

Research Paper

Insilico Structural and Functional Profiling of the *HerA* (Helicase) Enzyme in *Pyrobaculum ferrireducens*

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Abstract

DNA double-strand breaks (DSBs) are significant DNA lesions that, if left unrepaired, compromise the integrity of the genome, while the role of DNA helicases in DNA unwinding during DNA repair processes cannot be overstated. This study aims to investigate the structural and functional role of the DNA helicase *HerA* in the repair of DNA double-strand breaks in the thermophilic archaeon *Pyrobaculum ferrireducens* using an *insilico* approach. *Insilico* studies help to understand the role of *HerA* in DNA double-strand break repair, including the binding site of the protein with its interacting partners, as well as the impact of point mutations on the function of the DNA helicase. The homology of the DNA helicase *HerA* with other DNA repair enzymes, as well as its structural homology with other DNA helicases, indicates that it plays a significant role in DNA double-strand break repair in the thermophilic archaeon *Pyrobaculum ferrireducens*, possibly as a result of evolutionary adaptations to survive in extreme environments under stress conditions. The results provide a computational framework for cross-species helicase research and validate *HerA* crucial role in DSB end resection for homologous recombination, reflecting evolutionary adaptations for extremophile survival. By addressing gaps in our understanding of archaeal DNA repair, synthetic biology for robust enzymes, and possibly eukaryotic repair defects associated with cancer, will get advanced. Through optimized commercial production of thermostable *HerA* for high-temperature industrial processes such as PCR, biofuel production, and diagnostics, it benefits biotechnology socially. Future prospects include directed evolution for improved variants, experimental validation, and applications in anti-cancer therapies that target repair helicases.

1. Introduction

The survival and evolutionary adaptation of species, particularly those in extreme habitats, rely on their ability to mend DNA damage. One of the three major domains of life, Archaea, is well-known for its flexibility and ability to thrive in habitats as extreme as hydrothermal vents, acidic hot springs, and hypersaline lakes of this particular planet (Alhmoud et al., 2020). *Pyrobaculum ferrireducens*, a hyperthermophilic archaeon, has the ability to resist high-temperature and anaerobic conditions, making it a suitable candidate for the study of extremophiles. DNA double strand breaks (DSBs) are one of the most common and lethal types of DNA damage, which, if not repaired, can result in genomic instability, the loss of genetic information, and cell death (Iyama & Wilson, 2013). The primary method of DSB repair in archaea involves homologous recombination (HR). DNA end resection, which involves the generation of single-stranded DNA overhangs through the processing of the DNA ends, is an essential step in HR. In order to enable accurate repair, these overhangs have to function as substrates for strand invasion and mating with the complementary strands (Sun et al., 2020). An important component of this process is the *HerA-NurA* complex, which has *NurA* as a nuclease to degrade the processed ends of the DNA and *HerA* as an ATP-dependent helicase to unwind the DNA.

Besides its role in DNA repair, the *HerA-NurA* complex is of particular interest. Its role provides information on the evolution of the process of DNA repair. This is due to the highly conserved process and its similarity to eukaryotic systems. While archaea have the *HerA-NurA* complex to carry out end resection, bacteria have the RecBCD and AddAB complexes (Constantinesco, 2004). This underlines the mechanistic diversity of DNA repair processes across life domains.

Significant structural and functional information has been found to have been obtained through previous studies on *HerA* and *NurA* in model archaeal organisms such as *Sulfolobus solfataricus* and *Thermococcus kodakarensis*. The conserved ATPase motifs found in *HerA*, which is a member of the helicase superfamily II, are critical for its helicase activity (Bochman, 2014). On the other hand, the role of *NurA* is to ensure the production of ssDNA overhangs, and it is involved in 5'3' exonuclease activity. These enzymes combine to produce a dynamic complex, with *NurA* binding to the DNA ends that have been unraveled by *HerA* to ensure efficient processing (Cheng et al., 2015). Nevertheless, despite the ecological and evolutionary implications of the *HerA-NurA* complex in *P. ferrireducens*, little information has been reported about the structure and function of the complex.

The robustness and efficiency of the *HerA-NurA* complex have significant implications for hyperthermophilic archaea. Depurination, deamination, and strand breaks are spontaneous DNA damage events that are accelerated at high temperatures (Sirbu & Cortez, 2013). Thus, strong DNA repair systems are essential for preserving the integrity of the genome. Knowing the *HerA-NurA* complex's molecular makeup and interaction dynamics in *P. ferrireducens* can help us understand how extremophiles adapt to their surroundings and deal with genomic stress (White & Allers, 2018).

Besides this, insilico approaches also offer a useful tool in the characterization of protein complexes, especially in species in which technical challenges hinder experimental approaches. Protein structure prediction, functional domain identification, and protein-protein

and protein-DNA interaction studies are all facilitated through insilico approaches. The structural and functional characteristics of several DNA repair proteins in archaea have also been elucidated using these approaches, which may be followed in *P. ferrireducens* as well (Pérez-Arnaiz et al., 2020).

2. Materials and Methods

2.1. Sequence retrieval of *P.ferri-HerA* Helicase

The protein sequence of *P. ferrireducens* Helicase (*P.ferri-HerA*), has been looked up on the NCBI website using the gene [Id 11596116](#).

