



Journal of Research in Allied Life Sciences

Contents available at: <https://www.swamivivekanandauniversity.ac.in/jrals/>

Role of artificial intelligence and machine learning in combating MDR

Sayan Mondal¹, Debanjan Roy², Samudra Pal¹, Priyanka Pal¹, Debjit De¹, Rupesh Dutta Banik^{2*}

¹Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, India

²Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, India

*Corresponding author mail: rupesduttabanik99@gmail.com

Abstract

Multi drug resistance (MDR) refers to a situation in which various organisms, including viruses, fungi, parasites, and particularly bacteria, exhibit immunity to the specific drugs intended to eliminate them. The inappropriate and excessive use of drugs in animals, humans, agriculture, and the environment has hastened the emergence and proliferation of multidrug resistance. MDR pathogens develop when antibiotic treatment is interrupted or when antibiotics are discontinued before completing the full clinical course or trial for the disease in question. During this time, bacteria, viruses, and other parasites are altering their responses to drugs intended to eliminate them, undergoing structural modifications to develop resistance against these medications or antibiotics. MDR represents a significant global health issue that requires immediate attention through practical solutions. In 2019, it is estimated that there were 4.95 million fatalities globally due to bacterial multidrug resistance, with 1.27 million deaths directly linked to this issue. The emergence of drug-resistant microorganisms poses a significant challenge for modern medicine. Consequently, algorithms for machine learning and artificial intelligence have emerged as powerful tools in the battle against drug resistance. This review aims to explore the role of advanced computational techniques in managing multidrug-resistant pathogens, focusing on identifying pathogens, understanding resistance patterns,

Keywords: Multi-drug resistance (MDR), pathogens, pathogen identification, antibiotics, machine learning (ML), artificial intelligence (AI), bacterial MDR.

1. Introduction

Microorganisms possess the capability to survive without being eliminated or having their growth inhibited by antimicrobial agents, a phenomenon referred to as antimicrobial resistance (AMR). AMR occurs when bacteria undergo changes, making previously effective medications for infections caused by those bacteria ineffective. The excessive use of antibiotics fosters the proliferation of superbugs, which encompass bacterial strains that exhibit extensive drug resistance (XDR) and multidrug resistance (MDR). The emergence of these superbugs has led to repeated rises in mortality and illness, presenting a significant challenge to global public health [1]. This growing crisis threatens to undermine decades of medical progress, as common infections become increasingly difficult to treat and routine surgical procedures carry heightened risks of post-operative complications. The global spread of resistant pathogens has been accelerated by factors including international travel, inadequate infection control measures in healthcare settings, and the widespread use of antibiotics in agriculture and animal husbandry.

In 2019, there were approximately 5 million deaths worldwide attributed to antimicrobial resistance, with bacterial antimicrobial resistance responsible for 1.27 million of those fatalities [2]. Western Sub-Saharan Africa experienced the highest all-age mortality rate attributed to resistance, recording 27.3 deaths per 100,000 individuals [2]. These alarming statistics underscore the disproportionate burden borne by low- and middle-income countries, where limited access to diagnostic tools, quality-assured medicines, and infection prevention resources exacerbate the problem. The economic implications are equally concerning, with AMR imposing substantial healthcare costs through prolonged hospital stays, more expensive treatments, and decreased workforce productivity. Furthermore, the geographic variation in resistance patterns reflects disparities in healthcare infrastructure, antibiotic stewardship programs, and public health surveillance systems, highlighting the need for globally coordinated efforts to address this multifaceted challenge.

Accurate and timely bacterial identification, along with antibiotic susceptibility testing, is crucial for enhancing patient outcomes in the management of infectious illnesses. Traditional diagnostic methods, while reliable, often require extended incubation periods ranging from 24 to 72 hours, during which empirical broad-spectrum antibiotic therapy may be administered, potentially contributing to further resistance development. The delay in obtaining definitive diagnostic results can lead to inappropriate antibiotic selection, inadequate dosing, or unnecessarily prolonged treatment durations. Moreover, conventional culture-based methods may fail to detect fastidious organisms or those present in polymicrobial infections, limiting their clinical utility. The advancements in AI have significantly enhanced diagnostic accuracy through the analysis of extensive datasets, enabling the identification of trends and the formulation of predictions [3]. AI algorithms, particularly those incorporating machine learning capabilities, provide quicker and more precise diagnoses compared to conventional methods [3,4]. These technologies can process complex microbiological data, including genomic sequences, mass spectrometry profiles, and digital microscopy images, to rapidly identify pathogens and predict their antibiotic susceptibility patterns with unprecedented accuracy.

