Highlights in BioScience
ISSN:2682-4043
DOI:10.36462/H.BioSci.202304

Review Article

Open Access

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Received: October 10, 2023
Accepted: December 24, 2023
Published: December 30, 2023

Citation: Mary AS, Patil MM, Kundu G, Rajaram K. Machine Learning Mediated Advanced Phage and Antimicrobial Therapy - A Futuristic Approach. 2023 Dec 30;6:bs202304

Data Availability Statement: All relevant data are within the paper and supplementary materials.
Funding: The authors have no support or funding to report.
Competing interests: The authors declare that they have no competing interests.

Machine Learning Mediated Advanced Phage and Antimicrobial Therapy - A Futuristic Approach

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Abstract

The emergence of antimicrobial resistance (AMR) has overwhelmed the contemporary curatives and have turned into one of the major challenges in the biomedical sector. With increasing deaths being associated with AMR every year; early detection of pathogens and development of novel drugs and alternative therapies, have all become *ad hoc* in diagnosis, prognosis and patient survival. Bacteriophage therapy remains a viable strategy to counteract AMR, yet unduly restrained by phage resistance. Phage infection is a natural phenomenon and can be widely manipulated *in vitro* using advanced techniques including the CRISPR/Cas systems which renders phage therapy an upper hand in comparison to conventional drugs. Phage identification, host range detection, determination of phage-receptor binding efficiency, adsorption rate, phage genome analysis are crucial stages in phage selection and phage cocktail preparation and moreover pivotal in flourishing phage therapy. The ascent of translational research and omics has allowed the development of quick, reliable and precise strategies for phage-based diagnosis and treatment techniques. However, *in vitro* evaluation of AMR and phage factors as well as storing, processing and analyzing large laboratory data outputs are expensive, time-consuming and labor-intensive. Machine learning (ML) is a utilitarian strategy to organize, store, analyze data sets and more importantly allows prediction of certain features by recognizing patterns in the data sets. With the huge number of research been carried out around the globe and enormous data sets being published and stored in databases, ML can utilize the available data to perform and guide in developing alternative therapeutics. Several ML based tools have been developed to predict resistance in host, phage grouping for cocktail preparation, resistance and lysogenic genes detection, phage genomic evaluation and to understand phage-host interactions. ML also allows the *in silico* analysis of large samples (drug/phage) and reduces sample size for *in vitro* evaluation thereby reducing overall costs, time and labor. The present review summarizes the available ML algorithms and corresponding databases used in AMR and phage research. It also emphasizes the status quo of antimicrobial and phage resistance in the healthcare sector and analyses the role of ML in analyzing biological databases in order to predict possible phage/drug-host interaction patterns, phage susceptibility, suitability of phage strains for therapy and recommends the most efficient drug combinations and treatment strategies.

Keywords: Antimicrobial, AMR, Bacteriophage, Resistance, Machine learning, Database, Phage, Bacteria, Pathogen, Infection

Background

An alarming hike in morbidity and mortality due to bacterial infections have been reported worldwide in the past decade [1]. The Centre for Disease Control and Prevention and the World Health Organisation have arbitrated in this global health threat, and have identified and listed the priority pathogens entitled with the acronym ESKAPE, and have implemented strategies to combat pan drug-resistant (PDR), multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria [2; 3]. The Clinical and Laboratory Standards Institute (CLSI) has disclosed the ineffectiveness and failure of antibiotics against ESKAPE pathogens overtime [4].

Development of alternative drugs is on the horizon and in 2019, Mulani *et al.,* catalogued the emerging approaches like antimicrobial peptides, antibiotic combination therapies, photodynamic light therapy, bacteriophage therapy, nanoparticles and phytochemicals to combat antimicrobial resistance (AMR) [4]. Additionally, state-of-the-art treatment strategies like CRISPR/Cas9 and bacterial vaccines have also been surfaced and are under exploratory research and development [5].

Bacteriophage are ubiquitous and are present alongside the host and are pivotal in regulating bacterial populations; thereby maintaining microbial balance. Phage therapy has been largely neglected during the antibiotic era; however, with the emergence of drug-resistant bacteria it has regained its lost glory. On one hand, bacteriophage remains a logical and sustainable remedy for AMR, whereas bacterial evolution and fitness in presence of phage allows the persistent cells/mutants to grow and propagate [6]. Bacteriophage resistance can also be associated to bacterial abortive mechanisms, receptor mutations, Restriction-Modification (RM) systems and CRISPR-Cas systems [7]. While bacteriophage resistance is a backlash for phage based treatment regimen, certain clinical implications incurred due to phage resistance are of therapeutic importance. In a clinical setting, phage resistance does not only result in treatment failure but can also aid cross-resistance across other phage and antibiotics [7]. In 2018, Wright *et al.,* demonstrated the modular network of cross-resistance in spontaneous mutants of *P. aeruginosa* against 27 distinct phage; and emphasized the role of cross-resistance network based prediction of mutation frequency and phage combinations for successful therapy [8]. Screening and identifying putative phage for effective host inhibition is yet another major challenge where conventional methods can turn out to be unreliable, time-consuming and labour-intensive. Melo *et al.,* in 2022, evinced the use of Flow Cytometry for fast, reliable and high-throughput phage screening [9]. Genomic analysis associated to receptor synthesis of *P. aeruginosa* phage (K8) resistant-mutants by Pan *et al.,* in 2016, revealed the absence of O-antigen (serve as receptor) in mutants [10]. Similarly, innumerable research has documented the genes associated to the receptors modification in host [11; 12; 13], receptor binding proteins (RBP) [14; 15], antimicrobial genes (ARGs) [16; 17], cross-resistance network [8], phage-host interaction [18; 19], endotoxins [20; 21], lysins [22; 23; 24; 25], pharmacokinetics [26; 27], whole genome data [28; 29; 30], gene expression data [31; 32] and structural information [33; 34] all of which are paramount information in establishing phage therapy. The advancements in research strategies, subsequent outputs and innumerable data has been largely controlled by computational intervention and developments in bioinformatics [35]. Even when bioinformatics provides large range of data storage, indexing, analysis and data retrieval; recent developments in machine learning including deep learning and artificial neural network (ANN) have allowed the unprecedented prediction by analysing massive data sets [36]. Biological databases or repositories are key prerequisites in machine learning and are classified into primary, secondary and composite, and typically reserve molecular sequences (GenBank, DDBJ, PIR), structures (PDB), metabolic pathways (KEGG, MetaCyc), enzyme structure and interactions (BRENDA), molecules (PubChem), microarray gene expression data (GEO), taxonomic data (Catalogue of life), disease data (OMIM), model organisms (RGD, Flybase) and bibliographic data (PubMed) [37]. Machine learning algorithms learns from these data sets by analysing and identifying patterns; and this is particularly useful in prediction, classification, feature identification/selection and clustering [38]. ML algorithms have remarkable applications in biomedical research including disease diagnosis, drug discovery and development, personalized medicine, medical image analysis, electronic health record analysis and supreme role in analysing raw data in genomics and proteomics [39]. Several concerns arise in using machine learning and deep learning for biological data analysis, including ethical integrity and analysis of noise data along with selected features [40]. This review, elaborates the use of Machine learning in devising efficient therapeutic strategies to combat AMR as well as its applications in exploratory and basic research. It also briefs the potential of phage therapy and corresponding databases and ML algorithms to aid in the development of phage based curatives and strategies to overcome phage resistance by predicting bacterial susceptibility, phage host range and infectivity. This review also summarizes currently used ML algorithms and databases for research and medical purposes.

