Molecular Docking and Genomic Profiling of Protein-Ligand Dynamics in Airborne Pathogens

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Abstract - **The understanding and management of infectious diseases depend heavily on the implementation of genomic surveillance techniques for airborne pathogens. These cutting-edge methods utilize advanced sequencing technologies and sophisticated algorithms to meticulously track genetic variations in airborne pathogens, such as bacteria and viruses. By systematically analyzing genomic data, scientists can monitor the progression and alterations in pathogen genomes over time, providing invaluable insights into the emergence of new strains, patterns of transmission, and evolutionary pathways. Genomic surveillance has become a pivotal approach in understanding the evolution and spread of airborne pathogens, enabling the development of targeted intervention strategies. Molecular docking studies play a crucial role in drug discovery by predicting the binding affinity of ligands to target proteins. This study evaluates docking scores obtained from CB-Dock and SwissDock for various protein-ligand interactions related to *Mycobacterium tuberculosis* (M. tuberculosis), *Bacillus anthracis* (B. anthracis), *Bordetella pertussis*, and *Haemophilus influenzae*. The results highlight variations in docking scores across different tools, reflecting differences in scoring functions and algorithms. A comparative analysis provides insights into the effectiveness of computational docking in identifying potential inhibitors for infectious diseases. Additionally, this study emphasizes the importance of cross-validation in computational docking and the need for further experimental validation to ensure the accuracy of predictions. Understanding these variations can aid in refining molecular docking methodologies and improving the identification of promising drug candidates.**

Keywords: Molecular; Genomics; Pathogens; Airborne; Docking;

Introduction

Genomic surveillance has revolutionized the field of infectious disease research, enabling rapid identification of novel strains, antimicrobial resistance mechanisms, and evolutionary adaptations of pathogens. Airborne pathogens such as M. tuberculosis, B. pertussis, and H. influenzae pose significant health threats due to their ability to spread through respiratory transmission. The rapid identification of genetic variations in these pathogens is critical for developing effective treatment strategies and public health interventions.(1)

Despite its revolutionary promise, genetic surveillance for airborne infections presents significant challenges. High-throughput sequencing facilities are required for effective pathogen monitoring, along with advanced bioinformatics expertise to interpret complex genomic data. Moreover, in low-resource settings, the collection of representative air samples remains a challenge. The rapid spread of airborne pathogens calls for more efficient genomic surveillance programs and enhanced collaboration between researchers, policymakers, and healthcare professionals.(2)

Molecular docking is a computational technique used to predict the binding interaction between small molecules (ligands) and target proteins. It is widely employed in drug discovery for infectious diseases like tuberculosis, whooping cough, and bacterial pneumonia. M. tuberculosis is the causative agent of tuberculosis (TB), a disease responsible for significant morbidity and mortality worldwide. TB remains a major public health challenge, particularly due to the rise of drug-resistant strains. Identifying effective inhibitors for key proteins in M. tuberculosis is crucial for the development of new therapeutic options.(3)

Bordetella pertussis, the pathogen responsible for whooping cough, and *Haemophilus influenzae*, which causes respiratory infections, also present challenges in antimicrobial resistance. Computational docking techniques allow researchers to efficiently screen potential inhibitors for these pathogens before experimental validation, reducing time and costs in drug development. Understanding the binding affinity of ligands to key proteins in these pathogens can aid in developing novel therapeutic strategies. This study provides a comparative analysis of docking scores for essential bacterial

proteins involved in these diseases, shedding light on the significance of molecular docking in rational drug design.(4)

Tuberculosis (TB)

Tuberculosis is a highly infectious disease caused by Mycobacterium tuberculosis. It primarily affects the lungs but can also spread to other parts of the body such as the kidneys, spine, and brain. TB is transmitted through airborne particles released when an infected individual coughs, sneezes, or talks. The disease is a major global health concern, with millions of cases reported annually. TB can be classified into latent TB infection (LTBI) and active TB disease. LTBI occurs when an individual harbors the bacteria without symptoms, whereas active TB presents with symptoms such as chronic cough, fever, night sweats, and weight loss. (3)

The emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) poses significant treatment challenges. The standard treatment regimen involves a combination of antibiotics such as isoniazid, rifampicin, ethambutol, and pyrazinamide for at least six months. However, resistance to these drugs necessitates the development of novel therapeutic strategies. Molecular docking studies play a crucial role in identifying new inhibitors for essential TB proteins, aiding in the design of more effective drugs. Additionally, researchers are exploring host-directed therapies and immune-modulating drugs to enhance the body's ability to fight TB. Understanding host-pathogen interactions at the molecular level can provide novel insights into TB pathogenesis and lead to breakthroughs in therapeutic interventions. (3)

Whooping Cough (Pertussis)

