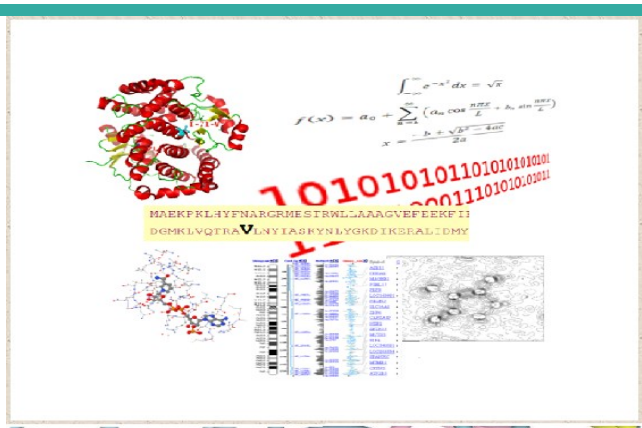
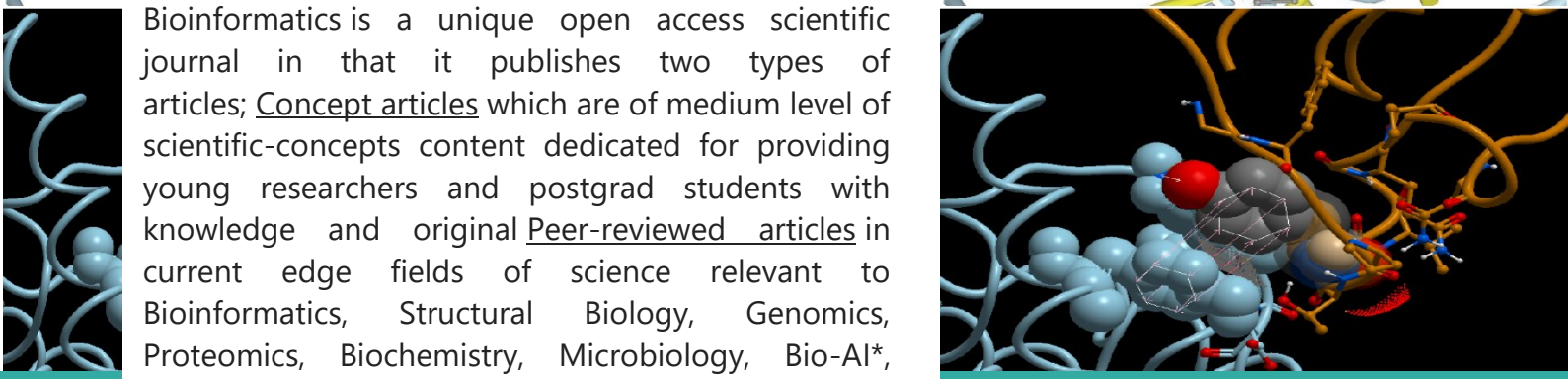
The Journal of Concepts in Structural Biology & Bioinformatics – JSBB

ISSN 2830-8832





The journal of Concepts in Structural Biology & Bioinformatics is a unique open access scientific journal in that it publishes two types of articles; Concept articles which are of medium level of scientific-concepts content dedicated for providing young researchers and postgrad students with knowledge and original Peer-reviewed articles in current edge fields of science relevant to Bioinformatics, Structural Biology, Genomics, Proteomics, Biochemistry, Microbiology, Bio-AI*, Biomathematics, Nutrition & Health and ultimately to Biology and Biotechnology themes and applications.

* Artificial Intelligence

JSBB is a monthly journal that aims to publish at least one peer-reviewed paper and four concept articles in each issue..

UNIVERSITY of SAIDA Dr MOULAY TAHAR

Volume 2 Issue 1 2023 JSBB Journal

EDITORIAL BOARD - 2023-2024:

Editor-in-Chief

Associate-Editors

EDITORIAL BOARD - 2022-2023:

Editor-in-Chief

Associate-Editors

External editors

Prof. Benbouza Halima, see also ORCID.

halima.benbouza@univ-batna.dz, h.benbouza@cnrst.dz

Prof. Mohammed Bey BABA-HAMED

beybabam@gmail.com

Table of content **Page**

Articles – Month of June:

Journal of **Concepts in Structural Biology & Bioinformatics**

BIO-DATABASES, STRUCTURE & FUNCTION ARTICLES

Research article: *Revisited research*

The NALD database: A Comprehensive Resource for Understanding Molecular Interactions.

RACHEDI Abdelkrim

Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Natural and Life Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

Correspondence: RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz
Published: 01 April 2023

Abstract

The Nucleic Acids and Ligands Database (NALD) is a comprehensive resource that provides information on the interactions between nucleic acids and ligands. This paper describes the development of NALD and its features, including the types of data it contains and the user interface. NALD is a valuable resource for researchers in the fields of molecular biology, biochemistry, and drug design.

The NALD database is concerned with the identification of ligands (drugs) that bind nucleic acids (NA) and provide users with a verity of binding information existing between both molecules. The database annotates nucleic acids in complexes with drugs in terms of detailed binding interactions, binding motifs where binding occurs, binding properties, binding modes and classes and links to diseases. These were calculated from entries of NA/Ligand complexes from the protein data bank (PDB) and also extracted by both automatic and manual means from scientific literature sources such as the PubMed web site (PMID) and publications. NALD provides online access to these types of information while it focuses on ligands that bind nucleic acids with implications on diseases of high prevalence such as HIV/AIDS, cancer, hepatitis, malaria and tuberculosis.

This paper is a revisit of the research paper **NALD: Nucleic Acids and Ligands Database** (Rachedi & Madida, 2013). The revisit highlights new improvements to the database including DNA/RNA-ligands binding motifs data growth, data-integration and the implementation of a customized 3D-graphics tool using the PDBe-RCSB Mol* (Sehnal D. et. al., 2021).

Availability: https://bioinformatics.univ-saida.dz/bit2/?arg=SB1

Key words: Bioinformatics, Database, Data mining, Data integration, Nucleic acids, Binding motifs, Ligands, Drugs, Diseases.

Introduction

The interactions between nucleic acids and ligands play a crucial role in various biological processes, such as gene expression and DNA replication. Understanding the nature of these interactions is essential for the development of new drugs and therapies. To facilitate research in this area, Nucleic Acids and Ligands Database (NALD) was developed as a comprehensive resource that provides information on the molecular interactions between nucleic acids and ligands.

Nucleic acid molecules are biologically important found in all living organisms. They contain genetic material that must be synthesized and reproduced with high fidelity to ensure its proper function. Failure to do so conditions of compromised health and disease arise and for this reason nucleic acids are points of interest for therapeutic drug targets during specific binding events. The protein data bank (PDB) (Berman et al., 2000) is an international repository of a large number of 3D structures for macromolecules including protein, nucleic acids and their complexes.

Many of the compounds binding nucleic acids known in general as ligands are considered drugs either designed as therapeutics or as additives for structural and functional investigation. This project deals with the development of an online database, Nucleic Acids and Ligands Database (NALD), which annotates the nucleic acid (NA) in complexes with ligand (drugs) in terms of detailed binding interactions, NA motifs where binding occurs, binding properties, binding modes and classes and links to diseases. Focus will be centered on ligands that bind nucleic acids with implications on diseases of high prevalence region such as HIV/AIDS, cancer, hepatitis, malaria and tuberculosis. The database provide data integration in links to the PDB, PDBeChem (Dimitropoulos et.al., 2006) and other literature resources such as UniProt and PubMed databases.

Methods

NALD was developed by collecting data from various sources, including the Protein Data Bank (PDB), the Cambridge Structural Database (CSD), and the literature. The data was then curated and organized into a user-friendly database that provides detailed information on the interactions between nucleic acids and ligands. The database consists of two models of information storage;

MySql Relational Module and FlaFiles modules. The relational module, created in MySQL database platfrom, is where tables, governed by a database schema, are used to store related information and the linking of the table components is via unique identifier columns or primary keys. The second module, flatfile structure, stores information in plain text files, Figure 1.

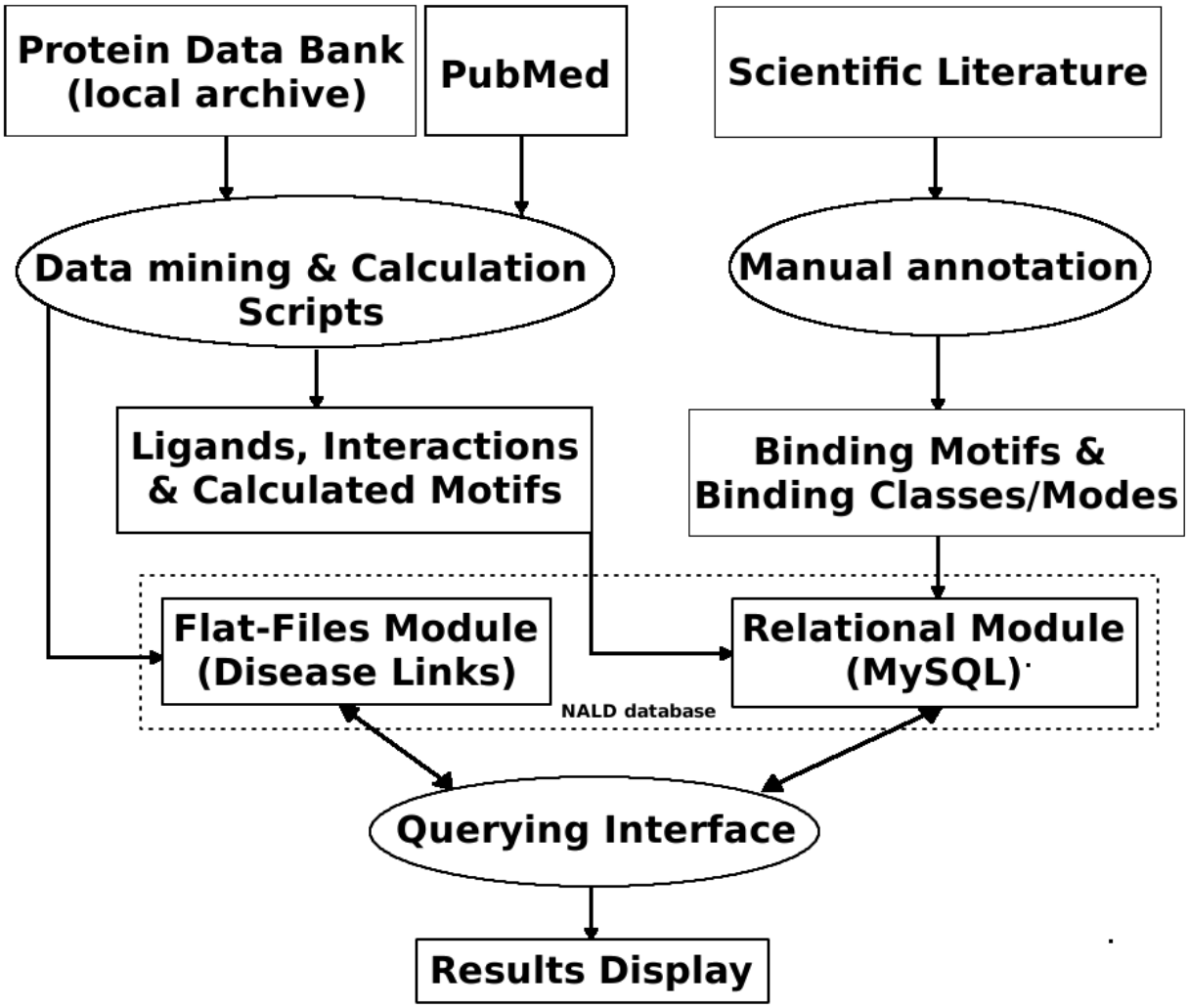


Figure 1 Diagram description of components that make the NALD database. Data is mined from the PDB and PubMed using PHP scripts and conduct calculation of NA/Ligands interaction, calculated binding motifs. Scientific literature is also used for manual extraction of empirical information about NA/Ligands binding motifs and binding binding and properties. The data are then stored into a MySQL based tables. Information about disease links to ligands which is extracted automatically from PubMed is stored in flatfiles format.

The tables present in MySQL were created using PHP scripts that acquire data and simultaneously create and loaded information directly into the MySQL tables. The tables were populated by the data mined from the Ligands Sites Explorer (LSE) website which is a locally developed online system that uses an archive version of the Protein Data Bank (PDB) data. The tables are created with a hierarchical structural component from the PDBid table cascading down to the classes of the ligands. The information pertaining to calculated binding motifs and ligand interactions with nucliec acids are based on exclusively complexes of nucleic acids (DNA, RNA and hybrids) with ligands as found in the PDB. Data related to binding motifs, binding modes/classes and properties have been manually mined from scientific literature and then loaded in MysSQL tables. Disease links data have been mined from the PubMed database.

Results

The database is updated on regular basis and currently contain 2258 NA/Ligands complexes and 917 unique ligands, Figure 3C. Annotated classes of NA–Ligands binding covers Intercalation, Modification, Addition and Cavity fitting in addition to binding modes of ligands to the DNA's Minor Groove, Major Groove and both Minor/Major Grooves. Annotation included binding motifs, binding sites and properties (Figure 3B). In this late version of the NALD database, the PDBe-RCSB Mol* (Sehnal D. et. al., 2021) customized 3D graphics is implemented and used to illustrate the binding of ligands to their NA targets, Figure 4D.

Querying the NALD database:

NALD database offers two ways for data retrieval; “Find Binding details & Disease links:” which is a search box, Figure 2A., and “Browse Ligand/Drug Binding Motifs and Classes:”, which offers links for details of modes of binding, Figure 2B.

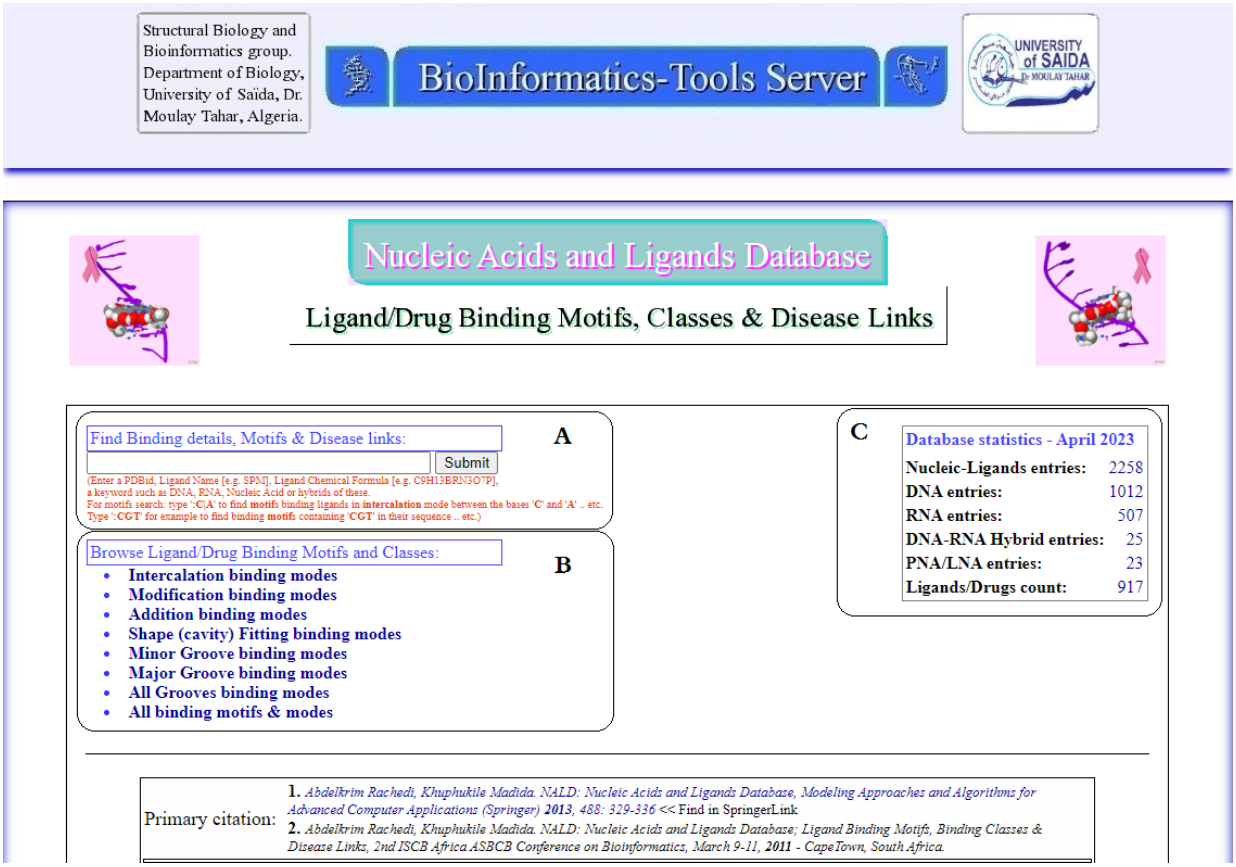
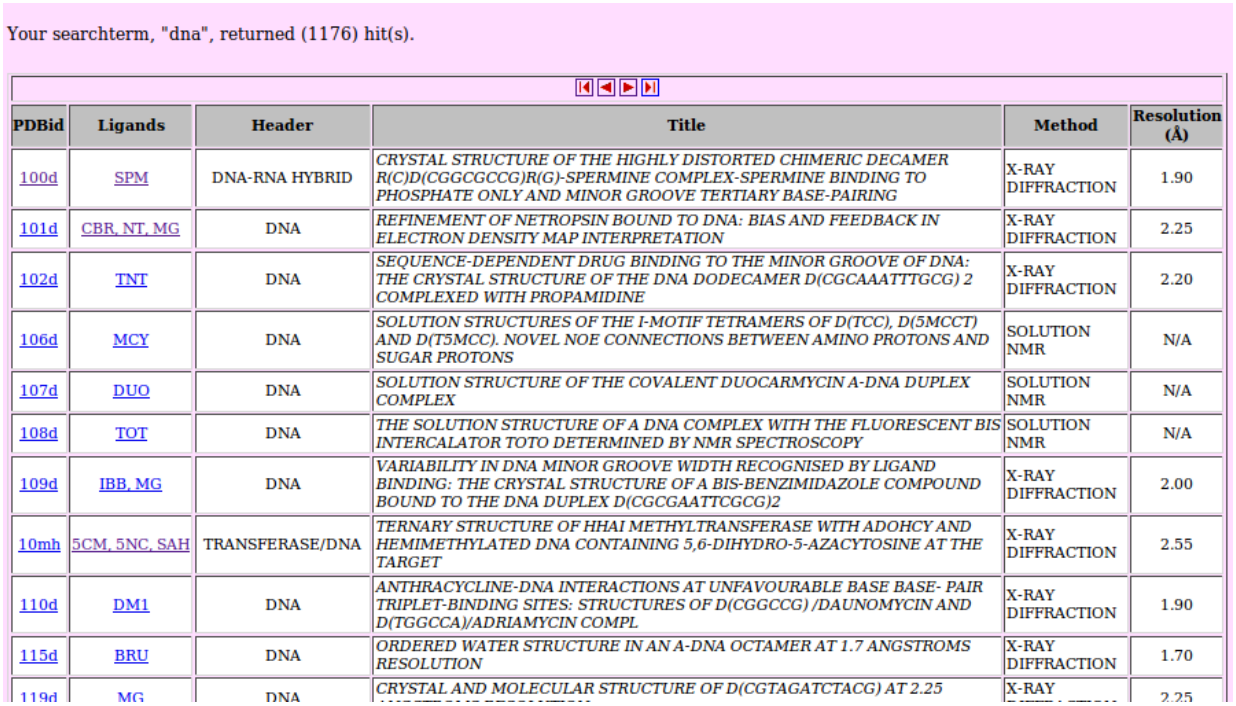


Figure 2. Screenshot from NALD main interface. **A.** search box for information retrieval; "Find Binding details & Disease links:" and **B.** Browse Ligand/Drug Binding Motifs and Classes:. **C.** Monthly updated statistics of the database content.

Find Binding details & Disease links:

This search box allows for both general and specific querying and browsing of the database. Keywords used in the search can be general like 'DNA', 'RNA', 'hybrid' or specific like ligand names such as 'SPM' (3 letter code for the drug known as SPERMIN), full names such as 'Spermin' and chemical formula like 'C10H26N4' (for SPM) and analogues.

NALD displays a results list, Figure 3, which gives a summary list of known 3D structures in the PDB database for nucleic acid molecules (first column), bound ligands (second column) and other useful information such as the title of the published molecules, method used to solve the structures and Resolution at which the structures were solved.



Your searchterm, "dna", returned (1176) hit(s).