2.2. Protein parameters

The protein parameters have been determined by using the Expasy Protparam web service. By using the address <https://web.expasy.org/protparam/> it is possible for a user to access the Protparam tool, as it is one of the tools provided by the Expasy server. The Protparam tool is used by providing an amino acid sequence in the FASTA format, and the parameters are recorded as a consequence (Gasteiger et al., 2005).

2.3. Multiple sequence alignment

Using CLUSTAL OMEGA, the multiple sequence alignment of five protein sequences from *P.ferri-HerA* from various archaeal and eukaryotic species was carried out. The website <https://www.ebi.ac.uk/Tools/msa/clustalo/> was used to access the internet server. The alignment of helicase sequence of *P. ferrireducens* was done against helicase from twenty-five archaeal species, *Sulfolobus solfataricus*, *Pyrococcus furiosus*, *Caldisphaera lagunensis*, *Acidianus hospitalis*, *Metallosphaera sedula*, *Methanobrevibacter ruminantium*, *Hyperthermus butylicus*, *Saccharolobus shibatae*, *Sulfolobaceae*, *Sulfolobus islandicus*, *Metallosphaera prunae*, *Thermococcus barophilus*, *Acidianus manzaensis*, *Pyrococcus yayanosii*, *Methanocaldococcus*, *Thermococcus sp*, *Thermococcus thioireducens*, *Thermococcus gorgonarius*, *Thermococcus gorgonarius*, *Thermococcus radiotolerans*, *Thermococcus barossii*, *Thermococcus eurythermalis*, *Thermococcus paralvinellae*.

2.4. Protein structure analysis

UCSF Chimera was downloaded following the instructions using the following website: www.cgl.ucsf.edu/chimera/download, for the investigation of the molecular structure and interactive visualization of the protein models. The protein structures were imported during the installation of the software using the codes from the RCSB PDB database or those generated by AlphaFold3.0 during the prediction of the protein structures. The 3-D structure of *S.solfataricus HerA-NurA* was downloaded and imported to UCSF Chimera for further analysis using the PDB ID number 4D2I for further investigations, whereas the 3-D structures of *P.ferri-HerA* and *P.ferri-NurA* were predicted by the AlphaFold3.0 program (Pettersen et al., 2004).

2.5. InSilico Characterization of *P. ferri-HerA*

InSilico characterization of *P.ferri-HerA* is done by using different available software's (Online/offline). The protparam Expasy server (<https://web.expasy.org/protparam/>) was used to analyze the statistics. The protein structure prediction is done by using the AlphaFold3.0

(<https://alphafoldserver.com/>) (Abramson et al., 2024). Protein structural analysis was being performed by using Chimera (<https://www.cgl.ucsf.edu/chimera/>) and COOT (<https://www2.mrc-lmb.cam.ac.uk/personal/pemsley/coot/>) software's.

2.6. Molecular Docking

The docking of the helicase protein with the nuclease protein is done by using cluspro (<https://cluspro.org/>). Further, the result of the docked compound is analyzed by using Chimera. This analysis provides a clear idea about the interaction of amino acids, resulting in the attachment of the protein for the DNA repair process (Jones et al., 2022).

2.7. Molecular Dynamic Simulation

To provide a more comprehensive and validated view of such protein-protein interactions and their validity, simulations of docked protein complexes were performed using IMOD software (<https://imods.iqf.csic.es/>) that uses Normal Mode Analysis (NMA) within internal coordinates (i.e., torsional space) for studying the collective motion of proteins and nucleic acids.

3. Results

3.1. Computational Protein Interaction Mapping

For the understanding of the interactions between proteins in a biological system, the need for the use of an important bioinformatics tool, which is referred to as the STRING study, cannot be overemphasized. It creates a network to show and explain the way proteins cooperate to perform biological functions, as shown in figure 1.

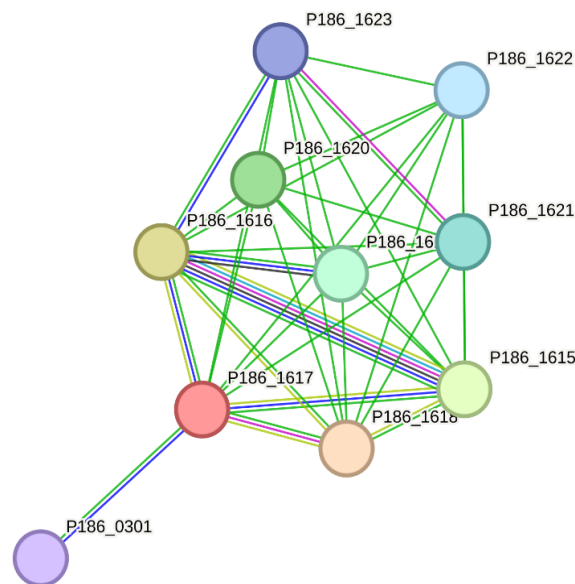


Figure 1. HerA helicase (P186_1617) in *Pyrobaculum ferrireducens*. Functional enrichment and protein-protein interaction network based on the STRING database. It appears that, as a major hub, the HerA helicase (P186_1617) has strong interactions with a number of proteins that could potentially play roles in DNA-related processes. From the functional enrichment, proteins associated with DNA repair, e.g., P186_1618 (Nuclease), and those with ATP-dependent activities on DNA, e.g., P186_1615 (RadA), were significantly overrepresented.

