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CHIMERA_NA: A Customizable Mutagenesis Tool for Structural Manipulations in Nucleic Acids and Their Complexes

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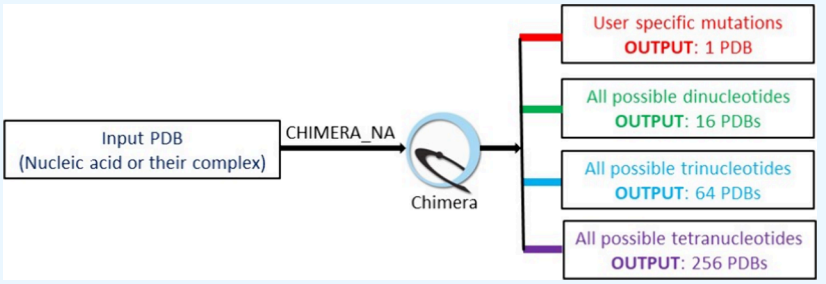

ABSTRACT: Studying the structure and dynamics of nucleic acids and their complexes is crucial for understanding fundamental biological processes and developing therapeutic interventions. However, the limited availability of experimentally characterized nucleic acid structures poses a challenge for exploring their properties comprehensively. To address this, we developed a customizable mutagenesis tool, CHIMERA_NA, to manipulate nucleic acid structures and their complexes. Utilizing the user-friendly CHIMERA_NA, researchers can perform mutations in nucleic acid structures, enabling the exploration of diverse structural configurations and dynamic behaviors. The tool offers the flexibility to generate all possible combinations of mutations or specific user-defined mutations based on research requirements. CHIMERA_NA leverages the capabilities of UCSF Chimera software, a widely used platform for molecular structure analysis, to facilitate the generation of mutations in nucleic acids. Our tool modifies the reference structure of nucleic acids or their complexes to generate initial coordinates of mutated structures/complexes within seconds for further computational exploration. This capability allows users to extend their investigations beyond structural repositories, enabling the study of DNA/RNA drug recognition, nucleic acid−protein interactions, and the intrinsic structural and dynamic properties of nucleic acids. By providing a user-friendly and customizable approach to nucleic acid mutagenesis, CHIMERA_NA contributes to advancing our understanding of nucleic acid biology and facilitating drug discovery efforts targeting nucleic acid-based mechanisms. CHIMERA_NA is freely available in the Supporting Information of this article.

INTRODUCTION

DNA and RNA serve as fundamental molecules in biological systems, governing essential cellular processes such as replication, transcription, and translation.[1−4] DNA acts as the repository of genetic information, encoding the instructions necessary for the development, growth, and functioning of living organisms.[4,5] On the other hand, RNA plays versatile roles, including mRNA, which carries genetic information from DNA to ribosomes for protein synthesis, tRNA, which transports amino acids to the ribosome during translation, and rRNA, which forms an integral part of the ribosome structure.[6,7] Both DNA and RNA exhibit intricate structures and dynamic behaviors, influencing their interactions with other molecules and the overall functioning of the cell.[1,8]

Understanding the interactions of nucleic acids with other molecules such as proteins and drugs is crucial for elucidating molecular mechanisms underlying diseases and developing effective therapeutic interventions.[4] DNA−drug interactions, for instance, are central to the design of anticancer agents and antimicrobial drugs, where small molecules target specific DNA sequences to inhibit DNA replication or induce DNA damage in diseased cells.[4,8] Similarly, DNA−protein interactions play pivotal roles in gene regulation, DNA repair, and chromatin remodeling, affecting cellular processes that govern cell fate and function.[9,10] RNA also forms complexes with drugs and proteins, contributing to gene expression regulation, RNA processing, and RNA interference pathways.[11,12] Investigating these complex interactions provides valuable insights into disease mechanisms and helps strategizing the development of targeted therapies for a wide range of human diseases.[13,14]

While nucleic acids and their complexes play pivotal roles in understanding biological processes and drug discovery, the

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scarcity of experimentally determined structures and complexes poses challenges in nucleic acid-based studies.[15] Addressing this need, we propose the development of a mutagenesis tool to generate a repertoire of modeled nucleic acid structures. Our approach utilizes an experimentally known nucleic acid structure/complex and allows for user-specific mutations or all of the possible combinations, enabling the generation of initial coordinates for computational exploration of nucleic acid research.

