Big Data to Expand the Antimicrobial Therapeutic Arsenal:
De Novo Discovery and Drug Repurposing

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INTRODUCTION

The current Big Data era implies the presence of vast and intricate amounts of data that cannot be analyzed with traditional tools and analysis techniques (Gandomi A, *et al.*, 2015). Between these data, we can find those related to biomedicine, which can be used for synthesis and compound selection in the discovery and design of drugs (Kim S, *et al.,* 2021). Some examples of these databases include ChemSpider (more than 26 million registered molecules), ChEMBL (data on bioactive molecules and their pharmacological properties), ZINC (commercial chemical compounds especially prepared for virtual screening), BindingDB (intermolecular binding data such as protein-ligand interactions) and Protein Data Bank (PDB) (protein and nucleic acid tridimensional structures).

The high throughput screening (HTS) has been one of the most important processes in the discovery of biologically active molecules (Pinzi L, *et al.,* 2019). Improved computational techniques used for HTS, such as artificial intelligence (AI) and machine learning (ML), also contribute to improved data management by accelerating and refining the process (Gupta R, *et al.,* 2021). Another relevant process in the search for new drugs, and that AI and ML techniques (along with databases such as PDB) have helped to optimize, is the determination of target molecules. Predicting and identifying the drug-target interaction (DTI) is a crucial step in the discovery and design of new drugs, as it reduces the costs of experimental validation (Thafar MA, *et al.,* 2021). The new drugs are designed based on the analysis and observation of the binding of ligands to the three-dimensional structure of molecules such as amino acids and their sequences, proteins, DNA or RNA (Robichaux JP, *et al.,* 2021). This translates into faster discovery of effective drugs, with a higher success rate and a reduction in computational costs related to traditional methods, such as molecular docking or virtual screening (VS) (Gupta R, *et al.*, 2021). An example of this is found in recent studies on computational analysis for the identification of effective

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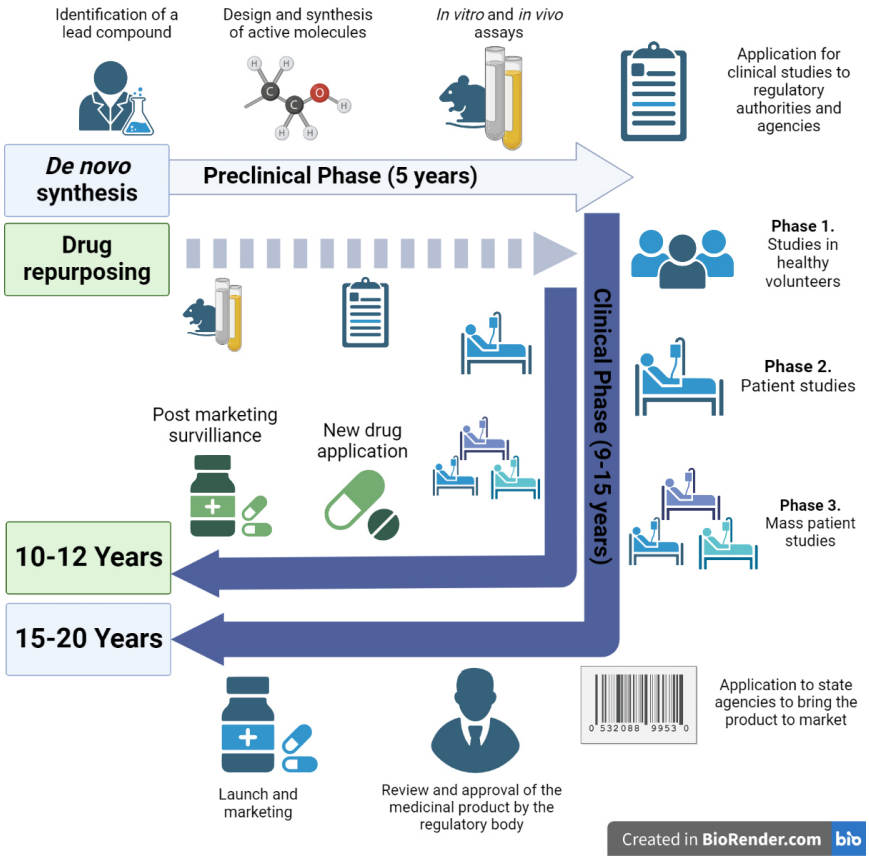
drugs against the SARS-CoV-2 coronavirus, where active molecules against this pathogen were identified (Pérez-Moraga R, *et al.,* 2021).

Another interesting factor in the design and discovery of drugs is the development of relationships between chemical structures and their physicochemical properties with biological activities. Mathematical prediction models, which characterize the structural, physical, chemical, and biological properties of molecules, have become an essential tool for this issue, becoming the key to the success of ML models targeting both drug design and repurposing (Suay-Garcia B, *et al.,* 2020a). Drug repositioning is the generation of new clinical opportunities for molecules already known and/or approved, providing a new therapeutic indication different from the usual one (Suay-Garcia B, *et al.,* 2019). The repositioning of drugs that have undergone extensive toxicological and pharmacological analysis is an effective method to reduce the time, cost, and risks of de novo synthesis, moving directly to preclinical testing and clinical trials (Liu Y, *et al.,* 2021) (Figure 1). This method has proven useful for identifying a new clinical use against different diseases in molecules already known or commercialized (Suay-Garcia B, *et al.,* 2020b). In addition, new molecules have been detected through in silico homology studies that could be reused as lead compounds from which to obtain new molecules with greater efficiency (Troeman DPR, *et al.,* 2019). An important feature of this method is that it can re-evaluate molecules considered as failed in previous studies, adding value to a lost investment by providing new indications for these drugs (Natalie KB, *et al.,* 2021). In addition, trials that can be conducted by repositioning drugs could reveal new therapeutic targets and improve knowledge of known therapies.