PDBid	Ligands	Header	Title	Method	Resolution (Å)
100d	SPM	DNA-RNA HYBRID	CRYSTAL STRUCTURE OF THE HIGHLY DISTORTED CHIMERIC DECAMER R(C)D(CGGCGCCG)R(G)-SPERMINE COMPLEX-SPERMINE BINDING TO PHOSPHATE ONLY AND MINOR GROOVE TERTIARY BASE-PAIRING	X-RAY DIFFRACTION	1.90
101d	CBR, NT, MG	DNA	REFINEMENT OF NETROPSIN BOUND TO DNA: BIAS AND FEEDBACK IN ELECTRON DENSITY MAP INTERPRETATION	X-RAY DIFFRACTION	2.25
102d	TNT	DNA	SEQUENCE-DEPENDENT DRUG BINDING TO THE MINOR GROOVE OF DNA: THE CRYSTAL STRUCTURE OF THE DNA DODECAMER D(CGCAAATTTGCG) 2 COMPLEXED WITH PROPAMIDINE	X-RAY DIFFRACTION	2.20
106d	MCY	DNA	SOLUTION STRUCTURES OF THE I-MOTIF TETRAMERS OF D(TCC), D(5MCCT) AND D(T5MCC). NOVEL NOE CONNECTIONS BETWEEN AMINO PROTONS AND SUGAR PROTONS	SOLUTION NMR	N/A
107d	DUO	DNA	SOLUTION STRUCTURE OF THE COVALENT DUOCARMYCIN A-DNA DUPLEX COMPLEX	SOLUTION NMR	N/A
108d	TOT	DNA	THE SOLUTION STRUCTURE OF A DNA COMPLEX WITH THE FLUORESCENT BIS INTERCALATOR TOTO DETERMINED BY NMR SPECTROSCOPY	SOLUTION NMR	N/A
109d	IBB, MG	DNA	VARIABILITY IN DNA MINOR GROOVE WIDTH RECOGNISED BY LIGAND BINDING: THE CRYSTAL STRUCTURE OF A BIS-BENZIMIDAZOLE COMPOUND BOUND TO THE DNA DUPLEX D(CGCGAATTCGCG)2	X-RAY DIFFRACTION	2.00
10mh	5CM, 5NC, SAH	TRANSFERASE/DNA	TERNARY STRUCTURE OF HHAI METHYLTRANSFERASE WITH ADOHCY AND HEMIMETHYLATED DNA CONTAINING 5,6-DIHYDRO-5-AZACYTOSINE AT THE TARGET	X-RAY DIFFRACTION	2.55
110d	DM1	DNA	ANTHRACYCLINE-DNA INTERACTIONS AT UNFAVOURABLE BASE BASE- PAIR TRIPLET-BINDING SITES: STRUCTURES OF D(CGGCCG) /DAUNOMYCIN AND D(TGGCCA)/ADRIAMYCIN COMPL	X-RAY DIFFRACTION	1.90
115d	BRU	DNA	ORDERED WATER STRUCTURE IN AN A-DNA OCTAMER AT 1.7 ANGSTROMS RESOLUTION	X-RAY DIFFRACTION	1.70
119d	MG	DNA	CRYSTAL AND MOLECULAR STRUCTURE OF D(CGTAGATCTACG) AT 2.25	X-RAY	2.25

Figure 3. Screenshot of the results page for “dna” pdb in the NALD.

Detailed exploration of the ligand binding details with the NA molecule, calculated binding motif and disease links in addition to other useful information about the ligand itself can be generated by clicking on ligand ids, second column, Figure 4. Further information about each PDB entry can be displayed by clicking on the first column which retrieves the entry's summary from the LSE system.

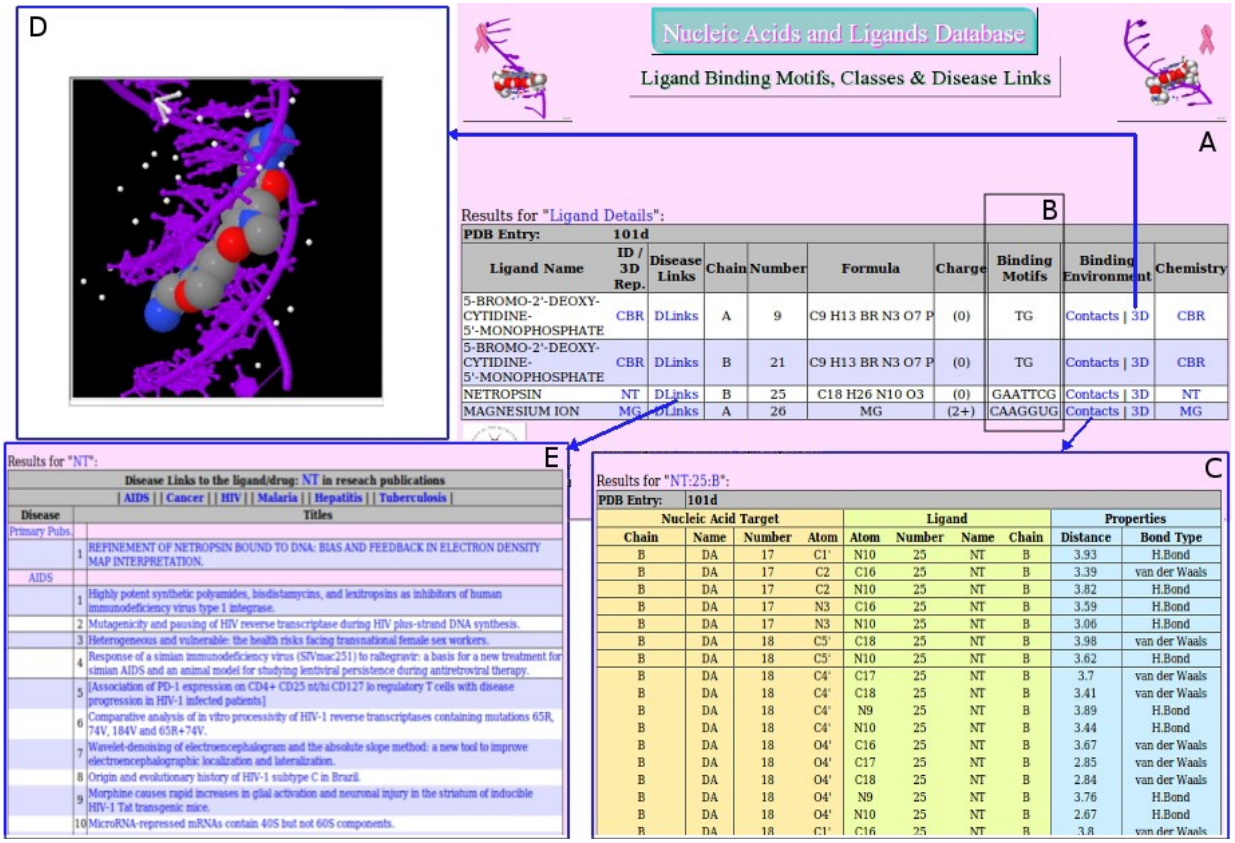


Figure 4. Screenshot of result pages for ligands in the PDB entry 101d; DNA/Ligands complex. **A.** overall list of ligands in the 104d. **B.** Calculated binding NA sequence motifs for each ligand. **C.** Binding details with bond distances and possible types of bonds between the ligand Netropsin (NT) and DNA. **D.** Jmol 3D representation of the DNA/NT binding. **E.** Disease links in relation with the ligand NT pointing to PubMed abstracts.

Find Binding Motifs & Binding Classes:

NALD offers two types of binding motifs, the calculated binding motifs seen above (Figure 4B) and empiric binding motifs reported in scientific literature (e.g. Clark et.al., 1996 and Bunkenborg et.al., 2002) with detailed annotation of the motifs, binding sites, modes, classes and properties (Figure 5A). Classes of NA–Ligands binding covers Intercalation, Modification, Addition and Cavity fitting in addition to binding modes of ligands to the DNA's Minor Groove, Major Groove and both Minor/Major Grooves.

Detailed annotation is associated with each binding motif which includes the NA sequence, binding mode position(s) and types of NA bases involved in the binding, Figure 5B. This is also reflected in the 3D representation, Figure 5C.

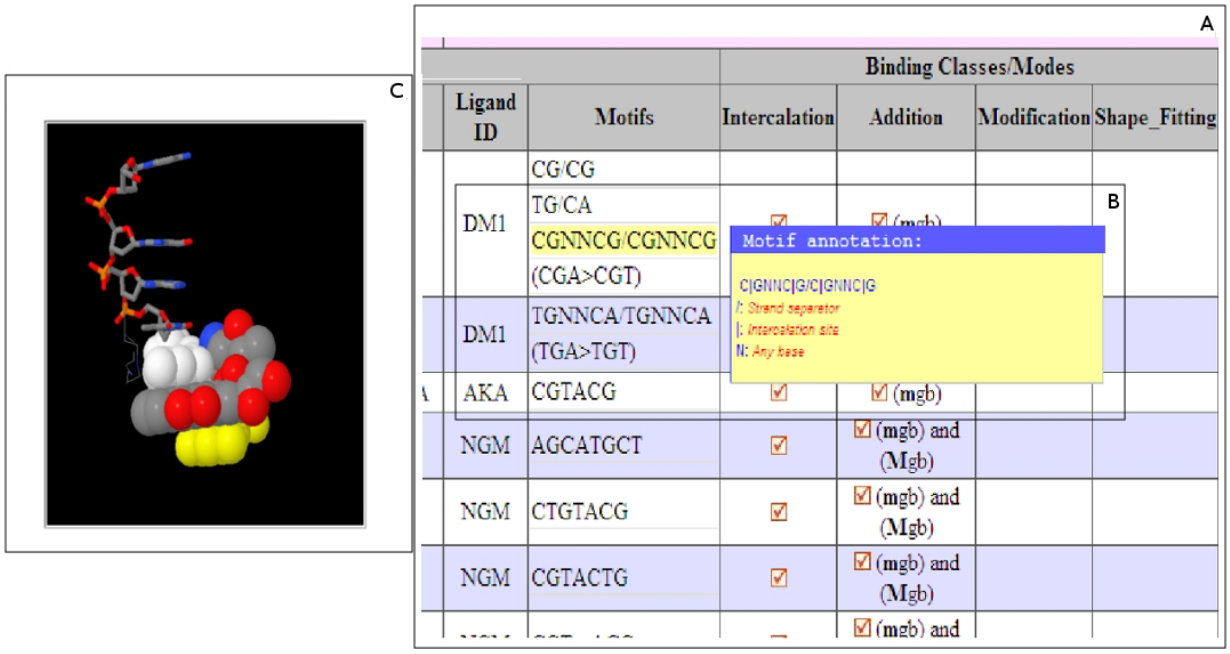


Figure 5. The APHM 3D-viewer displaying the predicted model created based on the DHFR sequence shown in Figure 1 and core regions suitable to the template structure 1U70.

The search box also allows users to search for DNA, RNA or hybrid molecules that binding motifs containing particular bases such as 'CGC' or searching for existing classes and modes of binding adopted by ligands such as typing 'Intercalation' or just 'I:' for finding those ligands that binds in “Intercalation modes” and nucleic acids motifs binding them, and modification ('M:') for finding those ligands that causes “modification” when biding nucleic acids.

Discussion

Nucleic acids are of great biological importance in all organisms and the inability to maintain integrity or tampering with nucleic acids leads to disease. Small chemical molecules or ligands bind nucleic acids in various ways and thus therapeutic strategies are designed from the the identification and study of binding details of these ligands including motifs bound to and modes of binding.

The NALD database, through the numbers of features described above, summarized in points below, has the potential to be instrumental in helping with studies and processes involving the

identification of potential nucleic acids targeted drugs and novel design of new drugs in the fight against diseases currently thriving in the SADC region including the HIV/AIDS pandemic, cancer and other conditions such as tuberculosis (TB), malaria and hepatitis.

NALD is a valuable resource for researchers in the fields of molecular biology, biochemistry, and drug design. One of the main advantages of NALD is its user-friendly interface, which allows researchers to search for specific interactions of interest using various criteria, such as the type of nucleic acid or ligand, the binding affinity, or the three-dimensional structure of the complex. The database is also regularly updated with new information and features, making it a valuable resource for researchers in the field.

Conclusion

NALD represents a significant contribution to the field of molecular biology and biochemistry, providing a comprehensive resource for researchers interested in the interactions between nucleic acids and ligands. By providing detailed information on the molecular interactions between these important biomolecules, NALD can aid in the development of new drugs and therapies.

In conclusion, NALD offers the following features important in biology in general and in relevant area of research including insights into structure-function relationship and rational drug design considerations into fighting high profiled diseases:

1. NALD provides a point of acquisition for categorized information about nucleic acid binding ligand categories including binding motifs, types and classes of the ligands and drugs.

2. The information contained and level of annotations provided in NALD paves the way to drug design strategies and identifying potential in various ligands and drugs.

3. NALD supplies links to medically applicable information related to the ligands centered on current diseases facing large populations of SubSaharan Africa.

4. NALD facilitates crossreferencing with other currently larger databases such as the PDB, UniProt and PubMed and provides a user friendly environment for fast integrated data retrieval from a single system.

References

- Rachedi, A., Madida, K. (2013). NALD: Nucleic Acids and Ligands Database. In: Amine, A., Otmane, A., Bellatreche, L. (eds) Modeling Approaches and Algorithms for Advanced Computer Applications. Studies in Computational Intelligence, vol 488. Springer, Cham. Available at: https://doi.org/10.1007/978-3-319-00560-7_36

- Berman, H.M., Westbrook, J., Freng, Z., Gilliland., Bhat, T.N., Weissig, H., Shindyalov, I. N. and Bourne, P.E. (2000). The Protein Data Bank. Nucleic Acids Res., 28, 235242.

- Bunkenborg,J., Behrens,C., Jacobsen,J.P. (2002). NMR Characterization of the DNA Binding Properties of a Novel Hoechst 33258 Analogue Peptide Building Block. Bioconjugate Chem., 13 (5), pp 927–936

- Clark,G.R., Squire,C.J., Gray,E.J, Leupin,W., Neidle, S. (1996). Designer DNAbinding drugs: the crystal structure of a metahydroxy analogue of Hoechst 33258 bound to d(CGCGAATTCGCG)2. Nucleic Acids Res., 24(24), 4882–4889.

- Dimitropoulos, D., Ionides, J. and Henrick K. (2006). Using PDBeChem to Search the PDB Ligand Dictionary. Current Protocols in Bioinformatics; Chapter 14:Unit14.3., 14.3.114.3.3

- Sehnal, D., Bittrich, S., Deshpande, M., Svobodová, R., Berka, K., Bazgier, V., Velankar, S., Burley, S.K., Koča, J., Rose, A.S. (2021) Mol* Viewer: modern web app for 3D visualization and analysis of large biomolecular structures. Nucleic Acids Research. Available at: https://doi.org/10.1093/nar/gkab314

- NALD. Nucleic Acids and Ligands Database. [Online] Available at: https://bioinformatics.univ-saida.dz/bit2/?arg=SB1

- LSE: http://emboss.bioinf.wits.ac.za/lse

- MySQL: The MySQL RDBMS. http://www.mysql.com

- PMID: http://www.ncbi.nlm.nih.gov/PubMed

Journal of **Concepts in Structural Biology & Bioinformatics**

STRUCTURE & FUNCTION ARTICLES

Concept article

How does the antidepressant ESCitalopram work & Prospects for Rationally Designing of new 'Antidepressants' .. the 3D-structural perspective.

RACHEDI Abdelkrim

Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Natural and Life Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

Correspondence: RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz

Published: 11 April 2023

Depression is a major public health issue, affecting over 300 million people worldwide. While antidepressant medications have been available for decades, their efficacy and tolerability are variable, and many patients require multiple trials of different medications before finding one that works for them. Furthermore, many of the currently available antidepressants, including escitalopram, have significant side effects.

Escitalopram, Figure 1, is a selective serotonin reuptake inhibitor that increases the availability of serotonin in the brain, leading to increased activation of serotonin receptors and a reduction in symptoms of depression and anxiety. However, it is not effective for all patients, and its side effects can be significant. Therefore, there is a need for the development of new and better antidepressant medications.

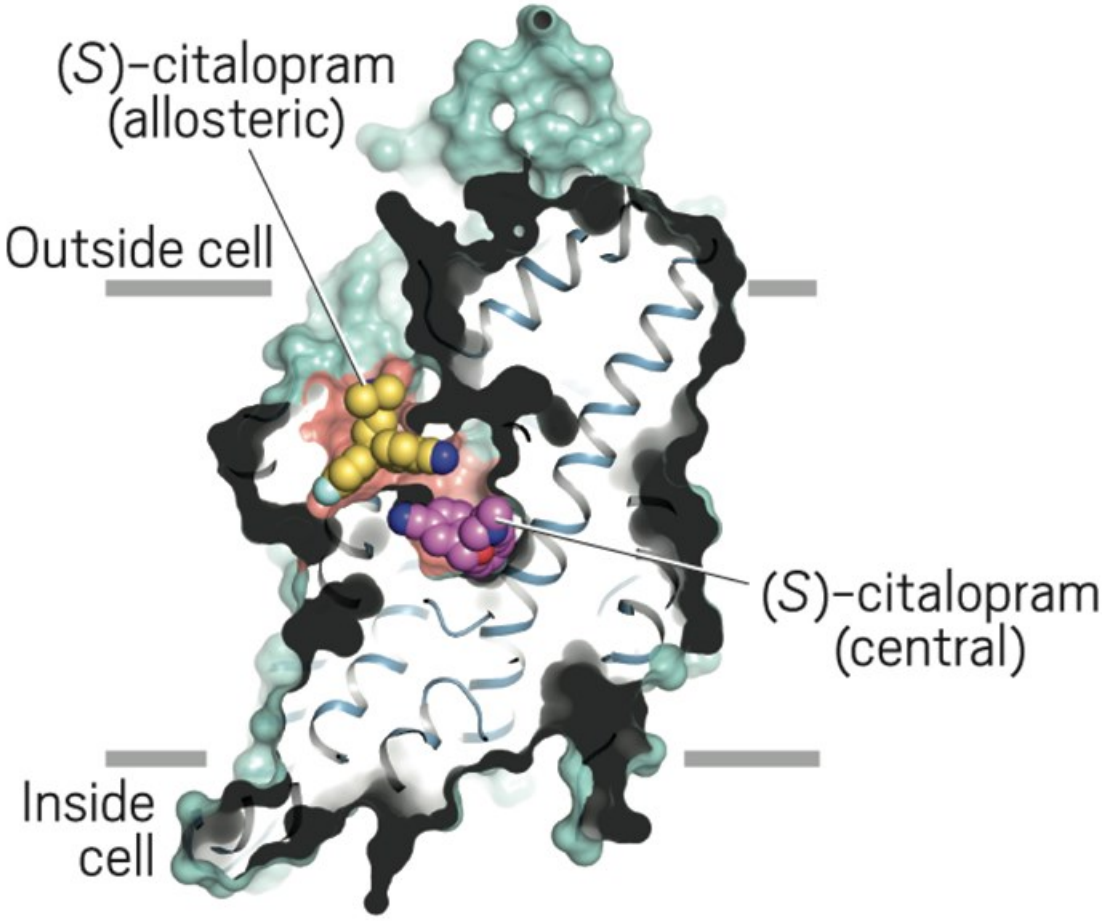


Figure 1. (S)-citalopram binds to both the central (green) and allosteric (blue) binding sites. (Nature) see: https://cen.acs.org/articles/94/i15/last-scientists-solve-structure-protein.html

A number of 3D-structures have been determined, using x-ray crystallography, 2016, of the Human Serotonin Transporter (SERT) many in complex forms bound with selected derivatives of the antidepressant ESCitalopram, Figuer 2. The structures contribute towards gaining incites into the working mechanism of the antidepressant and analysing the intriguing discovery that ESCitalopram can also bind to the allosteric site of the Serotonin transporter in addition to the central active site (S1) !! Follow the SSFS tool links provided below and see the attached images.

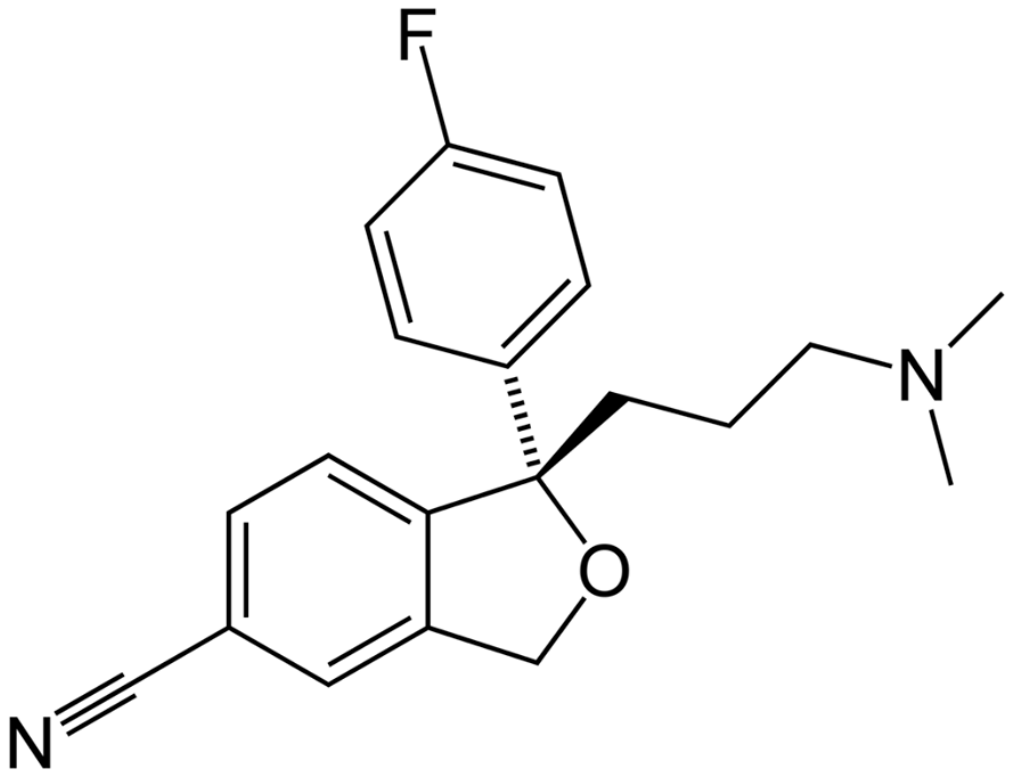


Figure 2. Chemical formula of the (S)-citalopram

Such discovery has set this protein as important target for the new and more effective antidepressants via the Rational Drug Design and alike techniques. For more details, follow the link:

☛ At last, scientists solve structure of protein that antidepressants target
https://cen.acs.org/articles/94/i15/last-scientists-solve-structure-protein.html

The technical papers is available in Nature:

☛ X-ray structures and mechanism of the human serotonin transporter
https://www.nature.com/articles/nature17629

The paper describes the determination of the three-dimensional structure of the SERT, which is a protein that plays a crucial role in the regulation of serotonin levels in the brain. The researchers used X-ray crystallography to determine the structure of the protein, which revealed important insights into how it functions at the molecular level.