METHODS

The tools for generating a modified library of nucleic acid structures, where one or more nucleotide residues are replaced with another, are not very common, posing a challenging situation for exploring these systems. One approach involves changing the residue name to the desired nucleotide followed by removing the atoms that are not present in the modified nucleotide and allowing the force fields to add the updated residue to the structure template. However, this approach is time-consuming, requires expert supervision, and is not always accurate. This is particularly problematic in the case of DNA, as the modified template added may not maintain the helical form and may protrude outside the intended helical structural core. An alternative approach is to use Chimera software, a powerful visualization tool with several built-in utilities to analyze the molecular structure and related data, which offers a feature called swapna.[16] The swapna command changes the nucleotide to the desired one while preserving the existing torsion angles around the base-sugar (glycosidic) bond and the position of the base nitrogen involved in that bond.[17−19] This approach is advantageous for double-helical DNA or RNA and for mutating nucleic acid base pairs, as it retains the conformation of the base pairs after mutation. However, the swapna command mutates only one residue at a time and is not efficient for performing multiple mutations simultaneously. For example, in the case of generating a library of modified DNA structures where multiple nucleotides need to be mutated to study their collective effect, using the swapna command for each mutation individually would be laborious and inefficient. When dealing with RNA molecules that require simultaneous mutations at multiple sites to investigate their structural stability or binding affinity to their cognate partner, the single-residue limitation of swapna significantly slows the process. Further, in computational studies aimed at understanding the role of specific nucleotide sequences in protein−DNA interactions, the need to mutate several nucleotides at once highlights the inefficiency of the swapna command for large-scale modifications. These examples underscore the need for more advanced tools and methods that can efficiently handle multiple nucleotide mutations while preserving the structural integrity of the nucleic acid molecules.

We introduce CHIMERA_NA, a tool that utilizes the UCSF Chimera swapna command to generate mutated structures of nucleic acids or their complexes in a high-throughput and user-specific manner. For instance, consider DNA bound to a drug where the DNA tetrameric segment interacts with the drug molecule. CHIMERA_NA can generate a comprehensive library of 256 possible DNA−drug complexes within seconds, which serve as initial coordinates for further computational exploration. This allows the user to evaluate the specificity of the drug for each DNA tetramer segment of the DNA by utilizing the generated DNA−drug complex models as starting points for conducting molecular dynamics (MD) simulations followed by energy estimations. In this way, CHIMERA_NA enables users to scan through all structural possibilities, a task that would otherwise be impossible by using the limited complexes available in structural repositories. CHIMERA_NA can generate all structural combinations of DNA dimers, trimers, tetramers, and their complexes while performing multiple mutations on a provided DNA structure or complex. The tool can also create multiple mutations on RNA/RNA complexes for exploring structural, conformational, or binding proclivities of mutated RNA molecules. To use CHIMERA_NA, the user first executes the CHIMERA_NA.sh script while supplying the residue IDs and chain IDs where mutations are to be performed along with the information on required mutations and the directory where the output PDBs should be placed. Thereafter, the user specifies the PDB code information (if available), which the script fetches from the RCSB PDB,[20] or provides the location of the file in the local directory. Depending on the input, whether all combinations of mutations are required or a single mutant structure is desired, the output will be a CHIMERA_NA.py code. This code is then directly executed using the Chimera visualizer, generating all of the desired structures within seconds at the user-specified directory. CHIMERA_NA thus offers a powerful and efficient solution for generating and exploring a wide array of nucleic acid mutations, facilitating advanced computational studies of nucleic acid structures and their interactions and beyond. The overall CHIMERA_NA pipeline is outlined in Figure 1.