The integration of AI and ML in healthcare encompasses real-time monitoring, decision support systems, and medication development [5–7], facilitating proactive interventions and focused antimicrobial stewardship. Machine learning models can analyze electronic health records to identify patients at high risk of developing resistant infections, enabling targeted preventive measures and optimized treatment protocols. Clinical decision support systems powered by AI can provide evidence-based recommendations for antibiotic selection, dosing adjustments based on patient-specific factors, and alerts for potential drug interactions or adverse effects. These intelligent systems continuously learn from new data, refining their predictions and recommendations to reflect emerging resistance patterns and clinical outcomes. Furthermore, AI-driven surveillance platforms can detect outbreaks of resistant organisms in real-time, enabling rapid public health responses and infection control interventions to prevent further transmission.

The application of AI and machine learning is transforming the field of drug discovery, particularly in the area of antimicrobial peptides, which exhibit significant antibacterial properties [8,9]. Traditional drug development processes are time-consuming and costly, often taking over a decade and billions of dollars to bring a new antimicrobial agent to market. AI algorithms can dramatically accelerate this process by screening vast chemical libraries, predicting molecular interactions, and identifying promising candidate compounds with optimal pharmacological properties. The use of computational modeling and predictive analytics can enhance the efficiency of AMP identification and optimization, leading to the development of novel treatments for drug-resistant infections [10]. Deep learning approaches can predict the three-dimensional structures of antimicrobial peptides, assess their potential toxicity, and optimize their stability and bioavailability. These computational tools enable researchers to explore chemical space more comprehensively and design molecules with tailored properties to overcome specific resistance mechanisms.

Advancements in AI and machine learning, combined with clinical experience, hold the promise of mitigating the effects of antimicrobial resistance and enhancing patient outcomes [6,7]. The synergy between artificial intelligence capabilities and human expertise creates a powerful framework for addressing the AMR crisis through improved diagnostics, optimized treatment strategies, and accelerated development of novel antimicrobial agents, ultimately contributing to better healthcare delivery and global health security.

ML approaches for combating MDR

Machine learning offers various strategies and applications to address antimicrobial resistance (**Fig. 1**) (**Table 1**).

Through structure-based design, it is possible to pinpoint new therapeutic targets, evaluate compound libraries, and enhance lead candidates for antibacterial properties. Machine learning algorithms applied to antimicrobial datasets forecast bioactivity, pharmacokinetic properties, and safety profiles of novel drug candidates, accelerating the drug development process and lowering costs in comparison to conventional approaches [11-13].

Supervised learning, a widely utilized method in machine learning, involves training models on labeled datasets such as microbial genomes or patient records to forecast antibiotic susceptibility or treatment responses (Fig. 1). In order to forecast the sensitivity of *Streptococcus pneumoniae* to β -lactam antibiotics, a correlation was established between penicillin-binding protein (PBP) sequences and minimum inhibitory concentration (MIC) values utilizing labeled data. Sequences in the NCBI database lacking MIC values were utilized as unlabeled data. This method revealed the connection among the resistance phenotypes, serotypes, and sequence types of *S. pneumoniae* [14]. Utilizing supervised machine learning, genetic traits associated with antibiotic susceptibility in *Escherichia coli* were identified across various sequence types (ST). Genetic markers provide valuable insights into the dissemination of STs within clonal complexes characterized by elevated transmission rates [15]. López-Kleine et al. identified 12 potential virulence factors in *Streptococcus pyogenes* using an objective approach, free from subjective filters or specific biological processes. These genes present significant potential for subsequent biological validation and the advancement of medication development [16]. Unsupervised learning examines unlabeled data to uncover concealed patterns or clusters within microbial populations. This contributes to the comprehension of resistance mechanisms and the identification of novel resistance genes [17, 18] (Fig. 1). Clustering algorithms, including K-means Clustering, classify bacteria according to their resistance profiles or genetic characteristics [19]. A recent study categorized β -lactamases into resistant and wild type, highlighting distinct clusters with specific strain characteristics [20]. K-means clustering is capable of identifying emerging resistance clusters or outbreaks, facilitating timely interventions to curb the spread of antimicrobial-resistant diseases. A study revealed that *Salmonella enterica* can demonstrate resistance to both metals and antibiotics [21].

