


A New Hope in the Fight Against Antimicrobial Resistance with Artificial Intelligence

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Abstract: Recent years have witnessed the rise of artificial intelligence (AI) in antimicrobial resistance (AMR) management, implying a positive signal in the fight against antibiotic-resistant microbes. The impact of AI starts with data collection and preparation for deploying AI-driven systems, which can lay the foundation for some effective infection control strategies. Primary applications of AI include identifying potential antimicrobial molecules, rapidly testing antimicrobial susceptibility, and optimizing antibiotic combinations. Aside from their outstanding effectiveness, these applications also express high potential in narrowing the burden gap of AMR among different settings around the world. Despite these benefits, the interpretability of AI-based systems or models remains vague. Attempts to address this issue had led to two novel explanation techniques, but none have shown enough robustness or comprehensiveness to be widely applied in AI and AMR control. A multidisciplinary collaboration between the medical field and advanced technology is therefore needed to partially manage this situation and improve the AI systems' performance and their effectiveness against drug-resistant pathogens, in addition to multiple equity actions for mitigating the failure risks of AI due to a global-scale equity gap.

Keywords: antibiotic, antimicrobial resistance, infection, artificial intelligence

Introduction

In recent years, following the development of technology, artificial intelligence (AI) has shown remarkable effectiveness in controlling antimicrobial resistance (AMR),¹ one of the top ten global public health threats that humans have to face in this century.² This implies a positive signal in our fight against drug-resistant bacteria, right amid this global crisis. Although the research and deployment of AI-based applications might require modern technology, the resultant products, algorithms, or procedures are more accessible to the end-users, even in poor quality healthcare settings, thanks to AI's automation and efficiency, therefore, confirming its influence and equity role in AMR control.

Implementation of Healthcare and Antimicrobial Data

First, the role of AI starts with one of its unique features: data. Clinical data, aside from being a critical element in AI,³ can also give us a good track of the situation inside a healthcare setting, especially about the epidemiology and characteristics of the pathogens. Coincidentally, and luckily, before deploying any AI-driven systems, the data collection process itself has set the foundation for other fields and disciplines in health sciences by providing a large amount of information and insights, which could promote other potential infection control strategies.

One of the most prominent secondary applications of AI-deploying data is to support antimicrobial stewardship program (AMS), an approach to optimize antibiotic use, improve patient outcomes, and mitigate AMR, healthcare-associated infections, and healthcare costs.⁴ Healthcare and microbial data can be applied in many different ways to maximize the effects of AMS, specifically in countries that lack access to effective antimicrobial treatments. With a vast amount of daily healthcare data, not only can we efficiently deploy AI-based systems but also AMS to more

comprehensive and more profound extents, which could possibly predict the epidemiology of nosocomial pathogens. This would allow us to prevent many multidrug-resistant bacterial infections, lowering antibiotic use and eventually limiting the prevalence and spread of AMR.⁵

Identification of Potential Antimicrobial Molecules

Second—and probably one of AI's most well-known applications—AI-based systems can assist critically in selecting and identifying molecular structures, proving their important role in drug discovery and, in this case, antibiotic discovery. In recent decades, private sectors have shown fewer preferences in developing new antibiotics due to the lack of economic incentives,⁶ making the threat of antimicrobial resistance more intimidating in the upcoming years. With assistance from AI models, scientists can now shorten this process with an increasing accuracy rate of lead compound identification at a much lower screening cost. Initially, Stokes et al had discovered halicin, a broad-spectrum antibacterial molecule that is highly effective against various drug-resistant strains, using a subfield of AI.⁶ Without using any pharmacological assumptions of the classical way, AI models can learn new structural patterns to identify new agents with new mechanisms of action, allowing us to regain the upper hand over bacteria.

Following this, recently, International Business Machines (IBM) Corporation Research team has created an AI system capable of accelerating the discovery of new, functional, and non-toxic antimicrobial molecules.⁷ Noticeably, IBM researchers have proposed Conditional Latent (attribute) Space Sampling (CLaSS), a simple, fast, and generic approach to the generation of targeted molecules.⁷ With additional benefits in repurposability, CLaSS also expresses a high potential in designing broad-spectrum antimicrobial agents.⁷ As a result, within 48 days, this system had identified, synthesized, and tested two highly potent antimicrobial peptides against various Gram-positive and Gram-negative pathogens, without increasing the risk of triggering resistance in *Escherichia coli*.⁷ Given these achievements, this AI-driven approach is highly expected to pull pharmaceutical corporations back into the fight against multidrug-resistant pathogens.