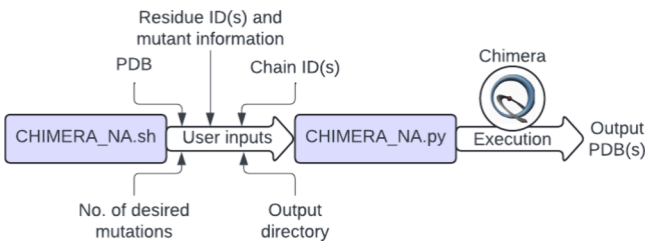

Figure 1. CHIMERA_NA pipeline to generate mutant PDBs utilizing a reference PDB.

RESULTS AND DISCUSSION

The CHIMERA_NA tool was demonstrated using several case studies where reference structures were sourced from the RCSB PDB Web server[20] to generate initial coordinates of mutants in PDB format. The following cases illustrate its application.

Case 1. To assess the selectivity of an intercalator molecule for DNA, it is essential to evaluate its binding to all 16 possible dinucleotide base pair steps at the intercalation site. Experimental structures for all 16 steps are challenging to obtain. However, using CHIMERA_NA, all 16 complexes can be generated as initial coordinates for computational studies, enabling meaningful conclusions. The crystal structure of proflavine bound to a DNA hexamer duplex (PDB ID: 3FT6) was used, where proflavine intercalates at the intercalation site formed by residue IDs 1 and 2 of chain A and residue IDs 6 and 5 of chain B, respectively.[21] CHIMERA_NA can be utilized to generate all 16 drug−DNA complexes (the overlay is shown in Figure 2).

Case 2. Zinc finger (ZF) proteins typically bind to three base pairs of double-stranded DNA.[22] To investigate the specificity and selectivity of a ZF protein, it is crucial to study its binding to all 64 possible DNA triplets. Generating initial coordinates for all 64 protein−DNA complexes is challenging. Using

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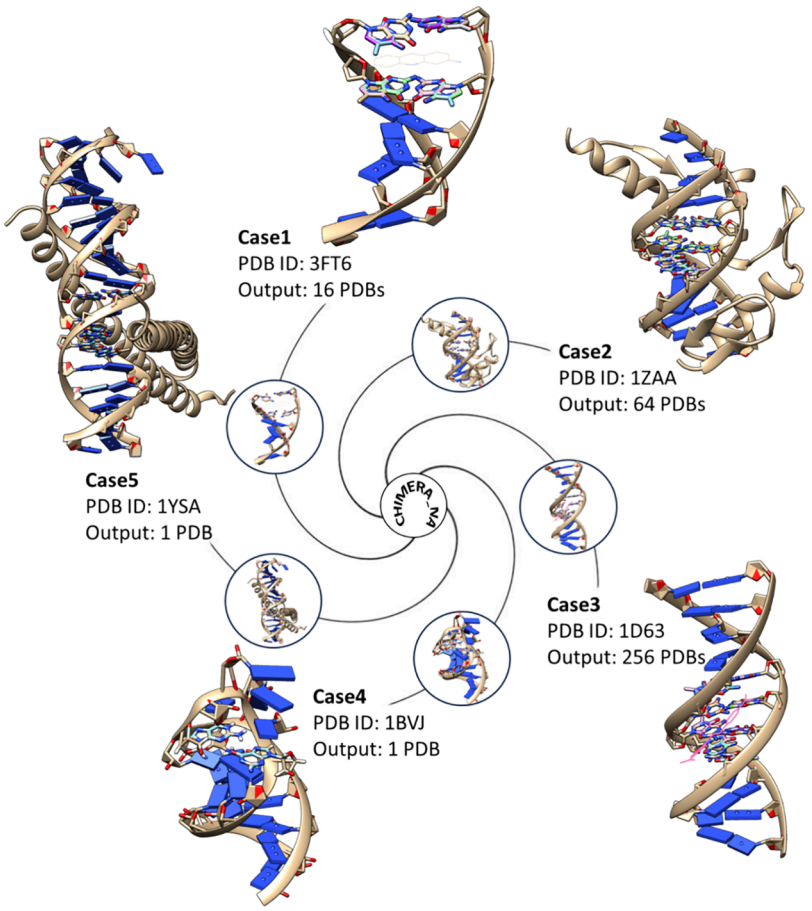

Figure 2. Input and output structures for Case 1 to Case 5 generated using the CHIMERA_NA approach. The site of interest is displayed in stick representation, while the rest of the molecule is shown in cartoon representation. Water molecules and ions of crystallization are removed for clarity.