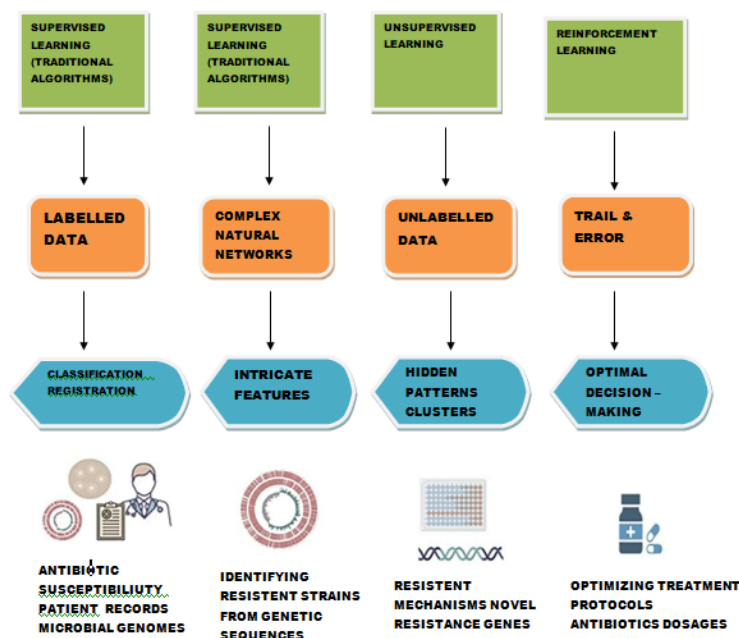


Fig. 1: ML methods and applications in the fight against antimicrobial resistance.

Deep learning algorithms, such as CNNs and RNNs [22], extract complex information from genomic sequences to identify resistant strains and predict resistance mechanisms (Fig. 1). CNNs accurately classify bacterial strains as resistant or susceptible based on genomic sequences, whereas RNNs predict antimicrobial susceptibility based on

treatment history or microbial evolution over time. CNN models can discover functional genetic differences, provide physiological explanations, and have clinical uses [22]. A CNN was used to predict *Mycobacterium* TB resistance to 13 medications by evaluating 18 previously unassociated genomic regions [23]. Deep learning techniques such as generative adversarial networks (GANs) have shown encouraging outcomes in the analysis of antimicrobial peptides [24]. GANs can synthesize anti-bacterial peptides by modifying the probability distribution of generated sequences. Tucs et al. [25] created six peptide variants, one of which demonstrated substantial antibacterial action against *Escherichia coli*.

Reinforcement learning (RL) optimizes antibiotic treatment regimens and drug combinations against resistance through trial-and-error feedback [26] (**Fig. 1**). RL techniques can maximize tasks with minimal understanding of system dynamics, such as evolutionary simulations of bacterial populations. Using *E. coli* as a model, a study found that each genotype in a population corresponded to a certain fitness landscape in simulations of evolution. The scientists found that increased genome size did not limit the decline in population fitness caused by medication cycles [27]. The RL method has been shown to provide reasonable antibiotic treatment recommendations for sepsis that align with clinical experience [28].

ML approaches provide distinct advantages in combating AMR, including detecting genetic markers, forecasting resistance trends, and optimizing treatment options in real-time. Methods for creating new antimicrobial drugs are tailored to the specific problem and factors, leading to increased efficiency and precision [29, 30].