Phage therapy

The antibiotic pipeline has shown seldom growth with very few novel compounds being commercialized in the recent years [41]. It is safe to say that the 'post-antibiotic era' is approaching, and the development of effective alternative therapies is essential. The discovery of the mighty penicillin and the subsequent development of other broad-spectrum antibiotics marked the beginning of the golden age of antibiotics, and as a result, the then-used alternatives like phage and other therapeutics have been sidelined since the 1940s [42]. Lytic phages are potential bactericidal agents and have been successfully used in clinical practices. The phage-bacterial interactions are commonly observed to be obligate lytic (virulent), pseudolysogenic, lysogenic, and chronic [43]. Lytic phages are bacterial viruses that replicate immediately after entering the host cell and release the progenies; on the other hand, lysogenic phages are viruses that integrate the phage genome with the bacterial genome for generations and can resume the lytic life cycle [44]. Pseudolysogeny occurs when the host cells are deprived of nutrients, and the phage genome neither enters the lytic nor lysogenic cycle but stays inactive [45]. Chronic life cycle is also known as the carrier state where the progeny is released through the host cell membrane without rupturing or damaging the cell, resulting in a long-term infection [44]. While lytic phages are the only bacterial viruses that could be translated for therapy, lysogenic conversion of phage in bacteria has allowed the acquisition of undesirable genes. For

instance, *Corynebacterium diphtheria* and enterohaemorrhagic *Escherichia coli* acquired toxin-producing genes - diphtheria toxin (siphovirus β-phage) and Shiga toxin (lambdoid phage) respectively from the integrated phage genome [46; 47]. Besides the type of phage life cycle, the optimal bactericidal efficacy of phage is also dependent on factors like adsorption rate, latency period, multiplicity of infection (MOI), and burst size. However, bacterial features including the host outer membrane (LPS, capsule, peptidoglycan), receptors, presence or absence of flagella or pili can alter the fate of phage infectivity. Xuan *et al.,* through their experiment in 2022, proved that quorum sensing upregulated the synthesis of lipopolysaccharides (typically for biofilm production) which are receptors for phage adsorption, thereby promoting phage infection [42]. Phage-encoded enzymes like depolymerases are capable of degrading the glycan protective layer in bacteria to establish infection [48]. At a clinical setting, the use of phage cocktails and lysins are also potential strategies to ensure bacterial growth suppression.

In 2019, Aslam *et al.,* reported the use of bacteriophage cocktails for treatment against *P. aeruginosa* and *Burkholderia dolosa* infection in lung transplant recipients [49]. Similarly, independent studies have evaluated the use of CT-PA (P. *aeruginosa* cocktail), AB-SA01 and NOV012 (*Staphylococcus aureus* cocktail) for treatment against chronic rhinosinusitis [50; 51; 52]. Uyttebroek *et al.,* in 2021, also summarized the use of bacteriophage against recalcitrant chronic rhinosinusitis due to *S. aureus* and *P. aeruginosa* colonization and biofilm formation [53]. A recent study in 20 patients positive for *Mycobacterium* infection treated with intravenous phage administration, 11 patients showed a favorable response, and phage neutralizing antibodies were found in 8 patients [54].

Topical phage administration is a reliable strategy to ensure maximum phage stability, with minimal immune responses. PP1-131 , phage cocktail used against *P. aeruginosa* burn wound infections, was found to reduce the bacterial load, but at a significantly lower rate in comparison to the standard of care treatment. The drop in the phage performance was linked to the loss of titer during manufacturing where the participants received low phage concentrations than intended [55]. FAGOMA (Spanish Network of Bacteriophages and Transducing Elements) in its regard to bacteriophage therapy advised the use of phage-based therapy only for patients infected with MDR pathogens or in case of antibiotic hypersensitivity and infection in antibiotic reluctant areas such as the prosthetics [56].

Even with a vast number of *in vivo* and clinical studies, commercialization of phage-based therapy has been under scrutiny due to the heterogeneity in the outcome and also due to the lack of unreported adverse effects. From the stage of selection of phages (single phage/cocktails), mode of administration to the treatment duration, no standards have been established till date. Onsea *et al.,* in 2021, devised a multidisciplinary strategy to overcome aforementioned hurdles in establishing phage therapy as a standard of care treatment [57]. Consecutive reports have been updated on the status of phage therapy in Germany from the 1930s till date along with the present challenges in phage production and commercialization on a large scale [58]. Phage-based therapeutic product development should ensure high quality, efficacy, and safety for clinical usage and, moreover, should be GMP-certified [59].

Another widely accepted aspect of phage application in clinical practice is the adjunct use of phage with antibiotic. Liu *et al.,* in 2020, evaluated the phage-antibiotic interactions (antagonism, synergy, additive) by analyzing the stoichiometry and among different classes of antibiotics. Through specific real-time readout synograph', they concluded that the mechanism of phage-antibiotic synergy is antibiotic class dependent, and the synergistic activity can be suppressed by bacterial growth conditions [60]. The resensitization of antibiotic-resistant strains during phage-antibiotic combination therapy is attributed to the trade-off costs during bacterial fitness. Wang *et al.,* in 2021, demonstrated the use of colistin-phage (Phab24) combinations against *Acinetobacter baumannii*, and reported that phage Phab24 was capable of eliminating both colistin-sensitive and resistant strains along with increased sensitivity of phage-resistant mutants to colistin [61]. Emerging proofs are indicative of successful phage therapy, whereas resistance is a significant factor in establishing the same.

Antimicrobial and phage resistance

The resurrection of *phage therapy* and augmentation of antibiotics have shown potential in developing efficient bactericidal therapeutics; whereas, *phage* and antibiotic/drug resistance prevails as a major concern. Bacteria attain antimicrobial resistance by employing one or more mechanisms that may involve either drug alteration/inactivation, overcoming intracellular drug accumulation, modification of the drug binding sites, efflux pumps, or by forming biofilms, Figure 1 [62]. ESKAPE pathogens also acquire novel resistance mechanisms which are not part of their natural intrinsic defense methods. *Enterococcus faecium* produces penicillin-binding-protein 5 (*PBP5*) that provides protection against β-lactam drugs (penicillin, ampicillin, and cephalosporins). *E. faecium* also resists the combined doses of aminoglycosides and β-lactam/glycopeptides by chromosomal AAC (6')-I enzyme [63]. The clonal complex 17 (CC17) strains of *E. faecium* are assigned to be responsible for hospital-acquired *E. faecium* infection and contain virulence and resistance genes conferring protection against a series of antibiotics, including ampicillin and quinolones [64]. Similarly, *S. aureus* have attained resistance against penicillinase-resistant drugs like methicillin, cloxacillin, and oxacillin (*MRSA* strains) but remain susceptible to glycopeptides. Resistance towards β-lactam drugs is conferred by plasmid-encoded *blaz* gene as well as through *PBPs* (*mecA* & *mecC*) [65]. Last resort drugs like colistin and tigecycline are used for *ESBL* (extended-spectrum β-lactamases) and carbapenemase-producing *Klebsiella pneumoniae* infections; whereas, colistin resistance is also reported (*mcr* gene) giving rise to untreatable pan-drug infections [66].

