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Artificial Intelligence in Battle against Antimicrobial Resistance: Opportunities and Challenges

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Abstract—Due to the overuse and abuse of antibiotics, antimicrobial resistance (AMR) poses a serious risk to socioeconomic development and public health. A paradigm shift is required to address this dilemma, and artificial intelligence (AI) appears as a possible remedy. AI, including machine learning (ML) and deep learning (DL), has demonstrated significant promise in several medical research fields, especially in the fight against AMR. Applications of AI in AMR use cutting-edge computational methods to analyze gene expression and whole-genome sequencing data, assisting in discovering infectious disease etiology and disease subtypes. These AI-driven systems have several advantages over more conventional ones, including less need for human involvement, more accuracy, and lower costs. However, they also encounter difficulties, such as inconsistent performance across datasets, with data volume critically influencing model efficacy. The accessibility and expense of high-throughput sequencing data, particularly next-generation sequencing data, also pose challenges to the wider application of AI models for AMR investigation. Despite these difficulties, AI has significant promise in the fight against AMR, and its advantages and disadvantages must be carefully considered in order to build successful tactics for dealing with this urgent worldwide problem. We assess research papers on AMR analysis using AI on various datasets and contrast the effectiveness of various AI models. We thoroughly reviewed the DL models used up to this point in the field of AMR, and we additionally discussed the challenges that come with deploying these approaches. This paper offers a thorough overview of AI's applications in AMR analysis, highlighting both its benefits and drawbacks.

Keywords- Antimicrobial resistance (AMR); Artificial intelligence (AI); Machine learning (ML); Deep learning (DL); Whole-genome sequencing (WGS); Next-generation sequencing (NGS).

I. INTRODUCTION

An urgent threat to treating bacterial diseases is the emergence of antimicrobial resistance (AMR) in bacteria, affecting people and animals used for food production, agriculture, and the environment. Fighting against antibiotic-resistant infections requires accurately identifying strains that are susceptible to or resistant to particular antibiotics. The Centers for Disease Control and Prevention (CDC) estimates that AMR caused 35,900 fatalities in the United States in 2018, and that number will likely rise as the population ages [1], [2]. According to statistics, an astounding 700,000 people die each year around the entire globe [3], [4]. In every region of the world, antibiotic resistance is increasing to dangerously high levels. The emergence and global dissemination of new resistance mechanisms threaten our ability to cure widespread infectious diseases. As antibiotics lose their effectiveness, many illnesses, including UTI, pneumonia, TB, blood poisoning, gonorrhea, and foodborne diseases, are becoming difficult and occasionally impossible to cure [5]. AMR has become a major issue for public health worldwide. Most major pathogenic human and animal pathogens today, including E. coli, Salmonella, Staphylococcus, Pseudomonas, etc., exhibit multi-drug resistance (MDR). Many terms are associated with the AMR analysis; a few key terms commonly used during the discussion of AMR are shown in Figure 1.

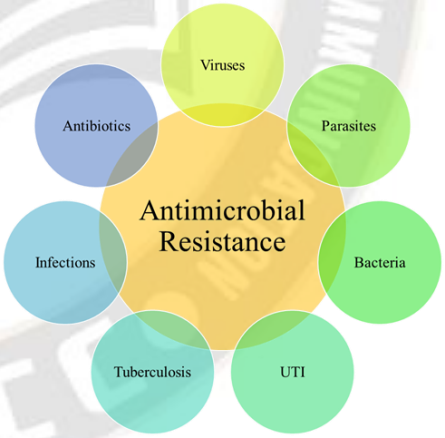

Figure 1. Widely used keywords for AMR study

AMR is one of the top 10 dangers to world health, according to the World Health Organization (WHO). The environment, the security and safety of food and nutrition, economic growth, and racial fairness are all threatened by AMR [6]. The mortality rate due to AMR is also a major global threat. The current mortality rate in AMR is 1.27 million (2019), and according to WHO, the deaths due to AMR in 2050 will be 10 million. The deaths from AMR, cancer, and other diseases, including road accidents, are shown in Figure 2 [3], [7].

Similarly, antimicrobial susceptibility (part of AMR) is often assessed using disc diffusion or minimum inhibitory concentration (MIC) assays. Since numerous distinct genes can

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frequently impart resistance to a particular antimicrobial drug, identifying resistance-specific markers by PCR or microarray mapping is helpful for epidemiological purposes in addition to correlating phenotypic results [8]. Although the introduction of a new era of antibiotics has given patients and medical professionals optimism, progress must still be made in the area of medication research due to bacterial evolution. Furthermore, there is a pressing need for generalizable AMR prevention strategies due to the high cost of new medicines and the lack of accessibility in environments with low resources.

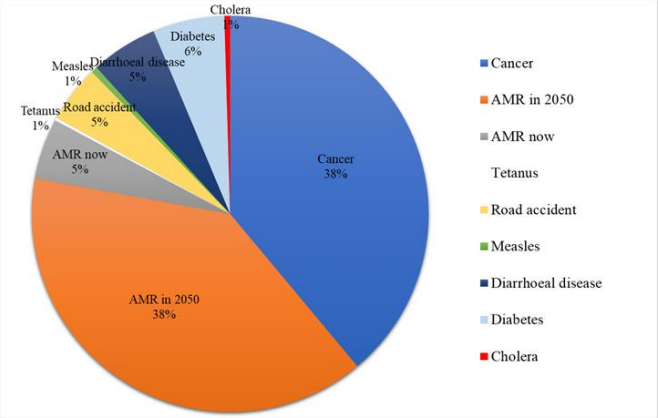

Figure 2. Deaths due to AMR compared to other common deaths in 2019.