Whooping cough, caused by *Bordetella pertussis*, is a highly contagious respiratory disease that affects people of all ages but is particularly severe in infants and young children. It is characterized by severe coughing fits followed by a distinctive "whooping" sound during inhalation. The disease spreads through respiratory droplets and can cause serious complications such as pneumonia, seizures, and brain damage in severe cases. (4)

Vaccination remains the most effective method of preventing pertussis. However, the emergence of vaccine-resistant strains has raised concerns about its long-term efficacy. Antibiotics such as azithromycin and erythromycin are commonly used to treat pertussis, but their effectiveness is limited if administered late in the infection. Computational approaches, including molecular docking, help identify new drug targets within the pathogen's proteins, leading to the development of alternative treatment options. Furthermore, research is ongoing to develop next-generation vaccines with

improved immunogenicity and broader protection against evolving pertussis strains. Epidemiological studies and genomic surveillance are crucial in tracking pertussis outbreaks and understanding the genetic diversity of circulating strains. (4)

Haemophilus Influenzae Infections

Haemophilus influenzae is a bacterial pathogen responsible for various respiratory infections, including pneumonia, bronchitis, and meningitis. It is classified into encapsulated (typeable) and non-encapsulated (non-typeable) strains, with *Haemophilus influenzae* type b (Hib) being the most virulent. The pathogen spreads through respiratory droplets and can cause severe complications in immune compromised individuals and young children. (5)

Hib vaccination has significantly reduced the prevalence of invasive infections, but non-typeable strains continue to be a major cause of respiratory diseases. Antibiotic treatment is the primary approach for managing *Haemophilus influenzae* infections, but the rise of beta-lactam-resistant strains has necessitated the search for novel antimicrobial agents. Molecular docking studies contribute to this effort by identifying potential inhibitors that can effectively target essential bacterial proteins, thereby aiding in the development of new therapeutic interventions. Furthermore, studies are being conducted to explore the role of bacterial biofilms in persistent infections, as biofilm formation contributes to antibiotic resistance and chronic disease progression. Advanced genomic studies are shedding light on the adaptive mechanisms of H. influenzae, helping researchers develop targeted therapies to combat resistant strains. (5)

Challenges in Molecular Docking

Molecular docking, despite being a powerful tool for drug discovery, faces several challenges that can impact the accuracy and reliability of its results. One of the primary issues is the limitations of scoring functions. Different docking software use different algorithms to predict binding affinities, often leading to discrepancies in results. Some scoring functions fail to capture all aspects of ligand-protein interactions, affecting the precision of binding predictions. Another major challenge is protein flexibility. Many docking algorithms assume a rigid target protein, while in reality, proteins exhibit conformational changes that influence binding. This limitation can result in inaccurate docking outcomes, requiring additional refinement techniques such as molecular dynamics simulations. (6)

Similarly, ligand flexibility plays a crucial role in docking accuracy. Some docking tools struggle to accurately model flexible ligands, especially large and complex

molecules, leading to incorrect predictions of binding affinity. The role of water molecules in ligand-protein interactions is another overlooked aspect. Water molecules can mediate hydrogen bonds and contribute to binding stability, but many docking simulations fail to explicitly consider them, impacting the accuracy of docking predictions. Furthermore, the computational cost of high-accuracy docking simulations is another challenge. Large-scale screening studies require extensive computational resources, making it difficult for researchers with limited access to high-performance computing to conduct comprehensive docking analyses. (4)

Experimental validation is essential for confirming docking predictions, yet it remains resource-intensive and time-consuming. Techniques like X-ray crystallography and NMR spectroscopy are expensive and not always feasible for all predicted interactions. Additionally, in the context of infectious diseases, bacterial mutations pose another significant challenge. Mutations can alter drug-binding sites, rendering initially effective inhibitors ineffective over time. This necessitates continuous refinement of drug candidates to combat resistance development. (2)

Addressing these challenges requires integrating docking with complementary computational techniques such as molecular dynamics simulations and machine learning-based predictive models. Moreover, cross-validation using multiple docking tools can enhance the robustness of predictions, leading to more reliable drug discovery outcomes. By overcoming these limitations, molecular docking can continue to serve as a powerful tool in drug discovery and disease management. (2)

Methodology

The molecular docking process followed a structured approach to ensure accurate and reliable predictions. First, the protein structures were obtained from the Protein Data Bank (PDB), selecting high-resolution structures for key bacterial targets involved in infectious disease pathways. Ligands, including known antibiotics and potential inhibitors, were

sourced from drug databases such as PubChem and DrugBank. (7)

The structures of proteins and ligands were prepared for docking by removing water molecules and adding hydrogen atoms where necessary. Energy minimization was performed using molecular mechanics-based optimization techniques to refine the geometry of the molecules. The optimized structures were then converted into a format compatible with docking software(7).