CHIMERA_NA, initial coordinates for these systems can be generated within seconds. The crystal structure of a zinc finger (Zif268) complexed with DNA (PDB ID: 1ZAA) was utilized, with a specific focus on the central trinucleotide region (TGG; residue IDs 5 to 7 of chain A with residue IDs 8 to 6 of chain B).[23] CHIMERA_NA generated all combinations, as shown in Figure 2.

Case 3. For a DNA−drug complex, where the drug binds to a tetrameric region of the DNA (minor groove), it is important to investigate drug interactions with all tetramer combinations to understand specificity/selectivity. The crystal structure of berenil complexed with d(CGCAAATTTGCG) (PDB ID: 1D63) was used, with berenil recognizing the central AATT region (residue IDs 5−8 of chain A and residue IDs 17−20 of chain B).[24] CHIMERA_NA generated all 256 possible mutants of the berenil−DNA complex, as shown in Figure 2.

Case 4. RNA hairpin folding stability is dependent on loop composition.[25] Studying this can enhance our understanding of RNA folding, which is crucial for RNA function and RNA-targeted drug discovery. CHIMERA_NA can generate initial coordinates for multiple mutations, as defined by the user. The HIV-1 RNA A-rich hairpin loop (PDB ID: 1BVJ) is stabilized by a noncanonical G-A pair and a U-turn motif.[26] For example, to investigate the effect of switching the G-A base pair (residue IDs 10 and 15 of chain A) to an A-G base pair on the stability of the hairpin loop, CHIMERA_NA can be utilized to generate the initial structure of the mutant, as shown in Figure 2.

Case 5. Analyzing key residues in protein−DNA recognition is fundamental to understanding the overall recognition mechanism. For example, basic region leucine zipper (bZIP) proteins form multiple types of contacts (salt bridges, hydrogen bonds, water-mediated hydrogen bonds, and van der Waals) for DNA recognition.[27] For the leucine zipper−DNA complex (PDB ID: 1YSA), Asn235 binds to DNA residue IDs 7 and 8 of chain A, and Arg243 binds to DNA residue ID 32.[28] One can swap these DNA bases with their complementary bases using CHIMERA_NA to generate modified system coordinates to study how these hydrogen bonds contribute to protein−DNA binding (Figure 2).

Case 1 to Case 5 demonstrate only a few applications of the CHIMERA_NA tool. The approach can be utilized to perform any user-specific structural manipulations in nucleic acids and their complexes.

Flowchart. The execution of CHIMERA_NA can be explained in three steps. In step 1 (selection), the user can select the desired operation. In step 2 (input description), depending on the selection in step 1, the user is required to provide several details, such as residue IDs, chain IDs, number of desired mutations, and types of mutations. In the final step (step 3: execution), the output python script (CHIMERA_NA.py) with reference PDB information is directly processed by using CHIMERA software to generate the mutant PDBs. The step-by-step process is demonstrated in Figure 3.

Each step (step 1 to step 3) of CHIMERA_NA is equipped with detailed explanations of all required inputs/arguments,