AI-powered AMP discovery

AMPs are small peptides that exhibit a wide range of structural diversity and possess antimicrobial properties. Amino acid residues in their sequence can range from a few to dozens, with or without modifications, and they operate through various mechanisms [31]. AMPs have the ability to destabilize membranes that are negatively charged and zwitterionic, leading to the permeabilization of the membrane. This memorandum of agreement highlights antimicrobial peptides as an innovative category of prospective antibacterial agents, complicating the emergence of resistance development [31, 32].

AMP extraction from existing sequence space

The advancement of novel antimicrobial peptides (AMPs) has been greatly supported by AI. Platforms such as Deep-AmPEP30, IAMPE, and DeepACP have significantly advanced the processes of peptide discovery and synthesis. Databases of antimicrobial peptides derived from genetic sequences, like the AMPer database, are curated for the purpose of designing innovative antimicrobial peptides. Advanced strategies for AMP design involve modifying existing AMPs, creating protein epitope molecules (PEMs), and utilizing biophysically motivated modeling studies. Natural Language Processing (NLP) has been utilized to comprehend AMP activity and to create AMPs. A study integrating machine learning with extensive meta datasets, including omics data, demonstrated the potential of this combination to enhance AMP prediction and pinpoint active therapeutic molecules. This study illustrates the significant potential of employing computational techniques to identify active therapeutic molecules from various omics data sources [33].

AMP harvesting from both extinct and simulated sequences

Microbes aren't the sole contributors to AMP mining. Maasch et al. [34] developed panCleave, a random forest model designed to predict proteome-wide cleavage sites for the identification of AMPs in both extinct and extant human

proteomes, utilizing the concept of “molecular de-extinction.” The AMPs identified through panCleave exhibited the ability to permeabilize membranes and showed effectiveness against *A. baumannii* in murine skin abscess and thigh infection models, highlighting the potential of the paleoproteome as a source for therapeutic candidates [34]. The process of AMP mining from current proteomes, irrespective of their origin, is fundamentally biased towards the sequence space of the proteome. Huang et al. [35] developed a sequential model ensemble pipeline that incorporates machine learning modules, employing a coarse-to-fine design strategy to explore the complete virtual library of peptides with lengths varying from six to nine amino acids. The tree lead hexapeptides from this pipeline exhibit considerable efficacy against multidrug-resistant clinical isolates in both in vitro and in vivo models, highlighting the substantial potential of the sequential model ensemble pipeline for objective peptide screening tasks [35].

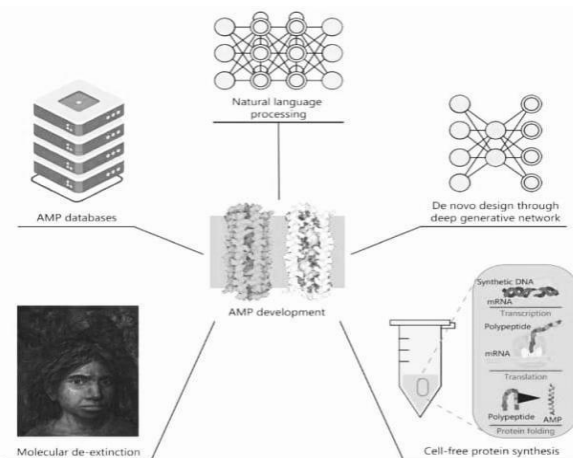


Fig 2: The application of artificial intelligence in the synthesis of antimicrobial peptides. The databases of AMPs have established a strong basis for training models using AI, including natural language processing and deep generative networks. AI models can be employed to explore a vast array of protein sequence space, encompassing the extinct human proteome, while high-throughput methods such as cell-free synthesis greatly enhance the speed of validating potential antimicrobial peptides.