3.2. Prediction of α -Helices and β -Sheets in *HerA*

The secondary structure of the *HerA* helicase enzyme has been predicted with the help of the Psi-Pred tool. After the prediction, it has been interpreted that there are approximately 23 alpha helices and 21 beta sheets and coils. The prediction has been done that the *HerA* protein, which has the coding for the helicase enzyme, has the tendency to interact with the membrane and the membrane, as shown in figure 2.

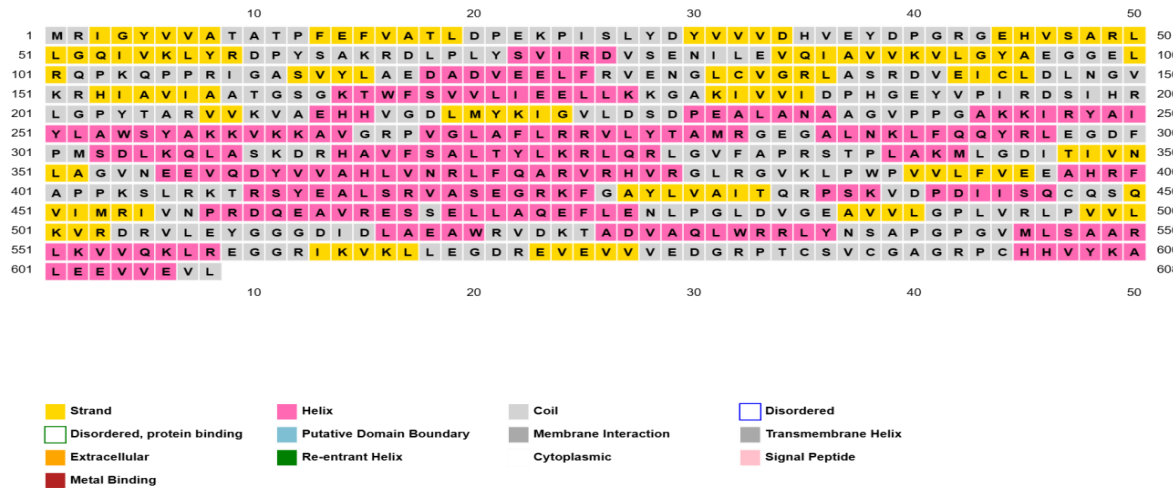


Figure 2. Protein 2D Structure prediction. Results showing the number of α -helix, β -sheets and coils in the Protein structure.

The *HerA* gene, which encodes the DNA helicase from the microorganism *Pyrobaculum ferrireducens*, has a mostly helical structure with distinct helical regions spanning the first 500 amino acids, based on the prediction by the MEMSAT-SVM algorithm. After the 501 to 560 amino acids, a flexible coil region appears, and thereafter, until the 600 amino acid, a C-terminal tail region is observed, as shown in figure 3. The protein, being a DNA helicase, is involved in genome repair and maintenance, and it is a soluble protein located in the cytoplasm, as indicated by the absence of transmembrane regions, signal peptides, and membrane-associated regions.

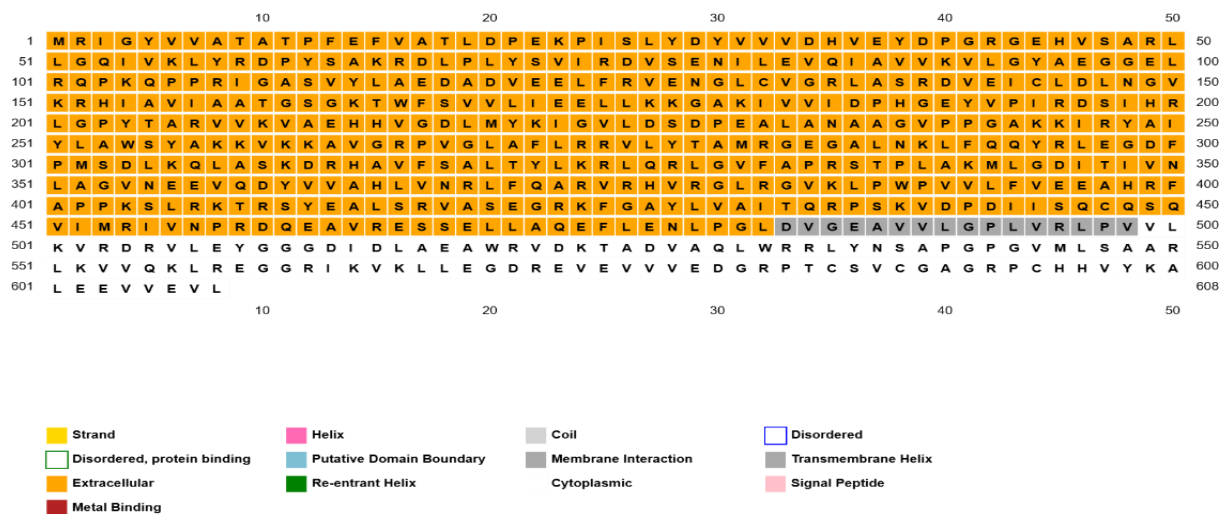


Figure 3. MEMSAT results of *HerA-NurA* complex. These results show the presence of transmembrane helix in the protein structure.