New methods for identifying strains that are susceptible to or resistant to specific antibiotics are crucial in the fight against antibiotic-resistant infections since AMR (AMR) is already becoming a major issue in nations worldwide. The expanded form of artificial intelligence (AI) has fundamentally altered research methods across many disciplines in the twenty-first century, including biomedical research. AI's machine learning (ML) and deep learning (DL) subfields have come to light as promising approaches to dealing with this complex phenomenon. In contrast to DL, which operates similarly to ML without any human involvement, ML primarily focuses on designing algorithms that can create predictive models employing training data sets [9].

Over the past ten years, there has been an increase in interest in using ML and DL to improve health care. This can be attributed to the increasing availability of biological and medical data, enormous computing power advances, and significant algorithm development advances.

Identifying and tracing the genes connected to AMR is challenging because it is such a complicated process. The development of an antibiotic-resistant gene involves both biological and environmental factors. AMR analysis has become a focus of research in recent years, and computational intelligence approaches offer sufficient technological breakthroughs to overcome the limitations of the conventional AMR analysis method. Modern computational methods, specifically ML and DL, have demonstrated their potential in several medical fields, including AMR analysis.

This work's main objective includes applying AI in various stages of AMR analysis. The availability of data and traditional tools is limited now-a-days. Thus, the emerging techniques of AI (ML and DL) are explored more in this work in order to find the key solution for AMR analysis. In this work, we took a few selective research articles in our literature that implemented ML or DL as the model to analyze the AMR in infectious diseases with the time span from 2018-2023. The research articles are selected based on ML and DL models used for the analysis of AMR, especially Antimicrobial Susceptibility Testing (AST), Identification of Antibiotic resistance genes (ARGs), SNP and small-indel calling, genetic components of the bacterial strain, the genetic relatedness of various strains.

The structure of the paper and key contribution are:

(i) How AMR is becoming the most powerful health hazard and the role of AMR in infectious disease.
(ii) AI for AMR analysis, what are the possible ways for AI to find the best analysis results for AMR (all the associated analyses of AMR)?
(iii) ML for AMR, the achievements, and limitations.
(iv) DL in AMR analysis and the promising factor associated with DL for AMR analysis.
(v) Critical findings and existing challenges in the application of AI in AMR research.

II. ANTIMICROBIAL RESISTANCE (AMR)

When bacteria, viruses, fungi, parasites, and other microorganisms continue to develop in a way that renders the drugs used to treat the infections, they enhance inefficient ratio, known as AMR [5]. AMR has been more prevalent in bacteria since the 1940s when antibiotics were initially administered. Horizontal gene transfer, most frequently through conjugation, is how AMR originates. It also spreads naturally and through transformation and transduction. Antimicrobials are discovered, isolated, and developed over years of clinical testing before being deemed safe for general use. Infectious diseases continue to severely threaten the public's health despite recent improvements in sanitation, vaccination, and antimicrobial therapy.

According to the World Health Organization (WHO), infectious illnesses remain an issue for all countries, resulting in many fatalities and sizable economic consequences. Infectious illnesses cause most juvenile mortality in lower-income and lower-middle-income nations. Dangerous microorganisms, including viruses, bacteria, protozoa, and fungi, cause infectious diseases. In response to interactions between the host and the pathogen, either a disease develops or the host's immune system wipes out the organism. Antibiotic-resistant pathogenic microorganisms are posing a severe threat to public health worldwide. On the other hand, genes for antibiotic resistance have been found in various bacterial populations across the

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ecosystem, not just in hospitals. In order to circumvent the body's defenses and propagate disease, pathogens modify vital biological processes in host cells. Determining the host genes regulated by the pathogen is crucial for better comprehending the mechanisms behind the emergence of infectious illnesses. The most crucial aspect of the analysis of AMR in this context is the discovery of antibiotic resistance genes (ARGs). Figure 2 shows the detailed phenomenon through which the AMR occurs.

Initially, there are various bacteria present in the human body, out of which few get the resistance to specific antibiotics which are generally used to kill them. The resistance of the bacteria against the antibiotics helps them to grow, and they may be able to transfer the same characteristics to other bacteria, as shown in Figure 3.