The study also explored the binding of different compounds to the serotonin transporter, including antidepressants and amphetamines, which are known to interact with the protein. The researchers found that these compounds bind to specific regions of the protein and alter its function, which can have therapeutic effects in the treatment of depression and other psychiatric disorders.

The paper also describes the development of a computational model that can predict the binding of different compounds to the serotonin transporter. This model could be used to design new drugs that target the protein and improve its function.

Exploration of the 3D-structures and binding detail is available via the SSFS tool, on the Bioinformaticstools.org web-site, University of Saida:

1- The TS2 Human Serotonin Transporter, the non-bound apo form, Figure 3.

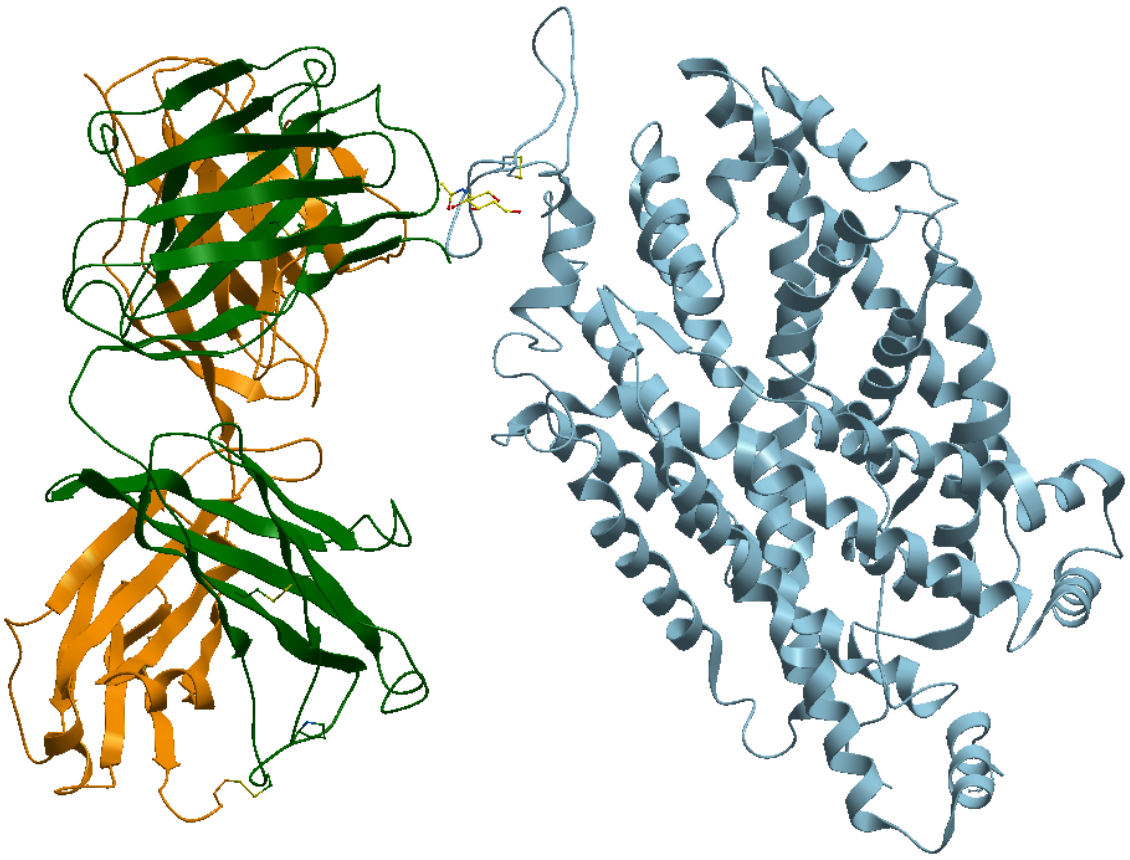


Figure 3. X-ray structure of the ts2 human serotonin transporter https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i6z

2- The TS3 Human Serotonin Transporter in bound form with the antidepressant Paroxetine known commercially as Paxil, Pexeva and Seroxat among other brands, Figure 4.

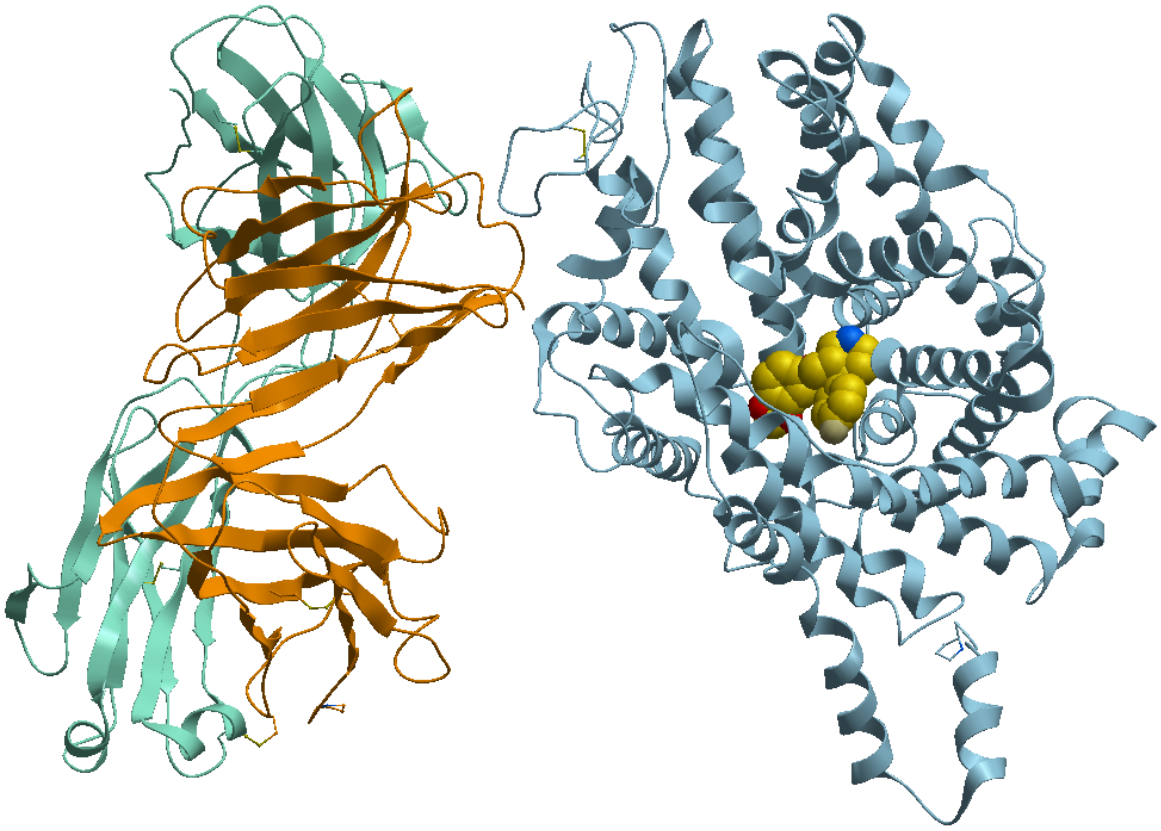


Figure 4. X-ray structure of the ts3 human serotonin transporter compl paroxetine at the central site. https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i6x

3- The TS3 Human Serotonin Transporter in bound form, at the S1, with the antidepressant S-Citalopram (the optical isomer S-(+)) known commercially as Cipralex, and Lexapro among other brand names, Figure 5.

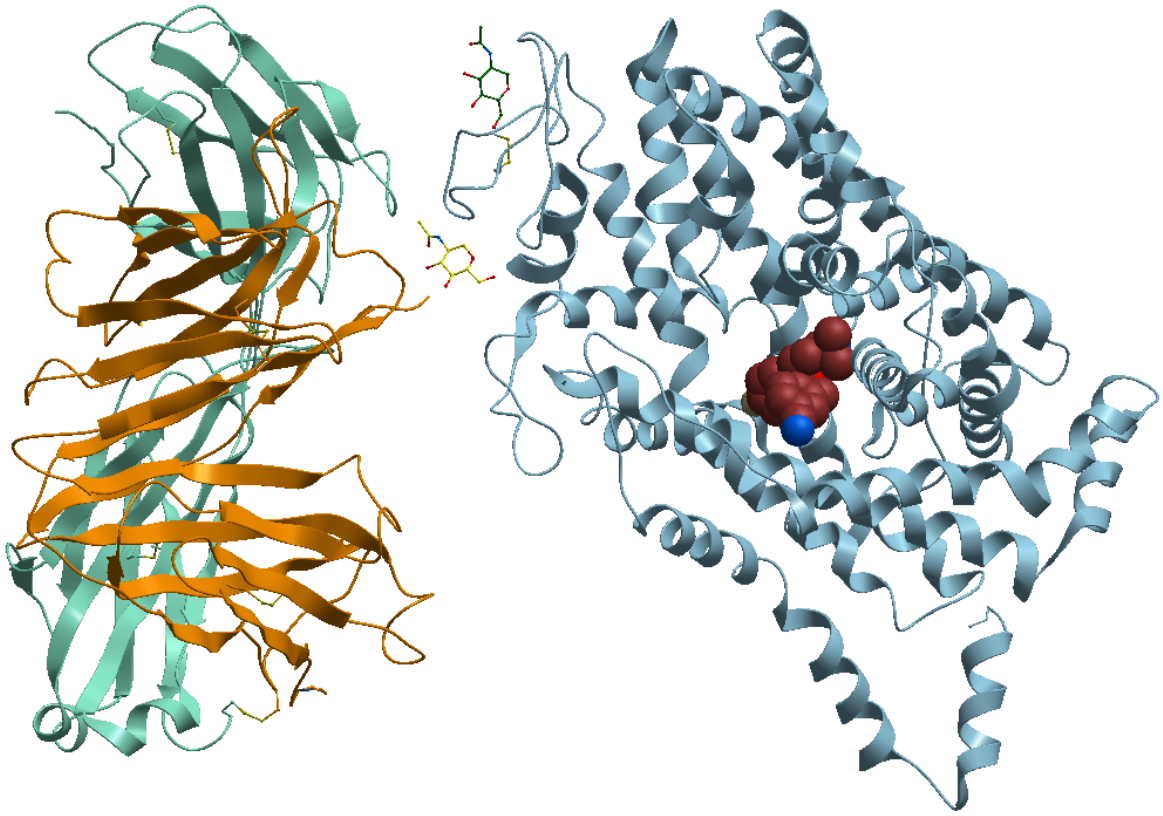


Figure 5. X-ray structure of the ts3 human serotonin transporter compl s-citalopram at the central site. https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i71

4- The TS3 Human Serotonin Transporter in bound form with the antidepressant S-Citalopram (the optical isomer S-(+)) at the two sites; the central S1 and allosteric site (S2), Figure 6.

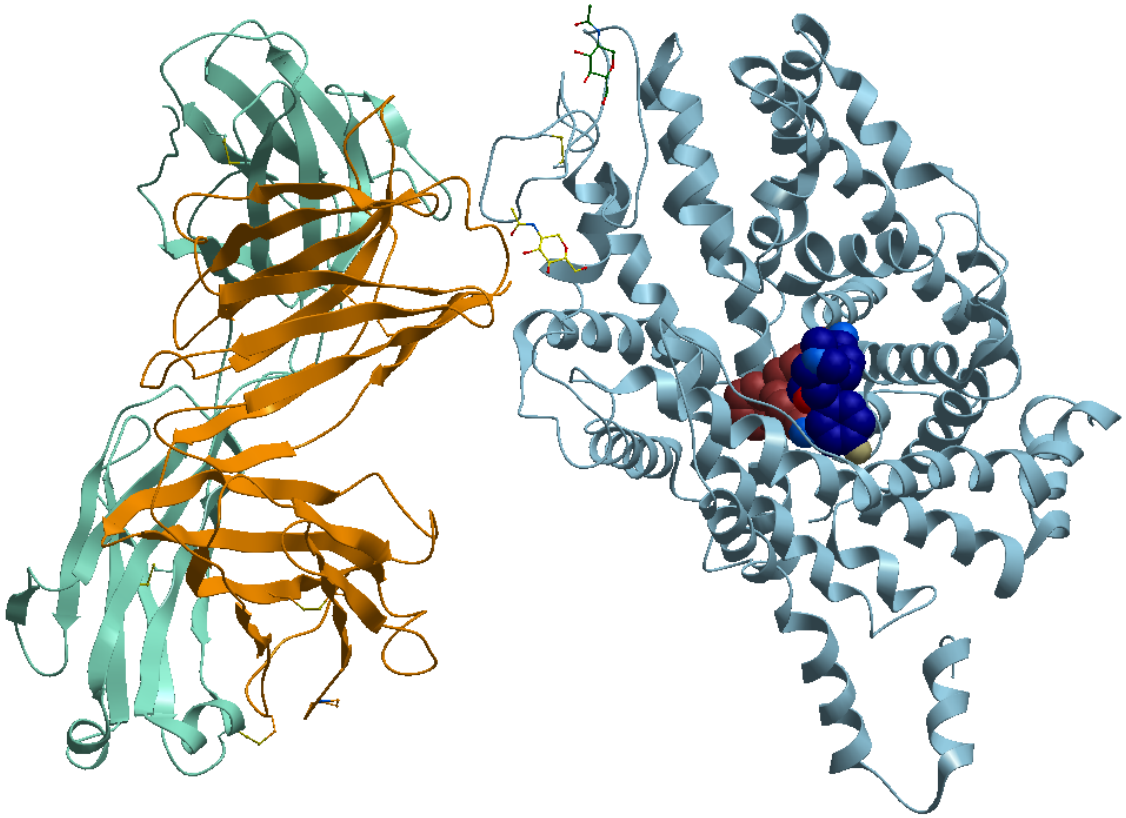


Figure 6. X-ray structure of the ts3 human serotonin transporter compl s-citalopram at the central and allosteric sites. https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i73

5- The TS3 Human Serotonin Transporter in a bound state with a drug under study, derived from the compound S-Citalopram which bear the name Br-Citalopram, where the fluoride group has been replaced by bromine. The binding is at the central active site, Figure 7.

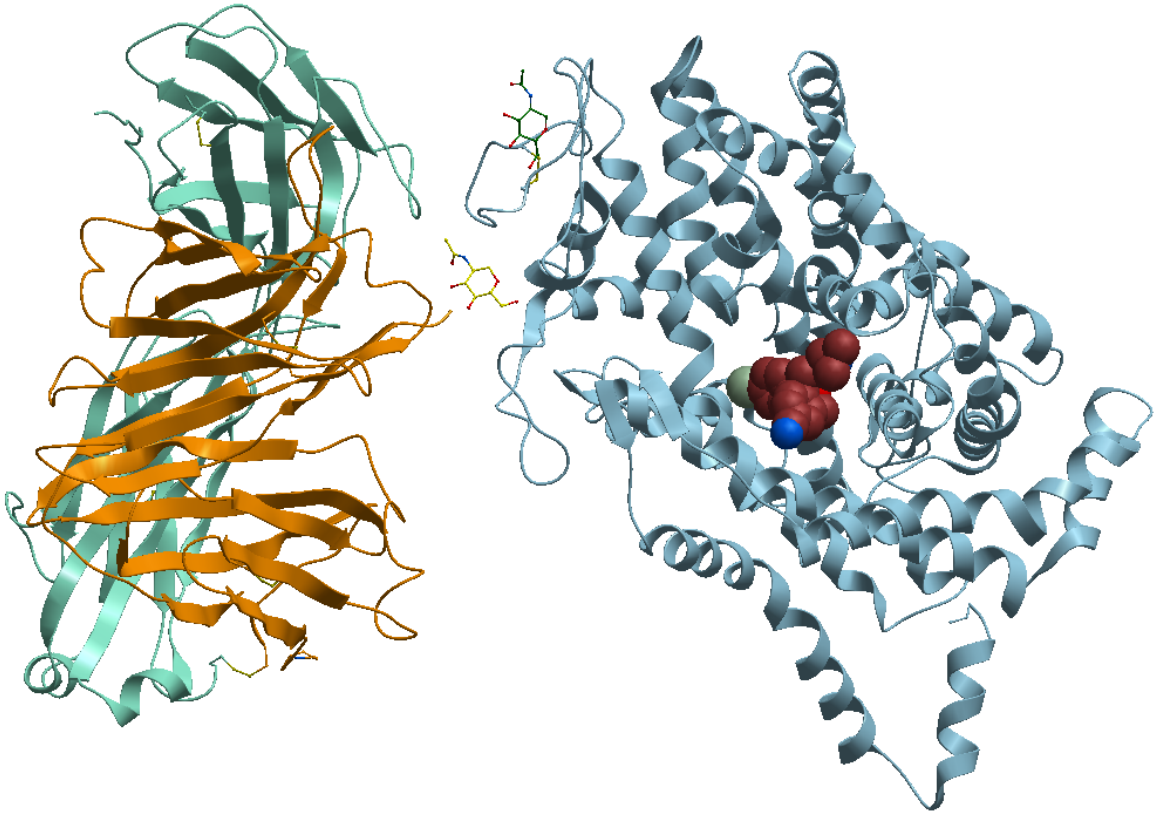


Figure 7. X-ray structure of the ts3 human serotonin transporter compl br-citalopram at the central site. https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i74

6- The TS3 Human Serotonin Transporter in a bound state with the drug S-Citalopram and the derivative Br-Citalopram both at the central active site, Figure 8.

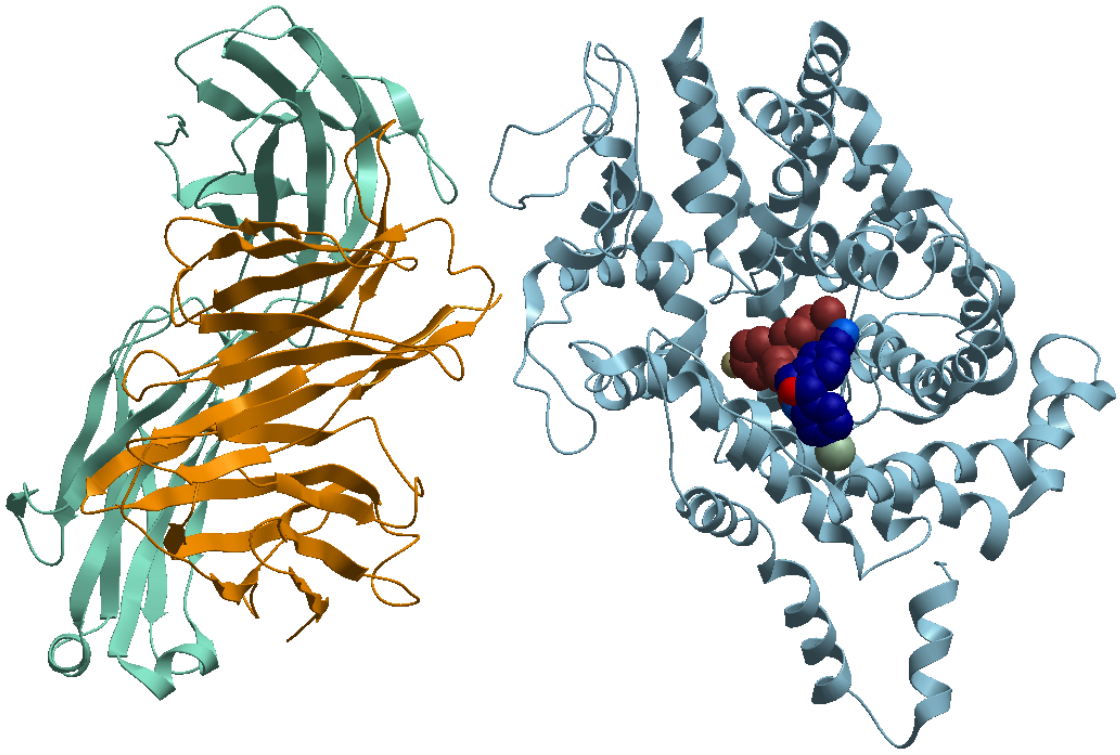


Figure 8. X-ray structure of the ts3 human serotonin transporter compl s-citalopram at the central site and br-citalopram at the a site.
https://bioinformaticstools.org/ssfs/ssfs.php?qry=5i75

The antidepressants and stimulants bind to specific regions of the serotonin

According to the paper the antidepressants and amphetamines bind to specific regions of the SERT through non-covalent interactions, including hydrogen bonds, salt bridges, and pi-pi stacking interactions. These interactions occur between the chemical groups on the compound and specific amino acids in the protein, particularly those located in the binding site of the transporter.

For example, antidepressants such as fluoxetine and paroxetine bind to the S1 site of the transporter, which is located in the extracellular vestibule of the protein. In this site, the compounds interact with several amino acids, including Asp98, Asp437, and Tyr176, through hydrogen bonds and salt bridges. These interactions stabilize the binding of the compound to the protein and prevent the reuptake of serotonin into the presynaptic

neuron, leading to increased levels of serotonin in the synaptic cleft.