De novo design of AMP

Antimicrobial peptides (AMPs) have been developed using deep generative neural networks [36]. International Business Machines Corporation employed two types of variational inference autoencoders, specifically the conventional Variational Autoencoder (VAE) and the Wasserstein Autoencoder, to create two novel and highly effective AMPs. This study addresses the peptide generation problem by conceptualizing it as a challenge in density modeling. The model efficiently samples the peptide sequence space, highlighting regions with high probability density. The density estimation technique has been improved to assign high likelihoods to identified trends while penalizing random, insignificant sequences [37]. The team employed 1.7 million peptide sequences sourced from the UniProt database for algorithm training. The frequency of interactions between positive residues and lipid bilayers is a predictor of antimicrobial activity [130]. After comprehensive in silico screening, 20 peptide sequences were selected. The samples were tested in wet laboratories to assess their antibacterial activity against different bacterial strains, including Gram-positive *S. aureus* and Gram-negative *E. coli*. Within 48 days, two novel antimicrobial peptides demonstrating broad antibacterial activity were identified [37]. Szymczak et al. [38] presented HydrAMP, a conditional VAE that demonstrates proficiency in analog and unconstrained AMP synthesis, functioning as a deep generative model for AMP design. The antimicrobial peptides exhibited effectiveness against five bacterial strains, including both Gram-positive and Gram-negative types, as well as strains resistant to antibiotics. HydrAMP signifies a significant development in the synthesis of high-potency antimicrobial peptides designed to combat antibiotic resistance [38].

Deep generative neural networks applied to de novo AMP design produce a significant number of candidate peptides for in vitro validation. DNA-based bioproduction significantly improves the efficiency of peptide screening compared to conventional chemical synthesis techniques. However, methods that depend on cells encounter limitations due to the toxic effects of peptides on bacteria [39]. Pandi et al. [39] utilized a cell-free protein synthesis pipeline to evaluate 500 de novo generated antimicrobial peptides using deep learning methodologies. Six of these AMPs demonstrated broad-spectrum activity against multidrug-resistant bacterial isolates, underscoring the potential of DL-based design.

The role of AI in the advancement of phage therapy

Alternative techniques, such as phage therapy, have played a crucial role in addressing antibiotic resistance, in conjunction with small-molecule medicines and AMPs [40, 41]. Bacteriophages, the natural predators of bacteria, have co-evolved with their hosts for 3.8 billion years and are essential to the human microbiome [42]. Phage treatment offers a higher level of specificity compared to broad-spectrum antibiotics, thereby minimizing disturbances to the microbiota and helping to prevent the spread of antibiotic-induced antimicrobial resistance. A number of investigations have demonstrated clinical success [45-48]. This section delineates phage therapy into four distinct steps: identifying phages, predicting phage virion proteins (PVPs), analyzing phage lifestyle, and exploring phage-host interactions. The discussion encompasses the application of artificial intelligence throughout each phase.

Conclusion

The One Health concept recognizes the interrelationship between human, animal, and environmental health, especially regarding antimicrobial resistance (AMR). The application of antibiotics in humans, animals, and agricultural practices can lead to the development and dissemination of resistant diseases. The use of antimicrobials in cattle for preventive measures and growth promotion has sparked significant concerns regarding the potential for antibiotic resistance in humans. This phenomenon can be attributed to the widespread occurrence of zoonotic diseases among animal populations. Integrating AI and machine learning into One Health initiatives can facilitate data-driven collaboration across various sectors, enabling efficient prediction, monitoring, and control of antimicrobial resistance threats.

The introduction of the exposome by Christopher Wild in 2005 is essential for comprehending the transmission of AMR. This category encompasses all environmental exposures, such as the use of antibiotics in healthcare, agriculture, and the broader environment. The analysis of exposome-related data through AI/ML techniques uncovers patterns that connect environmental variables to antimicrobial resistance. These models leverage clinical records, environmental monitoring, and genetic sequencing data to identify risk factors and forecast future trends in antimicrobial resistance. The One Health paradigm enhances risk assessment and environmental management through the integration of big data analysis, machine learning algorithms, and geographic information systems.

The integration of diverse data types, including genomic, phenotypic, clinical, and epidemiologic information, can enhance predictive models for AMR through the application of AI and ML techniques. These tools facilitate early detection of increasing resistance, allowing for timely intervention. The automation of the search for resistance mechanisms and medicines through AI/ML streamlines the process, reducing the need for manual testing and decreasing the likelihood of human error. Advanced algorithms and simulations enhance our capacity to combat AMR by pinpointing novel pharmacological and therapeutic targets. Furthermore, the application of AI and machine learning facilitates tailored antibiotic therapies by utilizing data from both patients and pathogens. The integration of various fields, including computer science, biology, and medicine, is enhanced by these technologies, leading to innovative and thorough approaches to addressing antibiotic resistance issues.

