found. Since singular value are good to choose for features. In this work SVD has lower computational cost. In SVD, the row belongs to proteins play good role in combination coefficients. In PCA the training proteins are altogether calculated the covariance between attributes. Suppose A={MO;ST} be the training dataset containing positive and negative examples, a matrix of size d*l is generated where d=p+n, it is the number of train vectors, p is the number of positive examples, n=number of negative examples, l= length of each vector. After

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extracting amino acid composition of different datasets, these results fed as input to Support vector machines and by performing feature selection and outlier detection. It's important to find the hyperplane which clearly distinguish are dataset from one another with respect to their negatives. For each run of SVM the classifier is developed and their performance is measured.

Performance evaluation: The performance of our classifier was judged by 10 fold cross validation. The LIBSVM provides a parameter selection tool using the RBF kernel: cross validation via grid search. For each Dataset 1, Dataset 2, and Dataset 3 grid search is performed using c and gamma. Test set was performed for 10% of all samples and remainder samples are used for training. Generally SVM faces the problem of "over- fitting" where the system converges on the set of rules but it can be solved efficiently. The test set and train set trees are identified properly. To know the correct classification cross validation process is used. This requires for each run 10% of sample is used as test set. Different rule set up test cases are classified. It was found that which rule has the most beautiful predictive ability to improve is raised as best model evaluator. Over fitting of the data leads to the pruning.[21]

Results & discussion

Machine learning algorithm for classification of antimicrobials for human medicine is implemented in this paper. All the three datasets run in LIBSVM. And best result is obtained in the form of model.

Model development

It is the final step when the data is classified as wanted. After labelling testing data and generating several classifiers. It's final to choose which fit best classification and develop model for future use. Figure 2 shows the model for critically important antimicrobials.

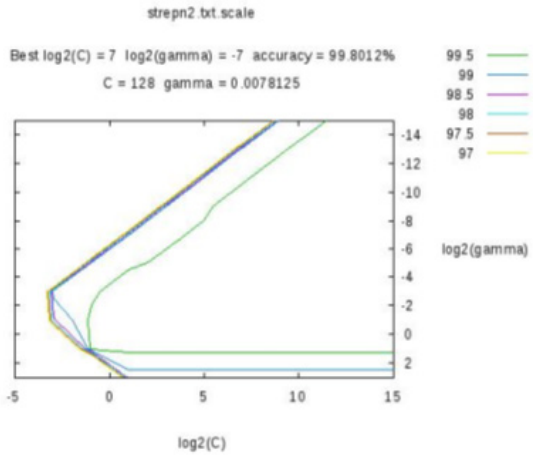

Figure 2 Model for critically important antimicrobials.

According to the model development in SVM, there c,g and accuracy are calculated simultaneously and can be written in the form of Table 3 and all the required details are described later in this paper.

Table 3 Support vector machine results

Dataset	C	G	Accuracy
Dataset 1	120	0.007813	99.8012
Dataset 2	120	0.0025	99.5
Dataset 3	120	0.0078	98.5

Figure 2 & Table 3 proves better that are datasets are classified accurately with great accuracy. As we focus on CIA, it was classified with 99.8012% accuracy. And also proves for similar sequences. Amino acid compositions are best suited to classify such sequences. Detail description is as follows:

Accuracy can be calculated as: $= \frac{tp + tn}{tp + tn + fp + fn}$

Where tp=all the true positives in the samples

tn=all the true negatives in the sample

fp=all the samples which behave as positive

fn=those samples which behave as negative

Precision and recall, accuracy all functions are inbuilt in LIBSVM. By choosing correct c,g, software calculate all parameters and reflect the correct answer within minutes as per the volume of data. As the result obtained clearly differentiate characteristics of antimicrobials in three different groups. Any new antibiotic discovered can be grouped in above defined these categories. The correct values of c,g and accuracy of all the three datasets identified. The c and g are the two parameters for RBF kernels. It can't be judged which is best. But the LIBSVM has the parameter selection tool which best finds the c,g, and accuracy. If good (c) is identified by the classifier then it is better prediction. The prediction accuracy indicates the performance on classifying an independent dataset. Hence it is good to know about 'unknown" dataset. Again cross-validation is performed. In this n-fold cross-validation the training set is first divided into n-subsets of equal size. It would work sequentially by (n-1) subsets. Therefore cross validation is the percentage of data which is accurately classified. This cross validation removes the over fitting. The grid search approach is used because (a) it avoids exhaustive parameter search by approximations or heuristics, (b) Computational time is less as there is only two parameters. (c) Both c and g are independent. Hence SVM is one of the best computational methods which reduce the cost of CV and best is biological data classification.

Conclusion

Machine learning being an active area of research requires experts that handle data safely and understand the data as information retrieval system. Here machine learning model is developed for antimicrobials which are used in human medicine. Hence WHO initiates how to recommend critically important antimicrobials for human medicine? It's a need to describe importance of human medicine publically. So in this paper author well tried to classify critically important antimicrobials for human medicine with great accuracy. Future treatment should be given by seeing the effect of antimicrobials. And any other microbe or antimicrobial is generated it should be grouped according to its amino acid composition based category as the machine learning model is being developed.

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None.

Conflicts of interest

The author declares there is no conflicts of interest.

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