On the other hand, amphetamines such as methamphetamine and MDMA bind to the S2 site of the transporter, which is located deeper within the protein. In this site, the compounds interact with amino acids such as Phe335, Tyr350, and Ser422 through pi-pi stacking interactions and hydrogen bonds. These interactions induce a conformational change in the protein, leading to the reverse transport of serotonin out of the presynaptic neuron and into the synaptic cleft.

The specific regions of the protein that these compounds bind to and the type of interactions involved can determine their mechanism of action and potential therapeutic effects.

Function alteration of the SERT upon antidepressants bounding

Alteration to the function of the SERT occurs upon binding the compounds such as antidepressants and amphetamines. Once bound, these compounds can modulate the activity of the transporter in different ways.

Antidepressants such as fluoxetine and paroxetine block the reuptake of serotonin into the presynaptic neuron by binding to the S1 site of SERT. This prevents the serotonin from being removed from the synaptic cleft, leading to increased levels of serotonin in the brain. The binding of antidepressants to SERT can also induce conformational changes in the protein, which can further affect its function. For example, the binding of fluoxetine has been shown to increase the affinity of SERT for serotonin and decrease the rate of serotonin transport.

Amphetamines such as methamphetamine and MDMA, on the other hand, bind to the S2 site of SERT and induce the reverse transport of serotonin out of the presynaptic neuron and into the synaptic cleft. This causes a rapid increase in the levels of serotonin in the brain, which can lead to a feeling of euphoria. The binding of amphetamines to SERT also induces conformational changes in the protein, which can further enhance their activity. For example, the binding of methamphetamine has been shown to increase the rate of serotonin transport and decrease the affinity of SERT for serotonin.

The binding of these compounds to specific regions of SERT alters the activity of the transporter by blocking or enhancing the reuptake of serotonin, inducing conformational changes in the protein, and affecting the affinity and rate of serotonin transport. These effects can lead to changes in the levels of serotonin in the brain

and have therapeutic implications for the treatment of depression and other psychiatric disorders.

X-ray structural based computational modelling and Prospects for new antidepressant drugs.

The paper study describes the development of a computational model that can predict the binding of different compounds to the serotonin transporter (SERT) based on its three-dimensional structure. This model was developed using molecular dynamics simulations and docking studies, which allowed the researchers to predict the interactions between the protein and different compounds.

The computational model was based on the X-ray crystallography data of the human SERT in complex with various ligands, including antidepressants and amphetamines. The researchers used this data to create a molecular model of SERT, which was then subjected to molecular dynamics simulations to simulate the behavior of the protein in a dynamic environment.

Docking studies were then performed to predict the binding of different compounds to SERT based on their chemical structure and the interactions observed in the X-ray crystallography data. The researchers validated the computational model by comparing its predictions to experimental data on the binding of different compounds to SERT.

The computational model was shown to accurately predict the binding of different compounds to SERT, including those with high affinity for the protein such as antidepressants and amphetamines. The model can be used to design new compounds that target SERT and improve its function, as well as to predict the potential side effects of existing drugs that target the protein.

Overall, the determination of the structure and function of the SERT has important implications for our understanding of brain function and the development of new treatments for psychiatric disorders.

The development of this computational model provides a powerful tool for understanding the molecular interactions between SERT and different compounds, which can help in the development of new treatments for psychiatric disorders.

The structures can also be explored using the PDB database;

☛ https://pdbe.org

☛ https://www.rcsb.org

References

- Coleman, J., Green, E. & Gouaux, E. X-ray structures and mechanism of the human serotonin transporter. Nature 532, 334–339 (2016). https://doi.org/10.1038/nature17629
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Apr 7;391(10128):1357-1366. doi: 10.1016/S0140-6736(17)32802-7.
- Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry. 2017 Sep;4(9):409-418. doi: 10.1016/S2215-0366(17)30135-1.

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ANTIBIOTICS RESISTANCE ARTICLES

Concept article: Review

Antibiotic Resistance: A Global Public Health Crisis and Current Strategies for Combatting It

BENABBOU Taha Ahmed[1], BENREGUIEG Mokhtar[1], BELLIL Yahia[1,2], CHAHROUR Wassila[1,2]

1. Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants Compus Ain El Hadjar, Faculty of Sciences, Department of Biology, University of Saida Dr Tahar Moulay, 20100 Saida, Algeria.
2. Laboratory of Applied Microbiology, Department of Biology, Faculty of Nature Science and Life, University of Oran 1 Ahmed BENBELLA, B.P. 16, Es-Sénia,31100 Oran, Algeria.

Correspondence:
E. mail : t.a.benabbou@gmail.com , taha.benabbou@univ-saida.dz

Abstract

Antimicrobial resistance is a significant global public health problem. Antibiotic-resistant bacteria have emerged as a result of inappropriate and excessive use of antibiotics, rendering treatment ineffective and increasing morbidity and mortality rates. The effectiveness of currently available antibiotics has already been compromised due to the emergence of multi-resistant bacteria. Steps have been taken globally to prevent and combat antibiotic resistance by promoting best practices in infection control, encouraging the judicious use of antibiotics, developing new antibacterial drugs, and raising public awareness. Current approaches to combating antibiotic resistance are reviewed in this article, including methods for improving antibiotics, halting the spread of antibiotic resistance, and investigating unconventional therapies such as antimicrobial peptides, riboregulators, nanoparticles, and phage therapy. Current problems and future prospects in the fight against antibiotic resistance are also discussed.

Key words: Antibiotic-resistant, antimicrobial peptides, ATP synthase inhibitors, Riboregulators, Nanoparticles, Phage therapy, CRISPR-Cas

Introduction

Antibiotic resistance is a growing public health issue on a global scale. Antibiotics were discovered more than 80 years ago and have saved millions of lives by treating bacterial illnesses (Martens & Demain, 2017). However, their inappropriate and excessive use has resulted in the development of bacteria resistant to antibiotics, rendering treatments ineffective and raising the rates of morbidity and mortality (Wang et al., 2021).

Antibiotic resistance can result from a variety of factors, including inappropriate or excessive antibiotic use, the spread of antibiotic-resistant bacteria from one person to another, a lack of infection prevention and hygiene measures, and the widespread use of antibiotics in farm animals (Bungau et al., 2021). However, due to multi-resistant bacteria, currently available antibiotics are already at their limit. According to OMS estimates, if superbugs continue to spread over the world, there will be 10 million infection-related deaths annually by the year 2050, with a cost to the global economy of more than $100 billion (Engström, 2021).

International action has been taken to create measures to avoid and combat antibiotic resistance as a result of this public health issue. Governments, health organizations, and health professionals are collaborating to promote good infection control procedures, advocate the prudent use of antibiotics, develop new antibacterial medications, and increase public awareness of the significance of antibiotic resistance (Engström, 2021).

We shall examine current tactics to tackle antibiotic resistance in this essay. We'll talk about several strategies for preventing antibiotic resistance as well as continuing initiatives to create new medications and enhance antibiotic prescribing procedures. Finally, we'll look at the ongoing issues and potential future developments in the fight against antibiotic resistance.

Current strategies to combat antibiotic resistance

Since the discovery of the first case of antibiotic resistance in the 1940s, pharmaceutical companies have continued to develop solutions and strategies, including pharmacological ones, to limit its occurrence. The main current strategies to fight antibiotic resistance can be summarized in several points (Fig. 1).

1. Strategies for improving antibiotics: optimizing existing structures and creating new molecules

Two crucial strategies in the battle against antibiotic resistance are altering the structure of existing antibiotics and developing novel ones.

The first strategy entails enhancing the chemical composition of outdated antibiotics. An antibiotic's structure can be changed by scientists to improve the antibiotic's capacity to kill resistant bacteria or to more effectively reach its bacterial target. Additionally, structural alterations can lessen the antibiotic's toxicity for the patient.

Penicillin was changed to produce β-lactam antibiotics as an illustration of how outdated antibiotics might be strengthened structurally. Although β-lactams are frequently used as antibiotics to treat bacterial infections, resistance to them is on the rise. Scientists have created third-generation cephalosporins, which are more potent and efficient against resistant bacteria, as new β-lactam antibiotics to address this issue.

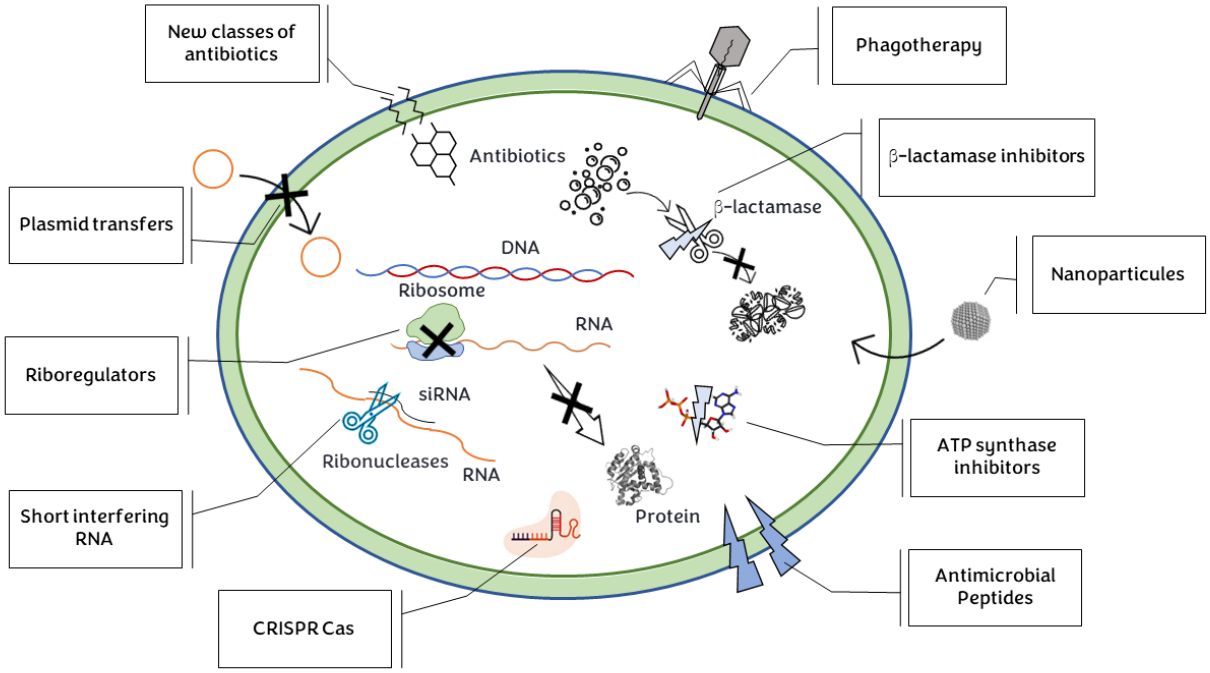


Fig. 1: Strategies and bacterial targets used to combat antibiotic resistance

In clinical investigations including more than 2,500 patients with skin and soft tissue infections as well as community-acquired bacterial pneumonia (File et al., 2011), ceftaroline, a chemical from the same family as beta-lactams that was created in 2008, was proven to be beneficial. An important step forward in the fight against antibiotic resistance is represented by this chemical (Zhanel et al., 2009).

In a similar vein, plazomicin is a brand-new chemical from the aminoglycosides class that was created to reduce antibiotic resistance (Becker & Cooper, 2013; Bush, 2012). Contrarily, eravacyline, a member of the new tetracycline generation, was created for the same goal as plazomicin, namely, to restrict bacterial resistance, notably against particular active efflux and ribosome protection (Grossman et al., 2015).

The use of β-lactamase inhibitors such as clavulanic acid (Matsuura et al., 1980), sulbactam (Bush, 2012), tazobactam (Kuti et al., 2015), avibactam (Olsen, 2015; Soroka et al., 2016), and relbactam can reinforce the structural improvement of older antibiotics (Lucasti et al., 2016; Olsen, 2015). These inhibitors allow for the neutralization of the enzymes that some bacteria produce in order to resist antibiotics. In addition, the use of selenium (sodium bismuth citrate) in conjunction with metronidazole and tetracycline can effectively combat *Helicobacter pylori*, the bacterium that causes gastrointestinal infections (Bouyssou, 2014). These tactics are crucial ways to increase the effectiveness of currently used antibiotics and make them more bacterial resistance-resistant.

2. The antimicrobial peptides (AMPs)

The discovery of the enzyme lysozyme in 1922 by Alexander Fleming was a major breakthrough in our understanding of how the immune system fights bacterial diseases. Lysozyme was the first example of an antimicrobial agent that was found to be naturally occurring in the body (Alexander Fleming, 1922). However, it took several decades for researchers to identify other antimicrobial peptides (AMPs), which are tiny molecules produced by the body in response to bacterial or fungal infections. The first AMPs were discovered in Drosophila in the 1990s, and this discovery paved the way for further research into the development of antimicrobial medications and a better understanding of how AMPs can prevent infections (Unckless et al., 2016).

AMPs are an important tool in the fight against a wide range of pathogens, including pathogenic bacteria and fungi. One of the most intriguing aspects of AMPs is their ability to combat antibiotic resistance, as they only result in limited bacterial resistance compared to conventional antibiotics. Most AMPs work by breaking down the bacterial cell membrane, causing permeabilization and cell lysis, which has a bactericidal effect (Fig. 2). Some AMPs can also penetrate the bacterial membrane and target anionic molecules, such as enzymes or nucleic acids, which disrupt the bacterial cell's biological functions. This dual mechanism of action makes AMPs a promising avenue for future research and drug development (Mahlapuu et al., 2016; Spohn et al., 2019).

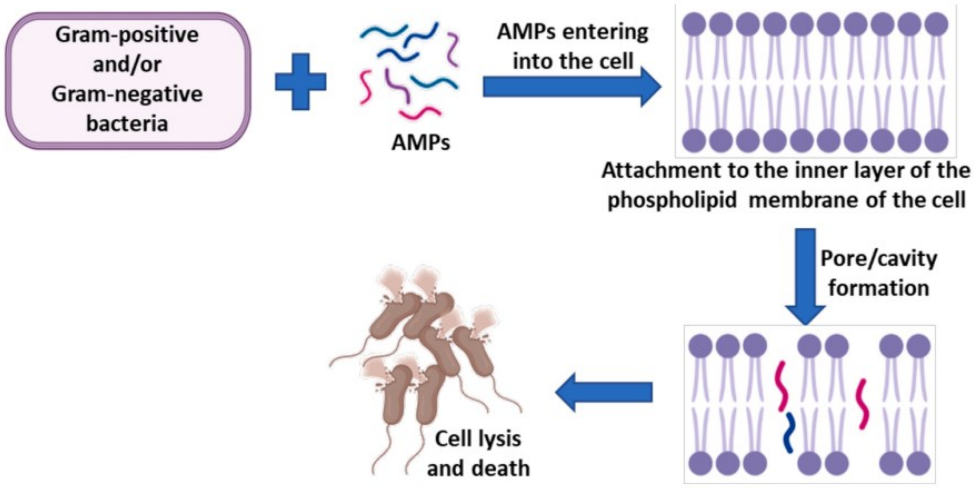


Fig. 2: Mechanism of action of antimicrobial peptides (Fatima et al., 2021)

3. Riboregulators

Riboregulators are RNA molecules that interact with target mRNAs to regulate the expression of certain genes. They can either stop protein synthesis by binding to the mRNA and blocking its translation or start it by allowing the mRNA to be translated. In 2007, researchers proposed the idea of using ribregulators as potential targets to interfere with the production of critical proteins in bacteria, using them as an alternative to the conventional strategy of targeting bacterial proteins (Ogawa & Maeda, 2007).

Complex mechanisms that trigger gene expression in response to antibiotic exposure frequently control antibiotic resistance genes. Recent research reveals that the expression of several resistance genes is significantly regulated by cis-active non-coding RNAs known as riboregulators. These RNAs, known as riboregulators, are found in the 5'UTR region of regulated genes and detect the presence of antibiotics by directing translating ribosomes to short, non-coding upstream reading frames (uORFs), which are embedded in the RNA. Antibiotics that limit translation cause the ribosomes to stop on the uORF, changing the structure of the regulator RNA and causing the expression of the resistance gene to become active (Fig. 3). The ability of these regulators to identify particular antibiotic classes depending on the size and make-up of the relevant uORF determines how specific they are (Dar & Sorek, 2017).

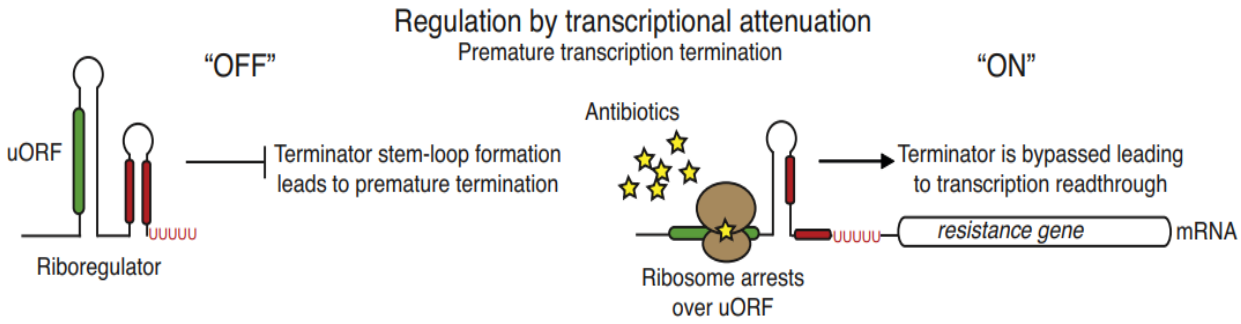


Fig. 3: By managing the creation of a premature transcription terminator, which is a stem-loop structure followed immediately by a poly uridine tract, transcriptional attenuation controls expression. Antibiotics are not present, so transcription starts but ends early. The resistance gene's transcription is aided by ribosome pausing over the uORF, which prevents the development of terminator stem loops (Dar & Sorek, 2017).

Studies have shown that specific binding of a chemical, PC1, to a guanine ribo regulator in *S. aureus* inhibits bacterial growth in vitro and in vivo in mice by binding to the regulatory region of the target RNA. These results suggest that rioregulators may be a promising target for the development of new antibiotics by interfering with the production of critical proteins in bacteria (Mulhbacher et al., 2010).

4. Prevention of horizontal genetic material transfer between bacteria

One of the main factors contributing to the spread of antibacterial resistance is the exchange of genetic material between bacterial communities. In fact, bacteria are capable of exchanging resistance genes with one another, allowing them to develop a resistance to new antibiotics. This strategy relies on the use of conjugation inhibitors since inhibiting proteins that participate in conjugation (such as relaxase, pili, and others) prevents the transfer of plasmides to different hosts, promoting the eradication of plasmides from bacterial populations (Fig. 4) (Cabezón et al., 2017; Dimitriu et al., 2014; Getino & de la Cruz, 2018). Several strategies, including the use of ionophores, chlortetracycline, bacitracin, and combinations of ionophores/antimicrobials, have been investigated to restrict the horizontal transfer of antibiotic resistance. According to studies, these techniques are particularly good at preventing the horizontal spread of antibiotic resistance in *E. coli*. Various natural substances, including flavonoids, plant extracts, and antimicrobial peptides, have been proven in other investigations

to be able to prevent horizontal gene transfer. Similar to this, artificial compounds have been created that precisely target the bacterial conjugation-related proteins.

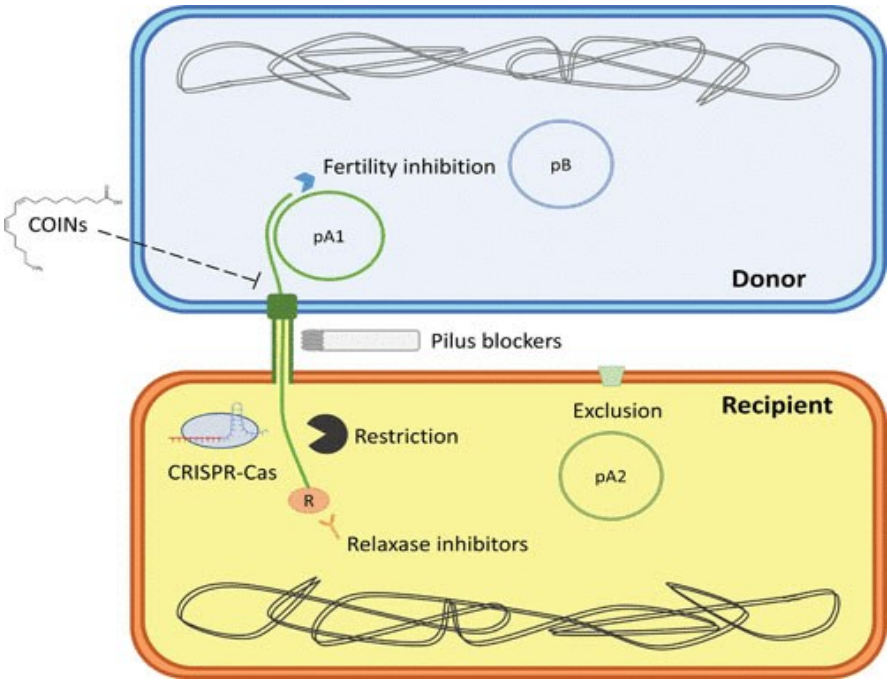


Fig. 4: Natural and Artificial Mechanisms Controlling Conjugative Plasmid Transmission: RM and CRISPR-Cas Systems, Exclusion Systems, and Fertility Inhibition Systems as Natural Mechanisms, and Relaxase, Pilus, and ATPase Interference as Artificial Mechanisms (Getino & de la Cruz, 2018)

5. ATP synthase inhibitors

A new class of antibiotics, known as ATP synthase inhibitors, includes the antitubercular drug Bedaquiline. It works by preventing the synthesis of ATP, a vital energy molecule for bacterial growth and survival, especially for *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Bedaquiline limits bacterial growth by obstructing its energy metabolism by selectively blocking ATP synthase. This approach works well against *Mycobacterium tuberculosis* strains that are resistant to widely used drugs (Hards et al., 2015).