Figure 1. Phase and time difference between drug development from de novo synthesis and the drug repurposing method. Created with BioRender.com



In vitro or *in vivo* experiments aimed at drug repurposing need a lot of time and work. *In silico* approaches, can study and calculate structures, properties, dimensions and geometries of target molecules. These can be combined with drug repurposing, becoming a methodology capable of providing new therapeutic approaches to molecules already known in a fast, effective, and economical way compared to other strategies (Tarín-Pelló A, *et al.,* 2022). This combination consists of collecting data and preprocessing it to generate the computational model. Subsequently, from the existing literature, proofs of concept are generated and used for the evaluation of models through cross-validation, case analysis and metrics evaluation. Finally, validation of repurposed drugs is performed through clinical trials and *in vitro* and *in vivo* studies (Gupta R, *et al.*, 2021). This sum of methods represents a great improvement in terms of economic savings and speed in the discovery and development of new drugs (Meng Z, *et al.,* 2020). In this sense, one of the most relevant lines of research of our era is the search for new antimicrobials, due to the progressive increase of bacteria that are multiresistant to the current therapeutic arsenal.

In the literature there are many ML techniques based on similarity calculation, matrix factorization, network models, feature vectors and deep learning (DL) models for DTI prediction (Islam SM, *et al.,* 2021). Therefore, the aim of this review is to present the different types of mathematical prediction models that have been used to develop new antimicrobials or repurpose drugs without known antibiotic activity as antibiotics. In this way, it is intended to prove the effectiveness of the combination of these two strategies to provide new therapeutic opportunities against various diseases with the databases that are currently presented.

BACKGROUND

Antimicrobial resistance has become one of the top 10 threats facing humanity worldwide (World Health Organization (WHO), 2016). WHO has been warning since 2016 that antimicrobial resistance (AMR) could cause 10 million deaths by 2050 if an early solution is not found (PhRMA, 2021). This figure would exceed those reached by diseases such as cancer and diabetes or traffic accidents and is equivalent to populations of countries such as Sweden, the Czech Republic, Greece, or Portugal (Eurostat, 2021). The most recent data can be found in the analysis by Murray *et al.* where they indicate that in 2019 the global burden of deaths associated with drug-resistant infections evaluated in 88 pathogen-antimicrobial combinations was approximately 4.95 million, of which 1.27 million could have been avoided if the pathogens had been sensitive to available antimicrobial treatments (Murray *et al.,* 2022). In 2017, WHO published a list of pathogens of global priority and classified these microorganisms as critical, high and medium priority bacteria depending on the urgency there is to find new antibiotics against them (WHO, 2017). *Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Mycobacterium tuberculosis* are examples of pathogens that present high resistance to the available treatment options (Terreni M, *et al.,* 2021, European Centre for Disease Prevention and Control (ECDC), 2015). The complicated health situation we face has pushed researchers to prioritize the search for alternative or complementary therapies to antimicrobials (Gutiérrez R, *et al.,* 2021). We currently find studies on alternative antimicrobial therapies to the traditional antimicrobial therapy (Table 1). However, these therapies still require clinical trials to ensure their safety and efficacy, remaining as complementary treatments to antimicrobials (Shang Z, *et al.,* 2020).

Table 1. List of alternative therapies to antibiotics. Adaptaded from: Tarín-Pelló, A. et al.,2022

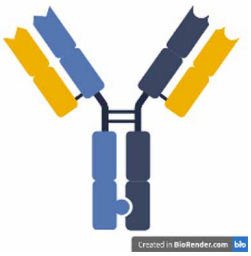
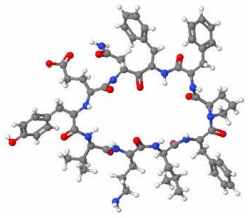
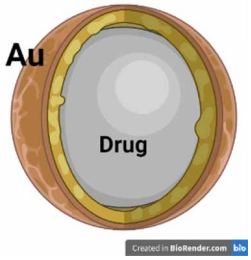
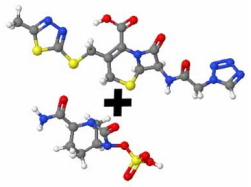
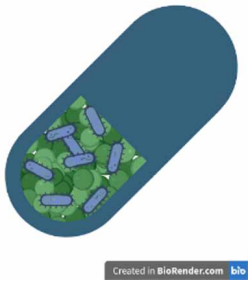
	Examples	General characteristics	Advantages	Structures	References
Monoclonal antibodies	17H12, 8F12, 2C7, SA-13, SA-15 and SA-17.	Application of antibodies that specifically target the external antigens of the pathogen.	Specific strategy without adverse effects on the body's microbiota. Reduction of the development of resistances.		Gulati S, *et al.,* 2019 Diago-Navarro E, *et al.,* 2018
Antimicrobial Peptides (AMP)	Thyrotricin, gramicidine, teixobactin.	Oligomers that target the bacterial membrane or intracellular components performing an antibacterial effect.	They do not interact with specific targets, slowing down the emergence of resistances.		van Gent ME, *et al.* 2021 Pacios O, *et al.* 2020 Vila J, *et al.*, 2020
Nanoparticles (NP)	AgNP, AuNP, ZnONP, TiO_2NP.	Small particles that can penetrate eukaryotic cells and target intracellular pathogens.	They have versatility in the loading and adaptability of the drug and adequate stability in physiological fluids. Improving the effectiveness of the drug and slowing down the emergence of resistance.		de Dicastillo CL, *et al.,* 2019 Tiwari V, *et al.,* 2018 Kumar R, *et al.,* 2016 Morones-Ramirez JR, *et al.,* 2013
Combination therapy	MCB3681, cadazolid, zaviceft.	Combination of molecules (antibiotics or not) that have an antibiotic effect.	Improving the effectiveness of current antibiotics. Better toxicity profile and efficacy of the molecules involved. Decrease in the appearance of resistance.		Bradley JS, *et al.,* 2019 Shapiro S., 2013
Microbiota therapy	Fecal microbiota transplant, modified *E. coli* strains.	Administration of beneficial microorganisms for the reestablishment of a healthy microbiota.	Antimicrobial effect, immunostimulant effect and improvement of the barrier function of the body's tissue. Low chances of emergence of resistances. Harmless to the human microbiota.		Hwang IY, *et al.,* 2017