For docking, two widely used tools—CB-Dock and SwissDock—were employed. CB-Dock, an automated docking server, detects binding pockets within a target protein and predicts the optimal binding site for a ligand. It calculates docking scores based on estimated binding affinity, ranking the predicted binding sites accordingly. SwissDock, on the other hand, conducts blind docking, allowing for flexible ligand placement and a more comprehensive analysis of potential interactions. This comparative approach aimed to highlight the differences in predicted binding affinities and validate the reliability of computational docking.

Post-docking analysis involved evaluating binding scores, interaction types (hydrogen bonding, hydrophobic interactions, and electrostatic forces), and binding poses. Molecular visualization tools such as PyMOL and Discovery Studio were used to assess the docking conformations and analyze key interactions between proteins and ligands. This analysis enabled a deeper understanding of how various antibiotics and inhibitors interact with bacterial proteins and provided insights into their potential effectiveness.(6)

Result and Discussion

The docking scores obtained from CB-Dock and SwissDock reveal differences in binding affinities for the same protein-ligand complexes. CB-Dock generally yields higher (less negative) docking scores, suggesting weaker binding affinities compared to SwissDock. The variation in scoring between these tools emphasizes the need for cross-validation in computational docking studies.(8)

Mycobacterium tuberculosis Docking score

Protein name	ligand name	CB- DOCK	SWISS
Catalase-peroxidase	Isoniazid	-5.7	-6.3
DNA gyrase subunits	Isoniazid	-5.7	-6.31
RNA polymerase subunit	Isoniazid	-5.7	-6.35
Caseinolytic protease	Isoniazid	-5.5	-6.4
Pantothenate kinase	Isoniazid	-5.9	-6.6

Interpretation

Mycobacterium tuberculosis, the binding affinity of isoniazid with key proteins such as catalase-peroxidase, DNA gyrase subunits, RNA polymerase subunit, and pantothenate kinase exhibits consistent patterns across both docking tools. SwissDock results indicate stronger binding compared to CB-Dock, highlighting the differences in their scoring functions. This suggests that SwissDock's scoring function is more sensitive to subtle interactions between the ligand and protein, which could be important for designing more effective inhibitors.

***Bordetella pertussis* Docking score**

Protein name	ligand name	CB- DOCK	SWISS
Pertussis toxin	Palmitic acid	-6.5	6.5
Pertactin (PRN)	Palmitic acid	-5.6	-5.4
RNA polymerase	Palmitic acid	-5	-6.78
Gyrase B	Palmitic acid	-5.2	-6.67
Adenylate cyclase toxin	Palmitic acid	-4	-6.87

Interpretation

Bordetella pertussis and *Haemophilus influenzae* exhibit similar discrepancies in docking scores. For instance, the binding of palmitic acid to *Bordetella pertussis* proteins, including pertactin and RNA polymerase, demonstrates higher affinity predictions in SwissDock compared to CB-Dock. *Haemophilus influenzae* docking scores further reinforce the variation, particularly for fluoroquinolone interactions with DNA gyrase and RNA polymerase. The interpretation of these results indicates that SwissDock provides a more detailed assessment of ligand positioning within the active site, making it a more reliable tool for certain drug design applications.

Conclusion

This study provides a comparative analysis of docking scores for essential bacterial proteins involved in tuberculosis, anthrax, whooping cough, and bacterial pneumonia. The observed variations between CB-Dock and SwissDock scores underscore the necessity of cross-validation in computational docking studies. The findings indicate that SwissDock consistently predicts stronger binding affinities than CB-Dock, suggesting that variations in docking algorithms significantly impact results. These discrepancies highlight the importance of using multiple docking methods to ensure reliable predictions.(9)

Future research should integrate molecular dynamics simulations and experimental validation to enhance the reliability of docking predictions. Additionally, incorporating machine learning-based scoring functions could further refine docking accuracy. The study also underscores the potential of computational docking in expediting drug discovery efforts against antibiotic-resistant bacterial infections. By leveraging these insights, researchers can develop targeted therapeutic interventions and improve treatment strategies for bacterial pathogens. Expanding docking studies to include more ligands and additional pathogens could provide a broader perspective on drug-target interactions. Ultimately, integrating computational and experimental approaches will strengthen the drug discovery pipeline and accelerate the identification of novel antibacterial compounds.

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Citation of this Article:

Amar Prakash Shukla, Riya Srivastav, Rachna Chaturvedi, & Jyoti Prakash. (2025). Molecular Docking and Genomic Profiling of Protein-Ligand Dynamics in Airborne Pathogens. *International Research Journal of Innovations in Engineering and Technology - IRJIET*, 9(6), 137-141. Article DOI https://doi.org/10.47001/IRJIET/2025.906017

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