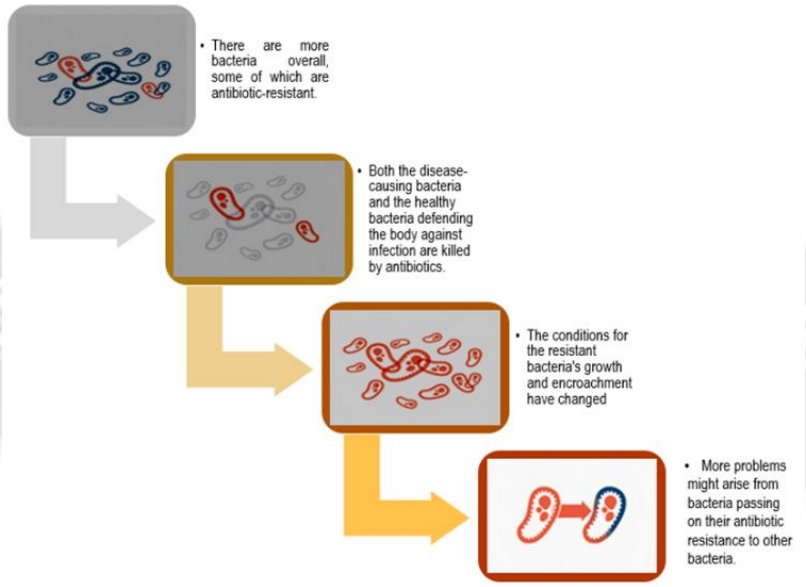

Figure 3. The process of how AMR occurs.

In addition to identifying ARGs, the primary phase of AMR analysis includes antimicrobial susceptibility testing (AST), which helps the diagnosis process become more effective with medical experts' proper medicine prescription.

III. Existing Challenges in AMR Analysis

Analyzing AMR or Antimicrobial susceptibility testing (AST) is a complex and expensive task. The major challenges in AMR analysis are listed below:

A. Data Availability

The entire analysis process depends on the data available for model feeding. In the case of AMR analysis, there is a limitation in the availability of gene expression and sequential data [10]. In addition to this, the data available openly in various repositories are noisy and require more effort for data cleaning and labeling.

B. Limited Tools

Another issue associated with AMR analysis is the biological tools availability. The number of tools available is very few, whereas the cost of the tool is very high. Some open-source tools are available, but the outcome of the analysis is less significant. Most importantly, the tools available for AST are very slow and depend on pure culture data [11]. The statement "There is no single major, or broadly accepted, a technological breakthrough that leads the field of rapid AST platform development" by PIAMR AMR- RDT Working Group on AMR and Rapid Diagnostic Testing is still valid [12] – [14].

C. Trained Manpower

Another challenge linked with the traditional AMR analysis is that it requires trained manpower to conduct the analysis process [15].

D. Cost

The cost associated with the traditional analysis is very large. It includes the data preparation, manpower, and tool costs [16].

E. Significant Result

The analysis result from any traditional biological tool and technique takes a very long time, and the accuracy is less biologically significant [17].

The above challenges in AMR analysis imply that researchers might have overestimated antibiotic resistance's excess costs and attributable mortality due to methodological limitations [12], [16], [18].

IV. How AI meets the challenges

AI has recently shown promise as a solution for controlling antibiotic resistance. For instance, to support clinicians in developing new drugs, boosting antibiotic therapy, and preventing the spread of resistant infections [19].

The AI approach has already accelerated the discovery of novel antimicrobial drugs. Generative models, a subset of next-generation AI, generate hypotheses for the final molecule required for a given new drug. These AI models are capable enough to understand the characteristics of the underlying data and can suggest novel molecules that have not yet been synthesized. They do not merely look for known molecules with relevant attributes, like the capacity to bind to and neutralize a

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virus or a bacterium. Because there are more potentially appropriate molecules than there are atoms in the cosmos, making search activities impractical, this design, as opposed to searching capabilities, is particularly transformational [20].

V. Application of Machine Learning (ML) in AMR

To ensure effective treatment due to the rising prevalence of AMR, regular antibiotic susceptibility testing (AST) is necessary. The gold standard for AST is phenotypic testing. However, bacterial isolation, culture, and subsequent drug exposure often take two days for non-fastidious bacterial infections and up to a few weeks for slow-growing bacteria like Mycobacterium tuberculosis. Despite the well-documented rise of resistance in some infections, such as Neisseria gonorrhoeae, it is not typically carried out. The microbial genotype, rather than the phenotype, is used to evaluate AMR in a different approach that is gaining popularity due to dropping sequencing costs and advancements in analytical techniques [21] – [24]. By avoiding laboratory culture, genotypic methods promise to not only be quicker than phenotypic methods. Still, they may also shed light on the mechanisms underlying AMR, allow for the early detection of transmission events, and provide crucial ancillary information like bacterial strain and virulence factors [25-28].

Several ML models are proposed in the literature to analyze the AMR [14], [16], [18], [19], [21], [23], [26], [27], [28], [29]. These works generally deployed the supervised and unsupervised ML models for the AMR analysis. The main purpose of this work involves the antibiotic resistance gene (ARG), identification, susceptibility gene classification, and infected sample classification. The overall architecture for AMR analysis using ML is shown in Figure 4.