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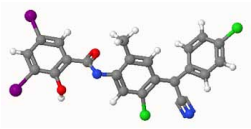
Table 1. Continued

	Examples	General characteristics	Advantages	Structures	References
Phagotherapy	ΦRGN_{ndm-1} and ΦRGN_{shv-18}.	Application of bacteriophages that target and penetrate pathogenic bacteria.	Specificity. Harmless to eukaryotic cells. Effectiveness in the eradication of biofilms. Improvement of the effectiveness of antibiotics.		Citorik RJ, *et al.,* 2014
Antivirulent therapy	Thioridazine, verapamil, and closantel.	Drug interaction in targets not essential for the pathogenic microorganism.	Improvement of current antibiotic treatments. Ability to decrease virulence and the appearance of resistance.		Rodrigues L, *et al.,* 2020 Rajamuthiah R, *et al.,* 2015a Rajamuthiah R, *et al.,* 2015b Rajamuthiah R, *et al.,* 2014

Due to the lack of alternatives to these drugs, the search for new antibiotics becomes the only way to alleviate this health crisis (Tarín-Pelló A, *et al.,* 2022). *De novo* synthesis is the most widely used strategy for the search for new drugs, including antibiotics. Unfortunately, in the last two decades, the economic and time investment in the development of new antimicrobials has been a setback in the pharmaceutical industry (Hamet P, *et al.,* 2017), because it is a slow procedure, with low success rates in terms of pharmacokinetic parameters, safety profiles and compound stability (Knoblauch R, *et al.,* 2020). This is because drug discovery and design comprise long and complex phases, such as target selection and validation, therapeutic detection and seeding optimization, preclinical and clinical trials, and manufacturing processes. All these steps present two major challenges for the pharmaceutical industry. First, the identification of effective antibiotics, and second, the management of the costs and speed of the entire process (Zhang D, *et al.,* 2017). Traditional computational approaches, despite having managed to reduce these problems, turn out to be inaccurate and deficient techniques (Hassanzadeh P, *et al.,* 2019). The implementation of novel techniques allows overcoming problems and obstacles in the process of drug design and discovery, in addition to improving the management of the immense information provided by complex biomedical databases (Duch W, *et al.,* 2007). This fast and relatively simple processing capacity leads us to the potential of this methodology to improve the drug repositioning strategy, which shares with computational models the advantage of reducing the costs and development periods of *de novo* synthesis because characteristics of these drugs such as mechanism of action, dose and toxicological profile are already known (Ohmoto A, *et al.,* 2021). In fact, the success rate of the drug repurposing method accounts for nearly 30% of all the new drugs approved by the FDA (Ashburn TT, *et al.,* 2004). There are countless examples of drug repositioning that have been a success for medicine, such as fin-

asteride, thalidomide, sildenafil, metformin, and hydroxychloroquine (Barbarossa A, *et al.,* 2022). Table 2 contains a compilation of studies that have described antimicrobial effects on drugs originally used for another indication in the usual therapeutics.

Table 2. Drugs studied by in vitro methods that have demonstrated antimicrobial properties. Adapted from: Barbarossa A, et al., 2022.

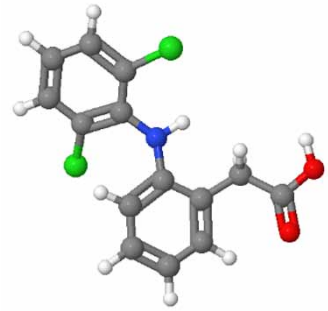
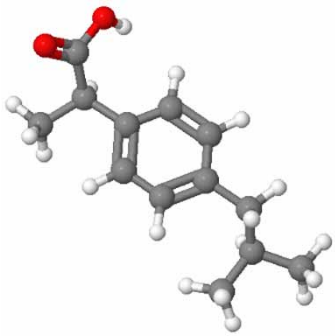
Molecules	Class of drug	Structures	References
Acetylsalicylic acid	NSAID*		Rosato A, *et al.,* 2016
Diclofenac	NSAID*		Rosato A, *et al.,* 2016 Rosato A, *et al.,* 2021 Ferrer-Luque CM, *et al.,* 2021
Ibuprofen	NSAID*		Chen H, *et al.,* 2018 Pereira AKDS, *et al.,* 2020

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Table 2. Continued

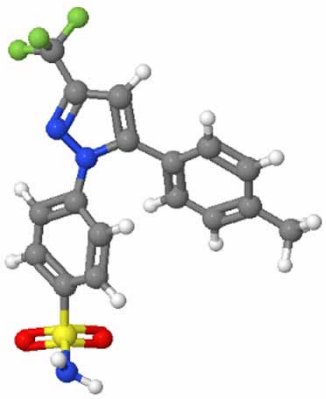
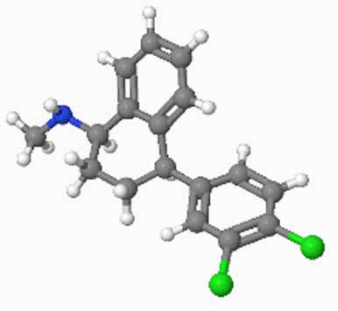
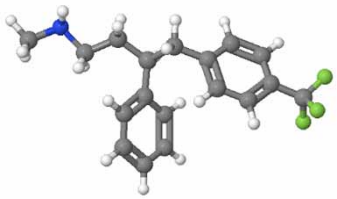
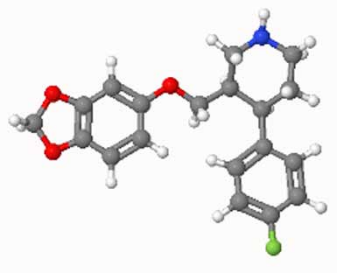
Molecules	Class of drug	Structures	References
Celecoxib	NSAID*		Mortensen R, *et al.,* 2019
Sertraline	Antidepressant		Ayaz M, *et al.,* 2015 Gowri M, *et al.,* 2020 Krzyżek P, *et al.,* 2019
Fluoxetine	Antidepressant		Hadera M, *et al.,* 2018 Karine de Sousa A, *et al.,* 2018 Foletto VS, *et al.,* 2020
Paroxetine	Antidepressant		Foletto VS, *et al.,* 2020