In regard to *Acinetobacter baumannii* and *P. aeruginosa*, the intrinsic defense is quite intriguing with impermeable outer membrane and enhanced efflux pumps. β-lactamases and *PBP* confer protection against β-lactam and carbapenem drugs in most cases [67]. In *P. aeruginosa*, *OprD* loss is associated with imipenem resistance [68].

Antibiogram is one of the most commonly used cost-effective in vitro resistance detection strategies. Other phenotypic methods include MIC detection (micro-dilution method), breakpoint agar method, biochemical tests, immunographic tests (CARBA-5, RESIST-4), electrochemical test (BYG test), motility test, staining, etc. MicroScan walk assay, BD Phoenix, and Vittek 2 are examples of semi-automated MIC determination approaches [69]. Bacterial strain identification and differentiation are carried out using MALDI-TOF analysis and strain-specific tests like MGP (*methyl-α-D-glucopyranoside*) test (*E. faecium*), slide agglutination test (*S. aureus*), modified Hodge test, and carbapenemase inhibition method (*P. aeruginosa* & *A. baumannii*), etc. Genotypic characterization is ad hoc and mostly targets the detection of genes including superoxide dismutase (*sodA*), vanA, vanB (glycopeptides resistance genes), mecA, mecC (methicillin resistance genes), bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, bla_{OXA-48} (carbapenem resistance), *mcr* (colistin resistance), *aphA6* , *armA* (amikacin resistance) through LAMP, microarray, real-time PCR, and whole genome sequencing (WGS) [69].

Bacteriophage resistance is a complex yet a natural evolutionary process in bacteria. Nevertheless, the implications of phage resistance have more arena of challenges than antimicrobial resistance. Phage resistance is associated with trade-off /fitness costs that can alter the genotypic and phenotypic characteristics of the bacterial strain. Studies have reported reduced virulence, enhanced cross-resistance, altered antibiogram, changes in biofilm formation, permeability variations, and several other modifications during phage exposure [70]. Hesse *et al.,* in 2020, evaluated 57 phage-resistant mutants (*K. pneumoniae*) and reported that each mutant had distinct genes involving in mutation but with similar function associated with assembly or synthesis of surface receptors which ultimately affected phage adsorption in mutants [71]. Phage-resistant *UPEC* (Uropathogenic *E. coli*) strains exhibited alterations in *LPS* (lipopolysaccharide) and were confirmed via WGS [72]. Garb *et al.,* studied the defense-associated sirtuin (DSR) proteins in 2022, and found that SIR2 (N-terminal sirtuin) domain acts as NAD+ depletors and helps bacteria to abort phage adsorption and propagation [73]. One of the major findings by Laure *et al.,* in 2022, on trade-off costs in *Salmonella typhimurium* was the increased β-lactamase activity of mutants obtained after phage and phage +ampicillin treatment [74]. Li *et al.,* in 2022, investigated multiple mutant strains of *P. aeruginosa* and revealed major mutations in *pilT* and *pilB* (type IV pili) genes and chromosomal deletions of approximately 294 kb involving *galU* (UTP-glucose-1-phosphate uridylyltransferase) and *hmgA* (homogentisate 1,2-dioxygenase) [75]. Enhanced DNA exonuclease activity through overexpression of *mpr* gene in *Mycobacterium smegmatis* was proved to confer resistance against phage [76]. Owen *et al.,* in 2021, identified BstA-phage-defense proteins encoded by prophage that inhibit exogenous lytic phage infections [77]. Similarly, Charity *et al.,* in 2022, correlated *mTmII* prophage genome integration in *Salmonella typhimurium* to cause increased fitness and drug resistance [78]. Aforementioned studies are rather a glimpse at the ongoing research to unravel phage-host interactions and resistance mechanisms. A compelling need to develop sophisticated strategies to control and allow the development of prediction models prevails. The data produced through these studies could be put in use to manifest a much clearer picture for the development of phage and other antimicrobial therapeutics.

Machine learning

Machine learning (ML) is a scale-up strategy in refining and developing Artificial Intelligence (AI). Contradictory to symbolic AI; ML focuses on learning from datasets and develops an algorithm that could be novel with a distinct understanding of certain features and their respective weights [79]. In biomedical research, computational methodologies have failed in analyzing enormous datasets and ML comes in handy where a labeled/unlabeled dataset is used to train, validate, and test algorithms. Interpretation using ML becomes more systematic and allows classification, clustering, and, more importantly, prediction [80]. Supervised, semi-supervised, unsupervised, and reinforcement learning are the major learning methods used in ML. In layman's terms, ML algorithms are fed with raw data, data that are labeled (input/output, cause/effect), or with unlabeled data; either way, ML identifies hidden patterns and allows classification/regression (supervised) grouping/clustering (unsupervised) [81]. Supervised learning uses a labeled dataset with identified features and targets, and unsupervised datasets use unlabeled (raw) data where the algorithm determines the best features and target [82]. Regression and classification are two common tasks in supervised learning. On the other hand, association, clustering, and anomaly detection are tasks in unsupervised ML. Reinforcement learning is a trial-and-error-based learning strategy and is regarded as the best attempt at modeling human-like learning experience [83]. Support vector machine (SVM), linear regression, logistic regression, naïve Bayes classifier (NB), ANN, k-nearest neighbor (kNN), random forest, and decision trees are ML algorithms that are used to understand the relationship among the features and outcome/target [84]. While linear regression (univariate/multivariate) uses a linear line to describe the relationship, logistic regression predicts a sigmoidal relationship between features and the probability of an outcome. Decision trees classify the data based on features, beginning from a root node and partitioning into decision and terminal nodes. Random forest is an ensemble producing several decision trees [83]. Deep learning is a subset of ML, where hidden neural layers perform learning and decision-making more efficiently without other intervention [85]. Stochastic models are more approachable in the case of