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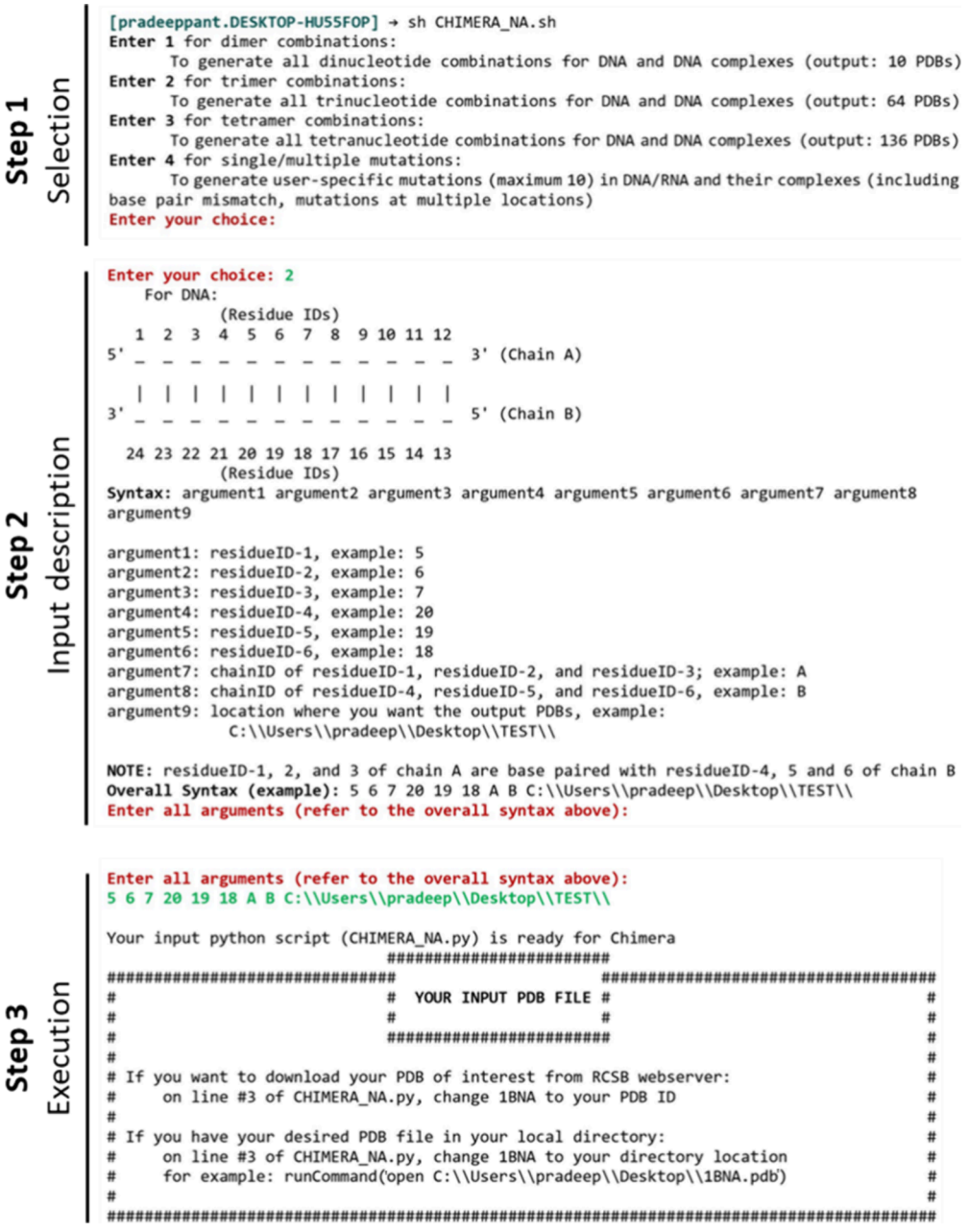

Figure 3. Step-by-step procedure of executing CHIMERA_NA to generate the structures of mutants.

facilitating user-friendly execution without the need for a separate tutorial document. The application of CHIMERA_NA extends beyond Case 1 to Case 5, demonstrating multifaceted capabilities in altering any nucleic acid structure or its complexes. For example, the approach can be utilized to initiate computational studies on aptamer design and optimization, understanding protein−RNA recognition, and investigating nucleic acid sequence-dependent metal ion binding. Overall, CHIMERA_NA is an excellent tool to generate initial coordinates for nucleic acid-based research. However, at present, it restricts mutations to nucleotide substitutions only, disallowing the insertion or deletion of nucleotide units. When a mutation is introduced, such as a base pair mismatch in double-helical DNA, additional steric clashes and close contacts may arise in the generated DNA mutant structure. In such instances, local refinement using force fields is recommended. Furthermore, in such cases, it is also anticipated that the glycosidic torsion angle of the mutated residue may require manual adjustment to restore stacking interactions with adjacent residues.

When the CHIMERA_NA.sh script is edited in a Windows environment and then transferred to a Unix/Linux environment, the different line-ending formats can cause processing issues due to carriage returns. Supplementary Note 1 provides several methods to resolve this issue. Additionally, for structures where the chain ID is not present, particularly in modeled structures or those generated by docking protocols, the mutations may not be directly achievable using the CHIMERA_NA code. To address this, missing chain IDs can be added to the input PDB file as discussed in Supplementary Note 2.