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Table 2. Continued

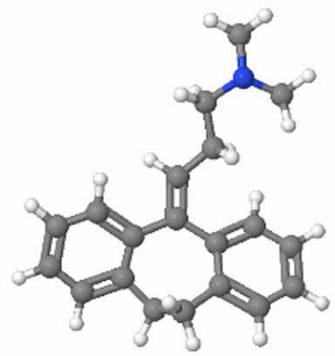
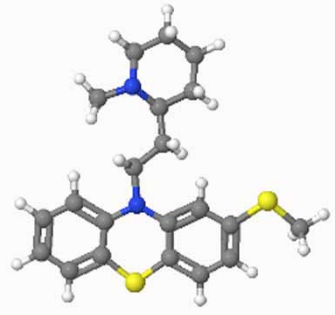
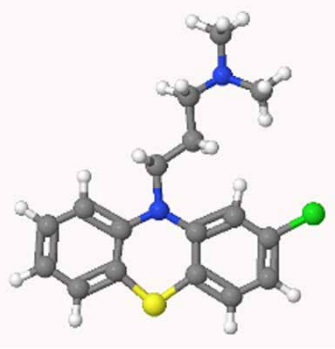
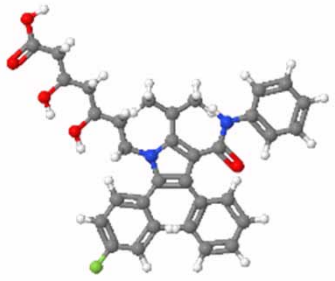
Molecules	Class of drug	Structures	References
Amitriptyline	Antidepressant		de S. Machado C, *et al.,* 2020
Thioridazine	Antipsychotic		Ruth MM, *et al.,* 2020 Tozar T, *et al.,* 2019
Chlorpromazine	Antipsychotic		Nistorescu S, *et al.,* 2020
Atorvastatin	Statin		Masadeh M, *et al.,* 2012 Sarkeshikian SS, *et al.,* 2020

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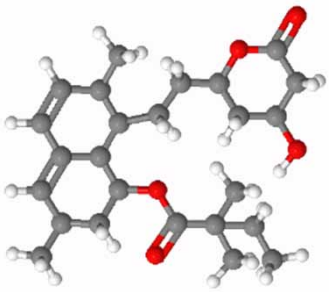
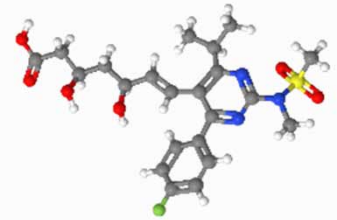
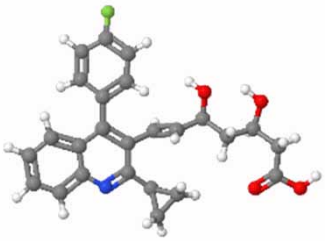
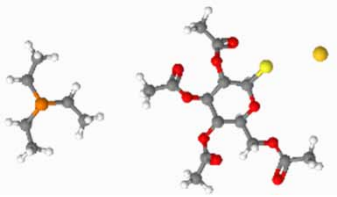
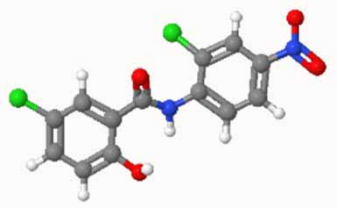
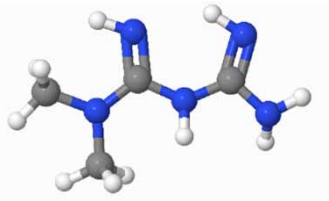
Table 2. Continued

Molecules	Class of drug	Structures	References
Simvastatin	Statin		Masadeh *et al.,* 2012 Graziano *et al.,* 2015 Ko *et al.,* 2018 Akbarzadeh *et al.,* 2021 Fan *et al.,* 2020 Figueiredo *et al.,* 2019 Rampelotto *et al.,* 2018
Rosuvastatin	Statin		Masadeh M, *et al.,* 2012
Pitavastatin	Statin		Ko HHT, *et al.,* 2018
Auranofin	Antirheumatic		Cassetta MI, *et al.,* 2014
Niclosamide	Antihelmintic		Rajamuthiah R, *et al.,* 2015 Tharmalingam N, *et al.,* 2018 Ayerbe-Algaba R, *et al.,* 2018
Metformin	Antihyperglycemic		He X, *et al.,* 2022

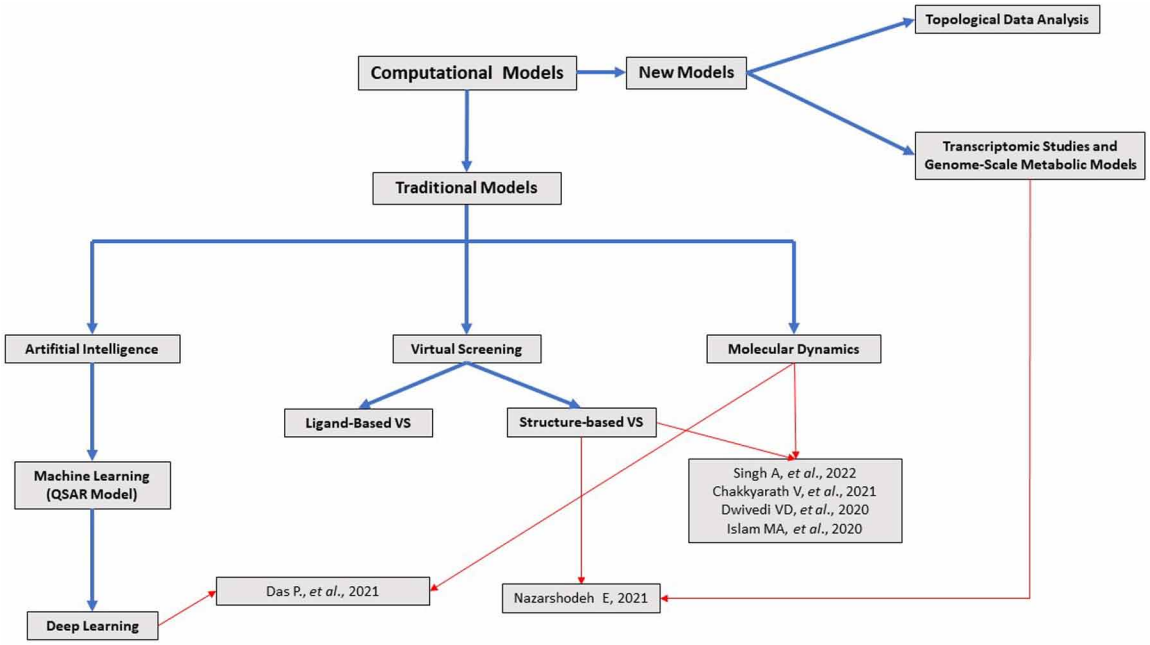
*NSAID: non-steroidal anti-inflammatory drug