3.3. Differential Modeling and Structural Interpretation of *HerA* and *NurA*

The monomeric structure of helicase producing enzyme *HerA* and Nuclease producing enzyme *NurA* in *Pyrobaculum ferrireducens* is interpreted with the help of software Alphafold3, and the presence of four domains in the enzyme makes it fit for the DNA double-stranded break repair pathway, as depicted in Figure 4.

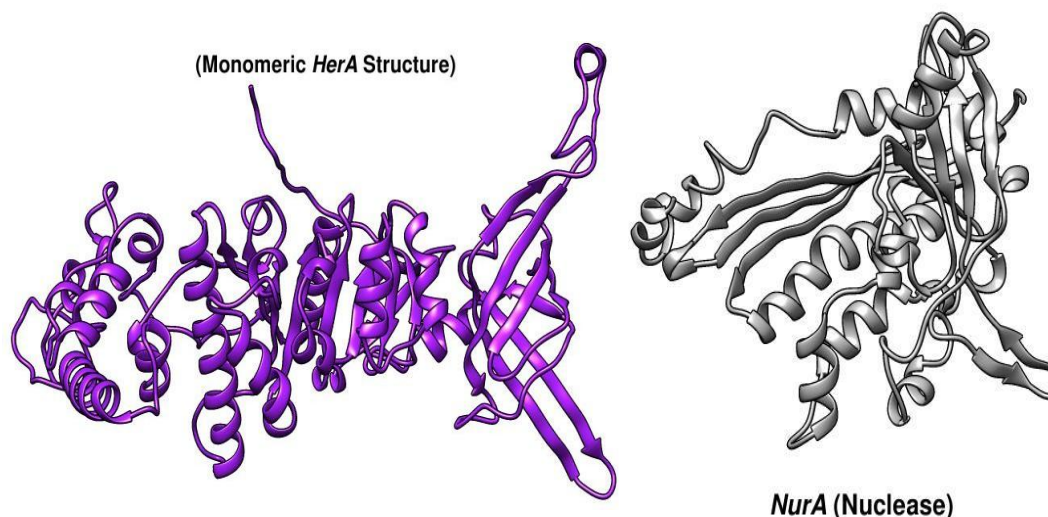
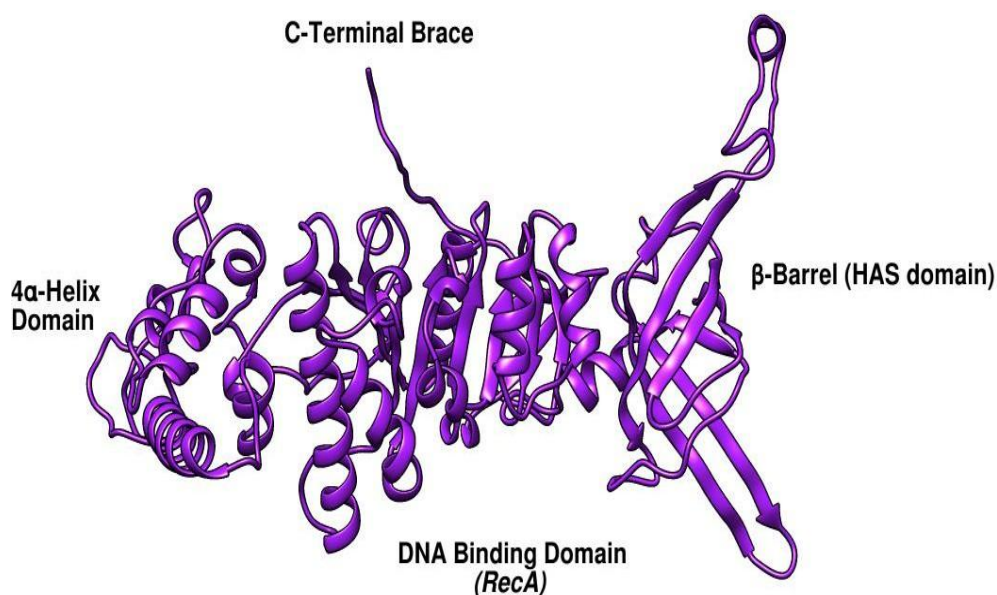


Figure 4. Protein structure Prediction. Monomeric structure of *HerA* and *NurA* proteins

The DNA repair helicase had crucial domains that were responsible for the binding of the *NurA* and *HerA* to perform the DNA repair mechanism. These domains were responsible for the formation of the hexamer, the attachment of the nuclease, and the DNA to enter for the DNA repair process, as depicted in figure 5.

Figure.5. Domain Analysis of *HerA* in *P. ferrireducens*



In *HerA* hexamer, AMP-PNP, a chemically stable ATP analog often utilized as a tool to study ATP binding and hydrolysis events in ATPases, binds to a helicase protein. Adenylyl-

imidodiphosphate, also known as AMP-PNP, mimics the natural substrate ATP by binding to the nucleotide-binding domain of the helicase, as indicated in figure 6.