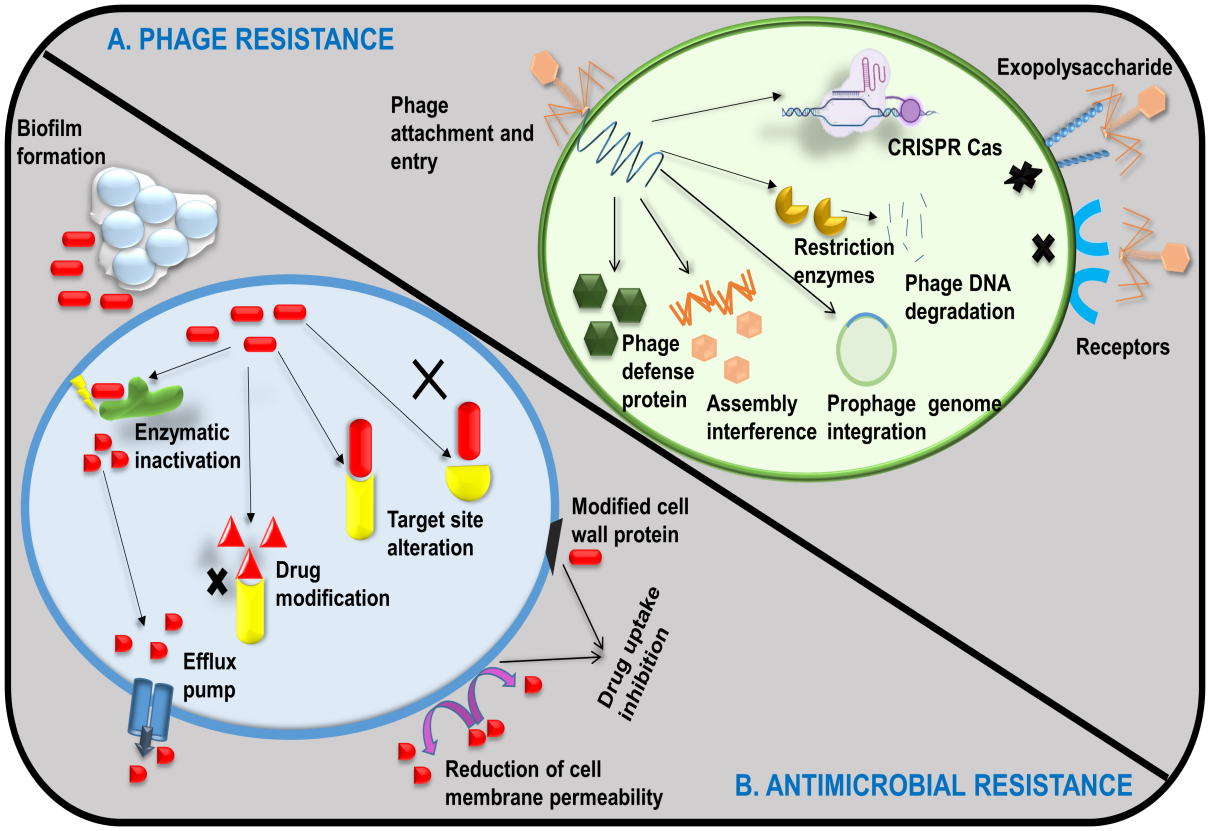

Figure 1. Antibiotic and Phage resistance mechanisms in bacteria. A) Intrinsic phage defence involves production of thick outer membrane and receptor modifications. After the phage genome enters the bacterial cell restriction modification (RM) system or CRISPR Cas system degrades or inactivates the genome and avoids further transcription, translation and phage assembly. B) Antibiotic or drug resistance mechanisms involves enzymatically inactivating the drugs, drug modification and target site alteration. Intrinsic mechanisms involve biofilm production, reduced drug uptake by altering membrane permeability and enhanced efflux pumps.

randomness and ambiguity in data. In 2021, Goodswen *et al.,* reviewed the uses of ML in biology, which included disease diagnosis, predicting outbreaks/vaccine candidate/drug targets, drug resistance identification, and microbial interactions [86]. With the assistance of some reliable methodological strategies, it will be more realistic to model the global pan-genome. The Expectation-Maximization (EM) algorithm is the multitude approach for determining maximum a posteriori estimates (MAP) or maximum likelihood estimates (MLE) for undocumented models in statistical analysis [87]. Reboredo *et al.,* in 2021, have updated the trends in the usage of ML in drug discovery; the authors also emphasized on the economic advantages of ML in detecting active compounds and thereby reducing the cost and effort in processing large sample sizes in pre-clinical and clinical studies [88]. Convolutional Neural Network (CNN) in ML is reportedly efficient in analyzing images (MRI, CT, PET scans) with significant application in nuclear medicine [89]. With unlimited application in the biomedical sector along with novel developments, ML has become a reliable tool. Among several other applications, ML in AMR and development of phage therapy is a growing area of interest.

Machine Learning and Antimicrobial Resistance

Computation of data ensures greater accuracy in analysis, which is the foremost requirement for data analysis in the biomedical sector. Several infectious diseases are frequently being treated with antimicrobial drugs; however, antimicrobial resistance in bacteria has become a generic reason for treatment failure. Developments in machine learning (ML) have allowed the detection and prediction-based applications in antimicrobial resistance [90]. Distinct tools for determining the antimicrobial resistance genes and virulence genes based on ML are currently available (Figure 2).

A specific approach of ML in AMR is by analyzing the suitable synergistic drugs for the development of possible combinatorial therapies. INDIGO (Inferring drug interactions using chemogenomics and orthology) uses the best-fitted synergistic drugs for the treatment of intra-abdominal infection using Gentamycin -Ampicillin developed using model predictions [91]. Another refined model that is a bit different in application is the MAGENTA (metabolism and genomics-based tailoring of antibiotic regimens), which facilitates the treatment of biofilm using combinatorial Rifampicin dosage [92]. Determination of antimicrobial resistance using ML is now being used in various