However, the contributions of traditional *in vivo* or *in vitro* methods, both in the synthesis of new drugs and in the repurposing of known molecules, remain scarce for the speed at which AMR appear (Monteiro NRC, *et al.,* 2021). Given the large amount of information reported on ligands, targets and diseases in publicly available databases, greater efforts have been made in the application of discovery strategies based on *in silico* repositioning during the last decades. These approaches have shown to provide valuable novel opportunities for drug discovery and development, becoming a key methodology for identifying and evaluating new seedings and new repurposed drugs in a reasonable time and in a relatively easy way (Nazarshodeh E, *et al.,* 2021). The emergence of AMR urgently requires rapid and effective therapeutic development. Drug reuse and redesign using existing computational analysis methods capable of processing thousands of target molecules is a way to speed up the process (Dey D, *et al.,* 2021).

FOCUS OF THE ARTICLE

There are different methods that apply computational models to improve the development of new antimicrobials or the repositioning of non-antibiotic drugs (Figure 2). All of them focus on the discovery of new drug-target interactions (DTI), as it is a key step in both the discovery and design and repositioning of antimicrobial drugs (D'Souza S, *et al.*, 2020). In this chapter we will present the methods most frequently used in the discovery and/or repositioning of drugs aimed at the investigation of new antibiotics. These methods can be divided into 4 large blocks. First, we find AI, which encompasses concepts such as ML, decision trees, neural networks and DL. Next, another important category because it is a common method of choice in the design and repositioning of drugs is virtual screening that encompasses molecular docking. Finally, we find molecular dynamics that analyzes the physical movement of atoms and molecules, as well as the interactions between them.

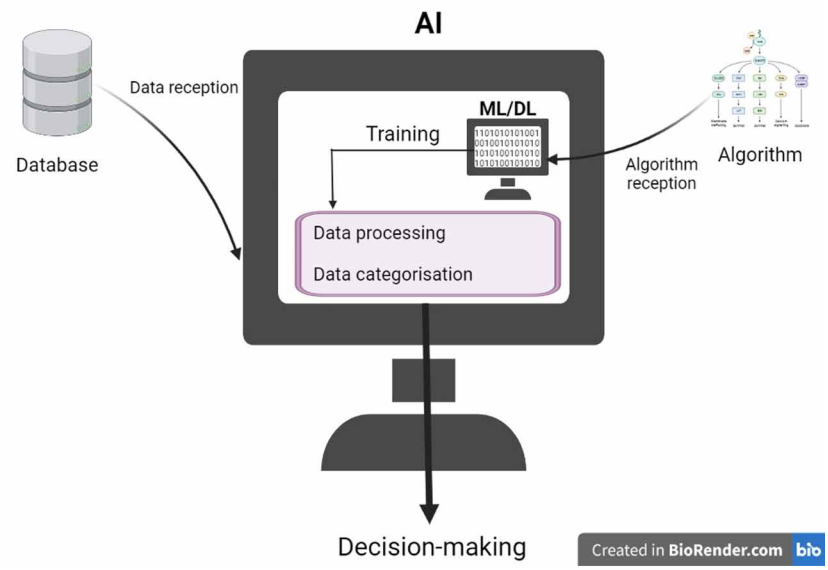
Figure 2. Tree diagram of models capable of contributing to the development of new molecules or re-positioning of targeted drugs in the search for new antimicrobials, both individually (blue arrows) and in combination (red arrows).



1. Artificial Intelligence

AI is a general term that includes any computer program capable of processing data autonomously and make decisions, or categorize data, after a learning process, which is generally continuous and adaptative (Goel AK, *et al.*, 2011). Computational modeling based on AI principles turns out to be a very useful avenue for the identification, development and repositioning of drugs, since it is able to recognize drugs and their physicochemical properties, as well as evaluate their efficacy and toxicity profile (Zhong F, *et al.*, 2018). Within AI one can find ML, which differs from the broader term in that data are inputted along with algorithms which help the machine learn without being explicitly programmed (Badillo S, *et al.*, 2020). These algorithms have proven to be interesting for designing models capable of identifying antimicrobial molecules or repositioning known drugs to antibiotics. (Gupta S, et al., 2019). Furthermore, DL appears as a subset of ML where vast volumes of data and complex algorithms are used to train a model (D'Souza S, *et al.*, 2020) (Figure 3).

