

# A novel frontier in computational approaches and personalised medicine interventions to overcome antibiotic resistance



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## 1. Introduction

The growing increase in antibiotic resistance is a health catastrophe that poses a direct challenge to global health. Programmes like Global Antimicrobial Resistance Surveillance System under WHO (World Health Organization), Global Health Security Agenda (GHSA), and Antimicrobial Resistance Action Package (GHSA Action Package Prevent-1) were created to address this problem (1). Antibiotics, sometimes called "miracle drugs," have prevented the needless deaths of many people from bacterial infections or diseases. The evolution of antibiotic-resistant bacteria, however, has been fuelled by the extensive and often improper use of antibiotics in human and animal healthcare and in agriculture (2). Some bacterial strains have developed resistance to antibiotics, making these life-saving medications useless against bacterial infections that were formerly readily treated (1). Bacteria are incredible survivors because of their innate capacity to adjust to new conditions, including exposure to antibiotics (3). Due to the high chances of survival by antibiotic resistant bacteria, genetic mutations that support antibiotic resistance have spread widely across bacterial populations. Furthermore, bacterial species may rapidly exchange resistance genes with one another through horizontal gene transfer mechanisms such as plasmid transfer. Determining how antibiotic resistance occurs is crucial for devising solutions to this significant global challenge (4). Although conventional methods have provided useful insights, they are inadequate to fully grasp the genetic and molecular complexities of antibiotic resistance. Consequently, computational methods have shown great promise as a paradigm shift in the battle against antibiotic resistance. Computational techniques provide better in-depth knowledge of the genetic basis of resistance and novel ways to design innovative therapies through the use of contemporary computers, data analysis, and sophisticated algorithms. Artificial intelligence (AI) may speed up the preclinical stage of drug development by generating numerous novel chemical

suggestions using algorithms developed with machine learning (ML) methods (5). Hence, the integration of computational methods and precision medicine has the potential to revolutionize how we tackle antibiotic resistance and safeguard the efficacy of antibiotics for future generations.

## **2. Use of computational approaches in antibiotic resistance**

The complex problems presented by antibiotic resistance have made computational methods significant. Researchers may analyse massive datasets, including genomic information, proteomic interactions, and microbiome data, to better understand the genetic basis of resistance mechanisms (6). Bacterial evolution to acquire resistance to antibiotics could be better understood by the combination of computational biology, bioinformatics, and artificial intelligence (7). In 2009, a team employed ML algorithms in conjunction with the quantitative structure-activity relationship (QSAR) approach to find novel antimicrobial peptides with antibacterial capabilities. With the ARGs (antibiotic resistant genes) data obtained from the COALA database (collection of all antibiotic resistance gene databases), an algorithm was developed to predict the class of antibiotics like sulphonamides, tetracyclines, beta-lactams, etc. using a DL (deep learning) derived ensemble method. This would cut down on the failure rate associated with empirical antibiotic treatment and save time compared to traditional antibiotic susceptibility testing (AST) (8).

## **3. Precision medicine**

Precision medicine has shown promise as a personalised and targeted strategy to combating the complicated issue of antibiotic resistance. The use of genetic testing to detect genetic markers linked with antibiotic resistance is a crucial component of precision medicine in the context of antibiotic resistance (9). The mechanisms of resistance can be analysed by studying the genetic composition of patients and that of the invading bacteria to help healthcare professionals in choosing the best antibiotic therapy and steer clear of drugs that the bacteria have developed resistance to. For instance, a patient presenting with a severe bacterial infection may undergo genetic testing to determine whether the infecting bacteria harbour specific resistance genes (10). Precision medicine is a patient-centred and data-driven healthcare system that employs a wide range of techniques to provide personalised treatment plans. Some forms of precision medicine are listed in table 1 with the computational tools that can be utilised for respective study.

### **3.1 Genetic based precision medicine**

Precision medicine based on genetic analysis seeks to determine how specific genetic compositions of patients affect their responses to antibiotics. Genes involved in drug metabolism, transport, and target interactions may be identified via genetic testing and the impact of variations in such genes on antibiotics can be studied. Antibiotic effectiveness and adverse effects might be affected by unique genetic makeup of an individual (11). Deciphering the huge amount of genetic data produced by genome sequencing relies heavily on computational methods. In order to determine which antibiotics should be used, sophisticated algorithms can detect important genetic variations and evaluate their clinical importance. Antibiotic resistance genes may be a target for novel drug discovery, and population-level investigations can reveal genetic patterns linked to antibiotic resistance (12).