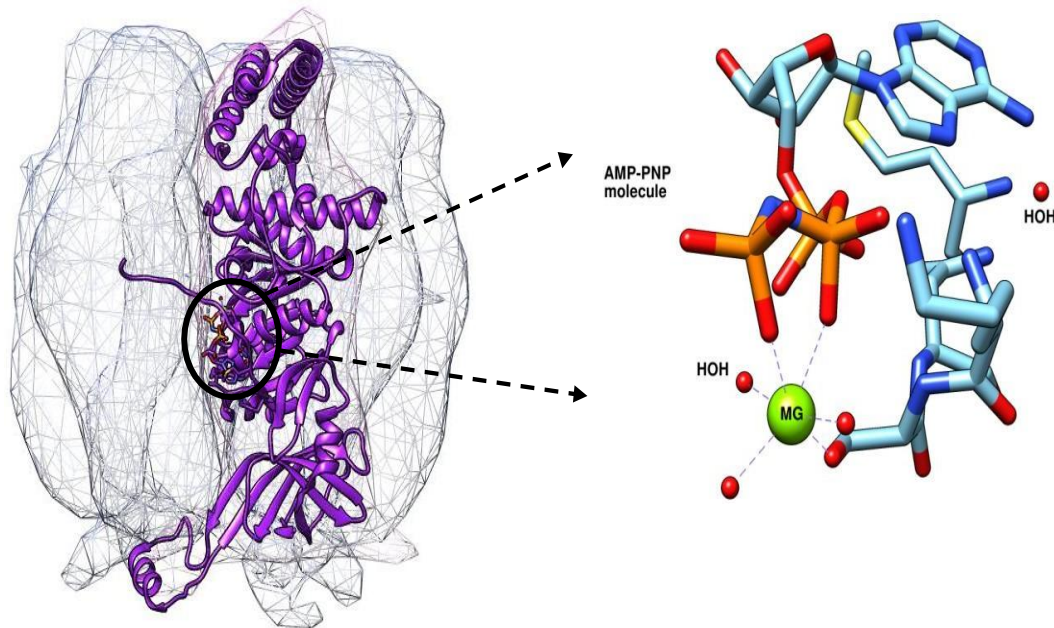


Figure 6. AMP-PNP molecule, a ligand binds with the *HerA* hexameric consisting of Magnesium molecule surrounded by water molecule.

From the structure, it is shown that the DNA binds to the Helicase enzyme at a specific site known as the binding pocket, which gives the DNA the ability to enter and bind so that the unwinding of the DNA gets started. This will allow the nuclease enzyme to start chopping the defected DNA to proceed the repair pathway as shown in figure 7.

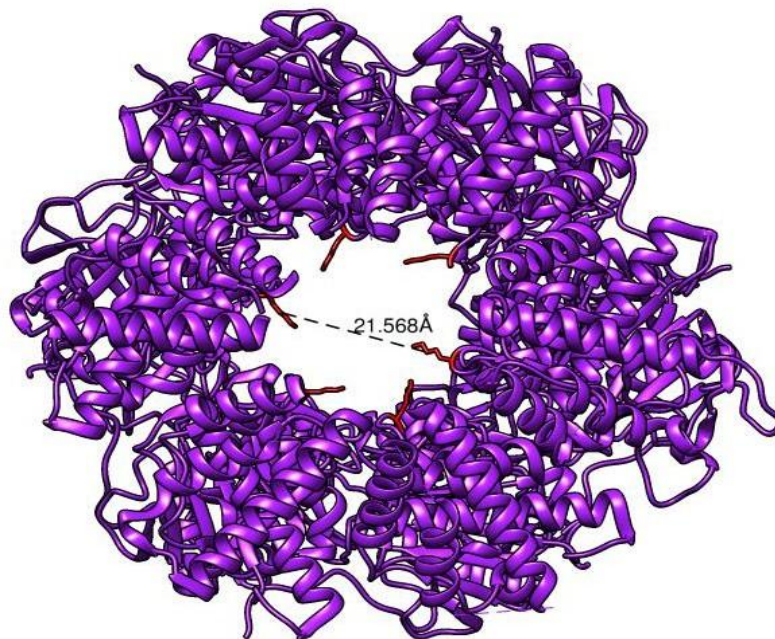


Figure 7. DNA binding Domain analysis. *HerA* hexamer provides the entering point of DNA in the protein by making a DNA binding Pocket. The distance of the pocket is 21.568 Å.

Interacting Residual Analysis of *HerA* in *Pyrobaculum ferrireducens* provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn shown in Figure 8.