Figure 3. Relationships between Artificial Intelligence, Machine Learning and Deep Learning and how these models operate. Created with BioRender.com



An example of a model within the AI methodology is the Tree-based Quantitative Structure-Activity Relationship (QSAR) model, which applies ML methods to compare a candidate ligand with the set of all known ligands to infer its binding capacity (Byvatov E, *et al.*, 2003). This method has proven to be suitable for the synthesis of new antimicrobials, specifically, antimicrobial peptides (AMP), one of the alternatives to traditional antibiotic therapy that is under development (Fleitas Martinez O, *et al.*, 2019). The natural and synthesized AMPs so far have disadvantages (physical-chemical instability, short half-life, rapid elimination, slow penetration into tissues...) that do not allow it to assert itself as an alternative treatment, but complementary to antibiotics (Oshiro KG, *et al.,* 2019). In order to find AMPs more suitable for optimal treatment, special attention has been paid to the QSAR model, because it uses physicochemical descriptors to predict the biological activity of peptides from their amino acid sequences (Mitchell JB, *et al.*, 2014). In our context, QSAR models can be used to identify determinants that are important for antimicrobial activities and, from these determinants, design new and more effective AMPs (Lee EY, *et al.*, 2017). This model has been applied to calculate the antimicrobial potential of different molecules, such as wasp venom-derived mastoparan analogues and peptoids (AMP mimics) (Czyzewski AM, *et al.,* 2016, Toropova MA, *et al.*, 2015). The QSAR model has also contributed to other alternatives to antibiotics such as nanoparticles. A study applied this model to identify peptides of interest that induced the production of silver nanoparticles with antimicrobial potential (Bozic AS, *et al.*, 2016). Another major finding attributed to this model is the development of antituberculous antimicrobials, such as peptide inhibitors of ribonucleotide reductase (RNR) of *M. tuberculosis* (Nurbo J, *et al.*, 2007). More recently, the QSAR model has also demonstrated its potential to improve drug repositioning. In a study the authors applied a tree-based classification method using linear discriminant analysis and discrete indices (Suay-Garcia B, *et al.,* 2020). This QSAR model was able to identify from the DrugBank database 134 drugs as possible antibacterial candidates against *E. coli.* Only 8 of these drugs were known as antibiotics, 67 were approved drugs for other pathologies and 55 were experimental stage drugs. In another study, the nicotinamide-nucleotide adenylyl transferase protein of the microorganism *M. tuberculosis* was selected as a target of interest, because it is an essential protein for the growth of this pathogen. From the structure

of this protein, an *in silico* model of virtual ligand detection was built in front of the Prestwick chemical library and the ZINC database, resulting in 155 molecules with potential interaction capacity with the protein (Cloete R, *et al.*, 2021). 5 of these molecules were introduced into a 3D-QSAR model that validated the inhibition properties of the compounds by comparing them with already known inhibitors. As a result of the entire in *silico* assay and after an *in vitro* test, it was confirmed that Novobiocin and derivatives of this drug as coumermycin could be considered for future cell trials and synthesis studies taking these molecules as serial heads for new antituberculous.

2. Virtual screening

Virtual Screening (SV) is a high-throughput experimental screening technique, which uses the early stages of the drug discovery process to search for libraries of small molecules to identify chemical compounds that are likely to bind to one or more drug targets (Shoichet BK, 2004). There are two categories of SV that encompass different screening techniques. First, we have ligand-based virtual screening (LGWS), which is based on molecular similarity through the comparison of different structural and physicochemical properties (Lill M, 2013). Second, there is virtual structure-based or target-based or molecular docking (SBVS or TBVS), which aims to predict the best interaction between ligands and a target to form a complex (Maia EHB, *et al.*, 2020). SBVS presents significant advantage in terms of de novo synthesis, as there is no need for physically existing molecules. In addition, it is a useful method to predict the possible mechanism of antimicrobial action that the compound of interest may have. There is literature that exposes the effectiveness of this method in reference to the repositioning of molecules already known. An example is a study where a computational approach of drug reuse guided by polypharmacology was applied to identify molecules with antituberculous potential (Madugula SS, *et al.*, 2022). After molecular docking of the targets considered important of *M. tuberculosis* to the molecules approved by the FDA, 34 drugs with antituberculous and antibacterial activity were observed. Of these molecules, 4 were not already recognized antibiotics (nitrofural, stavudine, quinine and quinidine)

A study expanded information on the repositioning of phenothiazine-derived drugs, a group of compounds used mainly to treat psychotic disorders, since they block dopaminergic receptors thus preventing binding to dopamine (Posso MC, *et al.*, 2022). However, chlorpromazine, thioridazine, and trifluoperazine had also demonstrated antibacterial activity. With molecular docking, Nistorescu *et al.* performed a simulation of interactions between chlorpromazine and laser-irradiated chlorpromazine with several clinically important microorganisms (Nistorescu S, *et al.*, 2020). As a result, irradiated chlorpromazine was shown to exhibit better antimicrobial activity than the unmanipulated molecule, in addition to reducing the formation of biofilms by *P. aeruginosa* and MRSA in impregnated catheters.

Dwivedi *et al.* analyzed by molecular docking the interaction between the Tap protein of the pathogen *M. tuberculosis* and 18 calcium blockers/channels (Dwivedi M, *et al.*, 2022). At the end of the analysis, five ligands were observed: glimepiride, flecainide, flupyritin, nimodipine and amlodipine as promising compounds for recovering the sensitivity of *M. tuberculosis* to antituberculous drugs. Singh *et al.* studied molecular docking the interactions between the protein diaminopimelase epimerase (DapF) of *Enterococcus faecalis* and the molecules acetaminophen and dexamethasone. After docking, both molecules were shown to potentially act as DapF inhibitors (Singh H, *et al.*, 2021). Another protein of interest for *M. tuberculosis* was cyclophilin peptidyl-propyl isomerase (PpiB), which Kumar *et al.* He studied, together with other homologous proteins, by *in silico* coupling its ability to create complexes with the molecules acarbose, cyclosporine-A and gallium. Through this analysis, it was observed that

the residues of the PpiB protein interacted with acarbose, cyclosporine-A and Gallium nanoparticles, exposing a potential capacity as modulators (Kumar A, et al., 2019).