Acknowledgement

I would like to express my special thanks of gratitude to the higher dignitaries of Swami Vivekananda University for allowing me to carry out the study.

Reference

- Almutairy, B. (2024). Extensively and multidrug-resistant bacterial strains: case studies of antibiotics resistance. *Frontiers in Microbiology*, 15, 1381511.
- Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., ... & Tasak, N. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325), 629-655.
- De la Lastra, J. M. P., Wardell, S. J., Pal, T., de la Fuente-Nunez, C., & Pletzer, D. (2024). From Data to Decisions: Leveraging Artificial Intelligence and Machine Learning in Combating Antimicrobial Resistance—a Comprehensive Review. *Journal of medical systems*, 48(1), 71.
- Ahmed, Z., Mohamed, K., Zeeshan, S., & Dong, X. (2020). Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. *Database*, 2020, baaa010.
- Bhattamisra, S. K., Banerjee, P., Gupta, P., Mayuren, J., Patra, S., & Candasamy, M. (2023). Artificial intelligence in pharmaceutical and healthcare research. *Big Data and Cognitive Computing*, 7(1), 10.
- He, S., Leanse, L. G., & Feng, Y. (2021). Artificial intelligence and machine learning assisted drug delivery for effective treatment of infectious diseases. *Advanced drug delivery reviews*, 178, 113922.
- Theodosiou, A. A., & Read, R. C. (2023). Artificial intelligence, machine learning and deep learning: Potential resources for the infection clinician. *Journal of Infection*.
- Wan, F., Wong, F., Collins, J. J., & de la Fuente-Nunez, C. (2024). Machine learning for antimicrobial peptide identification and design. *Nature Reviews Bioengineering*, 2(5), 392-407.
- Yan, J., Cai, J., Zhang, B., Wang, Y., Wong, D. F., & Siu, S. W. (2022). Recent progress in the discovery and design of antimicrobial peptides using traditional machine learning and deep learning. *Antibiotics*, 11(10), 1451.
- Agüero-Chapin, G., Galpert-Cañizares, D., Domínguez-Pérez, D., Marrero-Ponce, Y., Pérez-Machado, G., Teixeira, M., & Antunes, A. (2022). Emerging computational approaches for antimicrobial peptide discovery. *Antibiotics*, 11(7), 936.
- Anahtar, M. N., Yang, J. H., & Kanjilal, S. (2021). Applications of machine learning to the problem of antimicrobial resistance: an emerging model for translational research. *Journal of clinical microbiology*, 59(7), 10-1128.
- Jiang, Y., Luo, J., Huang, D., Liu, Y., & Li, D. D. (2022). Machine learning advances in microbiology: A review of methods and applications. *Frontiers in Microbiology*, 13, 925454.
- Wong, F., de la Fuente-Nunez, C., & Collins, J. J. (2023). Leveraging artificial intelligence in the fight against infectious diseases. *Science*, 381(6654), 164-170.
- Zhang, C., Ju, Y., Tang, N., Li, Y., Zhang, G., Song, Y., ... & Feng, J. (2020). Systematic analysis of supervised machine learning as an effective approach to predicate β -lactam resistance phenotype in *Streptococcus pneumoniae*. *Briefings in Bioinformatics*, 21(4), 1347-1355.
- Goodacre, R., Rooney, P. J., & Kell, D. B. (1998, April). Rapid analysis of microbial systems using vibrational spectroscopy and supervised learning methods: application to the discrimination between methicillin-resistant and methicillin-susceptible *Staphy*. In *Infrared Spectroscopy: New Tool in Medicine* (Vol. 3257, pp. 220-229). SPIE.
- López-Kleine, L., Torres-Avilés, F., Tejedor, F. H., & Gordillo, L. A. (2012). Virulence factor prediction in *Streptococcus pyogenes* using classification and clustering based on microarray data. *Applied microbiology and biotechnology*, 93, 2091-2098.
- Miraftabzadeh, S. M., Colombo, C. G., Longo, M., & Foiadelli, F. (2023). K-means and alternative clustering methods in modern power systems. *IEEE Access*.
- Aytan-Aktug, D. (2021). Machine learning of antimicrobial resistance.
- Tang, J. W., Liu, Q. H., Yin, X. C., Pan, Y. C., Wen, P. B., Liu, X., ... & Wang, L. (2021). Comparative analysis of machine learning algorithms on surface enhanced Raman spectra of clinical *Staphylococcus* species. *Frontiers in microbiology*, 12, 696921.
- Rath, S. L., Mohapatra, S., & Gayathri, V. (2024). Identifying Antibiotic-Resistant Mutants in β -Lactamases for Class