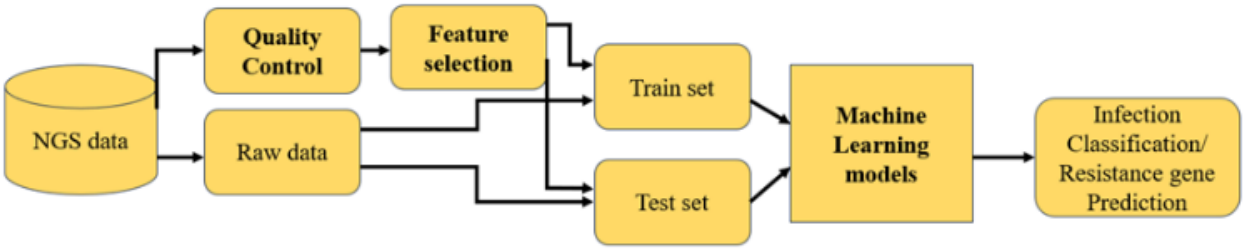

Figure 4. A general blueprint of various ML models for AMR analysis

A. Machine Learning (ML) techniques used with different AMR datasets

ML methods used on AMR datasets can potentially optimize antibiotic prescribing practices, spot new resistance trends, and deepen the understanding of the mechanisms underlying AMR. Numerous ML methods have been used in the analysis of AMR. To identify the genes in various bacteria that are differentially expressed in AMR analysis, ML approaches, including Random Forest (RF), Decision tree (DT), Support vector machine (SVM), and Linear Regression (LR), are among the top few models used in recent years and are shown in Table 1 [16], [23], [26], [27], [29] – [31].

TABLE I. ML techniques used for AMR analysis

Year	Author	Disease/Species	Dataset	Techniques Used	Analysis Type
2018	Danesh et al. [33]	Not specified	WGS	RF, Gradient-boosted decision trees, Deep neural networks, Rule-based baseline.	➢ Without making any assumptions about the underlying genetic pathways, this study tested the capacity of four different machine-learning methods to determine antibiotic resistance from pan-genome data in E. coli. ➢ These experiments showed that although population structure data alone can also be accurately forecasted, supplemental genomic data is generally required. ➢ This is especially useful when a novel strain's genetic relatedness is recognized. Still, the inherited genetic resistance mechanism is obscure or unknown, as is frequently the case with recently introduced antibiotics.
2019	Nguyen et al. [29]	Salmonella	WGS	XGBoost	➢ The model uses XGBoost, an ML-based MIC prediction technique for non-typhoid Salmonella genomes with overall accuracy ranges between 95% and 96% within a 1 to 2-fold dilution factor. ➢ It offers a sample method for MIC prediction using genome sequence data that can be used for additional human or veterinary infections.
2020	Liu et al. [10]	Actinobacillus pleuropneumoniae	WGS	SVM, Set Covering Machine (SCM)	➢ The findings of the correlation between phenotype and the simulated results of the five drugs showed that both SVM and SCM models could significantly distinguish the resistant isolates of the bacteria from the sensitive isolates (p 0.01). They could be used as potential tools in veterinary medicine for clinical diagnosis and AMR monitoring.
2020	Kim et al. [34]	E. cloacae, E. coli, K. pneumoniae and P. aeruginosa	Sequencing	Gradient boosting tree	➢ Can characterize the AMR-related variants at the protein level. ➢ Open reading frames (ORFs) were located and translated into amino acid sequences, and then protein BLAST utilizing the AMR mentioned above protein database was carried out on the sequences. ➢ Using a novel gene ortholog-based variant classification method, this study made a major advance compared to other prediction models like PATRIC, which depended on the adaptive boosting (AdaBoost) algorithm.

2021	Sunuwar and Azad [11]	K. pneumoniae AR_0107 strain	Sequencing	mNB, LDA, SVM, DT, RF, KNN, LR, gNB, ABC, GBC, ET	➢ Discovering the genetic components in bacterial strains that cause antibiotic resistance, especially when those strains do not have known resistance determinants. ➢ One of the main reasons for creating such a pipeline was that the ETC algorithm accurately predicted the resistance trait of over 85% of bacterial isolates that lacked genes known to be responsible for resistance to particular antibiotics.
2022	Han-Yi et al. [14]	Infectious disease (Covid-19)	Clinical data	DT, LR, LASSO, DNN	➢ The precise prediction criteria provided in the DT structures serve as helpful guides for creating efficient clinical strategies because the DT models can perform at par with the most advanced DNN models. ➢ The model findings demonstrated that, in terms of forecasting Influenza-like illness severity, the DT-based prediction models performed at par with the DNN models. Clinicians' decision-making process may be aided by the explicit prediction logic displayed in the DT structures.
2023	Hu et al. [35]	A. baumannii	Metagenomics NGS (mNGS) WGS (CARD and NCBI data base)	Random forest and LASSO regression model	➢ With the aid of reading simulated sequences from clinical isolates, the mNGS-Antibiotic Susceptibility Testing (AST) prediction model was subsequently developed, verified, and upgraded. ➢ For 230 retrospective samples, four mNGS-AST models had positive predictive values (PPVs) more than 0.97 and negative predictive values (NPVs) of 100% for imipenem, 86.67% for ceftazidime, 86.67% for cefepime, and 90.91% for ciprofloxacin. LASSO-DT method correctly identified the antibacterial phenotypes of imipenem, ceftazidime, cefepime, and ciprofloxacin with an accuracy of 97.65%, 96.57%, 97.64%, and 98.36%, respectively. ➢ When 50 prospective samples were tested, the mNGS-AST prediction results matched the phenotypic AST results exactly. The mNGS-based model may be utilized as a quick genotypic AST method to identify A. baumannii, predict resistance to and susceptibility to antibacterials, and apply to other organisms to promote wise antimicrobial use.