The efficacy of Bedaquiline in the treatment of tuberculosis has been supported by numerous studies, notably in patients with multidrug-resistant forms of the disease. To increase its potency and reduce the possibility of resistance forming, Bedaquiline is frequently used in conjunction with other antibiotics. Additionally, research continues to explore other ATP

synthase inhibitors and understand their mode of action to improve the treatment of tuberculosis and other bacterial infections (Hards et al., 2015; Maitre et al., 2017).

The mechanism of action of bedaquiline, the first drug to target mycobacterial ATP synthase, is illustrated in Fig. 5 ATP synthase is a crucial enzymatic complex for the production of ATP, necessary for cellular survival in both prokaryotes and eukaryotes. The complex consists of a transmembrane domain (F0) and a cytoplasmic domain (F1), and protonation through the F0 domain leads to a rotation of the c and γ subunits of the F1 domain, resulting in ATP synthesis. Bedaquiline binds to the binding site between the a and c subunits of the F0 domain and inhibits ATP production by blocking proton flow and subsequent conformational changes, resulting in cell death in both replicating and non-replicating mycobacteria. Despite the high similarity in protein sequence with the human homologue, bedaquiline is selective towards mycobacterial ATP synthase (Goulooze et al., 2015; Guglielmetti & Robert, 2015; Singh et al., 2017)

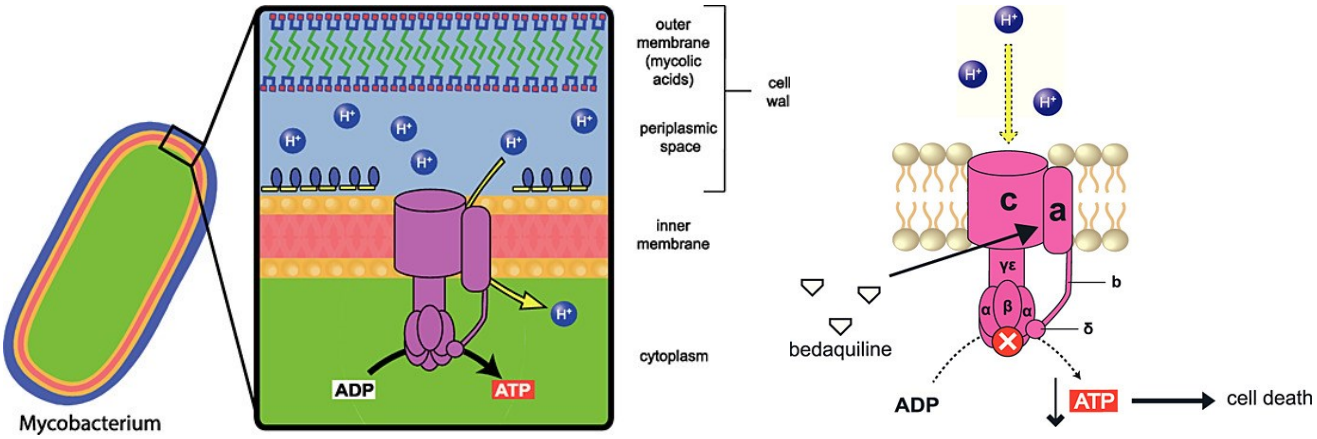


Fig. 5: Mechanism of action of bedaquiline (Goulooze et al., 2015)

6. Nanoparticles

The use of nanotechnology in medicine is a cutting-edge strategy that attempts to enhance the treatment of many serious diseases. Using nanovectors, which are incredibly small particles (on the scale of nanometers) capable of transporting active ingredients to their pharmacological target in the body, medications are administered using this technology (Haleem et al., 2023). In comparison to traditional medication administration techniques,

nanovectors have improved bioavailability and more controlled release of active components. They can also target diseased cells or damaged tissues directly, minimizing adverse effects and collateral harm to healthy organs (Damodharan, 2021).

The antibacterial activity of nanoparticles has been explained by a number of different mechanisms of action. The electrostatic interaction between positively charged nanoparticles and the negatively charged bacterial cell membrane, which can result in cell membrane breakdown, the release of poisonous metal ions, and the eradication of bacteria, is one of the most researched mechanisms (Staroń & Długosz, 2021). Nanoparticles can also interfere with biological functions like respiration, protein synthesis, and DNA replication in order to impair bacterial metabolic processes. Free radicals, unstable molecules with unpaired electron atoms that can harm bacterial membranes and proteins, can also be produced by nanoparticles (Sánchez-López et al., 2020). Additionally, bacterial biofilms, which are bacterial colonies enmeshed in a protective extracellular matrix, can interact with nanoparticles. Chronic infections are frequently linked to biofilms, which are notorious for their resistance to conventional medicines. By disrupting the extracellular matrix and penetrating biofilms, nanoparticles can make bacteria more susceptible to antibiotic therapy (Gudkov et al., 2021; Sánchez-López et al., 2020).

Recent studies have also emphasized the antibacterial characteristics of specific nanoparticle components such iron, zinc, copper, and silver oxide. Particularly against Gram-positive bacteria like *S. aureus* and *Bacillus subtilis* as well as Gram-negative bacteria like *P. aeruginosa* and *E. coli*, these capabilities have been noted (Franci et al., 2015; Marslin et al., 2015; Yu et al., 2020).

7. Short interfering RNA

Utilizing short interfering RNA (siRNA) is a potential strategy to combat antibiotic resistance (Edson & Kwon, 2014). This method targets specific DNA or RNA regions on a bacteria that are crucial for the development of proteins implicated in antibiotic resistance. Genes that make the β-lactamases, which degrade drugs from the β-lactam family, are potential targets (Edson & Kwon, 2014).

RNA segments of roughly 20 base pairs are produced when these places are found. The capacity of these RNA segments to accurately attach to specific sites results in the formation of a double-stranded RNA pair that can be recognized by ribonucleases. The double-stranded

RNA is subsequently destroyed, inhibiting the production of resistance-related proteins (Yanagihara et al., 2006).

8. Phage therapy

An old technique for treating bacterial illnesses called phage treatment uses viruses called phages to kill dangerous bacteria. Phages are viruses that target and particularly infect bacteria, lysing them or causing them to rupture. Even before the development of antibiotics, this approach was contemplated, but it was later abandoned due to its unfavorable immunological consequences. Phage treatment, however, has recently attracted renewed interest due to the growth in antibiotic resistance. Because they are unique to their bacterial target and don't disturb the gut flora, phages have the advantage of lowering the possibility of phage resistance (Brives & Pourraz, 2020).

Phage variety and the requirement to select the appropriate phage for each bacterial illness are two problems that must be overcome for phage therapy to be effective. A new phage must be chosen for every new resistant bacterial strain since bacteria can evolve phage resistance very quickly (Pires et al., 2020; Torres-Barceló, 2018).

Utilizing phage-derived peptides, which are protein fragments produced from phages that are capable of cytolyzing or rupturing bacterial cell membranes, is an additional strategy. These peptides can be created in a lab and have the benefit of being more stable than whole phages. They can also be changed to more effectively and steadily target particular bacterial strains or to make them more stable (Lin et al., 2017).

9. CRISPR-Cas

It may be possible to use the revolutionary method of genome editing known as CRISPR-Cas to combat antibiotic resistance. Researchers can target and cut specific DNA areas in bacteria using the CRISPR-Cas system. If the genes in bacteria that make them resistant to antibiotics were targeted and rendered dormant, drugs might become effective once more (Uribe et al., 2021).

The CRISPR-Cas system has shown promise in the fight against antibiotic resistance in a number of studies. The CRISPR-Cas system can directly kill bacteria since it can target genes on chromosomes and plasmids (Fig. 6) (Citorik et al., 2014; Vercoe et al., 2013). For instance, CRISPR-Cas was used in one study (Gomaa et al., 2014) to target and deactivate an antibiotic

resistance gene in *E. coli* bacteria, restoring the effectiveness of antibiotics against these pathogens. The CRISPR-Cas system can be used to target antibiotic resistance genes in dangerous bacteria like *S. aureus* and *S. pneumoniae*, as has been shown in prior studies (Bikard et al., 2012, 2014).

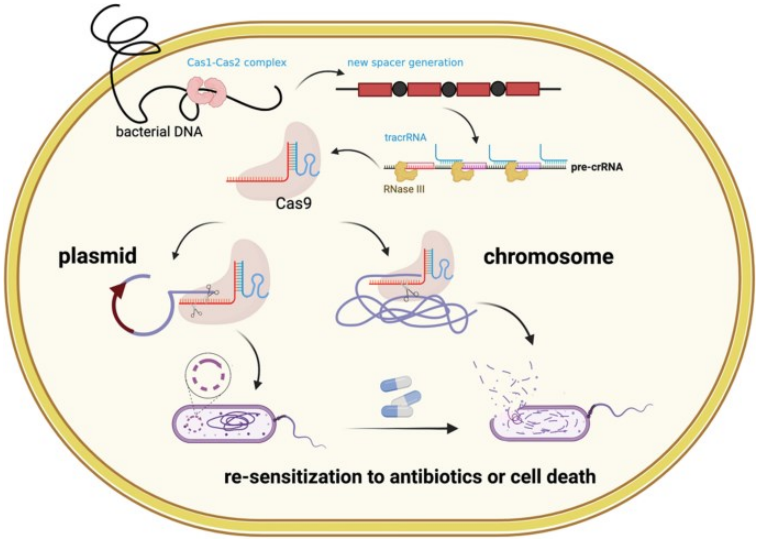


Fig. 6: Utilizing CRISPR-Cas systems as antibiotics. Together with the guide RNA that will instruct it to cut a target sequence, the Cas9 RNA-guided nuclease is expressed. The target may be carried on a plasmid or chromosome, which could result in cell death from chromosome disintegration or antibiotic resistance (Wu et al., 2021).

Conclusion

Antibiotic resistance is a major public health problem as bacteria have acquired resistance to all classes of antibiotics currently in use. This can pose significant therapeutic challenges for some infections, such as Staphylococci, Enterococci, and Acinetobacter. The responsibility for the discriminant use of antibiotics is often debated, but it is now accepted that it is essential to use these drugs prudently to prolong their effectiveness.

As is mentioned in this article, new strategies are currently being developed to combat antibiotic resistance. In vitro and in vivo studies have shown that these strategies could be promising for the future of antibiotic therapy, as well as for the development of new classes of antibiotics. However, it is important to note that antibiotic resistance is a complex and multifactorial problem that requires concerted action by the medical community, policymakers, and the general public.

In order to combat antibiotic resistance, it is deemed essential that research and development of new classes of antibiotics continue to be invested in. Furthermore, effective strategies must be implemented to promote the prudent and responsible use of antibiotics, in order to preserve their long-term effectiveness. If these efforts are combined with increased public awareness of the seriousness of antibiotic resistance, a future where antibiotics remain an effective weapon against bacterial infections can be hoped for.

References

Alexander Fleming. (1922). On a remarkable bacteriolytic element found in tissues and secretions. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character*, *93*(653), 306–317. https://doi.org/10.1098/rspb.1922.0023

Becker, B., & Cooper, M. A. (2013). Aminoglycoside Antibiotics in the 21st Century. *ACS Chemical Biology*, *8*(1), 105–115. https://doi.org/10.1021/cb3005116

Bikard, D., Euler, C. W., Jiang, W., Nussenzweig, P. M., Goldberg, G. W., Duportet, X., Fischetti, V. A., & Marraffini, L. A. (2014). Exploiting CRISPR-Cas nucleases to produce sequence-specific antimicrobials. *Nature Biotechnology*, *32*(11), 1146–1150. https://doi.org/10.1038/nbt.3043

Bikard, D., Hatoum-Aslan, A., Mucida, D., & Marraffini, L. A. (2012). CRISPR Interference Can Prevent Natural Transformation and Virulence Acquisition during In Vivo Bacterial Infection. *Cell Host & Microbe*, *12*(2), 177–186. https://doi.org/10.1016/j.chom.2012.06.003

Bouyssou, C. (2014). Une nouvelle approche thérapeutique pour l'éradication de Helicobacter pylori. *Actualités Pharmaceutiques*, *53*(536), 31–35. https://doi.org/10.1016/j.actpha.2014.02.026

Brives, C., & Pourraz, J. (2020). Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures. *Palgrave Communications*, *6*(1), 100. https://doi.org/10.1057/s41599-020-0478-4

Bungau, S., Tit, D. M., Behl, T., Aleya, L., & Zaha, D. C. (2021). Aspects of excessive antibiotic consumption and environmental influences correlated with the occurrence of resistance to antimicrobial agents. *Current Opinion in Environmental Science and Health*, *19*. https://doi.org/10.1016/j.coesh.2020.10.012

Bush, K. (2012). Improving known classes of antibiotics: an optimistic approach for the future.

Current Opinion in Pharmacology, *12*(5), 527–534. https://doi.org/10.1016/j.coph.2012.06.003

Cabezón, E., de la Cruz, F., & Arechaga, I. (2017). Conjugation Inhibitors and Their Potential Use to Prevent Dissemination of Antibiotic Resistance Genes in Bacteria. *Frontiers in Microbiology*, *8*. https://doi.org/10.3389/fmicb.2017.02329

Citorik, R. J., Mimee, M., & Lu, T. K. (2014). Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases. *Nature Biotechnology*, *32*(11), 1141–1145. https://doi.org/10.1038/nbt.3011

Damodharan, J. (2021). Nanomaterials in medicine – An overview. *Materials Today: Proceedings*, *37*, 383–385. https://doi.org/10.1016/j.matpr.2020.05.380

Dar, D., & Sorek, R. (2017). Regulation of antibiotic-resistance by non-coding RNAs in bacteria. *Current Opinion in Microbiology*, *36*, 111–117. https://doi.org/10.1016/j.mib.2017.02.005

Dimitriu, T., Lotton, C., Bénard-Capelle, J., Misevic, D., Brown, S. P., Lindner, A. B., & Taddei, F. (2014). Genetic information transfer promotes cooperation in bacteria. *Proceedings of the National Academy of Sciences*, *111*(30), 11103–11108. https://doi.org/10.1073/pnas.1406840111

Edson, J. A., & Kwon, Y. J. (2014). RNAi for silencing drug resistance in microbes toward development of nanoantibiotics. *Journal of Controlled Release*, *189*, 150–157. https://doi.org/10.1016/j.jconrel.2014.06.054

Engström, A. (2021). Antimicrobial Resistance as a Creeping Crisis. In *Understanding the Creeping Crisis* (pp. 19–36). Springer International Publishing. https://doi.org/10.1007/978-3-030-70692-0_2

Fatima, H., Goel, N., Sinha, R., & Khare, S. K. (2021). Recent strategies for inhibiting multidrug-resistant and β-lactamase producing bacteria: A review. *Colloids and Surfaces B: Biointerfaces*, *205*, 111901. https://doi.org/10.1016/j.colsurfb.2021.111901

File, T. M., Low, D. E., Eckburg, P. B., Talbot, G. H., Friedland, H. D., Lee, J., Llorens, L., Critchley, I. A., Thye, D. A., Pullman, J., Giordano, P., Welker, J., Manos, P., Mehra, P., File, T., De Santo, J., Venkateswaralu, B., Gerald Schrock, C., Tillis, W., … Plutinsky, J. (2011). FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *Journal of*

Antimicrobial Chemotherapy, *66*(Supplement 3), iii19–iii32. https://doi.org/10.1093/jac/dkr096

Franci, G., Falanga, A., Galdiero, S., Palomba, L., Rai, M., Morelli, G., & Galdiero, M. (2015). Silver Nanoparticles as Potential Antibacterial Agents. *Molecules*, *20*(5), 8856–8874. https://doi.org/10.3390/molecules20058856

Getino, M., & de la Cruz, F. (2018). Natural and Artificial Strategies To Control the Conjugative Transmission of Plasmids. *Microbiology Spectrum*, *6*(1). https://doi.org/10.1128/microbiolspec.MTBP-0015-2016

Gomaa, A. A., Klumpe, H. E., Luo, M. L., Selle, K., Barrangou, R., & Beisel, C. L. (2014). Programmable Removal of Bacterial Strains by Use of Genome-Targeting CRISPR-Cas Systems. *MBio*, *5*(1). https://doi.org/10.1128/mBio.00928-13

Goulooze, S. C., Cohen, A. F., & Rissmann, R. (2015). Bedaquiline. *British Journal of Clinical Pharmacology*, *80*(2), 182–184. https://doi.org/10.1111/bcp.12613

Grossman, T. H., Murphy, T. M., Slee, A. M., Lofland, D., & Sutcliffe, J. A. (2015). Eravacycline (TP-434) Is Efficacious in Animal Models of Infection. *Antimicrobial Agents and Chemotherapy*, *59*(5), 2567–2571. https://doi.org/10.1128/AAC.04354-14

Gudkov, S. V., Burmistrov, D. E., Serov, D. A., Rebezov, M. B., Semenova, A. A., & Lisitsyn, A. B. (2021). A Mini Review of Antibacterial Properties of ZnO Nanoparticles. *Frontiers in Physics*, *9*. https://doi.org/10.3389/fphy.2021.641481

Guglielmetti, L., & Robert, J. (2015). Bédaquiline : de l'in vitro aux essais cliniques d'un nouvel antituberculeux. *Journal Des Anti-Infectieux*, *17*(2), 60–66. https://doi.org/10.1016/j.antinf.2014.12.003

Haleem, A., Javaid, M., Singh, R. P., Rab, S., & Suman, R. (2023). Applications of nanotechnology in medical field: a brief review. *Global Health Journal*. https://doi.org/10.1016/j.glohj.2023.02.008

Hards, K., Robson, J. R., Berney, M., Shaw, L., Bald, D., Koul, A., Andries, K., & Cook, G. M. (2015). Bactericidal mode of action of bedaquiline. *Journal of Antimicrobial Chemotherapy*, *70*(7), 2028–2037. https://doi.org/10.1093/jac/dkv054

Kuti, J. L., Pettit, R. S., Neu, N., Cies, J. J., Lapin, C., Muhlebach, M. S., Novak, K. J., Nguyen, S. T.,

Saiman, L., & Nicolau, D. P. (2015). Microbiological activity of ceftolozane/tazobactam, ceftazidime, meropenem, and piperacillin/tazobactam against Pseudomonas aeruginosa isolated from children with cystic fibrosis. *Diagnostic Microbiology and Infectious Disease*, *83*(1), 53–55. https://doi.org/10.1016/j.diagmicrobio.2015.04.012

Lin, D. M., Koskella, B., & Lin, H. C. (2017). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*, *8*(3), 162. https://doi.org/10.4292/wjgpt.v8.i3.162

Lucasti, C., Vasile, L., Sandesc, D., Venskutonis, D., McLeroth, P., Lala, M., Rizk, M. L., Brown, M. L., Losada, M. C., Pedley, A., Kartsonis, N. A., & Paschke, A. (2016). Phase 2, Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-abdominal Infection. *Antimicrobial Agents and Chemotherapy*, *60*(10), 6234–6243. https://doi.org/10.1128/AAC.00633-16

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. *Frontiers in Cellular and Infection Microbiology*, *6*. https://doi.org/10.3389/fcimb.2016.00194

Maitre, T., Aubry, A., Jarlier, V., Robert, J., Veziris, N., Bernard, C., Sougakoff, W., Brossier, F., Cambau, E., Mougari, F., & Raskine, L. (2017). Multidrug and extensively drug-resistant tuberculosis. *Médecine et Maladies Infectieuses*, *47*(1), 3–10. https://doi.org/10.1016/j.medmal.2016.07.006

Marslin, G., Revina, A. M., Khandelwal, V. K. M., Balakumar, K., Sheeba, C. J., & Franklin, G. (2015). PEGylated ofloxacin nanoparticles render strong antibacterial activity against many clinically important human pathogens. *Colloids and Surfaces B: Biointerfaces*, *132*, 62–70. https://doi.org/10.1016/j.colsurfb.2015.04.050

Martens, E., & Demain, A. L. (2017). The antibiotic resistance crisis, with a focus on the United States. *The Journal of Antibiotics*, *70*(5), 520–526. https://doi.org/10.1038/ja.2017.30

Matsuura, M., Nakazawa, H., Hashimoto, T., & Mitsuhashi, S. (1980). Combined antibacterial activity of amoxicillin with clavulanic acid against ampicillin-resistant strains. *Antimicrobial Agents and Chemotherapy*, *17*(6), 908–911. https://doi.org/10.1128/AAC.17.6.908

Mulhbacher, J., Brouillette, E., Allard, M., Fortier, L.-C., Malouin, F., & Lafontaine, D. A. (2010). Novel Riboswitch Ligand Analogs as Selective Inhibitors of Guanine-Related Metabolic

Pathways. *PLoS Pathogens*, *6*(4), e1000865. https://doi.org/10.1371/journal.ppat.1000865

Ogawa, A., & Maeda, M. (2007). Development of a New-type Riboswitch Using an Aptazyme and an anti-RBS Sequence. *Nucleic Acids Symposium Series*, *51*(1), 389–390. https://doi.org/10.1093/nass/nrm195

Olsen, I. (2015). New promising β-lactamase inhibitors for clinical use. *European Journal of Clinical Microbiology & Infectious Diseases*, *34*(7), 1303–1308. https://doi.org/10.1007/s10096-015-2375-0