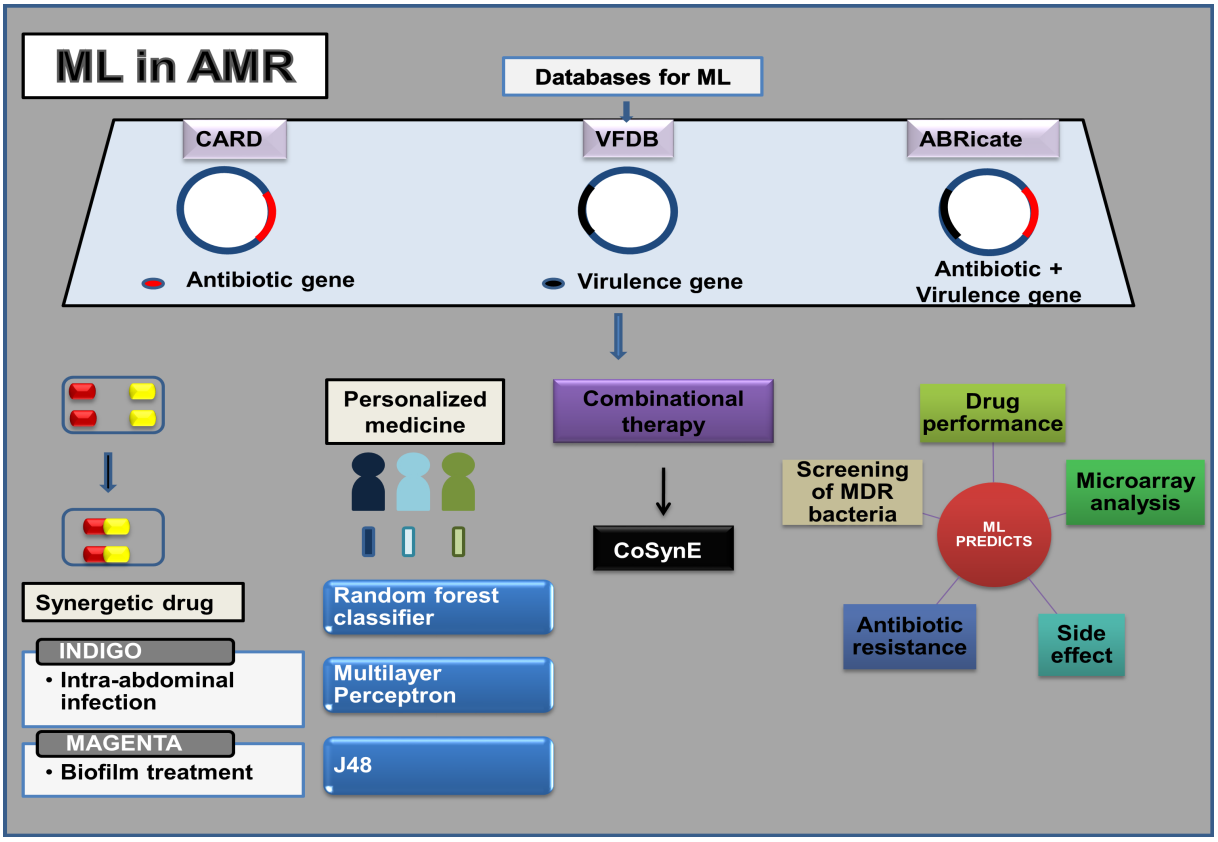

Figure 2. Machine learning algorithm utilized antibiotic and/or virulence gene databases to predict antimicrobial resistance, alternative therapies and its corresponding side effects. The Machine learning algorithms can be used to develop personalized medicine and also can predict the synergistic effects of certain combinatorial therapies.

sectors, including the first line of intensive care. ML is not only limited to a targeted approach but also narrows down the frequent use of multiple antibiotics under the same diseased conditions [93]. For medical professionals, ML has now become the key predictor for antimicrobial resistance, where ML-based tools are taken into consideration for allowing the screening of the best-suited antibiotics for the pathogens. Recursive partitioning is applicable for the prediction-based analysis of ESBL production from *Klebsiella sp.* and *E. coli* [94]. Modified recursive partitioning models are found to be advantageous for developing the logistic regression models [95]. XGBoost, one of the openly accessible platforms for ML-based algorithms, has guided the prediction-based analysis of antibiotic resistance for some of the gram-negative bacterial species [96]. The predicted performance by XGBoost is better than other risk assessment tools; however, the prediction model is a bit selective and applicable to limited antibiotics. The ML system can also be futuristic for determining the extent of antibiotic resistance during the culture collection. ML would capture the empowerment for the upcoming advancement of antimicrobials determination. ML enables the development of personalized medicinal approaches to cut down frequent uses of antibiotics. The Random Forest Classifier, one of the most supervised ML algorithms, is allocated to accelerate the screening of MDR bacteria among the patients in ICU [97]. The associated empirical data of the ML-based algorithm can also be implemented for local antimicrobial susceptibility assessment. Some of the ICU antimicrobial susceptibility-based ML algorithms are Multilayer Perceptron and J48 [98].

As discussed earlier, the principles of ML-based systems are i.) being trained from the existing datasets (supervised) and ii.) analyzing or giving output based on unlabeled data (unsupervised). Information regarding the underlying drug interactions has to be made available for ML to learn and develop algorithms for predicting the best combinatorial treatment approach. Primarily, certain attributes like changes in gene expression, response to the drugs, etc., need to be characterized before computerized for decision-making [99]. Based on the available datasets of drug information like chemical structure and function, the algorithms are trained to determine the combinatorial therapy. Among multiple algorithms, CoSynE (Combination Synergy Estimation) governs the direct structural analysis for an individual drug candidate to analyze the overall combinatorial therapy. Basically, to have knowledge of every aspect of the combinatorial compounds, there should be prior data for the drug and the target as well [100]. With the CoSynE approach, the level of application can be extended towards diversified combinatorial drug designing against

drug-resistant *E. coli* and also against malarial parasite *Plasmodium* [99]. Through consistent records, the ML algorithms were able to predict drugs to counteract antimicrobial resistance in *Mycobacterium* and *Salmonella* [101]. The predictability is well-curated to reframe the ML so that antibiotic resistance can lay the foundation for the model-based prediction.

The extent of genetic variations and drug resistance can be supervised using Machine Learning algorithms. The drug resistance predictability is done so far in accordance with IC50 indicators. The various searches are based upon the retrieval of different sequence databases. Tuberculosis, caused by *M. tuberculosis*, is one of the infectious diseases which could be eradicated using antibiotics, but due to the dosage's dysfunctionality and random uses of antibiotics, it concludes with a highlighted remark towards the development of MDR Tuberculosis [102]. Administration of fluoroquinolones is currently considered, but the usage could lead to after effects due to reported toxicity. ML predicts novel drugs, mechanistic performance of the drugs, microarray data construction and analysis, side effect prediction, etc. Based upon the existing known dataset, ML-based algorithms can display the futuristic blind prediction. The performance based on the suggestive prediction can confer the right indication towards clarifying the Single Nucleotide Variance followed by the mutation within the genome of *Mycobacterium tuberculosis*. Sequenced based algorithms and structure-based simulations employ the right directive approach to analyze the genomic variation, so that suitability for selecting the target gene can be obtained. Deep learning is efficient in predictable analysis to distinctively diagnose the inherent antimicrobial peptide (AMP) to combat antimicrobial resistance. Deep Learning was able to evaluate AMPs as antimicrobial agents and predicted that AMP can surpass MDR in carbapenemase-producing *E. coli*. Deep learning is also capable of simulating the newer versions of AMPs from the existing peptides [103]. With access to different databases like ARGs, a number of Deep Learning models have been recruited so far to deliberately screen the best-hit searches for antimicrobial genes. A summary of the ML tools for antimicrobial resistance and its associated factors is depicted in Table 1.