ML techniques have been progressively applied to various AMR datasets to address this important global health issue. These methods are essential for foretelling, comprehending, and thwarting AMR across many data types:

1) Genomic Data: ML is widely utilized to analyze genomic data and find genes and mutations linked to antibiotic resistance. Based on genetic data, classification techniques like Support Vector Machines (SVMs) and Random Forests (RF) forecast antibiotic susceptibility.

2) Metagenomic Data: Metagenomic datasets representing microbial communities are analyzed using dimensionality reduction methods like Principal Component Analysis (PCA) or clustering algorithms like k-means to find AMR patterns in complex microbiomes.

3) Clinical Data: Clinical data and patient records are used to comprehend the use of antibiotics and patient outcomes. Clinical narratives are analyzed using Natural Language Processing (NLP) models to extract insights, and patient history is used in logistic regression and decision trees to forecast the risk of AMR.

4) Integration of Multi-Omics Data: DL techniques, such as Multi-Omics Neural Networks, allow for integrating genomes, proteomics, and metabolomics data to provide a comprehensive knowledge of AMR mechanisms.

Additionally, ML approaches make feature selection, model optimization, and result interpretation easier [67] - [69]. These ML techniques make it possible to recognize AMR patterns, predict drug susceptibility, and create tailored interventions in the battle against AMR [32].

B. Issues with Traditional ML Techniques:

In most of the literature, we observed that the performance of various ML models depends on the dataset's quality. Due to the non-linearity in genomics data, the linear ML model performance decreased significantly. The curse of dimensionality is a major issue with various ML models while dealing with the huge unlabeled dataset. It is also observed that data cleaning plays a crucial role in each ML model. However, ML data preprocessing and model training require trained manpower and high computational time, increasing the analysis pipeline's cost [36], [37].

It is also observed from the literature that the dataset (expression and sequencing) available for AMR analysis has very high dimensions. It includes a very small number of samples concerning the huge number of features. Thus, feature extraction is crucial to bring the data to an appropriate standard for various ML analysis models [38]. Manual feature extraction needs trained manpower as well as high computational time.

The major limitations of the ML models for AMR analysis insist the researchers look into various DL models to bridge the gap. The limitations of ML models associated with AMR analysis are [39], [40],

- Data quality is a major issue affecting various ML models' outcomes.
- Few ML models like DT are not sensitive to outlier data.
- The learning rate of SVM is very slow compared to other models.
- The classification accuracy of the linear ML model is very low due to the nonlinearity of AMR data.
- In most cases, the genes selected by the ML model have less percentage of a chance of being an ARG.
- Manual feature extraction burdens the whole analysis process in terms of computational time.

In addition to the problems mentioned above, there are other crucial aspects to consider while implementing ML models for AMR analysis [15, 16, 18, 40, 41],

1) Feature Engineering: Pre-processing, or feature engineering, is the process used in ML to turn raw data into features that may be used to build predictive models. Inaccurate feature extraction may affect the ML model performance. Thus, it requires input from domain experts for its operation in order to extract important and valid features [70], [71].

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2) Performance: High-dimension data processing challenges various ML models. It requires more computational time.

3) Scalability: ML models that perform very well for a specific data set hardly guarantee that accuracy will rise as data set size increases (addition of new data to the existing data set).

VI. Application of Deep Learning (DL) in AMR

Recent breakthroughs in AI (AI) have significantly increased performance in data-driven applications across various fields, particularly in the areas of deep neural networks and DL. In recent years, DL technologies have been extensively used in clinical and public health studies. At the same time, it might take medical professionals months or even years to collect adequate expertise to establish a decision-making process; DL algorithms successfully analyze relationships among various complicated variables in clinical datasets and make correct predictions [18], [42] – [44]. However, other DL algorithms have many unique properties and design objectives. In the past few years, the rising success of DL has motivated many biomedical researchers to implement various DL models in the research field of AMR.

DL models can analyze genomics and metagenomics data to identify resistant genes and predict their potential impact on antimicrobial treatment. Additionally, they can help in the discovery of novel antimicrobial compounds. DL models play a crucial role in analyzing AMR (AMR) by leveraging their capabilities in handling complex biological data. They can help predict and identify AMR mechanisms, enabling faster and more accurate antibiotic susceptibility testing. The basic pipeline for DL models in AMR analysis and identifying resistance genes is shown in Figure 5.

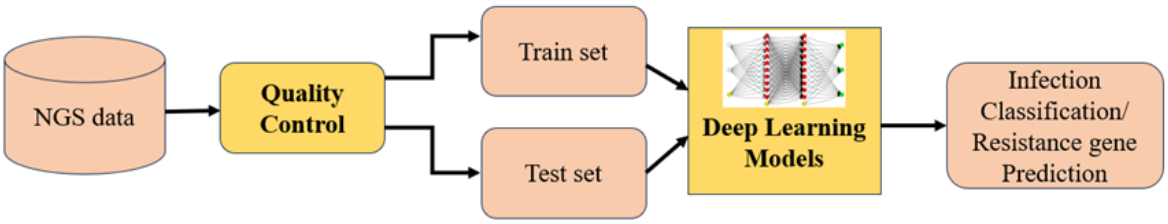

Figure 5. Pipeline of DL models in AMR analysis

The DL models proposed for AMR analysis can be of different stages, but the above DL pipeline has mainly the following phases;

1) Quality Control and Sequence Alignment: Quality control is first applied to NGS data to remove low-quality reads and sequences. In order to accurately complete the downstream analysis, sequence alignment is then carried out to map the reads to a reference genome or database.