Pires, D. P., Costa, A. R., Pinto, G., Meneses, L., & Azeredo, J. (2020). Current challenges and future opportunities of phage therapy. *FEMS Microbiology Reviews*, *44*(6), 684–700. https://doi.org/10.1093/femsre/fuaa017

Sánchez-López, E., Gomes, D., Esteruelas, G., Bonilla, L., Lopez-Machado, A. L., Galindo, R., Cano, A., Espina, M., Ettcheto, M., Camins, A., Silva, A. M., Durazzo, A., Santini, A., Garcia, M. L., & Souto, E. B. (2020). Metal-Based Nanoparticles as Antimicrobial Agents: An Overview. *Nanomaterials*, *10*(2), 292. https://doi.org/10.3390/nano10020292

Singh, P., Kumari, R., & Lal, R. (2017). Bedaquiline: Fallible Hope Against Drug Resistant Tuberculosis. *Indian Journal of Microbiology*, *57*(4), 371–377. https://doi.org/10.1007/s12088-017-0674-0

Soroka, D., Ourghanlian, C., Compain, F., Fichini, M., Dubée, V., Mainardi, J.-L., Hugonnet, J.-E., & Arthur, M. (2016). Inhibition of β-lactamases of mycobacteria by avibactam and clavulanate. *Journal of Antimicrobial Chemotherapy*, dkw546. https://doi.org/10.1093/jac/dkw546

Spohn, R., Daruka, L., Lázár, V., Martins, A., Vidovics, F., Grézal, G., Méhi, O., Kintses, B., Számel, M., Jangir, P. K., Csörgő, B., Györkei, Á., Bódi, Z., Faragó, A., Bodai, L., Földesi, I., Kata, D., Maróti, G., Pap, B., … Pál, C. (2019). Integrated evolutionary analysis reveals antimicrobial peptides with limited resistance. *Nature Communications*, *10*(1), 4538. https://doi.org/10.1038/s41467-019-12364-6

Staroń, A., & Długosz, O. (2021). Antimicrobial properties of nanoparticles in the context of advantages and potential risks of their use. *Journal of Environmental Science and Health, Part A*, *56*(6), 680–693. https://doi.org/10.1080/10934529.2021.1917936

Torres-Barceló, C. (2018). Phage Therapy Faces Evolutionary Challenges. *Viruses*, *10*(6), 323.

https://doi.org/10.3390/v10060323

Unckless, R. L., Howick, V. M., & Lazzaro, B. P. (2016). Convergent Balancing Selection on an Antimicrobial Peptide in Drosophila. *Current Biology*, *26*(2), 257–262. https://doi.org/10.1016/j.cub.2015.11.063

Uribe, R. V., Rathmer, C., Jahn, L. J., Ellabaan, M. M. H., Li, S. S., & Sommer, M. O. A. (2021). Bacterial resistance to CRISPR-Cas antimicrobials. *Scientific Reports*, *11*(1), 17267. https://doi.org/10.1038/s41598-021-96735-4

Vercoe, R. B., Chang, J. T., Dy, R. L., Taylor, C., Gristwood, T., Clulow, J. S., Richter, C., Przybilski, R., Pitman, A. R., & Fineran, P. C. (2013). Cytotoxic Chromosomal Targeting by CRISPR/Cas Systems Can Reshape Bacterial Genomes and Expel or Remodel Pathogenicity Islands. *PLoS Genetics*, *9*(4), e1003454. https://doi.org/10.1371/journal.pgen.1003454

Wang, J.-Q., Yang, Y., Cai, C.-Y., Teng, Q.-X., Cui, Q., Lin, J., Assaraf, Y. G., & Chen, Z.-S. (2021). Multidrug resistance proteins (MRPs): Structure, function and the overcoming of cancer multidrug resistance. *Drug Resistance Updates*, *54*, 100743. https://doi.org/10.1016/j.drup.2021.100743

Wu, Y., Battalapalli, D., Hakeem, M. J., Selamneni, V., Zhang, P., Draz, M. S., & Ruan, Z. (2021). Engineered CRISPR-Cas systems for the detection and control of antibiotic-resistant infections. *Journal of Nanobiotechnology*, *19*(1), 401. https://doi.org/10.1186/s12951-021-01132-8

Yanagihara, K., Tashiro, M., Fukuda, Y., Ohno, H., Higashiyama, Y., Miyazaki, Y., Hirakata, Y., Tomono, K., Mizuta, Y., Tsukamoto, K., & Kohno, S. (2006). Effects of short interfering RNA against methicillin-resistant Staphylococcus aureus coagulase in vitro and in vivo. *Journal of Antimicrobial Chemotherapy*, *57*(1), 122–126. https://doi.org/10.1093/jac/dki416

Yu, B., Wang, Z., Almutairi, L., Huang, S., & Kim, M.-H. (2020). Harnessing iron-oxide nanoparticles towards the improved bactericidal activity of macrophage against Staphylococcus aureus. *Nanomedicine: Nanotechnology, Biology and Medicine*, *24*, 102158. https://doi.org/10.1016/j.nano.2020.102158

Zhanel, G. G., Sniezek, G., Schweizer, F., Zelenitsky, S., Lagacé-Wiens, P. R. S., Rubinstein, E., Gin, A. S., Hoban, D. J., & Karlowsky, J. A. (2009). Ceftaroline. *Drugs*, *69*(7), 809–831. https://doi.org/10.2165/00003495-200969070-00003

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

Biomimetic: nature's promise for Artificial Intelligence

ADJOUDJ Réda[1,*]

[1] Evolutionary Engineering & Distributed Information System Laboratory, University Sidi Bel-Abbes, Algeria

[*]**Correspondence:** ADJOUDJ Réda – Email: adjreda@yahoo.fr

Received 19 April. Accepted and published: 05 May 2023

Abstract

Biomimetic, or imitation of the living, consists of taking inspiration from natural solutions and transposing their principles and processes to human engineering, and more particularly to artificial intelligence. The approach aims to favor "choices" proven by nature, in order to develop applications and solutions in artificial intelligence in better harmony with efficiency and feasibility. Biomimetic can therefore be summed up in a few words as the transfer of biological models and mechanisms to technology and in particular to computer science and artificial intelligence. Here, two concrete examples are illustrated:

The first is how to design an IDS (intrusion detection system) for a computer network bio-inspired by the offensive defense of bees. The second is how to solve the multi-objective shortest path problem by simultaneously taking into account several objectives and by exploiting the solution of the natural marking of the living (to indicate the possession of an area).

Key words: Bio-inspired, AI, IDS, shortest path

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

LGVP histograms for text-independent writer Identification

BAHRAM Tayeb [1,*]

[1] Geometry, Analysis, Control and Applications Laboratory, Faculty of Sciences, Department of mathematics, University of Saida - Dr Tahar Moulay, 20100 Saida, Algeria

[*]**Correspondence:** BAHRAM Tayeb – Email: Tayeb.bahram@univ-saida.dz, tbahram@laposte.net

Received 19 April. Accepted and published: 05 May 2023

Abstract

The problem of authenticating a writer from his/her writing samples has been the most important and prevalent subject of active research in the field of handwriting biometrics for the last decade. In this paper, we have focused mainly on the forensic document analysis, more precisely, the offline automatic writer identification in a truly text-independent mode. Two new and simple potential textural descriptors have been analyzed for characterising handwriting style of the writers, so as to be used to describe the intra and inter-writer variability by calculating the similarity measurements. In order to capture the textural information in a scanned image, two effective statistical texture descriptors are extracted from binary connected-components: the first one is based on the Black pixels of the connected components Local BLack Patterns (LBLP), while the second is based on the White pixels of the latter Local WHite Patterns (LWHP); after that, a combination of these descriptors Local Black and White Patterns (LBWP) is performed. Classification is carried out using k-nearest neighbors and the Chi-Square distance with the simplest kind of cross validation: Holdout. The experimental results obtained on four well-known databases show that the proposed scheme achieves a very satisfactory performance and thus reflecting that our approach is among the best compared in the state-of-the-art.

Key words: Feature extraction, Local Black Patterns, Local White Patterns, Writer identification, Texture analysis

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

Arabic Natural Language Processing and Machine Learning

DOUMI Noureddine [1*,2]

[1] Evolutionary Engineering & Distributed Information System Laboratory, University Sidi Bel-Abbes, Algeria
[2] University Dr Moulay Tahar of Saida, Algeria.

[*]**Correspondence:** DOUMI Noureddine – Email: ndoumi2006@gmail.com

Received 19 April. Accepted and published: 05 May 2023

Abstract

The object of this work is to give reader an overview on the state-of-the-art methods and techniques used in Arabic Natural Language Processing (ANLP). As a branch of artificial intelligence, NLP is at the heart of scientific research that tries to mimic, in the computer, the human ability to produce and understand textual and spoken linguistic data.

A general overview on the three major approaches to solve an NLP problem was given. In particular, the ANLP problem particularities were explained while giving the Arabic language families. Despite the effort made by the ANLP research community, Arabic is still considered by rating companies as an under-resourced language. The terrible lack of linguistic resources and processing tools for Arabic leads ANLP researchers to adopt the new techniques of machine learning and deep learning.

ANLP community, like other languages, tends to promote Arabic NLP tools and resources. Nowadays, we are witnessing a remarkable demand for new technologies such as machine learning, deep learning and word embedding to process Dialectal Arabic textual data.

In the purpose of recommending these techniques to reader, a review of these new techniques is also given.

Key words: Arabic Natural language Processing, Machine Learning, Deep Learning, FNN, RNN

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

Artificial intelligence for improving the performance of computer networks

BELKHIRA Sid Ahmed Hichame*

Institute of Sciences, Department of Technology, Nour Bachir University Center of Elbayadh Algeria

***Correspondence:** BELKHIRA Sid Ahmed Hichame – Email: s.belkhira@cu-elbayadh.dz

Received 19 April. Accepted and published: 05 May 2023

Abstract

Optimizing a network means improving its functioning in terms of security and reliability, performance and speed, quality of service (Qos) and of course in terms of energy consumption. Network architectures are increasingly managed in a centralized structure with management functions handled in a control plan separate from data plan, such as in cloud-managed networks and Software Defined Networking (SDN). Artificial Intelligence (AI) and machine learning are essential to collect the full benefits of these centrally managed network architectures.

AI and machine learning are now used to continuously analyse large amounts of data using sophisticated algorithms to determine what exactly is happening on the network, to make predictions and to react to events gradually as they occur. This ability to intelligently analyse network data and to derive detailed insights into network performance without human intervention is at the heart of its attraction. The combination of AI and centralized software networking is pushing us towards fully automated networking. AI can also provide a contribution in the field of cybersecurity, allowing real-time visualization of threats. It makes it possible to correlate a certain amount of information that a human expert is no longer able to do. In addition, AI techniques can be used as an attack simulation tool in the detection of vulnerability or for guessing passwords in order to detect computer network failures or data in order to improve and strengthen its security.

Key words: Computer networks, vulnerability, centralized network management, machine learning, artificial intelligence.

References

AMRAOUI, A., & BENMAMMAR, B. (2020). Optimisation des réseaux à l'aide des techniques de l'intelligence artificielle. Gestion et contrôle intelligents des réseaux: Sécurité intelligente, optimisation multicritères, Cloud Computing, Internet of Vehicles, Radio Intelligente, 71.

SEMMOUD, A., & BENMAMMAR, B. (2020). La sécurité intelligente des réseaux informatiques. Gestion et contrôle intelligents des réseaux: Sécurité intelligente, optimisation multicritères, Cloud Computing, Internet of Vehicles, Radio Intelligente, 1.

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTICIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

ChatGPT - A Powerful AI Language Model

The Transformative Power of AI in Biology

RACHEDI Abdelkrim [*,1]

[1] Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

[*]**Correspondence:** RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz

Received 19 April. Accepted and published: 11 May 2023

Abstract

Artificial intelligence (AI) has revolutionized numerous domains, and its impact on biology, bioinformatics, and protein structure analysis is particularly remarkable. This review explores the wide-ranging applications of AI in these fields, focusing on notable examples such as ChatGPT and AlphaFold. We delve into the historical background of AI, the concept of deep learning, and its relationship to ChatGPT and other language models. Furthermore, highlight the invaluable role of ChatGPT in assisting customers, generating content, enhancing educational experiences, and aiding healthcare professionals.

In the field of biology and bioinformatics, AI technologies, including ChatGPT, have become indispensable. They facilitate the analysis of biological data, prediction of protein structures, exploration of gene expression patterns, and identification of drug targets. With advancements in natural language processing, ChatGPT promotes collaboration and knowledge sharing among scientists, enhancing communication in complex biological research.

One exemplary AI technology that has garnered significant attention is AlphaFold. Developed by DeepMind, AlphaFold leverages deep learning algorithms to predict protein structures with unprecedented accuracy. Its potential applications in drug discovery, protein engineering, and disease understanding are immense. AlphaFold's ability to rapidly and accurately determine protein structures marks a significant milestone in scientific research.

This review highlights the transformative power of AI in biology and underscores the need for continued research and development. As AI technologies continue to evolve, there is immense potential for advancements in understanding biological systems, accelerating drug discovery, and shaping the future of personalized medicine. The integration of AI, exemplified by ChatGPT and AlphaFold, offers a promising pathway for scientific progress and innovation in the biological sciences.

Key words: Artificial intelligence, ChatGPT, Transformer architecture, Deep learning, AlphaFold, Bioinformatics, Protein structure prediction

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

*Communication abstract – for the **I2A University Day 2023, 19 April 2023**, University of Saida, Algeria*

Open Source at the service of Artificial Intelligence

BAHLOUL Ahmed[1,*] & BAHRAM Tayeb[2]

[1] Department of computer science, University ORAN 1, Algeria
[2] Geometry, Analysis, Control and Applications Laboratory, Faculty of Sciences, Department of mathematics, University of Saida - Dr Tahar Moulay, 20100 Saida, Algeria

[*]**Correspondence:** BAHLOUL Ahmed – Email: bahlouldea@gmail.com

Received 19 April. Accepted and published: 05 May 2023

Abstract

The rise of artificial intelligence would probably not have been possible without the Free Software Ecosystem: open-source code, open data and open science have made it accessible and improved technologies by pooling efforts.

The dynamics of the Free Software Ecosystem have driven the development of so-called artificial intelligence (AI) technologies in recent years. Whether creating, training, or evaluating models, Free Software communities are widely mobilized.

Open source is fertile ground for pioneering software, especially in cutting-edge areas like artificial intelligence (AI) and machine learning (ML). Open source ethics and collaboration tools make it easier for teams to share code and data, and build on the success of others. In this article, we will present the main open source projects that are transforming the world of AI and machine learning.

Today, more than 44,788 open-source projects are referenced on Github behind the keyword "artificial intelligence". Many of these projects are developed in Python, supported by three flagship projects: Tensorflow (and its simplified interface, Keras), Scikit-learn and PyTorch.

Key words: Artificial Intelligence, Open Source, Tensorflow, Scikit-learn, PyTorch, Huggingface.

Journal of **Concepts in Structural Biology & Bioinformatics**

ANTIBIOTICS RESISTANCE

Concept article.

Teixobactin an antibiotic from soil bacteria for fighting Multiple Antibiotic Resistance phenomena.

RACHEDI Abdelkrim

Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Natural and Life Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

Correspondence: RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz
Published: 01 June 2023

Abstract

The emergence of antibiotic-resistant bacteria is a growing threat to public health, and there is an urgent need for new antibiotics with novel mechanisms of action. Teixobactin is a promising relatively new antibiotic that was discovered in 2015 with a unique mechanism of action that makes it effective against multiple antibiotic-resistant bacteria. The antibiotic is produced by *Eleftheria terrae*, a Gram-negative bacterium, and is structurally distinct from other antibiotics, containing nonstandard amino acid residues. Teixobactin has shown potential in killing highly pathogenic and multidrug-resistant gram-positive bacteria, such as Methicillin-resistant Staphylococcus aureus (MRSA), Oxacillin-resistant Staphylococcus aureus (ORSA), and Mycobacterium tuberculosis (MTB). This article provides an overview of the discovery and potential uses of Teixobactin in the context of combating antibiotic resistance.

Key words: Teixobactin, Antibiotics, Soil bacteria, Antibiotic-resistance, MRSA, ORSA, MTB, Drugs, Diseases

Introduction

Antibiotic-resistant bacteria pose a significant threat to public health worldwide, as they are responsible for an increasing number of infections that are difficult to treat due to bacteria evolving mechanisms to evade the effects of commonly used antibiotics. The overuse and misuse of antibiotics have contributed to this problem, leading to the emergence of multidrug-resistant bacteria. In response to this problem, scientists have been searching for new antibiotics with novel mechanisms of action that can effectively kill antibiotic-resistant bacteria. To illustrate the gravity of the situation, it's perhaps important to mention the large preclinical development projects, as of 1 May 2019, 407 antibacterial projects from 314 institutions organized in pipeline discovery tool, Figure 1. The pipeline's focus is on Gram-negative pathogens, particularly bacteria on the WHO priority bacteria list. Teixobactin is one such antibiotic, which was discovered in 2015, harvested from soil bacteria, has shown potent activity against a range of gram-positive bacteria that are resistant to multiple antibiotics.

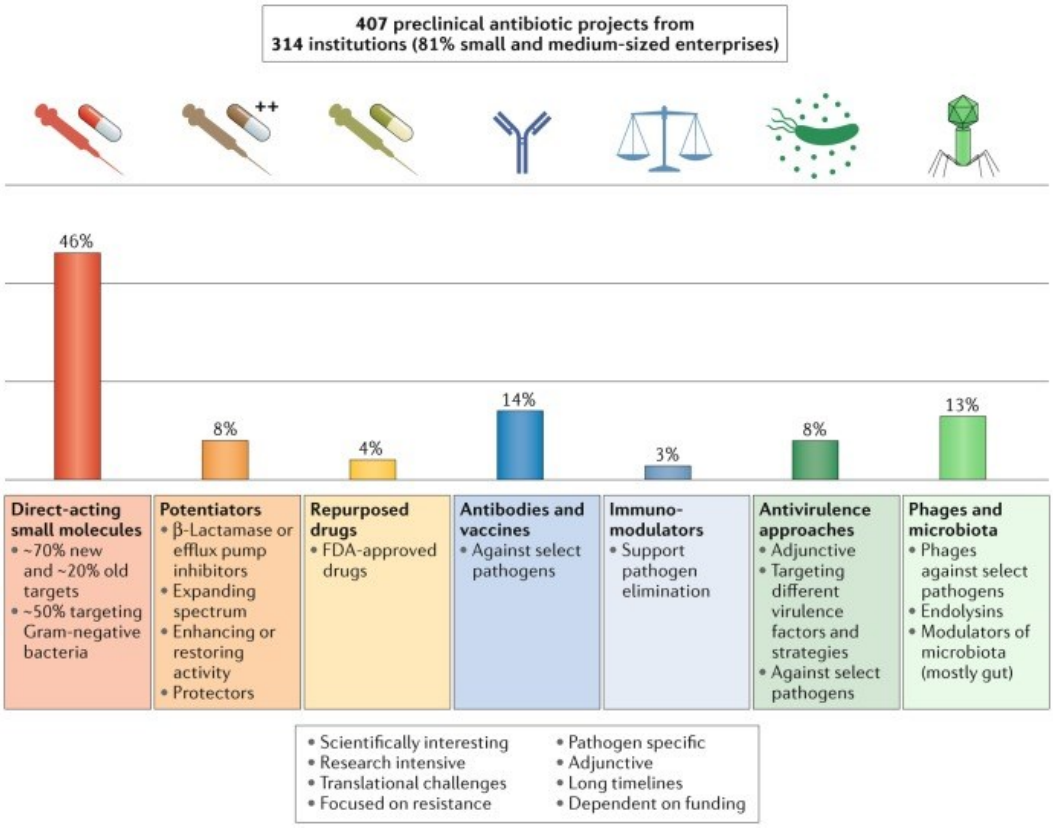


Figure 1. Overview of the preclinical antibacterial pipeline.
Source: The global preclinical antibacterial pipeline
https://www.nature.com/articles/s41579-019-0288-0

Discovery of Teixobactin

Teixobactin was discovered in 2015 by researchers from Northeastern University and NovoBiotic Pharmaceuticals, Ling et al., who developed a novel technique to isolate bacteria from soil samples, Figure 2. The bacterium that produces Teixobactin was named *Eleftheria terrae* and it is a gram-negative bacterium that had not been grown before in laboratory conditions, Figure 3. Teixobactin is a 'peptide-like' secondary metabolite produced by the bacterium, and it has a unique structure that includes several nonstandard amino acids.

Teixobactin has a unique mechanism of action, targeting cell wall biosynthesis and lipid II, a precursor for the peptidoglycan layer in bacterial cell walls. The antibiotic has shown potent activity against a range of highly pathogenic and multidrug-resistant gram-positive bacteria, including MRSA, ORSA, and MTB, without detectable resistance development.