Table 1. Computational tools for study of precision medicine to overcome antibiotic resistance

S. No	Type of precision medicine technique	Computational tools				
		Use	Tool name	Link		
1.	Genetic-based precision medicine	Genomic sequencing and variant calling	Burrows-Wheeler Aligner	<a href="https://bio-bwa.sourceforge.net/">https://bio-bwa.sourceforge.net/</a>		
			Bowtie	<a href="https://bowtie-bio.sourceforge.net/index.shtml">https://bowtie-bio.sourceforge.net/index.shtml</a>		
			GATK (Genome analysis toolkit)	<a href="https://gatk.broadinstitute.org/hc/en-us">https://gatk.broadinstitute.org/hc/en-us</a>		
			Samtools	<a href="http://www.htslib.org/">http://www.htslib.org/</a>		
		Variant annotation and interpretation	ANNOVAR	<a href="https://annovar.openbioinformatics.org/en/latest/">https://annovar.openbioinformatics.org/en/latest/</a>		
			SnEff	<a href="http://pcingola.github.io/SnpEff/">http://pcingola.github.io/SnpEff/</a>		
			Variant Effect Predictor (VEP)	<a href="https://asia.ensembl.org/info/docs/tools/vep/index.html">https://asia.ensembl.org/info/docs/tools/vep/index.html</a>		
		Population-level genetic analysis	PLINK	<a href="https://zzz.bwh.harvard.edu/plink/">https://zzz.bwh.harvard.edu/plink/</a>		
			Genome-wide Complex Trait Analysis (GCTA)	<a href="https://yanglab.westlake.edu.cn/software/gcta/">https://yanglab.westlake.edu.cn/software/gcta/</a>		
		2.	Microbiome-based precision medicine	Microbiome data analysis	QIIME2	<a href="https://qiime2.org/">https://qiime2.org/</a>
MetaPhlan 4.0	<a href="https://huttenhower.sph.harvard.edu/metaphlan/">https://huttenhower.sph.harvard.edu/metaphlan/</a>					
HUMAnN 3.0 (HMP Unified Metabolic Analysis Network)	<a href="https://huttenhower.sph.harvard.edu/humann/">https://huttenhower.sph.harvard.edu/humann/</a>					
Functional analysis of microbiome data	PICRUSt 2.0 (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States)			<a href="https://huttenhower.sph.harvard.edu/picrust/">https://huttenhower.sph.harvard.edu/picrust/</a>		
	Tax4Fun			<a href="http://tax4fun.gobics.de/">http://tax4fun.gobics.de/</a>		
Microbial co-occurrence network analysis	CoNet			<a href="http://raeslab.org/software/conet.html">http://raeslab.org/software/conet.html</a>		
	SparCC			<a href="https://web.mit.edu/almlab/sparcc.html">https://web.mit.edu/almlab/sparcc.html</a>		
	WGCNA			<a href="https://bio.tools/wgcna">https://bio.tools/wgcna</a>		
3.	Pharmacogenomics			Pharmacogenetic analysis	CPIC	<a href="https://cpic.pgx.org/">https://cpic.pgx.org/</a>
					PharmGKB	<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>
		PharmVar	<a href="https://www.pharmvar.org/">https://www.pharmvar.org/</a>			
		Genetic variant-drug interaction prediction	PolyPhen-2	<a href="http://genetics.bwh.harvard.edu/pph2/">http://genetics.bwh.harvard.edu/pph2/</a>		
			SIFT	<a href="https://sift.bii.a-star.edu.sg/">https://sift.bii.a-star.edu.sg/</a>		

Table 1. Computational tools for study of precision medicine to overcome antibiotic resistance (continued)

4.	Proteomics and biomarker-based precision medicine	Proteomics data analysis	<a href="https://www.maxquant.org/">MaxQuant</a>	<a href="https://www.maxquant.org/">https://www.maxquant.org/</a>
			Proteome Discoverer	<a href="https://www.thermofisher.com/in/en/home/industrial/mass-spectrometry/liquid-chromatography-mass-spectrometry-lc-ms/lc-ms-software/multi-omics-data-analysis/proteome-discoverer-software.html">https://www.thermofisher.com/in/en/home/industrial/mass-spectrometry/liquid-chromatography-mass-spectrometry-lc-ms/lc-ms-software/multi-omics-data-analysis/proteome-discoverer-software.html</a>
			Skyline	<a href="https://skyline.ms/project/home/software/Skyline/begin.view">https://skyline.ms/project/home/software/Skyline/begin.view</a>
		Pathway and functional enrichment analysis	DAVID	<a href="https://david.ncifcrf.gov/">https://david.ncifcrf.gov/</a>
			Panther	<a href="https://pantherdb.org/">https://pantherdb.org/</a>
			<a href="https://reactome.org/">Reactome</a>	<a href="https://reactome.org/">https://reactome.org/</a>
		Biomarker discovery and validation	Lasso regression	<a href="https://www.xlstat.com/en/solutions/features/lasso-regression">https://www.xlstat.com/en/solutions/features/lasso-regression</a>
			ROC analysis	<a href="https://www.rocplot.org/">https://www.rocplot.org/</a>
5.	Systems biology and network pharmacology	Network analysis	<a href="https://cytoscape.org/">Cytoscape</a>	<a href="https://cytoscape.org/">https://cytoscape.org/</a>
			<a href="https://networkx.org/">NetworkX</a>	<a href="https://networkx.org/">https://networkx.org/</a>
			Gephi	<a href="https://gephi.org/">https://gephi.org/</a>
		Network-based drug target prediction Or Network-based Inference of Drug Similarity (NIDS)	<a href="https://netcap.io/">NetCBP</a>	<a href="https://netcap.io/">https://netcap.io/</a>
			<a href="https://services.healthtech.dtu.dk/services/NetPhos-3.1/">NetPhos</a>	<a href="https://services.healthtech.dtu.dk/services/NetPhos-3.1/">https://services.healthtech.dtu.dk/services/NetPhos-3.1/</a>
		Pathway and network analysis	STRING	<a href="https://string-db.org/">https://string-db.org/</a>
			Ingenuity Pathway Analysis (IPA)	<a href="https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-ipa/">https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-ipa/</a>
<a href="https://reactome.org/">Reactome</a>	<a href="https://reactome.org/">https://reactome.org/</a>			