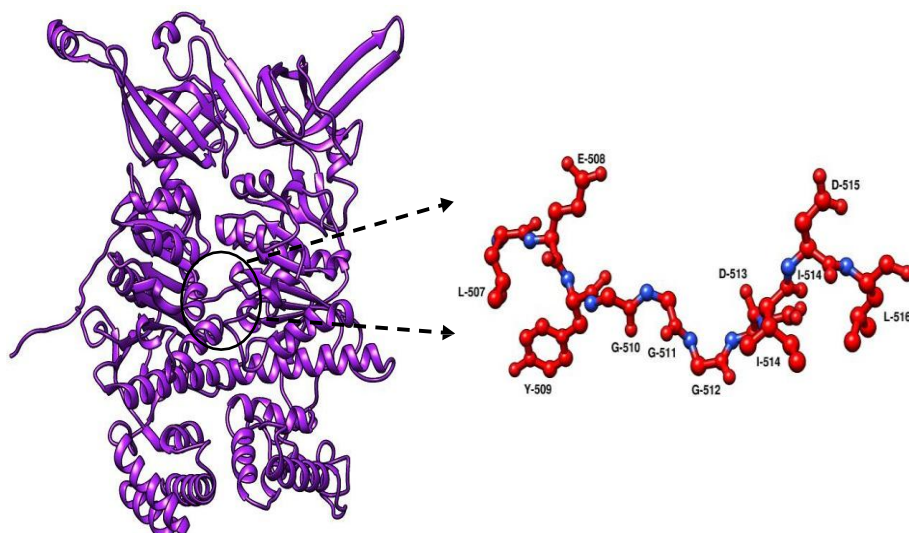


Figure 8. Mechanism Regulating Residues in *HerA*. The red color highlighted amino acids in (A) are the important residues in *HerA* that are responsible for binding to *NurA*. The spatial orientation of the highlighted residues in (B) emphasizes their importance in the hexameric structure's flexibility and the interaction with the DNA.

HerA C-terminal brace is a crucial structural component that maintains the stability of the protein complex in its hexameric form. Enabling the complex's helicase activity and the integrity of the complex are its responsibilities, as shown in Figure 9.

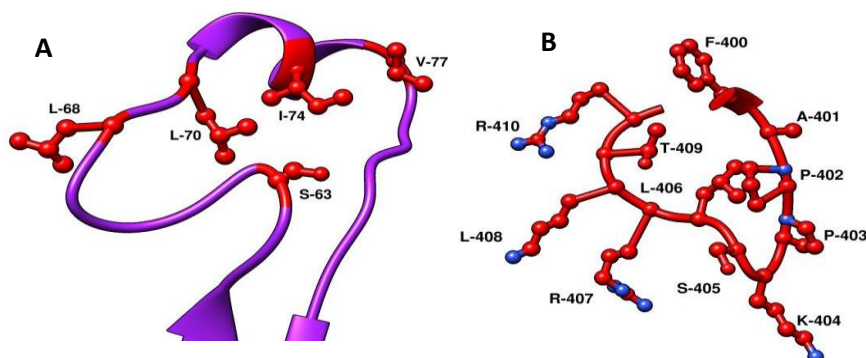


Figure 9. C-Terminal Brace representation of monomeric *P. ferri-HerA* with its C-terminal brace. Analysis of C-terminal brace residues and key residue D-513 (in red) for salt bridge formation and severe DNA destruction upon mutation Docking Analysis of *HerA-NurA* complex.

Docking analysis for the complex formed by the protein complex of *HerA* and *NurA* indicates the involvement of the active site in the interaction as depicted in the figure below. Approximately 104 contacts are observed for the protein-protein interactions, with the most

significant interaction being the (GLY 591.A O ILE 3.A H) for the complex formed by the helicase protein and the nuclease protein as depicted in Figure 10.

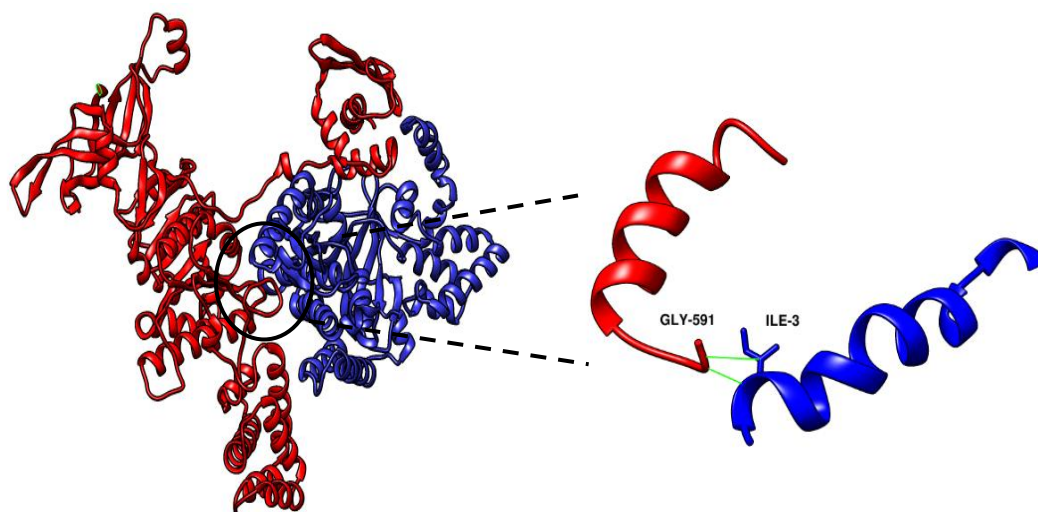


Figure 10. *HerA-NurA* docked complex. (A) Illustration shows the docked complex of both DNA repair proteins while the (B) shows the Only hydrogen bond formed between Glycine of helicase and isoleucine of nuclease.

Other observed interactions between these protein-protein docked molecule are mentioned in Table 1.