As we have already pointed out, computational models are not always used individually. In this case, in combination with acoupling analysis of a genome-scale metabolic model integrated with protein structures (GEM-PRO), a study was able to identify 92 *Escherichia coli* target proteins that interacted with 1405 FDA-approved drugs that could be repositioned as antibiotics against this bacterium. These molecules showed affinity for one or more of the proteins resulting from the *in silico* assay. Among the drugs selected by the model, Grazoprevir and Retapamulin appeared, anti-infective molecules already known, which could demonstrate the validation of this work to reposition drugs to antibiotics (Nazarshodeh E, 2021).

3. Molecular Dynamics

Molecular dynamics simulation provides a useful approach when simulating DTIs and by evaluating the molecular characteristics of the elements present in the interaction (Singh D, *et al.,* 2020). It is a hybrid technique that provides the key properties of formulations before experimental setup, providing information on the stable attributes of such interaction. Molecular dynamics, together with AI, have been shown to be capable of developing new antimicrobial drugs (Okada K, *et al.*, 2019).

A rational design that facilitated *de novo* synthesis of AMP was guided by simulations generated by molecular dynamics, which predicted and detailed at the atomic level structures formed by peptide designs with potential antimicrobial activity (Chen CH, *et al.*, 2019). One of the designs obtained by this model demonstrated an AMP with a small size (four amino acids) but with a powerful biocidal capacity through the formation of pores in microbial membranes against both large-positive and Gram-negative pathogens.

An enzyme of interest that occurs in several bacteria is DNA gyrase B (GyrB) as a target in antibiotic treatment. Islam *et al.* conducted a computational study where benzothiazole and N-phenylpyrrolamide derivatives were collected which, according to the literature and after a trial by molecular docking, demonstrated a stable interaction with GyrB (Islam MA, *et al.*, 2020). From the 10 most stable complexes, 6 de novo chemical analogues were screened and the stability of the ITD was confirmed by molecular dynamics simulation and promising drugs were considered subject to experimental validation *in vitro*.

Molecular dynamics have also been shown to be, with the help of other models, useful in drug repositioning, as well as assessing DTI and binding stability quickly and accurately. After a previous *in silico* assay where four broad-spectrum AMPs were developed and synthesized. They performed a model that combined molecular dynamics, docking and simulation to confirm their affinity to *Klebsiella aerogenes* beta-lactamases. These AMPs were found to have more affinity than some beta-lactams already registered with the FDA. This represents an improvement in treatments against bacteria resistant to beta-lactams due to the presence of beta-lactamase, one of the most widespread resistances in the world (Chakkyarath V, *et al.*, 2021)

Due to the emergence to find new antituberculous drugs, Dwivedi *et al.* conducted a computational study to evaluate the binding affinity of 38 phytomolecules to select more effective ligands against the resuscitation-promoting factor B (RpfB) of *M. tuberculosis* (Dwivedi VD, *et al.*, 2020). To this end, molecular docking and molecular dynamics models were combined to examine the stability of DTI. As a result of the study, it was observed that diospirin, 2'-nortiliacorinin, 5,4'-dihydroxy-3,7,8,3'-tetramethoxyflavone and tyliacorin showed binding affinity to the target protein, indicating its ability to inhibit it and therefore highlighting a possible treatment for *M. tuberculosis* infections. Recently, Singh

et al. examined phytochemicals from *Withania somnifera* to find possible inhibitors of the enzyme CTP synthase (Mtb PyrG). After performing molecular docking combined with simulation by molecular dynamics it was observed that the molecules quercetin 3-rutinoside-7-glucoside, rutin, chlorogenic acid and isochlorogenic acid C presented stable binding energies in the interaction with the target enzyme (Singh A, *et al.*, 2022). Currently, these molecules are being considered for future *in vitro* and *in vivo* trials to confirm their anti-tuberculosis effectiveness. With a similar strategy, the recent study by Shailaja *et al.* shown that adapalene interacted with high binding energy with key residues of the enzyme New Delhi metallo-beta-lactamase 1 (NMD-1) (Shailaja S, et al., 2022). Another example of computational models combined with molecular dynamics is the study by Das *et al.*, which DL and molecular dynamics were combined to encode molecules with antibacterial activity. Through this model, 20 candidate AMPs were identified and synthesized, of which two showed activities against different Gram-positive and Gram-negative pathogens (including multidrug-resistant *Klebsiella pneumoniae*) and a low propensity to induce resistance against *E. coli* (Das P, et al., 2021). In addition, these molecules demonstrated low toxicity in subsequent *in vitro* and *in vivo* tests.

All the models present in this chapter demonstrate an optimal capacity to provide, through a relatively quick and simple process, antimicrobial molecules capable of helping to combat current AMR, increasing the therapeutic arsenal available, and providing a more than attractive opportunity for the pharmaceutical industry to invest in R+D aimed at these design tools, from which the antibiotics (and other drugs) of the future will emerge.

SOLUTIONS AND RECOMMENDATIONS

Thanks to techniques such as computational design, it was possible to combat infectious diseases in the so-called Golden Age of antibiotics (Mohr KI, 2016). However, these microorganisms have been developing resistances to the therapeutic arsenal currently available, which has barely been updated with new antimicrobial molecules for more than 30 years. These resistances have been reducing the efficacy and, consequently, the antibiotic treatment options. It is important to note that one of the most worrying factors of AMR is the speed at which they appear, currently much faster than the rate of development of new antibiotics (Liu Y, *et al.*, 2021, Pérez-Gracia MT, 2021). All the results presented in the focus of the article have been obtained new potential antibiotic in a relatively easy and fast way. The simplicity and speed of these models are very attractive factors for the pharmaceutical industry in terms of increasing investment in R+D to develop antimicrobial molecules. Therefore, the computational models presented could easily, with the support of the pharmaceutical industry, reach the goal presented by several organizations of placing between 2 and 4 new antimicrobials on the market by 2030. (Plan Nacional Resistencia Antibióticos, 2022, United Nations, 2021, Priorities of the global leaders group on AMR for 2021-2022, 2021).