- A and Class B Using Unsupervised Machine Learning. *Engineering Proceedings*, 59(1), 146.
- Fenske, G. J., & Scaria, J. (2021). Analysis of 56,348 genomes identifies the relationship between antibiotic and metal resistance and the spread of multidrug-resistant non-typhoidal *Salmonella*. *Microorganisms*, 9(7), 1468.
- Popa, S. L., Pop, C., Dita, M. O., Brata, V. D., Bolchis, R., Czako, Z., ... & Padureanu, A. M. (2022). Deep learning and antibiotic resistance. *Antibiotics*, 11(11), 1674.
- Green, A. G., Yoon, C. H., Chen, M. L., Ektefaie, Y., Fina, M., Freschi, L., ... & Farhat, M. (2022). A convolutional neural network highlights mutations relevant to antimicrobial resistance in *Mycobacterium tuberculosis*. *Nature communications*, 13(1), 3817.
- Lin, T. T., Yang, L. Y., Wang, C. T., Lai, G. W., Ko, C. F., Shih, Y. H., ... & Lin, C. Y. (2021). Discovering novel antimicrobial peptides in generative adversarial network. *BioRxiv*, 2021-11.
- Tucs, A., Tran, D. P., Yumoto, A., Ito, Y., Uzawa, T., & Tsuda, K. (2020). Generating ampicillin-level antimicrobial peptides with activity-aware generative adversarial networks. *ACS omega*, 5(36), 22847-22851.
- Rawson, T. M., Wilson, R. C., O'Hare, D., Herrero, P., Kambugu, A., Lamorde, M., ... & Holmes, A. H. (2021). Optimizing antimicrobial use: challenges, advances and opportunities. *Nature Reviews Microbiology*, 19(12), 747-758.
- Weaver, D. T., King, E. S., Maltas, J., & Scott, J. G. (2024). Reinforcement learning informs optimal treatment strategies to limit antibiotic resistance. *Proceedings of the National Academy of Sciences*, 121(16), e2303165121.
- Wang, Y., Liu, A., Yang, J., Wang, L., Xiong, N., Cheng, Y., & Wu, Q. (2024). Clinical knowledge-guided deep reinforcement learning for sepsis antibiotic dosing recommendations. *Artificial Intelligence in Medicine*, 150, 102811.
- Asnicar, F., Thomas, A. M., Passerini, A., Waldron, L., & Segata, N. (2024). Machine learning for microbiologists. *Nature Reviews Microbiology*, 22(4), 191-205.
- Liu, G. Y., Yu, D., Fan, M. M., Zhang, X., Jin, Z. Y., Tang, C., & Liu, X. F. (2024). Antimicrobial resistance crisis: could artificial intelligence be the solution?. *Military Medical Research*, 11(1), 7.
- Zhang, Q. Y., Yan, Z. B., Meng, Y. M., Hong, X. Y., Shao, G., Ma, J. J., ... & Fu, C. Y. (2021). Antimicrobial peptides: mechanism of action, activity and clinical potential. *Military Medical Research*, 8, 1-25.
- Fjell, C. D., Hiss, J. A., Hancock, R. E., & Schneider, G. (2012). Designing antimicrobial peptides: form follows function. *Nature reviews Drug discovery*, 11(1), 37-51.
- Liu, G. Y., Yu, D., Fan, M. M., Zhang, X., Jin, Z. Y., Tang, C., & Liu, X. F. (2024). Antimicrobial resistance crisis: could artificial intelligence be the solution?. *Military Medical Research*, 11(1), 7.
- Maasch, J. R., Torres, M. D., Melo, M. C., & de la Fuente-Nunez, C. (2023). Molecular de-extinction of ancient antimicrobial peptides enabled by machine learning. *Cell Host & Microbe*, 31(8), 1260-1274.
- Huang, J., Xu, Y., Xue, Y., Huang, Y., Li, X., Chen, X., ... & Ji, J. (2023). Identification of potent antimicrobial peptides via a machine-learning pipeline that mines the entire space of peptide sequences. *Nature Biomedical Engineering*, 7(6), 797-810.
- Blaschke, T., Olivecrona, M., Engkvist, O., Bajorath, J., & Chen, H. (2018). Application of generative autoencoder in de novo molecular design. *Molecular informatics*, 37(1-2), 1700123.
- Das, P., Sercu, T., Wadhawan, K., Padhi, I., Gehrmann, S., Cipcigan, F., ... & Mojsilovic, A. (2021). Accelerated antimicrobial discovery via deep generative models and molecular dynamics simulations. *Nature Biomedical Engineering*, 5(6), 613-623.
- Szymczak, P., Możejko, M., Grzegorzek, T., Jurczak, R., Bauer, M., Neubauer, D., ... & Szczurek, E. (2023). Discovering highly potent antimicrobial peptides with deep generative model HydrAMP. *Nature communications*, 14(1), 1453.
- Pandi, A., Adam, D., Zare, A., Trinh, V. T., Schaefer, S. L., Burt, M., ... & Erb, T. J. (2023). Cell-free biosynthesis combined with deep learning accelerates de novo-development of antimicrobial peptides. *Nature Communications*, 14(1), 7197.
- Gordillo Altamirano, F. L., & Barr, J. J. (2019). Phage therapy in the postantibiotic era. *Clinical microbiology reviews*, 32(2), 10-1128.
- Strathdee, S. A., Hatfull, G. F., Mutalik, V. K., & Schooley, R. T. (2023). Phage therapy: From biological mechanisms