Table 1. Strong hydrogen bonds with high overlap

Interaction	Bond Type	Distance (Å)	Overlap	Significance
ARG 582.A HH22 – ARG 7.A O	H-bond	1.689	0.791	Very strong H-bond
ASN 537.A OD1 – ARG 9.A HH11	H-bond	1.738	0.742	Strong, stable interaction
LEU 351.A O – ARG 111.A HH21	H-bond	1.753	0.727	Likely backbone interaction
GLU 190.A OE1 – ARG 78.A HH21	H-bond / Salt bridge	1.767	0.713	Important electrostatic contact
PRO 187.A O – ARG 111.A HH11	H-bond	1.775	0.705	Strong side/backbone interaction
ASP 580.A OD1 – ARG 11.A HH22	H-bond	1.777	0.703	Classical salt bridge, critical

3.4. Molecular Dynamic Simulation

In order to examine the dynamics of *HerA-NurA* docked complex, IMOD server has been used, which depicts the flexibility of *HerA-NurA* complex. Eigen value of *HerA-NurA* complex has been depicted in figure 11.

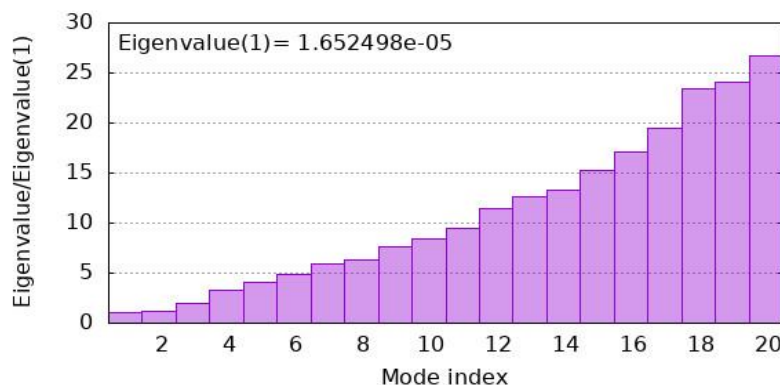


Figure 11. Low Eigen value suggesting the relevance of *HerA-NurA* complex collective motion and biological movements.

Relevance motion of one atom or residues of the other protein, i.e., depiction of the docked complex is given by the covariance of the docked complex. For the *HerA-NurA* complex, analysis of the covariance is shown in Figure 12, Along with the deformability analysis shown in Figure 13.

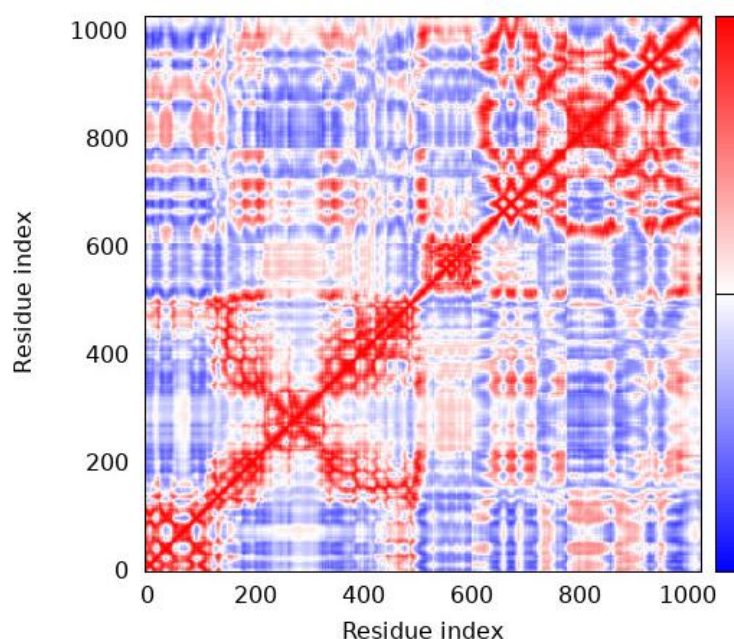


Figure 12. Atomic fluctuation covariance matrix for *Pyrobaculum ferrireducens'* *HerA-NurA* complex. Motions between residue pairs are shown to be favorably linked in red regions and negatively correlated in blue regions. While anti-correlated areas suggest possible hinge-like or opposing domain motions, strong off-diagonal correlations suggest coordinated inter-domain movements. The complex's structural connection and functional flexibility during DNA processing are reflected in these dynamic interactions.

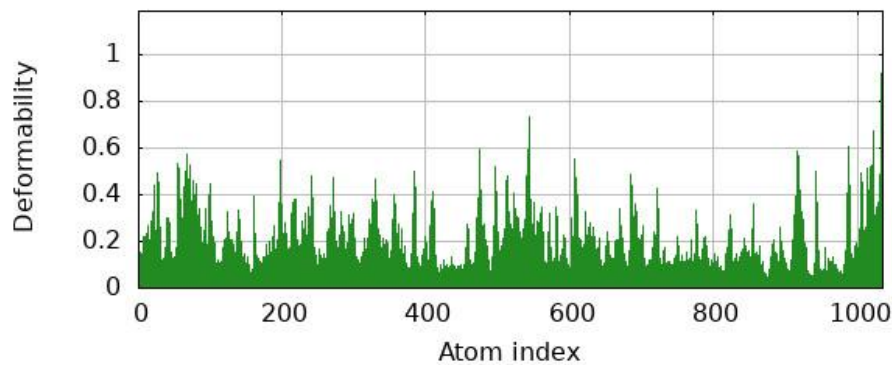


Figure 13. Atomic deformability profile of the *HerA-NurA* complex in *Pyrobaculum ferrireducens*. The peaks indicate the deformability of each atom in the protein chain, with indicating regions of higher deformability. Significant deformability is observed at the terminal regions and loop regions, which could act as the hinge regions for the protein complex.