Figure 2. Isolation of bacteria from soil samples using special
Source: Promising antibiotic discovered in microbial 'dark matter'
https://www.nature.com/articles/nature.2015.16675

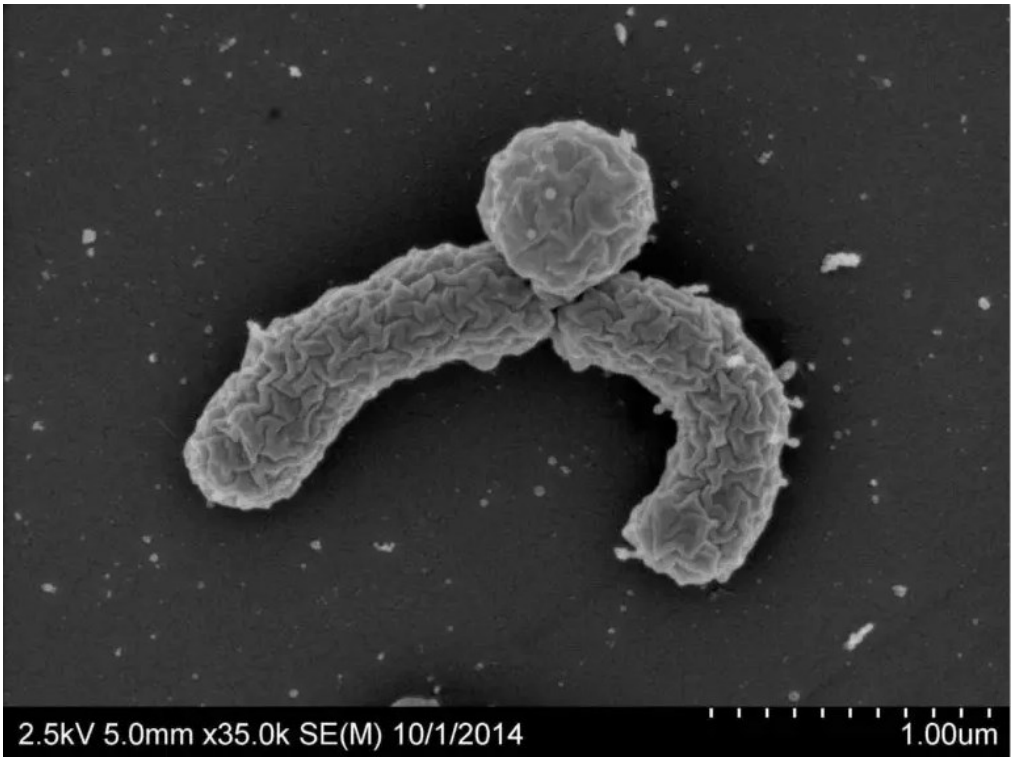


Figure 3. The soil bacteria *Eleftheria terrae*
Source : Teixobactina: un nuovo antibiotico contro i superbatteri ?
https://www.microbiologiaitalia.it/batteriologia/teixobactina-un-antibiotico-superbatteri/

Teixobactin Structure

The structural features of Teixobactin are quite interesting. It contains nonstandard amino acid residues, including three d-amino acids and l-allo-enduracididine, which makes it unique from other antibiotics, Figure 4. The distinctive pharmacological profile of Teixobactin is thought to contribute to its high activity against many known multi-antibiotic-resistant bacteria, as it adopts a different binding mode than most antibiotics, making it harder for the bacteria being attacked to develop resistance.

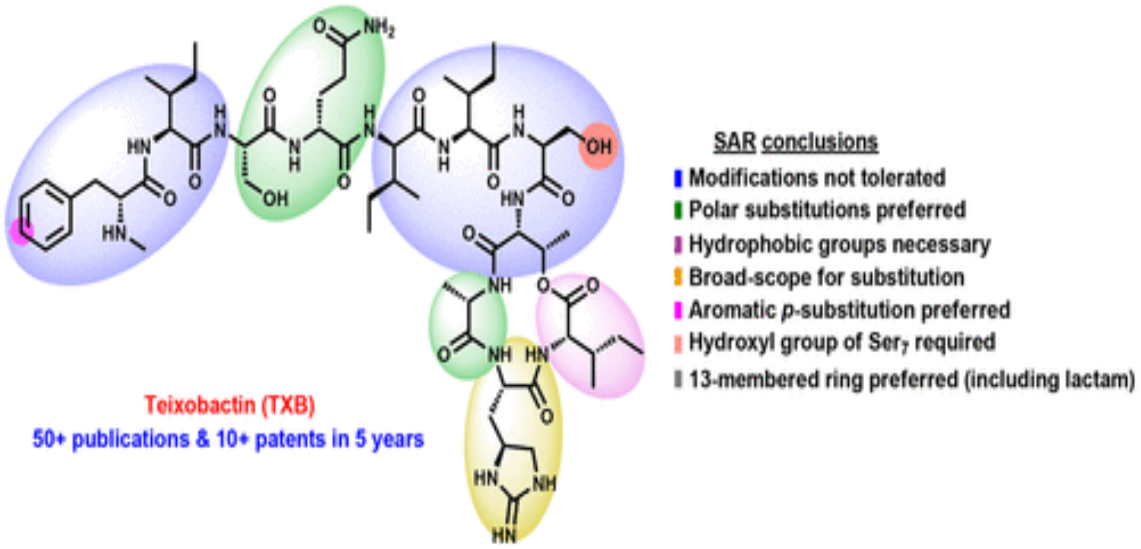


Figure 4. The structure of the antibiotic Teixobactin.
Source: Teixobactin: A Paving Stone toward a New Class of Antibiotics? https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00173

Mechanism of action

Teixobactin targets the cell wall of bacteria, preventing them from growing and replicating. This is in contrast to most antibiotics, which target specific proteins or enzymes in bacteria. Targeting the cell wall makes it much harder for bacteria to develop resistance, as the cell wall is a critical component of their survival.

Upon binding of lipid II, Teixobactin first forms small β-sheets then elongates into fibrils that eventually associate into lateral fibrillar sheets, obstructing biosynthesis of peptidoglycan and causing membrane defects, Figure 5. Teixobactin has been shown to be active against a range of gram-positive bacteria, including MRSA, ORSA, and MTB.

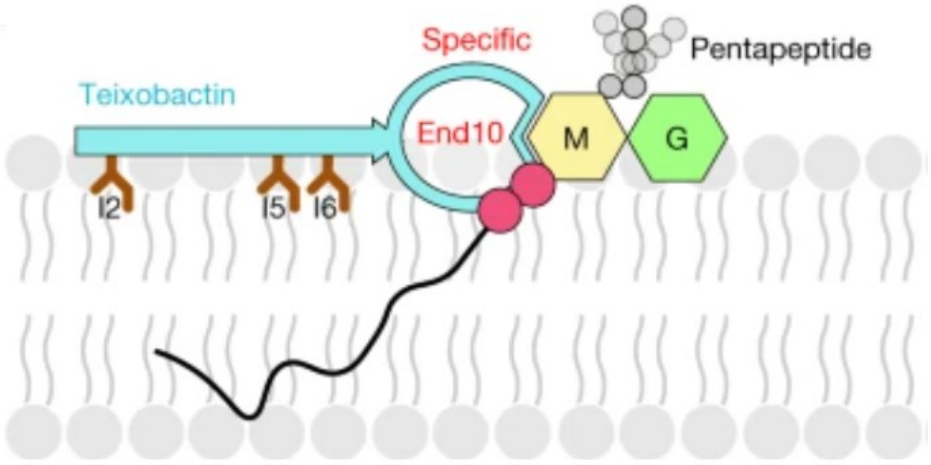


Figure 5. Illustration of the differential binding modes of natural Teixobactin.
Source: refer to Fig.3f at Model of the mode of action of teixobactin, https://www.nature.com/articles/s41586-022-05019-y

Pharmacology and potential for clinical use

Teixobactin has shown promise as a new antibiotic for the treatment of antibiotic-resistant infections. It has been shown to be active against a range of gram-positive bacteria, including those that are resistant to multiple antibiotics. Its unique mechanism of action and unusual structure make it difficult for bacteria to develop resistance, which is a major advantage over existing antibiotics. However, Teixobactin is still in the early stages of development, and further studies are needed to fully characterize its pharmacology and potential for clinical use.

The unique action mechanism of Teixobactin and its potency against multidrug-resistant bacteria make it a promising candidate for clinical use. Research is ongoing towards further exploring the potential uses of Teixobactin including its efficacy against other bacterial strains and its potential as a treatment for infections in humans.

Conclusion

Teixobactin is a promising new antibiotic that has the potential to revolutionize the way we combat antibiotic-resistant infections. Its unique mechanism of action and unusual structure make it a powerful tool in the fight against antibiotic-resistant bacteria. However, more research is needed to fully understand its pharmacology and potential for clinical use. With continued research and development, Teixobactin could eventually become an important new treatment option for patients with hard-to-treat infections.

The discovery of Teixobactin offers hope for the development of new antibiotics with novel mechanisms of action that can effectively combat antibiotic-resistant bacteria. Further research is needed to fully understand the potential uses of Teixobactin and to develop it into a clinically effective treatment.

References

Ling, L. L., Schneider, T., Peoples, A. J.et al. (2015). A new antibiotic kills pathogens without detectable resistance. Nature, 517(7535), 455–459. Available at: https://doi.org/10.1038/nature14098

Ledford, H. (2015). Promising antibiotic discovered in microbial 'dark matter'. Nature, Available at: https://doi.org/10.1038/nature.2015.16675

Cox, G., Wright, G. D. (2013). Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. International Journal of Medical Microbiology, 303(6-7), 287-292. Available at: https://doi.org/10.1016/j.ijmm.2013.02.009

Theuretzbacher, U., Outterson, K., Engel, A., Karlén, A. (2020). The global preclinical antibacterial pipeline. Nature Reviews Microbiology, 18(5), 275-285. Available at: https://doi.org/10.1038/s41579-019-0288-0

Vidya B. Gunjal, Ritesh Thakare, Sidharth Chopra, and D. Srinivasa Reddy (2020). Teixobactin: A Paving Stone toward a New Class of Antibiotics?, Journal of Medicinal Chemistry, 63 (21), 12171-12195. Available at: https://doi.org/10.1021/acs.jmedchem.0c00173

Shukla, R., Lavore, F., Maity, S. et al. (2022). Teixobactin kills bacteria by a two-pronged attack on the cell envelope. Nature 608, 390–396. Available at: https://doi.org/10.1038/s41586-022-05019-y

WHO. (2021). WHO global priority pathogens list of antibiotic-resistant bacteria Available at: https://www.doherty.edu.au/...who-global-list-of-antibiotic-resistant-bacteria

WHO. (2017). WHO publishes list of bacteria for which new antibiotics are urgently needed Available at: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

Journal of **Concepts in Structural Biology & Bioinformatics**

ANTIBIOTICS RESISTANCE

Concept article.

Antibiotic Resistance and the Ribosome: A key Target in the Battle against Pathogens.

RACHEDI Abdelkrim

Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Natural and Life Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

Correspondence: RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz
Published: 09 June 2023

Abstract

Antibiotic resistance poses a significant global threat to public health, necessitating innovative strategies to combat multidrug-resistant pathogens. In here we focuses on the ribosome as a key target in the fight against antibiotic resistance.

Ribosomes, can be referred to as the "ultimate molecular 3D printers", of the flesh and blood, are ancient molecular machines responsible for protein synthesis. Pathogenic bacteria heavily rely on ribosomes for survival and proliferation.

By disrupting ribosomal function, researchers aim to hinder bacterial protein synthesis, effectively impeding bacterial growth and reducing the spread of antibiotic-resistant strains. Targeting the ribosome offers a promising avenue for the development of novel antibiotics that can overcome resistance mechanisms employed by bacteria.

Ongoing research endeavors seek to understand the intricacies of ribosomal structure and function, identifying vulnerabilities that can be exploited for the design of more effective and specific drugs. We explore, in this article, the significance of ribosomes in biological processes and highlights the ongoing efforts to leverage ribosomal targeting in combating superbugs. Scientists aim to mitigate antibiotic resistance and safeguard public health through gaining insights into ribosomal mechanisms and advancing intervention strategies.

Key words: Antibiotic resistance, Ribosome, Protein synthesis, Multidrug-resistant pathogens, Superbugs, Drug development.

Introduction

Antibiotic resistance is an increasingly urgent global concern, undermining the effectiveness of existing antimicrobial therapies and posing a substantial threat to public health (Wilson, 2014). The emergence of multidrug-resistant pathogens has necessitated the development of innovative approaches to combat this critical problem. One promising avenue of research lies in targeting the ribosome, an ancient and essential molecular machine responsible for protein synthesis. Ribosomes are present in all living organisms and are often described as the "ultimate molecular 3D printers", of the flesh and blood, due to their ability to convert genetic information into specific three-dimensionally structured proteins that execute vital specialized biological functions.

Pathogenic bacteria, which cause a range of infectious diseases, rely heavily on ribosomes for their survival and proliferation. Disrupting the protein synthesis machinery within bacterial ribosomes can have a profound impact on bacterial growth, making ribosomes an attractive target for the development of new antibiotics (Jinzhong et al., 2018). Through interfering with ribosomal function, researchers aim to inhibit bacterial protein synthesis, thereby halting bacterial growth and reducing the spread of antibiotic-resistant strains.

Targeting the ribosome represents a promising avenue for combating antibiotic resistance due to its fundamental role in biological processes. Ribosomes are conserved across diverse bacterial species, making them an ideal target for the design of antibiotics that can circumvent resistance mechanisms employed by bacteria (Wilson, 2014). Scientists and researchers are actively studying the structure and function of ribosomes, Figures 1 and 3, to gain a comprehensive understanding of their mechanisms. Unravelling the intricacies of ribosomal biology can lead to the identification of vulnerabilities that can be exploited in the development of drugs with greater specificity and efficacy.

Of particular concern are superbugs, highly resistant bacterial strains that pose significant challenges in healthcare settings. Ribosomes have been found to play a key role in combating superbugs, and ongoing research efforts are focused on harnessing the potential of ribosomal targeting to overcome antibiotic resistance (Science Museum blog). Researchers aim at gaining deeper insights into ribosomal mechanisms and advancing intervention strategies, to mitigate the

spread of multidrug-resistant pathogens and protect public health.

This article delves into the significance of ribosomes in biological processes, highlighting their role as a focal point in the fight against antibiotic resistance. It explores ongoing research and advancements in ribosomal targeting, aiming to shed light on the potential of ribosome-based interventions in combating superbugs and overcoming antibiotic resistance. Scientists strive to develop effective strategies to safeguard public health and preserve the efficacy of antibiotic therapies by focusing on this critical area of study.

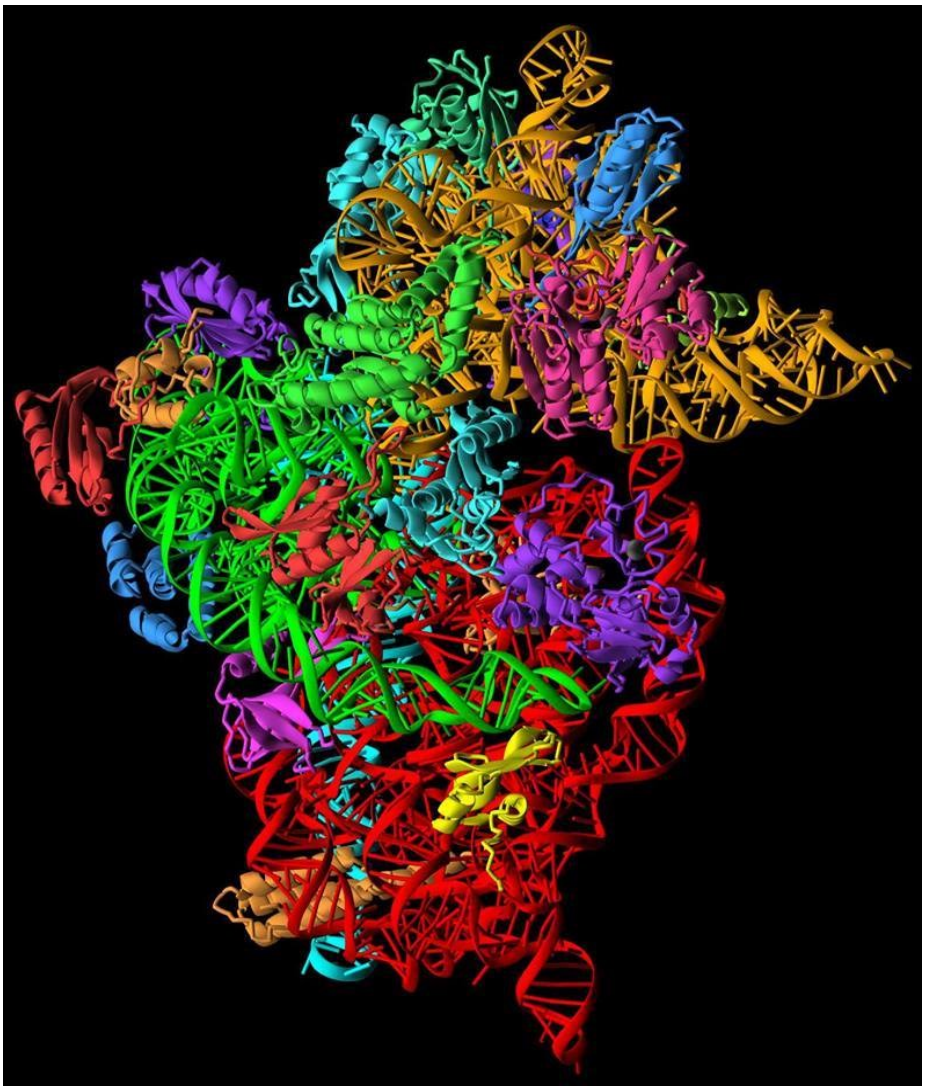


Figure 1. The 30S component, or 'brain' of the ribosome. Credit: Ramakrishnan Lab. https://blog.sciencemuseum.org.uk/ultimate-molecular-machine-plays-key-role-in-superbug-fight

The Ribosome; an Ultimate Molecular 3D Printer

The ribosome, often referred to as the "ultimate molecular 3D printer of flesh and blood" is a complex cellular structure found in all living organisms. It acts as a translation machine, converting genetic information encoded in RNA molecules into functional proteins with specific structures necessary for the correct biology to happen. Ribosomes accomplish this through linking together amino acids in the precise order dictated by the genetic code, Figure 2.

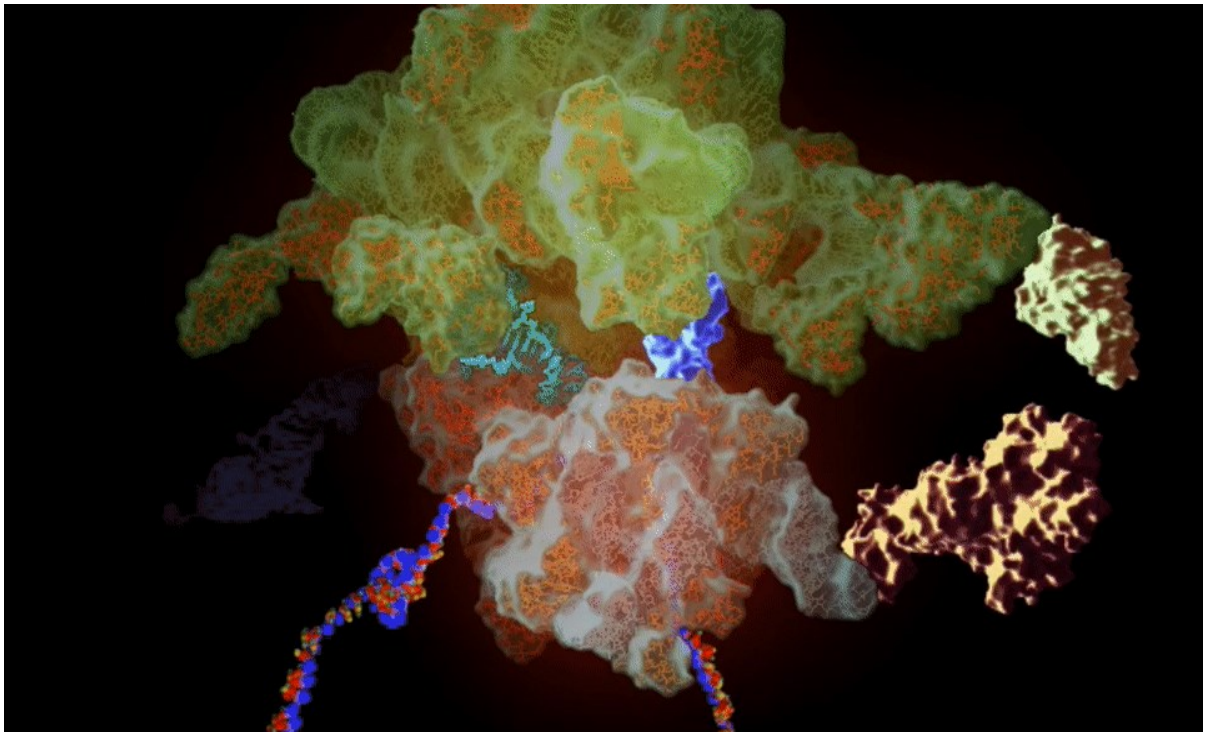


Figure 2. Animated model of protein synthesis by a Ribosome found in bacteria
Credit: Ramakrishnan Lab. https://blog.sciencemuseum.org.uk/wp-content/uploads/2016/05/ezgif.com-video-to-gif.gif

Ribosomes and Pathogenic Bacteria

Ribosomes play a critical role in the life cycle of pathogenic bacteria, which are responsible for causing various infectious diseases. These bacteria heavily rely on ribosomes for their survival and proliferation, making them an attractive target for therapeutic interventions. Disrupting the ribosomal machinery can impede the ability of pathogenic bacteria to synthesize proteins, leading to a significant impact on their growth and proliferation (Jinzhong et al., 2018).

One approach to targeting ribosomes is the development of ribosome-targeted antibiotics. These antibiotics specifically inhibit the activity of bacterial ribosomes, selectively disrupting protein synthesis in pathogenic bacteria while sparing the ribosomes of host cells. These antibiotics would selectively target the bacterial ribosomes and can effectively inhibit bacterial growth and prevent the spread of infections caused by resistant bacteria.