Machine Learning in phage therapy

Machine learning has arisen as a promising strategy in phage therapy prediction, intending to discern the most effective bacteriophage that can selectively target distinct bacterial strains. Currently, various techniques exist to measure bacteriophage-host interactions experimentally, such as PhageFISH-CLEM [113], microfluidic digital multiplex PCR [114], flow cytometry [115], agar overlay assay [116], RNA-sequencing [117], spot test, and efficiency of plating [118]. While these methods are highly accurate, they are costly, labor-intensive, time-consuming, and can turn out to be inconclusive. To overcome these limitations, researchers have developed high-precision computational methods for predicting phage-host interactions. The initial phase in phage therapy is the selection of suitable phage, characterized by three indicators that include 1. Presence of temperate markers 2. Presence of anti-microbial genes and 3. Presence of Virulence Gene. ML basically uses the whole phage genome and corresponding proteome analysis, and from the sequence similarity and analysis of the conserved domains, determines whether the phage undergoes lytic or lysogenic cycle. A recent approach has been developed to determine the suitability of phage for therapeutic purposes based on an online single-step predictor tool. This predictor tool utilizes the protein features such as integrase, Cro/CI repressor protein, anti-repressor proteins, immunity repressors, etc., along with ABRicat tools for determining the antibacterial and virulence genes. Apart from ML, other computational tools are also in use to identify host range and host-phage interactions. The alignment-free and alignment-based techniques are widely used tools, where the sequence homology and sequence similarity among host and phage are read by computational tools to predict its host range [119]. BLAST is a classic example of an alignment-based method. While the alignment-based method (e.g., Phirbo) is the most reliable strategy with the maximum prediction accuracy, certain factors like the prediction of multiple related hosts, spurious alignment, and artifacts lead to comparable false results. Alignment-free tools use similarity in the sequence composition of codons, oligonucleotide frequencies, etc. This tool comes in handy where the host and phage lack sequence homology, and thus alignment-based tools are not suitable.

ML develops algorithms based on dataset creation (phage genomes and its corresponding protein sequences), feature generation (custom scripts), and validation. Computational evaluation precedes other methods by allowing the comparison in a large dataset, especially advantageous for non-cultivable bacteria and the availability of limited host strains. HostPhinder examines phage genome sequences to predict the bacterial host of phage [120], VirHostMatcher measures CRISPR sequences and alignment-free similarity to predict virus-host interaction [121], WIsH outperforms VirHostMatcher at various taxonomic levels and predicts the host range of bacteriophages through genome sequences [122], Machine learning takes into consideration the measurable properties referred to as features'. Nucleotide sequence is a characteristic feature and is used by ML algorithms like Prokaryotic Virus Host Predictor (PHP) and Host Taxon Predictor (HTP) for phage-host interaction prediction. The absolute relative oligonucleotide frequencies and a Gaussian model are used to predict the host in HTP and PHP, respectively. Based on the virus-host associations, ILMF-VH and LMFH-VH integrate the virus and host similarity network [123], [124]. Leite's method uses a One-Class learning method to predict the host-viral interaction at the bacterial strain level [125], SpacePHARER (CRISPR Spacer PhageHost Pair Finder) predicts bacterial and viral interactions at the protein level by comparing spacers and phage [126]. On the other hand, VirSorter uses phage-host interaction signals to predict the phage-host interaction [127], and PredPHI (Predicting Phage- Host Interactions) predicts the prokaryote-phage interaction by sequence data [128]. PhageTB lever-

Table 1. Methods, Tools & Algorithms, Model Organisms, Genes, Databases, Applications, and References

Method	Tools & Algorithms used	Model organism	Genes	Database	Applications	Reference
Pan-genome construction, Random forest	Scoary, Prodigal, CD-HIT, Glimmer3, Naive-Bayes classifier	*E. coli*	AMR genes (from core and accessory gene clusters)	PATRIC, CARD	Analyses the accessory part of the genome to predict ARGs	[104]
WGS, Antibiogram	K-mer, Random forest, XGBoost	*S. aureus*	SCC mec genes	PATRIC	Predicts Antimicrobial Phenotype Resistance	[105]
Colony screening, RNA sequencing, DNA sequencing, SNP calling, Pangenome analysis and indel calling, Multilocus sequence typing	MSA2VCF, Illumina HiSeq 2500, MAFFT, SAMtools, BamTools, BCFtools	*P. aeruginosa*	PA14 gene	UCBPPPA14, MLST database	ML identified biomarkers assess AMR profiles through a molecular test system	[106]
Phylogenomics, and genome sequencing	mafft, raxml-ng, T-REX, TreeTime	*E. coli*	malT gene, manZ	BiMat software	Studies the phage-bacterial co-evolution dynamics (molecular and ecological mechanisms)	[107]
Oxford Nano-pore Technologies, Single Nucleotide Real Time (SMRT)	REBASE, DECIPHER, Clustal Omega	Cutibacterium acnes	Mob genes, Res gene	REBASE, NCBI Genome database, PFAM database, CRISPR-CAS Finder	Restriction-methylation and host protective mechanisms in *C. acnes* strains	[108]
Twitching motility assays, Swimming motility assay. Drosophila melanogaster virulence assays. Secreted enzyme assay. Antimicrobial resistance assay. Shearing assays.	MICROB Express kit, Agilent 2100 bioanalyzer, BEDTools software v2.16.2.	*P. aeruginosa*	Morons	CLC Genomics Workbench software v5.1	Bacterial and phage symbiotic interaction, Bacterial adaptation in various selective pressures	[109]
Mathematical model using an arbitrium-like communication system in a serial passage set up.	Matlab R2017b	Bacillus		GitHub	Small peptide mediated signal communication (phage-phage),phage life cycle prediction.	[110]
Antimicrobial susceptibility testing, Statistical analysis of multidrug resistance, Association set mining	SENTRY, Apriori	*S. aureus*	AMR genes		Analysis of Multidrug Resistance in Staphylococcus aureus	[111]
Serotyping, Antibiotic susceptibility testing, Set-covering machine, CMY-2 locus analysis	Python libraries, SISTR, IQTree, Prodigal v2.6.3, Kover v2.0.0, BWA-MEM	Salmonella enterica	AMR genes	Plasmidfinder database, DIAMOND v0.8.36	AMR genomic characterization of Non-typhoidal Salmonella serovars to train prediction models for AMR phenotypes.	[112]

ages accurately identifies hosts for bacteriophages using genomic sequences [129].

These user-friendly tools enable the study of phage interactions, identifying potential phages that can specifically target pathogenic bacteria, leaving beneficial bacteria intact. Machine learning-based approaches for phage therapy prediction have shown great promise in identifying effective bacteriophages for targeted treatment of bacterial infections. These methods offer faster and more cost-effective alternatives to traditional experimental techniques. However, challenges in data availability, model selection, evaluation metrics, interpretability, and user-friendliness must be addressed for their successful implementation in clinical settings [130]. Additionally, tools like PHACTS (Phage Classification Tool Set) and BACPHLIP (BACterioPHage LIfestyle Predictor) are widely used for determining phage lifestyle by annotating proteomes and classifying lifestyles based on conserved protein domains [131], [132].