4. Discussion

It is considered that DNA double stranded break repair is one of the crucial steps for the occurrence of anomalies like cancer. Archaea are considered as one of the most suitable organisms as they are comprised of a similar metabolic mechanism of eukaryotes (De Lise et al., 2023). They also have the tendency to survive in extreme conditions, making them more viable for studying enzymes (Garnier et al., 2021). In ancient research, *HerA-NurA* complex was studied in *Sulfolobus solfataricus*, which gave an idea about the key domains and residues of the complex, which can be considered as ground information for the evolving archaeal species (Rolfsmeier et al., 2010). In this research study, *HerA-NurA* complex was observed for the first time in *Pyrobaculum ferrireducens*. In which, specifically, the domain structures of *HerA* and *NurA* are studied using computational analysis. Important similarities in the structural characteristics of this species and the studied *Sulfolobus* are revealed, which provide new insights into the complex. An important functional component in *P. ferrireducens*, the *HerA-NurA* complex displays a novel yet evolutionarily conserved domain arrangement. The domains in *HerA* and *NurA* in *P. ferrireducens* resemble the domains in *Sulfolobus* species, which display thermophilic and extremophilic traits (De Falco et al., 2022). Thus, based on this discovery, *P. ferrireducens* could have employed similar mechanisms to ensure genome stability and DNA repair in harsh environmental conditions.

Genomic stability in the face of oxidative stresses and other forms of DNA damage requires the function of both the important nucleotide excision repair protein, *NurA*, and the helicase protein, *HerA* (Ahdash et al., 2017). The structural analysis of *HerA-NurA* complexes of *P. ferrireducens* revealed that these complexes have similar helix-turn-helix motifs and ATP-binding domains, which were also found in the already existing structure of *Sulfolobus* species (Huang et al., 2015). As the thermophilic archaea are constantly exposed to high temperatures, which could have a detrimental effect on their DNA, it is likely that these domains have a vital role to play in the DNA repair mechanisms of the thermophilic archaea (Makarova, 2002). In the face of oxidative stress and other DNA-damaging agents, genomic stability is ensured by the action of both *NurA*, which is a crucial element of nucleotide excision repair, and *HerA*, which is a helicase (De Falco et al., 2018). As these archaea are constantly exposed to high

temperatures that could damage their DNA, these conserved domains are likely to be a vital part of the DNA repair mechanisms of thermophilic archaea (Azam & Anjum, 2024).

Despite the similarities in the general domain organization of the *P. ferrireducens* and *Sulfolobus* enzymes, some unique structural features were observed. Specifically, the active site amino acids of the *P. ferrireducens* HerA-NurA complex were slightly different from those of *Sulfolobus* (Rzechorzek et al., 2014). These differences may be due to adaptive changes that enhance substrate specificity or enzyme stability, thus enabling *P. ferrireducens* to thrive in its unique biological niche, which is characterized by an abundance of iron and high temperatures.

In addition, the functional process of the HerA-NurA complex in *P. ferrireducens* appears to be regulated by its conformational flexibility. HerA and NurA have an exceptionally cooperative relationship that is likely to enhance DNA damage repair efficiency, thus promoting survival under severe environmental stress. The significance of the HerA-NurA complex in maintaining genomic integrity in thermophilic archaea is also supported by the fact that this cooperative process may be an adaptive response to *P. ferrireducens*' harsh environment.

5. Conclusions

This study offers an extensive insilico investigation of the HerA helicase enzyme of *Pyrobaculum ferrireducens*, which provides a detailed understanding of its structural and functional role in DNA double-strand repair. Using computational modeling, sequence homology, and molecular dynamics, this study focuses on the conserved regions of HerA, which are essential for its helicase function and interaction with the nuclease NurA. This study reveals that the complex of HerA and NurA shows a very cooperative mechanism, which helps in efficient DNA unwinding. Some of the important structural features of HerA, like its C-terminal brace, provide an understanding of the evolutionary adaptations of *Pyrobaculum ferrireducens* to extreme conditions, as DNA repair can be challenged by hyperthermic conditions. The docking and mutation analysis also reveal important interactions and residues that are crucial in maintaining the stability of the complex between HerA and NurA. This study is important in advancing the understanding of DNA repair mechanisms in archaea by combining the tools of bioinformatics and structural biology. This work is important in the broader understanding of the molecular adaptation of archaea. It also opens new avenues for experimental validations in the future, especially in the field of DNA repair and extremophile organisms. This study also shows the importance of computational methods in understanding complex biological systems, especially in organisms where experimental methods are limited. Further studies on the complex involving HerA and NurA will also be important in understanding the potential of the complex in understanding stress-induced DNA repair mechanisms in other extremophile organisms and eukaryotes.

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Data Availability Statement: More data related to this study can be accessed upon a reasonable request to the corresponding author or sabiyaazam92@gmail.com

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Conflicts of Interest: The authors declare no conflicts of interest.

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