2) Train-Test Split: A training set and a testing set are created from the dataset. DL models are trained using the training set, and model performance is evaluated using the testing set.

3) DL Models: The chosen characteristics are used to train DL models like deep neural networks (DNN), convolutional neural networks (CNNs), and recurrent neural networks (RNNs). These models discover intricate patterns and relationships that point to antibiotic resistance in the data.

4) Classification and Prediction: The classification and prediction of antibiotic resistance genes found in the NGS data are then performed using the trained DL models. Based on learned patterns, they can recognize specific gene variants or forecast the likelihood of resistance.

5) Model Evaluation: Data splitting, accuracy, sensitivity, specificity, the Receiver Operating Characteristic (ROC) Curve, cross-validation, domain-specific considerations, the importance of features, external validation, and interpretability are all factors that must be taken into account when evaluating DL models for antibiotic resistance gene identification.

6) Biological Annotation: The final findings shed light on whether antibiotic-resistance genes are present or absent in the NGS data. The biological validation boosts the adaptability of the DL model [45], [46]. These forecasts can help medical professionals track AMR trends and make educated decisions about the use of antibiotics.

Several research publications are available for AMR analysis, particularly for employing DL to find resistant and susceptible genes. In this section, we chose a few articles based on DL models for the AMR analysis. The decision was based on the DL models, the identification of the resistance genes, the identification of the susceptible genes, the prediction of the peptides, and the ARG annotation. The research in the last five years (2018-2022) carried out in the domain of AMR in infectious diseases where the DL techniques are implemented with the top most model accuracy and significant results are listed in Table 2.

TABLE II. DL techniques used for AMR analysis

Year	Author	Disease/Species	Dataset	Techniques Used	Analysis Type
2018	Poplin et al. [47]	Not specified	WGS	DeepVariant	➢ SNP and small-indel calling. ➢ By discovering statistical correlations between images of read pileups surrounding suspected variants and accurate genotype calls, it has been proposed that a deep convolutional neural network may detect genetic variation in aligned NGS read data.

2018	Chen et al. [48]	Tuberculosis	Sequencing Data	DNN	➢ This study's main objective was to use genomic data to build an extremely accurate model of drug resistance. ➢ This work uses data from whole genome sequencing and proposes a new DL architecture to detect MTB isolate resistance to 10 anti-tuberculosis medicines. ➢ On a sizable, aggregated TB dataset, the wide and deep neural network performed at the cutting edge, proving the effectiveness of DL as a diagnostic tool for MTB treatment resistance.
2020	Yan et al. [49]	Candida glabrata	Sequencing	Deep-AmPEP30	➢ Short Antimicrobial Peptides Prediction ➢ Using a deep convolutional neural network (CNN) with a restricted AAC, Deep-AmPEP30 predicts short-length AMP based on the reduced dataset (RAAC). ➢ To improve prediction accuracy for short functional AMPs, it combines the strength of CNN with various RAAC feature types.
2020	Thrift et al. [50]	P. aeruginosa and E. coli	Sequencing	SVM, DNN, CNN	➢ Rapid Antimicrobial Susceptibility Testing ➢ In SERS data, 10 min after antibiotic exposure, deep neural network models can distinguish with greater than 99% accuracy between treated and untreated cells in Escherichia coli and Pseudomonas aeruginosa's antibiotic responses.
2020	Brown et al. [51]	Staphylococcus aureus	WGS	LR, ANN	➢ Antimicrobial Susceptibility Testing ➢ The proposed system shows it can perform AST much more quickly than the industry-standard incubation procedure for 18–24 hr., accompanied by visual inspection.
2021	Jang et al. [52]	Not Specified	Environmental data	LSTM, LSTM-CNN hybrid model, and input attention (IA)-LSTM	➢ Identification of ARGs ➢ A traditional long short-term memory (LSTM), an LSTM-convolutional neural network (CNN) hybrid model, and input attention (IA)-LSTM are used to forecast the recurrence of ARGs. ➢ In contrast, the accuracy of the LSTM-CNN was 2–6 times better than that of the traditional L STM and IA–L STM. ➢ The IA-LSTM model outperformed LSTM-CNN regarding overall performance when predicting the simultaneous occurrence of all ARGs.
2021	Li et al. [53]	Pseudomonas aeruginosa, E. coli	Raw sequence encoding	Hierarchical Multi-task DL	➢ ARG annotation. ➢ First of its type DL model for ARGs annotation with model accuracy of 99%.
2022	Kuang et al. [54]	Mycobacterium tuberculosis (MTB)	10,575 MTB isolates' WGS (WGS) data was taken from the Sequence Read Archive (SRA) database.	Logistic Regression, RF, 1D-CNN	➢ Using three alternative ML algorithms and 24 binary classifiers across the eight (first- and second-line) medicines, the model was fine-tuned using tenfold cross-validation: RF, LR, and specialized 1D CNN. ➢ Compared to the cutting-edge rule-based method prediction, the proposed best ML classifiers significantly increased the F1-score for all four first-line medications and one second-line drug, according to our tenfold cross-validation. Mykrobe forecasting. ➢ Despite needing more intensive computing resources during training, the proposed 1D CNN architecture only slightly outperformed the conventional ML methods LR and RF; hence, feature selection was carried out in this study to lower computing resource requirements before training 1D CNN models. ➢ Proposed ML models may classify MTB resistance to the eight anti-TB medications with pretty high accuracy using only the computational power of a typical laptop, given the accessibility of WGS data and lineage information for MTB.
2023	Lu et al. [55]	methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE)	This study examined 130 Gram-positive cocci that were gathered from 2011 to 2021 in a clinical microbiology lab.	Long Short-Term Memory, DT., SVM, KNN, LR	➢ The authors constructed a binary LSTM classifier to distinguish between resistant bacteria and nonresistant organisms based on the susceptibility profiles towards commonly used antibiotics in order to develop a quick culture-free antibiotic susceptibility test utilizing Raman spectroscopy. ➢ The LSTM model outperformed the four ML algorithms in bacterial discrimination studies regarding accuracy in identifying E. faecalis and S. capitis (98.8% and 92.4%, respectively). ➢ According to the proposed LSTM model, the power of the LSTM-based Raman system was not great at the species level, as seen by the 12.7% of E. faecium's Raman spectra that were incorrectly classified as E. faecalis.
2023	Pei et al. [56]	ARG identification	CARD (v 3.1.2), AMRFinder, ResFinder, Megares, deepARG, and HMD-ARG.	ARGNet	➢ The proposed ARGNet is a deep neural network that combines an autoencoder model for unsupervised learning to identify ARGs and a multiclass classification convolutional neural network that does not rely on sequence alignment to classify ARGs. ➢ ARGNet is a deep neural network with two stages. An autoencoder model was created initially to identify ARGs from the input genomic sequence(s). A multi-class CNN was proposed in the second step to predict the categories of ARGs using genomic sequences classified as ARGs in the autoencoder model. ➢ ARGNet may be used for target and metagenomic sequencing because it takes amino acid and nucleotide sequences of various lengths, ranging from short (30–50 aa; 100–150 nt) sequences to full-length proteins or genes. In most application scenarios, ARGNet performed better than other DL models, such as DeepARG and HMD-ARG, particularly in measuring prediction consistency with phylogenetic trees and quasi-negative tests.