The advantage of targeting ribosomes lies in their conserved structure and function across different bacterial species. Ribosomes are ancient molecular machines that share fundamental characteristics, allowing researchers to develop broad-spectrum antibiotics that can combat a wide range of pathogenic bacteria. This broad-spectrum activity is particularly valuable in the face of antibiotic resistance, as it provides a versatile approach to combating resistant strains.

In recent years, research efforts have focused on gaining a deeper understanding of ribosomal structure, function, and the mechanisms by which ribosome-targeted antibiotics work. The identification of specific vulnerabilities that can be exploited for the design of more effective drugs is potentially within reach through understanding the intricate details of ribosomal biology. This knowledge has paved the way for the development of novel ribosome-targeted antibiotics with enhanced potency, reduced side effects, and improved resistance profiles.

The fight against Antibiotic Resistance

As bacteria evolve and develop resistance mechanisms against conventional antibiotics, finding alternative strategies to combat them becomes crucial. Targeting the ribosome presents a promising avenue, as it represents a fundamental and conserved biological process across diverse bacterial species. Research projects working on interfering with ribosomal function would potentially result in inhibiting bacterial protein synthesis and ultimately halting bacterial growth and reduce the spread of antibiotic-resistant strains (Wilson, 2014).

Ribosome-targeted antibiotics work by binding to specific sites within the ribosome, inhibiting its function and disrupting the accurate synthesis of proteins. This interference with protein synthesis compromises the survival and replication of bacteria, effectively reducing their ability to cause infections (Wilson, 2014).

Moreover, targeting the ribosome has the potential to overcome certain resistance mechanisms employed by bacteria. While bacteria can develop resistance to antibiotics through various mechanisms, such as modifying drug targets or enhancing efflux pumps, the ribosome represents a fundamental process that is difficult for bacteria to evade without severely impairing their own survival. Targeting the ribosome allowed researchers to circumvent some of the common resistance mechanisms employed by bacteria, making ribosome-targeted antibiotics a promising strategy in combating antibiotic-resistant strains.

Research and Advancements

Advancements in technology and techniques, such as cryo-electron microscopy and X-ray crystallography, have revolutionized the field of ribosomal research. These techniques enable researchers to visualize the three-dimensional structure of ribosomes at high resolution, providing insights into their molecular architecture and functional mechanisms, see the Figures 3 & 4. Scientific research in analysing these structures, would pinpoint specific sites within the ribosome that are critical for protein synthesis and can potentially be targeted by antibiotics.

Figure 3. Cryo-Electron Microscopy Structure of the 70s ribosome of *Enterococcus Faecalis*.
Source: the Protein Databank (PDB) entry code 6WUB; can be explored using the SSFS tool https://bioinformaticstools.org/ssfs/ssfs.php?qry=6WUB

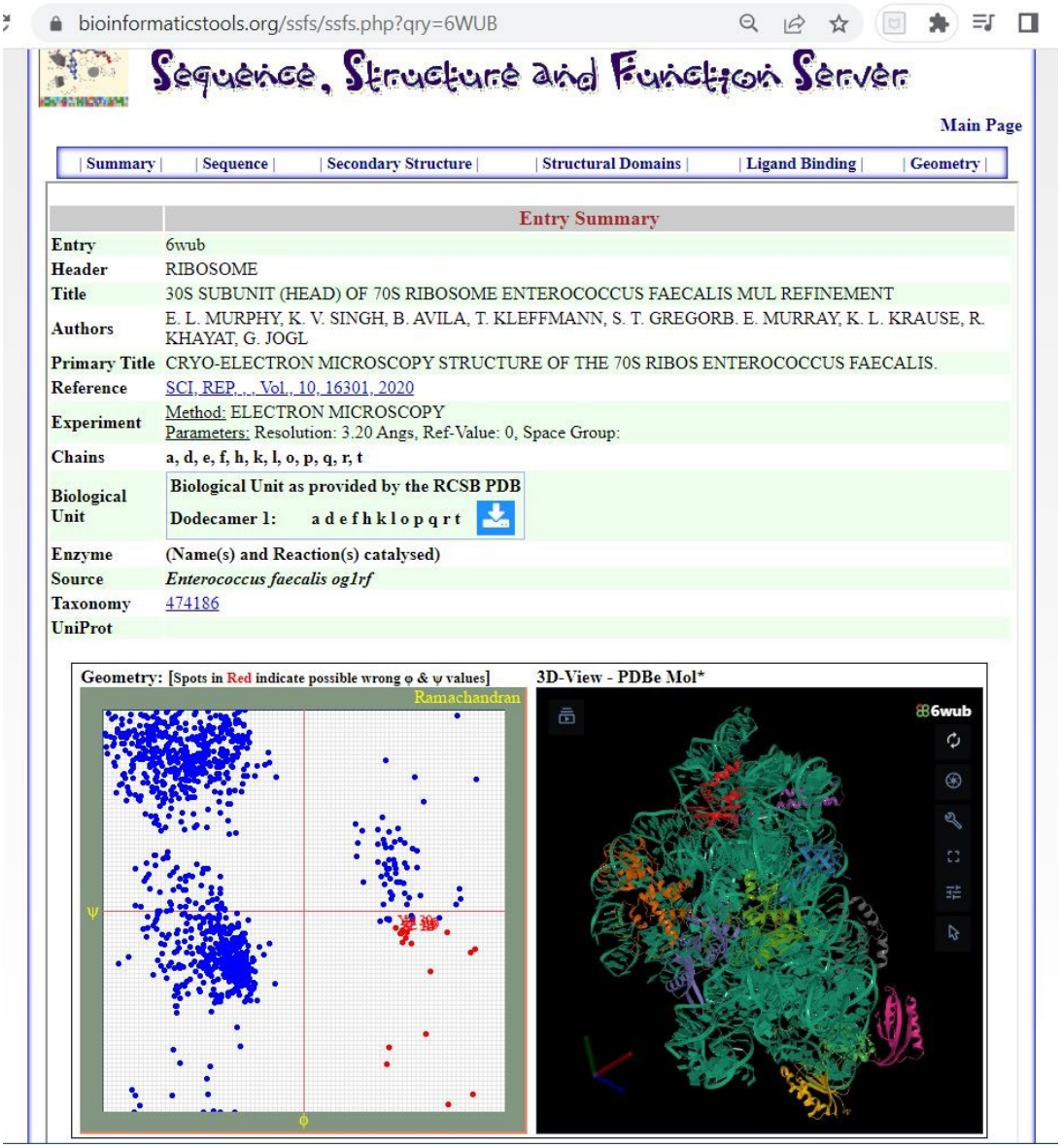


Figure 4. The SSFS✳ tool showing important details of the PDB entry 6WUB related to the 30S Ribosome structure. https://bioinformaticstools.org/ssfs/ssfs.php?qry=6WUB.

✳ SSFS: **Sequence, Structure and Function Server** by the Structural Biology & Bioinformatics Groups, Biology Dept, Faculty of Science, University of Saida, Algeria
نظام **التركيب الأولي، التركيب الفراغي والوظيفة البيولوجية**، فريق البيولوجيا ثلاثية الأبعاد و المعلوماتية الحيوية، قسم البيولوجيا، كلية العلوم، جامعة سعيدة، الجزائر
☛ https://bioinformatics.univ-saida.dz/bit2/?arg=SB3

Moreover, studying the ribosome allows researchers to understand the mechanisms by which ribosome-targeted antibiotics interact with the ribosome and inhibit protein synthesis. This knowledge aids in the design and optimization of antibiotics that can effectively bind to the ribosome and disrupt its function, thereby halting bacterial growth.

One area of focus in ribosomal research is the development of antibiotics that exhibit high specificity for bacterial ribosomes while sparing eukaryotic ribosomes found in human cells. This selectivity is crucial to minimize potential side effects and toxicity to the host organism. Understanding the subtle differences between bacterial and human ribosomes, can help in the design endeavours of novel antibiotics that selectively target bacterial ribosomes, enhancing their efficacy and safety profile.

A number of research projects are investigating novel mechanisms of action for ribosome-targeted antibiotics. Exploration of the different modes of interference with ribosomal function, such as inhibition of specific steps in the protein synthesis process or disruption of ribosome assembly, scientists aim also to expand the repertoire of antibiotics and overcome existing resistance mechanisms.

Furthermore, advancements in computational modelling and virtual screening techniques have facilitated the identification and optimization of potential ribosome-targeted antibiotics. Computational biology and computer simulations in addition to large-scale virtual screening of compound libraries, would result in vast number of molecules and predict their binding affinity and potential efficacy against the ribosome. This computational approach accelerates the discovery and development of novel antibiotics, potentially shortening the timeline for bringing new drugs to the market.

The link between Ribosomes and Superbugs

Superbugs, referring to highly resistant bacterial strains, pose a significant challenge in healthcare settings. Ribosomes have been found to play a key role in combating superbugs, and ongoing research efforts are focused on harnessing the potential of ribosomal targeting to overcome antibiotic resistance (Science Museum blog). For further information on this topic, the article "The Ultimate

Molecular Machine Plays Key Role in Superbug Fight" (source: Science Museum blog) offers a comprehensive overview.

Conclusion

The fight against antibiotic resistance requires innovative approaches that target the fundamental processes essential for bacterial survival. The ribosome, as the ancient molecular machine responsible for protein synthesis, has emerged as a crucial focal point in this battle. Understanding the intricate workings of ribosomes and developing targeted interventions, researchers aim to overcome antibiotic resistance and safeguard public health. Continued research and advancements in this field hold great promise for the development of effective strategies to combat multidrug-resistant pathogens.

References

- Jinzhong L, Dejian Z, Thomas AS, Yury SP, Matthieu GG. (2018). Ribosome-targeting antibiotics: mode of action, mechanisms of resistance, and implications for drug design. Annu Rev Biochem. Jun 20;87:451-478. doi: 10.1146/annurev-biochem-062917-011942. Available at: https://pubmed.ncbi.nlm.nih.gov/29570352/

- Wilson DN. (2014). Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nat Rev Microbiol. 12(1):35-48. doi: 10.1038/nrmicro3155. Available at: https://www.nature.com/articles/nrmicro3155

- Wimberly BT, Brodersen DE, Clemons WM Jr, Morgan-Warren RJ, Carter AP, Vonrhein C, Hartsch T, Ramakrishnan V. (2000). Structure of the 30S ribosomal subunit. Nature.407(6802):327-39. doi: 10.1038/35030006. PMID: 11014182. Available at: https://www.nature.com/articles/35030006

- Mishra S, Imlay JA. (2012) Why do bacteria use so many enzymes to scavenge hydrogen peroxide? Arch Biochem Biophys. 525(2):145-60. doi: 10.1016/j.abb.2012.02.028. PMID: 22405803. Available at: https://pubmed.ncbi.nlm.nih.gov/22609271/

- Benabbou TA, Benreguieg M, Bellil Y, Chahrour W (2023). Antibiotic Resistance: A Global Public Health Crisis and Current Strategies for Combatting It. JSBB 2(1). Available at: https://bioinformatics.univ-saida.dz/jsbb/blog-single.php?ar=April_2023LOLA_Global_Public_Health_Crisis_and_Current_Strategies_for_Combatting_It

- Rachedi A (2023). Teixobactin an antibiotic from soil bacteria for fighting Multiple Antibiotic Resistance phenomena. JSBB 2(1). Available at: https://bioinformatics.univ-

saida.dz/jsbb/blog-single.php?ar=April_2023LOLTeixobactin_Soil_Antibiotic_4_Multiple_Antibiotic_Resistance

- Science Museum blog. "The Ultimate Molecular Machine Plays Key Role in Superbug Fight." Available at: https://blog.sciencemuseum.org.uk/ultimate-molecular-machine-plays-key-role-in-superbug-fight/

Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ARTIFICIAL INTELLIGENCE & BIOLOGY ARTICLES

Concept article *– related to* ***the I2A University Day 2023, 19 April 2023****, University of Saida, Algeria*

ChatGPT - A Powerful AI Language Model

The Transformative Power of AI in Biology

RACHEDI Abdelkrim

Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants, Faculty of Sciences, Department of Biology, University of Saida - Dr Moulay Tahar, 20100 Saida, Algeria.

Correspondence: RACHEDI Abdelkrim – Email: abdelkrim.rachedi@univ-saida.dz, bioinformatics@univ-saida.dz

Published: 19 June 2023

Abstract

Artificial intelligence (AI) has revolutionised numerous domains, and its impact on biology, bioinformatics, and protein structure analysis is particularly remarkable. This review explores the wide-ranging applications of AI in these fields, focusing on notable examples such as ChatGPT and AlphaFold. A historical background is touched upon of AI, the concept of deep learning, and its relationship to ChatGPT and other language models. Furthermore, highlight the invaluable role of ChatGPT in assisting customers, generating content including of scientific relation, enhancing educational experiences, and aiding healthcare professionals.

In the field of biology and bioinformatics, AI technologies, such as ChatGPT, have become indispensable. They facilitate the analysis of biological data, prediction of protein structures, exploration of gene expression patterns, and identification of drug targets. With advancements in natural language processing, ChatGPT promotes collaboration and knowledge sharing among scientists, enhancing communication in complex biological research.

One exemplary AI technology that has garnered significant attention is AlphaFold. developed by DeepMind, AlphaFold leverages deep learning algorithms to predict protein structures with unprecedented accuracy. Its potential applications in drug discovery, protein engineering, and disease understanding are immense. AlphaFold's ability to rapidly and accurately determine protein structures marks a significant milestone in scientific research.

This review highlights the transformative power of AI in biology and underscores the need for continued research and development. As AI technologies continue to evolve, there is immense potential for advancements in understanding biological systems, accelerating drug discovery, and shaping the future of personalized medicine. The integration of AI, exemplified by ChatGPT and AlphaFold, offers a promising pathway for scientific progress and innovation in the biological sciences.

Key words: Artificial intelligence, ChatGPT, Transformer architecture, Deep learning, AlphaFold, Bioinformatics, Protein structure prediction

Background & Concepts

Artificial intelligence (AI) has witnessed remarkable advancements over the years, revolutionising various fields. In biology, the integration of AI techniques has opened new horizons for data analysis, pattern recognition, and knowledge generation. The historical development of AI, from its early stages to the emergence of deep learning, has laid the foundation for the powerful AI models we observe today. Deep learning, with its ability to process vast amounts of data and learn complex representations, has paved the way for transformative applications in biology.

In bioinformatics, ChatGPT can aid in the analysis of biological data by providing insights and generating hypotheses. It can assist researchers in exploring gene expression patterns, predicting protein structures, and identifying potential drug targets. By leveraging its language generation capabilities, ChatGPT can contribute to the interpretation of complex biological data and facilitate collaboration among scientists [1].

In the realm of protein structure analysis AlphaFold, developed by DeepMind, leverages deep learning and AI algorithms to predict protein structures with remarkable accuracy. Its ground-breaking capabilities have the potential to revolutionise fields such as drug discovery, protein engineering, and understanding the molecular basis of diseases. AI algorithms as implemented in AlphaFold, have shown the ability to rapidly and accurately determine protein structures which generated widespread attention and has been recognized for its significant contributions to scientific research [2].

In genomics, ChatGPT can assist in the annotation and interpretation of genomic sequences. It can provide functional annotations, predict the impact of genetic variants, and aid in the identification of disease-causing mutations. ChatGPT can also support genetic counselling efforts by generating understandable explanations for complex genetic concepts and findings.

Moreover, ChatGPT can find applications in biomedical research, where it can help researchers in reviewing and summarizing scientific literature, extracting relevant information from vast datasets, and facilitating knowledge dissemination among peers.

However, it is essential to acknowledge the limitations of ChatGPT, including the potential for bias in its responses and the necessity for human validation of its generated hypotheses or findings. Rigorous testing, validation, and continuous improvement are vital to ensure the reliability and accuracy of ChatGPT in biological applications.

Methods and Outcomes

The success of AI models like ChatGPT and AlphaFold can be attributed to the transformer architecture, a deep learning model that incorporates self-attention mechanisms [3]. Transformers utilize self-attention to capture contextual dependencies in natural language and generate coherent responses. ChatGPT is trained using large-scale datasets and employs autoregressive generation, predicting the next word based on the preceding context. On the other hand, AlphaFold utilizes deep learning techniques, such as convolutional neural networks and attention mechanisms, to predict protein structures [4]. By training on known protein structures, AlphaFold can accurately predict the 3D structure of proteins from their amino acid sequences [5].

Applications of AI in biology and highlight the impact of ChatGPT and AlphaFold. ChatGPT finds utility in customer service, where it can provide timely and accurate responses to customer inquiries, improving the overall customer experience [6]. Additionally, ChatGPT's language generation capabilities enable content creation, generating engaging and personalized materials for various purposes [7]. In education, ChatGPT facilitates interactive learning experiences by generating quizzes, study guides, and personalized educational content [8, 9]. In healthcare, ChatGPT assists medical professionals in diagnosing and recommending treatments by analyzing patient symptoms and medical literature [10].

AlphaFold has made significant contributions to protein structure prediction, advancing our understanding of protein folding and aiding drug discovery efforts. Its ability to predict protein structures with high accuracy has the potential to revolutionize areas such as protein engineering, enabling the design of novel enzymes and therapeutics [11]. Furthermore, AlphaFold's predictions can shed light on the molecular mechanisms of diseases, providing insights for personalized medicine and precision healthcare [12].

Discussion

AI brings immense opportunities to the field of biology, in vital and novel fields of genomic and proteomic analysis, remarkable structure and function prediction of macromolecules, potential rational design of new and effective drugs against diseases like cancers, antibiotics resistant microbes and biotechnology applications to mention few.

However, several considerations must be addressed. Biases in AI models, both in training data and algorithms, should be identified and mitigated to ensure fair and unbiased results [13]. Data privacy and security are of utmost importance, especially when handling sensitive biological and medical information [14]. The

responsible development and deployment of AI in biology necessitate collaborations between AI experts and domain specialists to ensure accurate and reliable results. Ethical considerations surrounding AI use in biology, such as transparency and interpretability of AI models, should also be addressed to foster trust and accountability [15]. Additionally, ongoing research and development are needed to improve the performance and applicability of AI models in biology.

Conclusion

AI has revolutionized the field of biology, offering transformative applications across various domains. ChatGPT and AlphaFold serve as prime examples of AI's impact in customer service, content creation, education, healthcare, and protein structure analysis. These AI models have demonstrated their ability to assist customers, generate personalized content, enhance educational experiences, aid healthcare professionals in diagnosis and treatment, and advance our understanding of protein structures. While there are challenges and ethical considerations associated with AI in biology, they can be addressed through collaborations, responsible development practices, and ongoing research.

References

1. Russell S, Norvig P. Artificial Intelligence: A Modern Approach. 3rd ed. Pearson; 2010. https://web.cs.ucla.edu/~srinath/static/pdfs/AIMA.pdf
2. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521(7553):436-444. https://www.nature.com/articles/nature14539
3. Vaswani A, Shazeer N, Parmar N, et al. Attention is all you need. In: Proceedings of the 31st International Conference on Neural Information Processing Systems. 2017:5998-6008. https://dl.acm.org/doi/10.5555/3295222.3295349
4. ChatGPT. OpenAI. https://openai.com/research/chatgpt. Accessed May 13, 2023.
5. Senior AW, Evans R, Jumper J, et al. Improved protein structure prediction using potentials from deep learning. Nature. 2020; 577(7792):706-710. https://pubmed.ncbi.nlm.nih.gov/31942072/
6. Vinyals O, Babuschkin I, Czarnecki WM, et al. Grandmaster level in StarCraft II using multi-agent reinforcement learning. Nature. 2019; 575(7782):350-354. https://www.nature.com/articles/s41586-019-1724-z
7. AlphaFold: Using AI for scientific discovery. DeepMind. January 15, 2020 https://deepmind.com/research/case-studies/alphafold
8. AlphaFold reveals the structure of the protein universe. DeepMind. July 28, 2022

https://www.deepmind.com/blog/alphafold-reveals-the-structure-of-the-protein-universe

9. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019; 25(1):44-56. https://www.nature.com/articles/s41591-018-0300-7
10. Chen M, Dai W, Sun YS, et al. Convolutional neural networks for automated annotation of cellular cryo-electron tomograms. Nat Methods. 2017; 14(10):983-985. https://pubmed.ncbi.nlm.nih.gov/28846087/
11. AlQuraishi M. AlphaFold at CASP13. Bioinformatics. 2019; 35(22):4862-4865. https://pubmed.ncbi.nlm.nih.gov/31116374/
12. Baek M, DiMaio F, Anishchenko I, et al. Accurate prediction of protein structures and interactions using a three-track neural network. Science. 2021; 373(6557):871-876. https://pubmed.ncbi.nlm.nih.gov/34282049/
13. Bolukbasi T, Chang KW, Zou JY, Saligrama V, Kalai AT. Man is to computer programmer as woman is to homemaker? Debiasing word embeddings. In: Advances in Neural Information Processing Systems. 2016:4349-4357. https://proceedings.neurips.cc/paper_files/paper/2016/file/a486cd07e4ac3d270571622f4f316ec5-Paper.pdf
14. Ohm P. Broken promises of privacy: responding to the surprising failure of anonymization. UCLA Law Rev. 2010; 57(6):1701-1777. https://www.uclalawreview.org/pdf/57-6-3.pdf
15. Ching T, Himmelstein DS, Beaulieu-Jones BK, et al. Opportunities and obstacles for deep learning in biology and medicine. J R Soc Interface. 2018; 15(141):20170387. https://pubmed.ncbi.nlm.nih.gov/29618526/

The Journal of Concepts in Structural Biology & Bioinformatics – JSBB

Volume 2 Issue 1 2023 JSBB Journal