to future directions. *Cell*, 186(1), 17-31.

Shkoporov, A. N., Clooney, A. G., Sutton, T. D., Ryan, F. J., Daly, K. M., Nolan, J. A., ... & Hill, C. (2019). The human gut virome is highly diverse, stable, and individual specific. *Cell host & microbe*, 26(4), 527-541.

Fishbein, S. R., Mahmud, B., & Dantas, G. (2023). Antibiotic perturbations to the gut microbiome. *Nature Reviews Microbiology*, 21(12), 772-788.

Liu, G., Thomsen, L. E., & Olsen, J. E. (2022). Antimicrobial-induced horizontal transfer of antimicrobial resistance genes in bacteria: A mini-review. *Journal of Antimicrobial Chemotherapy*, 77(3), 556-567.

Dedrick, R. M., Guerrero-Bustamante, C. A., Garlena, R. A., Russell, D. A., Ford, K., Harris, K., ... & Spencer, H. (2019). Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. *Nature medicine*, 25(5), 730-733.

Leitner, L., Ujmajuridze, A., Chanishvili, N., Goderdzishvili, M., Chkonia, I., Rigvava, S., ... & Kessler, T. M. (2021). Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. *The Lancet Infectious Diseases*, 21(3), 427-436.

Uyttendaele, S., Chen, B., Onsea, J., Ruythooren, F., Debaveye, Y., Devolder, D., ... & Metsemakers, W. J. (2022). Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review. *The Lancet Infectious Diseases*, 22(8), e208-e220.

Onallah, H., Hazan, R., Nir-Paz, R., Brownstein, M. J., Fackler, J. R., Hopkins, R., ... & Saharia, K. (2023). Refractory *Pseudomonas aeruginosa* infections treated with phage PASA16: A compassionate use case series. *Med*, 4(9), 600-61.