DL has been used mostly for learning challenges with big datasets. Various DL models based on the DNN, LSTM, RNN, and CNN are implemented successfully to analyze the AMR. The DL concept is inherited from the human neuron learning

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system. Simulating the neurons in the human nervous system gave rise to the concepts of DL and neural networks. These artificial neural networks (ANNs) process inputs quickly and output results using a complicated network of neurons (hidden layers). The input nodes take in inputs and look for nonlinear input-output relationships to determine the best possible solution to the problem at hand [43]. The literature shows that the DL models based on CNN are performing well on WGS data [42[, [44]. Convolutional neural networks (CNNs) and recurrent neural networks (RNNs) are two more categories of ANNs based on their design. The CNNs and RNNs are a subclass of ANN, with each node extracting specific information from the input vector, down-sampling the parameters, and integrating these features into a fully connected layer in the succeeding layers [42]. In this section, we describe a few DL models applied for various stages of AMR analysis.

A DL method was proposed by Veltri D. et al. (2018), which uses the concepts of deep neural network (DNN) for better antimicrobial peptides (AMPs) prediction [29]. The DNN model presented in this paper uses Conv and long short-term memory (LSTM) layers to record position-in-variant patterns along an amino acid sequence. In this work, the sequence dataset is used, which is in FASTA format. Due to the lack of a significant public archive of peptides that have been experimentally demonstrated to have AMR action, there is an issue with the availability of the required dataset for analysis. However, the authors use a strategy similar to prior work [30], [38], constructing a negative database of non-AMP sequences. The DL model's main advantage is that it also detects indirect AMP signatures more closely related to their structural characteristics than directly assessing their antibacterial activity.

Jang J. et al. (2021) proposed a DL model for identifying antibiotic resistance genes (ARGs). The model is hybrid in nature and uses conventional long short-term memory (LSTM), LSTM convolutional neural network (CNN) hybrid model, and input attention (IA)-LSTM. Ten categories of environmental variables were collected at 30-minute intervals, and intensity parameters for four primary ARG types were used to create the models. The purpose of this study is to forecast the occurrence of ARGs, which are primarily found around the coastline following rainfall. When LSTM and CNN sequentially converged, their performance in predicting single ARGs outperformed that of traditional LSTM. However, in terms of predicting single ARGs, LSTM-CNN outperformed IA-LSTM.