CONCLUSIONS

DNA and RNA are crucial biomolecules for sustaining life on earth. DNA, with its double-helical structure, encodes the

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genetic instructions necessary for the growth, development, and functioning of all living organisms.[4] It serves as a blueprint for the synthesis of proteins, which are vital for cellular structure, function, and regulation.[8,9] RNA, on the other hand, acts as a messenger molecule, translating the genetic information stored in DNA into functional proteins through the process of transcription and translation.[2,6] Beyond their roles in heredity and protein synthesis, DNA and RNA are involved in a myriad of cellular processes, including DNA replication, repair, and recombination, as well as gene regulation and signal transduction.[1]

Computational studies on nucleic acids have been thoroughly conducted to understand their structure and interactions with other molecules.[29−45] Although nucleic acid research is of paramount importance, the limited availability of experimentally characterized nucleic acid structures in structural repositories presents a significant challenge for thoroughly exploring their properties. To address this, we introduce CHIMERA_NA, a valuable tool for researchers interested in exploring the structure and dynamics of nucleic acids and their complexes in terms of predicting the effects of mutations on structure and complex stability and function. CHIMERA_NA is a user-friendly approach that leverages the capabilities of UCSF Chimera software for customizable mutagenesis of nucleic acids and their complexes to generate the initial coordinates of mutated structures/complexes for further computational exploration and hence helps us scan through beyond the structural repositories for studying DNA/RNA intrinsic structural properties, their dynamic properties, and nucleic acid interactions with other molecules. We demonstrate the utility of CHIMERA_NA by systematically mutating DNA−drug complexes, DNA−protein complexes, and RNA structure to generate the initial coordinates of the mutants; however, the approach is not limited to these cases and can be utilized to explore any nucleic acid structures/complexes. Overall, CHIMERA_NA enables researchers to perform systematic structural analysis and hypothesis-driven mutational studies, thereby advancing our understanding of nucleic acids and facilitating rational drug design efforts.

■ ASSOCIATED CONTENT

Data Availability Statement

The Chimera_NA codes are provided as a zipped folder in the Supporting Information. For Case 1 to Case 5, all the input files, case-specific CHIMERA_NA.py, log files, and output PDBs are also provided.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05954.

Chimera_NA codes (ZIP)

(Supplementary Note 1) Dos to Unix conversion and (Supplementary Note 2) processing structures with missing chain IDs (PDF)

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Author Contributions

P.P. conceived the idea, designed the study, analyzed the results, and wrote the manuscript.

Notes

The author declares no competing financial interest.

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■ REFERENCES

(1) Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P., 2002. From DNA to RNA. In *Mol. Biol. Cell*. 4th ed. Garland Science.

(2) Elliott, D.; Ladomery, M., 2017. *Molecular biology of RNA*. Oxford University Press.

(3) Watson, J. D.; Berry, A., 2009. *DNA: The secret of life*. Knopf Doubleday Publishing Group.

(4) Neidle, S.; Sanderson, M., 2021. *Principles of nucleic acid structure*. Academic Press.

(5) Watson, J. D.; Crick, F. H., 1953, The structure of DNA. In *Cold Spring Harbor symposia on quantitative biology* (Vol. *18*, pp 123−131). Cold Spring Harbor Laboratory Press.

(6) Noller, H. F. RNA structure: reading the ribosome. *Science* **2005**, *309* (5740), 1508−1514.

(7) Holbrook, S. R. RNA structure: the long and the short of it. *Curr. Opin. Struct. Biol.* **2005**, *15* (3), 302−308.

(8) Blackburn, G. M.; Gait, M. J.; Loakes, D.; Williams, D. M. ed., 2006. *Nucleic acids in chemistry and biology*. Royal Society of Chemistry.

(9) Maynard, S.; Fang, E. F.; Scheibye-Knudsen, M.; Croteau, D. L.; Bohr, V. A. DNA damage, DNA repair, aging, and neurodegeneration. *Cold Spring Harbor perspectives in medicine* **2015**, *5* (10), a025130.