Despite the demonstrated potential of the above computational tools for the search for new antimicrobials, there are issues that could be addressed to improve the operations performed by the methods exposed. The ability of these models to provide important information from data sets obtained from different databases is indisputable. Thanks to this immense amount of data, the tools have been able to calculate the characteristics of the different drugs and targets, in addition to evaluating through various metrics the possible orientations and stability of the different DTI. Unfortunately, this same information can be counterproductive, due to the difficulty in managing large amounts of data, along with the complications of design and development. In addition, most techniques use a different data sets to evaluate

the results (data processing at the atomic level, at the amino acid level, with 3D models...). This makes it impossible to quantitatively compare methods based on accuracy, precision, etc., as different data sets can produce different results (Sachdev K, *et al.*, 2019). That is why, to solve the limitations presented by each model individually, it is interesting to develop a model or combination of existing models. Historically, problems of inaccuracy and inefficiency have been observed in traditional approaches (Molecular docking and Virtual Screening) that today have been solved by incorporating AI algorithms into the process of drug design and discovery (Harrer S, *et al.*, 2019). In previous sections we have been able to observe how the combination of different models (Molecular docking with molecular dynamics, or Molecular dynamics with DL) allow to confirm key factors such as the stability of the DTI, so it would be interesting to make combinations that are consolidated in a single model to further optimize the processing and evaluation of data and results. The combination of models or the design of more complex models would cover the DTI with a much more extensive and complete information, without relatively affecting the operating time that the models we have seen individually would have.

FUTURE RESEARCH DIRECTIONS

As explained above, the key point for the design and development of new antimicrobials is the generation of faster and more effective models. There are methods with novel approaches capable of providing new methods of processing information about molecules, pharmacological targets, and their respective DTIs.

Topological Data Analysis is a computational model of mathematical prediction that applies geometry and topology to develop tools to study the qualitative characteristics of the data on molecules (Macalino SJY, *et al.*, 2020). One of the advantages of TDA is that it does not require a group of inactive compounds for the model to carry out its learning process. This is very favorable considering that negative activity results are not normally published, greatly complicating access to molecular structures that are known to be inactive for the construction and validation of models. Being a newer tool compared to other techniques, there are few studies in the literature where this model is applied in terms of the search for new antimicrobials. In one of them, they applied a TDA strategy to verify the possible antimicrobial activity of 55 new compounds against *Helicobacter pylori* (Hernández-Ochoa B, *et al.,* 2021). In this study, interactions were discovered with the enzyme glucose-6-phosphate dehydrogenase. After the results obtained, the compounds represent new candidates for promising drugs against this infection.

Another novel approach is that aimed at transcriptomic studies and genome-scale metabolic models (GSM), which are tools that could aid to better understand the resistance mechanisms of microorganisms, as well as the molecules involved in these AMR (Das S, *et al.*, 2022). These are in *silico* representations of the entire genome or of the metabolic reactions present in the microorganism (Thiele I, *et al.*, 2010). In this way, it is possible to predict and understand the changes that could happen in the microorganism by varying certain genetic, metabolic and environmental parameters (O'Brien EJ, *et al.*, 2015). Several studies demonstrate the potential of these tools to obtain antibiotics quickly and with very promising properties in terms of efficacy and safety (Nielsen J, 2017).

Despite finding no literature regarding the development of antibiotic molecules, several *in silico* chemogenomic studies have shown that genome-wide gene expression data can also represent a useful resource for identifying drugs and drug target genes that can potentially be used for drug repositioning (Bispo NA, *et al.,* 2013). For this reason, we have considered it of interest to expose this methodology as a future tool for the development of new antibiotics. The goal of chemogenomics is to establish molecular relationships between ligands and drug targets (Neves BJ, *et al.*, 2015). For this it is based on the same

concept presented by TDA, “similar targets have similar ligands”, the search based on homology using these databases helps to identify compounds that can act on a target and of which this DTI is unknown (Rognan D, 2007).

Another approach that could be taken to further increase the usefulness of the computational approaches discussed is to leverage them to accelerate the results of research aimed at alternative therapies to antimicrobials. Given the rapid development of computing tools over the years, it is hoped that high-precision methods will help researchers improve scoring functions to design new compounds such as AMP, monoclonal antibodies or NPs that are more effective and safer at a low cost. Taken together, all the features present in computational models prove to be more than valid tools for the design of real and effective drug candidates that are more likely to reach the market in the coming years.

CONCLUSION

The literature presented in this chapter reveals the importance of AMR as a global health threat, and the need for new antibiotics to effectively treat infections resistant to current drugs. Computational models have proven to play a key role in this problem. The presented models based on both, traditional and newer approaches, have proven to have potential for the discovery, design, and development of new antimicrobials. They also present the necessary tools to optimize the repurposing of known non-antibiotic drugs to antibiotics. The possibilities presented by these tools also aim to improve information on other topics of interest in the problem of ADR, such as alternative therapies to conventional drugs and the increase in knowledge of resistance mechanisms through the processing of omics and metabolomics data. To achieve a new battery of optimal antibiotic drugs on the market, it is necessary to reduce the limitations of the models that are known with greater investments in R+D. Another alternative to perfect current computational models is combining them in a single model to provide more to provide more complete information about the molecules, drug targets and DTI that may occur.

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KEY TERMS AND DEFINITIONS

Artificial Intelligence (AI): A branch of computer science dedicated to building machines capable of mimicking human intelligence processes, including reasoning, learning and deduction.

Deep Learning (DL): A class of ML algorithms that uses multiple layers to learn and make predictions. It differs from the general ML term in that DL can process unstructured data and automate feature extraction.

Machine Learning (ML): A subfield of AI in which machines are built with learning algorithms that allows the system to become mora accurate at predicting outcomes based on experience, without additional human intervention.

Molecular Docking: A molecular modeling technique used to predict how two or more molecules interact, determining the probability of a successful binding.

Molecular Dynamics: A simulation of how atoms and molecules move and evolve within a specific system.

Quantitative Structure-Activity Relationship (QSAR): A computational modeling method that can be built using different mathematical approaches and that is aimed at revealing the relationship between a chemical structure and its pharmacological activity.

Topological Data Analysis (TDA): A mathematical approach that uses topological methods to analyze large-scale datasets by extracting features of data based on the geometry and topology encoded in the distribution of datapoints.