Rapid antimicrobial susceptibility testing (AST) is a crucial technique for reducing the overuse of potent, broad-spectrum antibiotics, which fuels the spread of multidrug-resistant bacteria [42]. When utilizing sensor surfaces with carefully controlled nanogap spacing and chemistry, authors (William J. T. et al., 2020) have shown that the reaction of P. aeruginosa and E. coli bacterial communities to antibiotics is quickly identified in SERS spectrum data. Various models like DNN, CNN, and MLP are evaluated on the SERS data, and it is observed that the performance of CNN and DNN models is impressive in terms of prediction accuracy. Due to under-fitting, as there are only two features, MLP without transfer learning does not produce effective predictions from the variational auto-encoder (VAE, a supervised ML model encoding HD data into LD data) space.

Yu Li et al., 2021, proposed a complete hierarchical multi-task DL system for ARG annotation (HMD-ARG). In this study, HMD-ARG, which is based on DL, is used to annotate ARGs in detail from three key perspectives: the class of resistant antibiotics, the mechanism of resistance, and gene mobility. When given raw sequence encoding as input, HMD-ARG can determine multiple ARG properties simultaneously without querying through existing sequence databases, such as whether the input protein sequence is an ARG and, if so, what antibiotic family it is resistant to, what resistant mechanism the ARG uses, and whether the ARG is intrinsic or acquired. HMD-ARG predicts the subclass of beta-lactamase to which the ARG is resistant if the expected antibiotic family is beta-lactamase [61].

The above are some of the DL models that are applied to various parts of AMR analysis, and almost all the models have proven their potential for prediction, classification, and annotation phases of the analysis module. It is observed that the DL models outperformed the traditional ML models in multiple cases, including model accuracy, computational time, and cost. The key achievements of DL are discussed in section 7.

VII. ACHIEVEMENTS OF DL

A. Maximize classification accuracy

Maximizing classification accuracy is crucial for long-term, in-depth studies of genotypic alterations in connection to phenotype. When stable mutations are taken into account, this method is very valuable. It would make it possible to identify a genotypic fingerprint of a certain kind of AMR—a distinctive genetic string indicating a phenotype. This knowledge could be applied to creating a biological test (a device that provides rapid diagnosis in the field) [24], [62] – [64].

B. Selection of cumulative features

`The selection of features offers vital insight into the biological mechanisms that bestow AMR. It's still unclear how to cluster traits most effectively, a challenge that could provide biologists with crucial information. High levels of redundancy exist in the variables that make up the DL model of the issue, and grouping these redundant data into meaningful clusters or blocks yields a clear indication of the location of the mutation that causes AMR.

C. Maximize Model accuracy

Antibiotics are known to impact common genes and gene activities in bacteria, but little is known about how the AMR genes are spread among various bacteria. It is crucial to train the model with the data availability (unstructured data) to classify the AMR genes more accurately. However, from the literature, it is found that most of the DL models, especially the CNNs, outperform the traditional ML models regarding model accuracy [66].

VIII. CRITICAL OBSERVATIONS/ CHALLENGES FOR AI

The critical observations from the literature can be listed as:

- AI plays a crucial role in the battle against AMR by identifying the genes with antibiotic resistance, making drug therapy more convenient.
- Patients and society should want antibiotic resistance to be prevented, or else it may be the number one health hazard within a few decades
- As antibiotics used to treat them lose their efficacy, an increasing number of infections, including UTI, salmonellosis, gonorrhea, pneumonia, and tuberculosis, are becoming more challenging to treat.
- In the future (by the year 2050), it is estimated that 10 million people may die due to AMR [15].

- Methodological difficulties and problems with (i) estimating the overall number of infections, (ii) identification of ARGs, (iii) survival rate prediction, and (iv) antimicrobial susceptibility testing need to be fixed.
- Although we have seen in the literature how the Ml and DL models offered functioned accurately for a certain dataset and efficiently solved the problem, obtaining the adaptability of a model will remain a difficult challenge because of the wide range of data that is available today [66].

Most of the research is moving towards AI-centric; it plays an important role in almost all research areas. The following few key points need to be addressed with proper solutions,

- Researchers are exposed to several AI techniques in various biomedical research fields, including AMR analysis. In the current scenario, AI faces challenges regarding huge computational power, time, and cost requirements.
- These parameters related to AI model implementations must be taken care of to meet a more portable, robust, and sustainable research outcome.
- Most importantly, a well-operated quality control pipeline, as well as a robust AI model, need to be developed to deal with NGS data, which is noisy and complex in nature.

IX. Conclusion

AMR will be resolved by creating new antibiotics or other alternative therapies. Much research is currently being done to create an innovative antibiotic replacement to combat resistance. Anyone of any age in any nation can become susceptible to antibiotic resistance. Worldwide, the death rate from infections from resistant organisms has sharply increased among immunocompromised patients and newborns. Because prevention is always preferable to therapy, it is everyone's responsibility to take preventive and literate action while taking any antibiotics. AI has many applications for analyzing biomedical data and has proven its potential as a role model for disease prediction and drug design. It is found that ML and DL models have produced innovative analysis tools, and these technologies have significantly decreased the time and expense needed for the analysis of AMR. These models have now made way for more complex DL models, such as CNN, because of increased data accessibility and computing capacity. Many different DL models, including CNNs and other architectures, have been developed in the field of genomics and have implications for AMR analysis. With the rise of AI, the biomedical engineering community may be exploring even deeper into AMR analysis and lead the way for individualized, precise healthcare that is available to everyone on earth.

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