BacteriophageHostPrediction is one other ML which considers more features, including genomic sequences, protein sequences, protein secondary structures, and physiochemical properties. PHERI identifies bacterial host from phage sequence through annotated protein sequence clusters. PhageLeads are ML that focuses on predicting the lifestyle of phage (lytic or temperate) using protein features of temperate markers. The quick prediction times of PhageLeads make it a valuable tool for efficiently identifying phages suitable for combating antibiotic resistance, and its ability to detect resistance and virulence genes further enhances its utility [133]. Incorporating protein biological feature spaces may further enhance the functional similarities predictions [134]. Several databases like CARD [135], ShortBred AR [136], MEGARes [137], and VFDB [138] aid in detecting these genes. By overcoming these challenges, machine learning-based phage therapy prediction holds significant potential in combating antibiotic resistance and improving treatment outcomes for bacterial infections. After the development of ML, the usability is determined by several factors such as operating system restriction, automation, and reproducibility. PHP, HostPhinder are web-based prediction tools that are also available, which do not require a specific OS. Table 2 summarizes the ML algorithms developed for phage research.

Databases in antimicrobial resistance and phage research

In silico approaches for omics studies have become more widely available, which has in turn made it feasible to precisely recognize and catalog determinants in the case of antibiotic resistance and its associated genes. AMR archives, and software applications tools have been constructed for WGS-AST based on the available databases, which includes the Comprehensive Antibiotic Resistance Database (CARD), ResFinder and its companion database PointFinder, ARG-ANNOT, and many more (Table 3) [139]. The CARD offers an informatics paradigm for the notation and assessment of resistomes through integrating the Antibiotic Resistance Ontology (ARO) [140]. CARD is a database on the molecular basis of antimicrobial resistance that is ontology-focused. CARD has the potential to serve as both reference material and software instruments and resources for directing AMR investigation, particularly for ARG details and other findings from genomic information and metagenomic facts. This is made possible through the combination of an extensive modulated concept of ARO, with ARG [141]. The Resistance Gene Identifier (RGI), anticipates AMR from genome-wide facts and data using the bioinformatics prediction approaches and coordinated in CARD, and is a sophisticated strategy [142]. AMRFinderPlus, a tool of NCBI, analyzes protein annotations and/or gathered nucleotide sequence to find AMR genes, resistance-linked point mutations, and particular subclasses of genes. The Pathogen Detection operations make use of AMRFinderPlus, and these data are shown in NCBI's Isolate Browser [143]. AMRFinderPlus makes use of the carefully selected Hidden Markov Models and Reference Gene Database from the NCBI. The NCBI's Pathogen Detection Project incorporates the output of AMRFinderPlus to quickly group and locate associated pathogenic genetic patterns residing in food, environment, and people with illnesses. MicroBIGG-E (genomic data) together with the AMRFinderPlus; findings are provided in a more thorough manner, with extra data such as strain names and source of isolates [144]. In AMRFinderPlus the outcomes are provided for download by the users in two interfaces graphics [139]. Each unique isolate has a synopsis of its antimicrobial resistance, stress-related responses, and virulence gene sequence generated in the Isolates Browser, which may also be retrieved for more research.

Challenges and Opportunities

The use of machine learning in phage therapy faces several limitations and challenges. The future of health care system will be influenced by the intervention of AI and ML from organization to personalized precision care. The input of ML will also positively impact the diagnosis systems. One major obstacle is the need for diverse and unbiased datasets to train predictive models. Current datasets often suffer from data imbalance, leading to biased predictions and limited generalization to other bacterial species. Enriching a dataset with a broader range of phage-bacterium pairs involving different species and strains is essential for improving model accuracy and applicability [147]. Another limitation lies in the reliance on outdated databases to extract informative features that affect model relevance and performance. Incorporating up-to-date and comprehensive databases is crucial for generating more reliable predictions. Additionally, using deep learning models while achieving high accuracy presents challenges in model interpretability. These models are often considered "black boxes," creating challenges for users to comprehend the underlying decision-making process [152]. Balancing accuracy and interpretability is crucial for user trust and the real-world application of the models. The computational module for predicting phage lifestyle faces the limitation of uncer-

Table 2. Machine Learning based tools to aid bacteriophage research.

Machine learning predictors	Purpose of ML	Tools used	Major data sources - Algorithms	Predicting protein	Efficiency	Applications	References
Gradient Boosting Classifier (GBC)	Predict phage virion protein (PVPs) using phage protein sequences.	protlearn	AdaBoost Classifier (ABC),	Virion proteins	80 & 83 % accuracy for training and independent dataset.	Discovery of holins and other phage-driven proteins, endolysins, and exopolysaccharides Identification of phage virion proteins (PVPs)	[145]
PhageLeads	Determines the presence of temperate markers, antimicrobial resistance virulence genes	ABRicate tool,BACPHLIP	Plasmid Finder	Integrases, Cro/CI repressor proteins, immunity repressors	accuracy of 96.5%	Predicts the lifestyle of phageDetects lysogenic protein and temperate markers	[146]
PHACTS	Predicts the interaction of phage-bacterium	HostPhinder,K-Nearest Neighbors (K-NN), Random Forests (RF)], Support Vector Machines (SVM) , and Artificial Neural Networks(ANN)	GenBank, phagesDB.org, GeneMarkS, DOMINE, GeneMarkS, Pfam HMM, HMMER API	Receptor-binding proteins	86% to 90% accuracy	Predicts phage-host interaction	[147]
PhageTB, BLASTHost, BLASTPhage , CRISPRPred .	Predicts phage-host interactions	VirHostMatcher-Net	XGBoost, Multi-layer Perceptron		Accuracy of 67.9- 93.5%	Identifying hosts, assessing phage-host interactions, aids candidate phage therapy	[129]
AcrNET	Anti-CRISPR analysis	RaptorX,ESM-1b,POSSUM, PaCRISPR, AcRanker,DeepAcr, Hidden Markov Model (HMM) , MEME	anti-CRISPRdb, PaCRISPR, Acrs database, UniProt,UniParc, AlphaFold	Acr protein,anti-CRISPR proteins.	-	Determining Anti CRISPR from the large-scale protein database	[148]
PredPHI	Identification of phage-host interactions from sequence data	K-Means clustering	PhagesDB ,GenBank,		81.00%	Development of personalized treatment for bacterial infections.	[149]
Cryo-electron tomography (cryo-ET)	Phage based therapy against *K. pneumoniae* strains.	ChimeraX,HMMER,HHPred,Phyre2	Capsid and tail fibers of phage.	Receptor-binding proteins, protein gp118,protein gp119	IMOD,RoseTTAFold	Functional insight into Kp24 adaptation to variable surfaces of capsulated bacterial pathogens	[150]
Pred-BVP-Unb	Identification of BVPs within a huge volume of proteins	MATLAB tool,ADBoost, KNN,	Universal Protein Resource	Bacteriophage virion proteins	92.54% & 83.06% accuracy on benchmark and independent datasets	Designing antibacterial drugs Expedite discovery of BVP	[151]

Table 3. List of accessible databases for antimicrobial / phage resistant genes, receptor sequences, genomic sequences and SNPs.