(10) Jones, S.; Van Heyningen, P.; Berman, H. M.; Thornton, J. M. Protein-DNA interactions: a structural analysis. *Journal of molecular biology* **1999**, *287* (5), 877−896.

(11) Jones, S.; Daley, D. T.; Luscombe, N. M.; Berman, H. M.; Thornton, J. M. Protein−RNA interactions: a structural analysis. *Nucleic acids research* **2001**, *29* (4), 943−954.

(12) Sharp, P. A. RNA interference—2001. *Genes & development* **2001**, *15* (5), 485−490.

(13) Hartmann, G. Nucleic acid immunity. *Advances in immunology* **2017**, *133*, 121−169.

(14) Opalinska, J. B.; Gewirtz, A. M. Nucleic-acid therapeutics: basic principles and recent applications. *Nat. Rev. Drug Discovery* **2002**, *1* (7), 503−514.

(15) Burke, J. E.; Butcher, S. E. Nucleic acid structure characterization by small angle X-ray scattering (SAXS). *Curr. Protoc. Nucleic Acid Chem.* **2012**, *51* (1), 7−18.

(16) Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. UCSF Chimera—a visualization system for exploratory research and analysis. *Journal of computational chemistry* **2004**, *25* (13), 1605−1612.

(17) Rallapalli, K. L.; Komor, A. C.; Paesani, F. Computer simulations explain mutation-induced effects on the DNA editing by adenine base editors. *Sci. Adv.* **2020**, *6* (10), No. eaaz2309.

(18) Waltz, F.; Soufari, H.; Bochler, A.; Giegé, P.; Hashem, Y. Cryo-EM structure of the RNA-rich plant mitochondrial ribosome. *Nature Plants* **2020**, *6* (4), 377−383.

(19) Lebar, T.; Verbič, A.; Ljubetič, A.; Jerala, R. Polarized displacement by transcription activator-like effectors for regulatory circuits. *Nat. Chem. Biol.* **2019**, *15* (1), 80−87.

(20) Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. The protein data bank. *Nucleic acids research* **2000**, *28* (1), 235−242.

(21) Maehigashi, T.; Persil, O.; Hud, N. V.; Williams, L. D., 2009. *Crystal structure of proflavine in complex with a DNA hexamer duplex*. To be published.