Rapid Antimicrobial Susceptibility Testing

AI algorithms are gradually assisting physicians to quickly identify resistant strains through either standard Kirby-Bauer disk diffusion⁸ or whole-genome sequencing antimicrobial susceptibility testing (AST).¹ Though the former method is simpler and easier to implement, it usually takes about a day or more to generate the results, which considerably extends the empirical antibiotic regimen and could increase the risk of treatment failure due to ineffective therapy or the threat of antibiotic overuse-induced resistance. Several improvements using AI algorithms have been made, reducing the waiting period down to less than three hours (flow-cytometer AST) or even to only 30 minutes (infrared spectrometer).¹

Meanwhile, the whole-genome sequencing method is more efficient in identifying the resistance mechanism but requires big genome datasets and is more challenging to implement. To simplify this process, AI models have been applied, and eventually, have yielded more precise and easily interpretable results.¹ Therefore, both of these approaches are very promising in orienting the appropriate therapy timely as well as limiting the irrational use of antibiotics. Noteworthy, with the ability to transfer learning algorithms,⁹ these AI-based systems can be deployed and implemented with a meager cost at almost any laboratory traditionally running this type of susceptibility testing, thus lowering the inequity gap among healthcare settings.

Optimization of Combining Antibiotics

AI models, in the past few years, have shown their critical role in optimizing drug combinations.¹ The idea of combining therapy had long been used before, but not until the bloom of AI has it found the way to reach its full potential. Clinical practices have proved the enhanced effectiveness and resistance control of antibiotic combinations. Nevertheless, the strategies used in combining these agents have been limited by many factors, primarily due to the drug's toxicity, pharmacokinetics (PK), pharmacodynamics (PD), etc.

Surprisingly, with the assistance of AI, Smith et al have optimized the in vitro combination of meropenem and polymyxin B against the carbapenem-resistant *Acinetobacter baumannii*,¹⁰ showing another prospect of AI in this fight.

More critically, they also developed a genetic algorithm to identify optimal dosing strategies for both antibiotics,¹⁰ laying the foundation for optimizing AI-led combination therapy.¹¹

While only dosage was focused in Smith et al's work, there remain other aspects that could be utilized, such as choice of antibiotics, timing of administration, and synergistic effects with other medications. Furthermore, modeling will be essential to integrate PK/PD knowledge in complex simulations of *in silico*.¹² Information from these optimizations can then be transformed into knowledge, and eventually, guidelines, which can be practiced almost everywhere, especially in low- and middle-income countries, where the accessibility to new treatments is usually limited. With this simple and easily implemented approach, low-resource settings can also get access to economical and effective therapies for antibiotic-resistant microbes. The sooner we can fully optimize strategies of drug combinations, the better and more ethical we can control antimicrobial resistance and its burdens.

Interpretability of AI-Based Systems

Despite the outstanding benefits, in biomedical or healthcare fields, the applicability of these AI-based systems depends greatly on how well they can be interpreted in common sense.¹³ Nevertheless, while we can build or construct optimized AI networks with impressive accuracy, many interpretative mechanisms are still beyond our understandings. The quest for techniques or methods to address this issue is probably one of the most important steps to unlock the full potential of AI, address relevant ethical issues, and narrow the inequity gap among different settings when coping with AMR.

Certain attempts have been made to answer this question, but so far, none have shown to be completely robust. Fortunately, in 2017, Montavon et al proposed a tutorial covering an entry set of methods for interpreting and understanding a subfield of AI.¹³ Although no other similar efforts in AMR have been recorded since then, this is still a high potential approach for us to move one step closer to the victory against multidrug-resistant pathogens.

A more optimistic signal was recorded when Ribeiro et al proposed a novel technique for AI-based classifier models called Local Interpretable Model-Agnostic Explanations (LIME), which can explain the predictions of any complex model by locally approximating with an interpretable one.¹⁴ Following the assistance of LIME, we can now decide with confidence whether one should trust a computational prediction, choose what models/algorithms to implement, improve unreliable classification, or point out the reasons for untrustworthy classifiers.¹⁴ The only limitation here is that it may not always be applicable to other types of AI systems except for classification models. Despite that, these two novel techniques may have sowed the seeds for more advanced and robust methods in the future.

Collaboration Between Medicine and Advanced Technology

While various applications of AI in antimicrobial resistance control have been proposed and investigated, and certain achievements have been accomplished, yet there are still many things for us to improve and optimize in this long fight against rapidly mutating bacteria. Most importantly, there is a critical need for a harmonized combination of traditional medicine and advanced technology to implement our new tools in a standard and interpretable manner. Without the guidance and orientation of experienced clinicians, AI is nothing more but computer algorithms. By properly combining humans' clinical knowledge and experience with the processing ability of computer systems, we can improve our AI systems' performance and their effectiveness in AMR control.

Inequity Challenges

In spite of these advantages and opportunities that AI can provide amid the fight against AMR, certain inequity challenges are still ahead. AI and its associated components have long been considered as the "playground" for big corporations and wealthy countries with resources and technology. If low- and middle-income countries cannot get access to new efficient AI-based products due to high charges from these actors, sooner or later, microbes would find a way to evolve and take down our efforts. Therefore, we need multiple global equity actions to address the threats from AMR, from promoting and investing in AI research in low-resource settings to providing foreign aids and necessary supports, including new antibiotics or AST systems.

Conclusion

A multidisciplinary approach combining clinical medicine and AI could be the solution to the threats and burdens of this global AMR crisis. With appropriate measures and policies, we surely have higher chances to secure ourselves and, for later generations, a much brighter future.

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Disclosure

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