Databases	Type of Input Sequence	Format of the input sequence	Purpose	Developed/ Maintained by	Supporting Tools/ DB	Link of the website
Comprehensive Antibiotic Resistance Database (CARD)	Nucleotide, Amino acid	FASTA	SNPs, validated and curated reference sequencing details and molecular foundation of antimicrobial resistance	NCBI	RGI	https://card.mcmaster.ca/home
AMRFinder	Nucleotide, Amino acid	FASTA, GFF	Identifies AMR genes & resistance-associated point mutations	NCBI	-	https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/AMRFinder/
Pathosystems Resource Integration Centre (PATRIC)	Nucleotide, Amino acid	FASTA	Large database of infectious bacterial genomic information	BRCs by NIAID	-	http://www.patricbrc.org
MEGARes	Nucleotide	FASTQ	A metagenomics dataset consisting of AMR genes that are identified, characterized and evaluated.	-	AMR++ (Bioinformatics pipeline), CARD, ARG-ANNOT, LAHEY	https://megares.meglab.org/
ResFinder	Nucleotide	FASTA, FASTQ	Imports assembled contigs, data sequences or completed genomes and detects AMR genes.	-	web-based portal and Python script	https://cge.cbs.dtu.dk/services/ResFinder/
Food and Environment associated Anti-Microbial Resistance Database (FEAMR DB)	-	-	Nonclinical test results as well as dietary and surroundings related AMR data worldwide	Antimicrobial Research Lab, Department of Biotechnology, University of Mumbai	CARD, NDARO, MegaRes, NCBI	https://feamrudbt-amrlab.mu.ac.in/
National Databases of Antibiotic Resistant Organisms (NDARO)	-	-	A co-operative, centrally controlled, cross-agency center where researchers may obtain AMR data to enable real-time pathogen monitoring.	NCBI	AMRFinder	-
Functional Antibiotic Resistant Metagenomic Element Database (FARMEDB)	Nucleotide, Amino acid	FASTA	It explores functional metagenomics antibiotic resistant genetic variables, serves as an opportunity for investigating AR in the majority of bacteria that are difficult to culture in lab. It serves as a repository for globally available antibiotic resistance linked genome sequences, predicted amino acid sequences, regulatory factors, jumping genes, and predicted peptides associated with antibiotic resistant genes.	University of Washington	-	http://staff.washington.edu/jwallace/farme/index.html
LREfinder	Nucleotide	FASTA, FASTQ	Offers information on the genes and alterations that cause enterococci to become tolerant to linezolid.	Centre for Genomic Epidemiology	-	https://cge.cbs.dtu.dk/services/LRE-finder/
Galileo AMR	Nucleotide	FASTA	Offers quick and precise labelling of genes associated with AMR for any DNA fragment of gram-negative bacteria.	Arc Bio	MARA, RAC	https://galileoamr.arcbio.com/mara/
ARG-miner	-	-	Gathers and access all of the data from various ARG resources. It offers proof of ARGs, specifically plasmids, viruses, or prophages, that can be carried by MGEs.	-	ARDB, ARG-ANNOT, MEGARes, CARD, NDARO, ResFinder, UniProt, PATRIC	https://bench.cs.vt.edu/argminer/#/home
ShortBRED	Amino acid	FASTA	Facilitates the highly selective characterization of target protein families and AMR genes in shotgun metagomics sequence reading information.	The Huttenhower Lab, Department of Biostatistics, Havard T.H. Chan School of Public Health	ARDB, CARD	http://huttenhower.sph.harvard.edu/shortbred
Comprehensive β-lactamase Molecular Annotation Resource (CBMAR)	Nucleotide, Amino acid	FASTA	The approach groups beta-lactamases into classes and then subsequently subgroups them based on factors such as gene location, phylogenetic relationships, active site, parent fingerprints, mutational characteristics, antibiotic resistance characteristics, blocker vulnerability, and nucleotide diversity.	-	LAHEY, PDB, UniProt, GeneBank, LacED, ARBD,	http://proteininformatics.org/mkumar/lactamasedb/
DeepARG	Nucleotide, Amino acid	FASTA, FASTQ	It makes highly confident predictions about ARGs from quick reads and complete gene length sequences based on metagenomic study of environmental sources.	-	ARDB, CARD, UniProt	https://bench.cs.vt.edu/deeparg
INTEGRALL	Nucleotide	FASTA	gathers and arranges the integrons' data	-	-	https://integrall.bio.ua.ppt/?
Phage Receptor Database (PhReD)	-	FASTQ, SCF	It gathers bacterial receptors that are necessary for phage-host identification and interacting associations.	Bio-Conversion Databank Foundation	-	-
The Actinobacteriophage Database	-	-	It sequences, identities, defines and characterizes Mycobacteriophages.	Department of Biologicals Sciences at the University of Pitsburg	-	https://phagesdb.org/
Beta-lactamase database (BLDB) Lahey Clinic database	Nucleotide	-	It collects architectural and biochemical characteristics, along with sequencing data, for every known BL. It describes the genetic factors that give resistance to betalactam substances.	Part of Bacterial Antimicrobial Resistance Reference Gene Database, NCBI	PDB	http://bldb.eu http://www.lahey.org/Studies/
Antibacterial Biocide and Metal Resistance Genes Database (BacMet)	Nucleotide, Amino acid	FASTA	It aims to target genetic factor that provide resistance to metal-based substances and biocidal compounds.	-	-	http://bacmet.biomedicine.gu.se/

tain predictions owing to the variability from random sampling during classification. Continuously expanding the phage lifestyle database to include more known phage lifestyles will enhance prediction precision and sensitivity [153]. Furthermore, achieving high-precision rates for complex classification schemes, such as host strains and phage families, remains challenging [132]. Addressing these challenges requires refining the methodology and exploring novel classification methods. It is necessary to update the tool with new features and experimentally validated data to improve its accuracy and reliability [154]. The insufficient data on ssDNA and RNA phage is a significant limitation attributed to experimental constraints and resulted in the lack of respective genomic data in databases. Extensive research on phage clades and its diversity can bring much revolution in the collection of genetic information and databases [155; 156]. Furthermore, predicting phage-host relationships in complex microbial environments remains challenging because current methods often demand large amounts of homogeneous data. Developing more data-efficient techniques, such as similarity networks and machine learning, is crucial for accurate predictions [152]. Despite advances in computational methods, identification of phage-host interactions remains a central challenge for effective phage therapy. The application of deep learning techniques has shown promise, but their lack of interpretability hinders user understanding. Improving model interpretability while maintaining predictive performance is necessary for practical implementation. Integrating sequence similarity information and exploring novel features for phage-host interaction pairs could enhance model robustness and accuracy [129]. In conclusion, addressing the limitations and challenges of using machine learning in phage therapy, including dataset bias, outdated databases, model interpretability, and the need for continuous updates, will be pivotal in developing personalized therapies against antibiotic-resistant bacterial infections and in advancing the field of phage therapy.

Acknowledgements

I extend my sincere gratitude to the Central University of Tamil Nadu for its profound support for the successful completion of the manuscript.

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