(22) Elrod-Erickson, M.; Rould, M. A.; Nekludova, L.; Pabo, C. O. Zif268 protein−DNA complex refined at 1.6 Å: a model system for understanding zinc finger−DNA interactions. *Structure* **1996**, *4* (10), 1171−1180.
(23) Pavletich, N. P.; Pabo, C. O. Zinc finger-DNA recognition: crystal structure of a Zif268-DNA complex at 2.1 Å. *Science* **1991**, *252* (5007), 809−817.
(24) Brown, D. G.; Sanderson, M. R.; Garman, E.; Neidle, S. Crystal structure of a berenil-d (CGCAAATTTGCG) complex: an example of drug-DNA recognition based on sequence-dependent structural features. *Journal of molecular biology* **1992**, *226* (2), 481−490.
(25) Zhao, C.; Zhang, D.; Jiang, Y.; Chen, S. J. Modeling loop composition and ion concentration effects in RNA hairpin folding stability. *Biophys. J.* **2020**, *119* (7), 1439−1455.
(26) Puglisi, E. V.; Puglisi, J. D. HIV-1 A-rich RNA loop mimics the tRNA anticodon structure. *Nature structural biology* **1998**, *5* (12), 1033−1036.
(27) Ellenberger, T. E.; Brandl, C. J.; Struhl, K.; Harrison, S. C. The GCN4 basic region leucine zipper binds DNA as a dimer of uninterrupted α helices: crystal structure of the protein-DNA complex. *Cell* **1992**, *71* (7), 1223−1237.
(28) Fujii, Y.; Shimizu, T.; Toda, T.; Yanagida, M.; Hakoshima, T. Structural basis for the diversity of DNA recognition by bZIP transcription factors. *Nature structural biology* **2000**, *7* (10), 889−893.
(29) Pant, P.; Fisher, M. Marshall's nucleic acid: From double-helical structure to a potent intercalator. *Biophys. Chem.* **2021**, *269*, No. 106525.
(30) Pant, P.; Pathak, A.; Jayaram, B. Symmetric nucleosides as potent purine nucleoside phosphorylase inhibitors. *J. Phys. Chem. B* **2021**, *125* (11), 2856−2862.
(31) Pant, P.; Shaikh, S. A.; Jayaram, B. Design and characterization of symmetric nucleic acids via molecular dynamics simulations. *Biopolymers* **2017**, *107* (4), No. e23002.
(32) Pant, P.; Jayaram, B. C5′ omitted DNA enhances bendability and protein binding. *Biochemical and biophysical research communications* **2019**, *514* (3), 979−984.
(33) Pant, P.; Pathak, A.; Jayaram, B. Symmetrization of the backbone of nucleic acids: a molecular dynamics study. *J. Biomol. Struct. Dyn.* **2019**, *38*, 673.
(34) Pant, P.; Fisher, M. DNA triplex with conformationally locked sugar disintegrates to duplex: Insights from molecular simulations. *Biochemical and biophysical research communications* **2020**, *532* (4), 662−667.
(35) Pant, P.; Aggarwal, L. Assessing the DNA structural integrity via selective annihilation of Watson-Crick hydrogen bonds: Insights from molecular dynamics simulations. *Biophys. Chem.* **2022**, *282*, No. 106758.
(36) Etheve, L.; Martin, J.; Lavery, R. Protein−DNA interfaces: a molecular dynamics analysis of time-dependent recognition processes for three transcription factors. *Nucleic Acids Res.* **2016**, *44* (20), 9990−10002.
(37) Pant, P.; Pathak, A.; Jayaram, B. Bicyclo-DNA mimics with enhanced protein binding affinities: insights from molecular dynamics simulations. *J. Biomol. Struct. Dyn.* **2023**, *41* (9), 4040−4047.
(38) Pant, P.; Jayaram, B., 2021. A Rapid Computational Screening of Millions of Molecules to Identify Sequence-Specific DNA Minor Groove Binders via Physicochemical Descriptors. In *Biophysical and Computational Tools in Drug Discovery* (pp 341−367). Springer International Publishing: Cham.
(39) Shino, G.; Takada, S. Modeling DNA opening in the eukaryotic transcription initiation complexes via coarse-grained models. *Frontiers in Molecular Biosciences* **2021**, *8*, No. 772486.
(40) Sharma, S.; Pant, P.; Arya, R.; Jayaram, B.; Das, H. K. Bases immediate upstream of the TATAAT box of the sigma 70 promoter of Escherichia coli significantly influence the activity of a model promoter by altering the bending angle of DNA. *Gene* **2023**, *851*, No. 146968.
(41) Pant, P. Flexible RNA aptamers as inhibitors of Bacillus anthracis ribosomal protein S8: Insights from molecular dynamics simulations. *Biophys. Chem.* **2024**, *312*, No. 107273.
(42) Alagia, A.; Jorge, A. F.; Aviñó, A.; Cova, T. F.; Crehuet, R.; Grijalvo, S.; Pais, A. A.; Eritja, R. Exploring PAZ/3′-overhang interaction to improve siRNA specificity. A combined experimental and modeling study. *Chemical science* **2018**, *9* (8), 2074−2086.
(43) Pant, P.; Leese, F. Probing the nucleic acid flexibility to disarm the viral counter-defense machinery: design and characterization of potent p19 inhibitors. *J. Phys. Chem. B* **2023**, *127*, 8842.
(44) Pant, P. Design and characterization of neutral linker-based bis-intercalator via computer simulations: Balancing DNA binding and cellular uptake. *Chem. Biodiversity* **2024**, No. e202400768.
(45) Pant, P. Harmonizing Interstrand Electrostatic Repulsion by Conformational Rigidity in Counterion-Deprived Z-DNA: A Molecular Dynamics Study. *J. Phys. Chem. B* **2022**, *126* (48), 9956−9963.

https://doi.org/10.1021/acsomega.4c05954
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