### 3.2 Microbiome based precision medicine

The billions of bacteria found in and on the human body, collectively known as the human microbiome, have a major impact on our health and wellbeing. Antibiotic resistance may be fostered in part by bacteria in the gut that either directly harbour resistance genes or aid in the transfer of those genes to pathogenic bacteria. Large amounts of microbiome data can be analysed to find microbial fingerprints linked to antibiotic resistance through computational methods. Integration of microbiome data with patient-specific information, such as antibiotic exposure history and health status, could be implemented for the purpose of microbiome alteration and antibiotic medication optimisation. The use of antibiotics may alter the makeup

of the microbiome, and computer models can predict how this will affect the likelihood of resistance development, allowing for better informed treatment decisions (13).

### **3.3 Pharmacogenomics**

The field of pharmacogenomics studies the impact of individual differences in response to medications like antibiotics. Pharmacogenomics aids in antibiotics selection for individual patients by analysing changes in drug-metabolizing enzymes and drug transporters. By taking these precautions, harmful medication interactions may be avoided and treatment results can be improved (14). The field of pharmacogenomics uses computational algorithms to analyse genetic data in order to predict the pharmacological reaction of an individual. The effects of numerous genetic variations on drug metabolism may be evaluated using machine learning models, allowing for fine-tuned dosing for best therapeutic results (15). Pharmacogenomics is helpful in the setting of antibiotic resistance because it allows for the identification of people at greater risk of acquiring resistance and guides the selection of medicines that are less likely to induce resistance.

### **3.4 Proteomics and biomarker based precision medicine**

Proteomics is the study of all proteins expressed in a cell or tissue. Antibiotic treatment choices and the creation of tailored medicines may be aided by the identification of proteins or biomarkers linked with antibiotic resistance. Researchers can identify proteins that are essential to resistance mechanisms by comparing the proteomes of resistant and susceptible bacterial strains. This information can be used to create innovative and quick diagnostic techniques or to build tailored therapies to counteract resistance processes (16,17).

### **3.5 Systems biology and network pharmacology**

Systems biology computational methods investigate regulatory networks and metabolic processes in bacteria to identify points of weakness that might be exploited in the fight against resistance. Computational techniques uncover possible intervention locations for altering resistance mechanisms by modelling the interconnection of biological systems. In network pharmacology, computational approaches are used to investigate systems-level interactions between medicines, proteins, and genes. Using this method, scientists may find possibilities for repurposing existing drugs or formulate new medication combinations with enhanced efficacy against treatment-resistant illnesses (18).

## **4. Conclusion and future perspectives**

The meeting point of precision medicine and computational methods offers a game-changing chance to tackle the critical problem of antibiotic resistance. By tailoring medical interventions to individual patients based on their genetic makeup, microbiome composition, and other personalized factors, precision medicine offers the potential to optimize antibiotic treatment and minimize the risk of resistance development. Computational tools and advanced algorithms play pivotal roles in deciphering complex genomic, proteomic, and microbiome data, enabling researchers to predict antibiotic resistance, identify novel drug targets, and design innovative treatment strategies. These computational approaches empower healthcare providers to make informed decisions, anticipate the emergence of resistance, and implement proactive measures to combat antibiotic resistance effectively. The integration of precision medicine with computational techniques opens new frontiers in the fight against antibiotic-resistant infections. By leveraging the power of data-driven insights and personalized

approaches, we can revolutionize the way we combat antibiotic resistance and preserve the efficacy of these life-saving drugs for current and future generations. Moving forward, continued research and collaborative efforts between computational scientists, clinicians, and policymakers will be instrumental in advancing precision medicine interventions and computational tools to effectively tackle antibiotic resistance. As we embrace this innovative and patient-centric approach, we stand poised to revolutionize infectious disease management and ensure a healthier and more resilient future for all.

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