References

- [1] R. D. Hotchkiss, "The quantitative separation of purines, pyrimidines, and nucleosides by paper chromatography," *Journal of Biological Chemistry*, vol. 175, no. 1, pp. 315–332, 1948.
- [2] P. Barraud, A. Gato, M. Heiss, M. Catala, S. Kellner, and C. Tisne, "Time-resolved NMR monitoring of tRNA maturation," *Nature Communications*, vol. 10, no. 1, pp. 1–14, 2019.
- [3] S. Kumar, V. Chinnusamy, and T. Mohapatra, "Epigenetics of modified dna bases: 5-methylcytosine and beyond," *Frontiers in Genetics*, vol. 9, p. 640, 2018.
- [4] K. E. Sloan, A. S. Warda, S. Sharma, K.-D. Entian, D. L. Lafontaine, and M. T. Bohnsack, "Tuning the ribosome: The influence of rRNA modification on eukaryotic ribosome biogenesis and function," *RNA biology*, vol. 14, no. 9, pp. 1138–1152, 2017.
- [5] K. Kariko, M. Buckstein, H. Ni, and D. Weissman, "Suppression of RNA recognition by toll-like re-' ceptors: the impact of nucleoside modification and the evolutionary origin of RNA," *Immunity*, vol. 23, no. 2, pp. 165–175, 2005.
- [6] M. Yousefzadeh, C. Henpita, R. Vyas, C. Soto-Palma, P. Robbins, and L. Niedernhofer, "DNA damage—how and why we age?," *Elife*, vol. 10, p. e62852, 2021.
- [7] I. Barbieri and T. Kouzarides, "Role of RNA modifications in cancer," *Nature reviews Cancer*, vol. 20, no. 6, pp. 303–322, 2020.
- [8] C. Rinaldi and M. J. Wood, "Antisense oligonucleotides: the next frontier for treatment of neurological disorders," *Nature Reviews Neurology*, vol. 14, no. 1, pp. 9–21, 2018.
- [9] J. A. Kulkarni, D. Witzigmann, S. B. Thomson, S. Chen, B. R. Leavitt, P. R. Cullis, and R. van der Meel, "The current landscape of nucleic acid therapeutics," *Nature Nanotechnology*, vol. 16, no. 6, pp. 630–643, 2021.
- [10] J. Kim, C. Hu, C. Moufawad El Achkar, L. E. Black, J. Douville, A. Larson, M. K. Pendergast, S. F. Goldkind, E. A. Lee, A. Kuniholm, et al., "Patient-customized oligonucleotide therapy for a rare genetic disease," New England Journal of Medicine, vol. 381, no. 17, pp. 1644–1652, 2019.
- [11] T. C. Roberts, R. Langer, and M. J. Wood, "Advances in oligonucleotide drug delivery," *Nature Reviews Drug Discovery*, vol. 19, no. 10, pp. 673–694, 2020.
- [12] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, and P. E. Bourne, "The protein data bank," *Nucleic Acids Research*, vol. 28, no. 1, pp. 235–242, 2000.
- [13] E. L. Ulrich, H. Akutsu, J. F. Doreleijers, Y. Harano, Y. E. Ioannidis, J. Lin, M. Livny, S. Mading, D. Maziuk, Z. Miller, et al., "BioMagResBank," *Nucleic Acids Research*, vol. 36, no. suppl 1, pp. D402–D408, 2007.
- [14] A. T. Watt, G. Swayze, E. E. Swayze, and S. M. Freier, "Likelihood of nonspecific activity of gapmer antisense oligonucleotides is associated with relative hybridization free energy," *Nucleic Acid Therapeutics*, vol. 30, no. 4, pp. 215–228, 2020.

- [15] X. Bo, S. Lou, D. Sun, J. Yang, and S. Wang, "AOBase: a database for antisense oligonucleotides selection and design," *Nucleic Acids Research*, vol. 34, no. suppl 1, pp. D664–D667, 2006.
- [16] P. Boccaletto, M. A. Machnicka, E. Purta, P. Pikatkowski, B. Baginski, T. K. Wirecki, V. de Cr´ ecy-´ Lagard, R. Ross, P. A. Limbach, A. Kotter, *et al.*, "MODOMICS: a database of rna modification pathways. 2017 update," *Nucleic acids research*, vol. 46, no. D1, pp. D303–D307, 2018.
- [17] R. O. Dror, R. M. Dirks, J. Grossman, H. Xu, and D. E. Shaw, "Biomolecular simulation: a computational microscope for molecular biology," *Annual Review of Biophysics*, vol. 41, pp. 429–452, 2012.
- [18] N. R. Latorraca, N. M. Fastman, A. Venkatakrishnan, W. B. Frommer, R. O. Dror, and L. Feng, "Mechanism of substrate translocation in an alternating access transporter," *Cell*, vol. 169, no. 1, pp. 96–107, 2017.
- [19] H. S. Chung, S. Piana-Agostinetti, D. E. Shaw, and W. A. Eaton, "Structural origin of slow diffusion in protein folding," *Science*, vol. 349, no. 6255, pp. 1504–1510, 2015.
- [20] J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, O. Ronneberger, K. Tunyasuvunakool, R. Bates, A. Z´idek, A. Potapenko, *et al.*, "Highly accurate protein structure prediction with alphafold," *Nature*, vol. 596, no. 7873, pp. 583–589, 2021.
- [21] S. Bottaro and K. Lindorff-Larsen, "Biophysical experiments and biomolecular simulations: A perfect match?," *Science*, vol. 361, no. 6400, pp. 355–360, 2018.
- [22] M. Bonomi, "Promoting transparency and reproducibility in enhanced molecular simulations," *Nature Methods*, vol. 16, no. 8, pp. 670–673, 2019.
- [23] J. Sponer, G. Bussi, M. Krepl, P. Banas, S. Bottaro, R. A. Cunha, A. Gil-Ley, G. Pinamonti, S. Poblete, P. Jurecka, *et al.*, "RNA structural dynamics as captured by molecular simulations: a comprehensive overview," *Chemical Reviews*, vol. 118, no. 8, pp. 4177–4338, 2018.
- [24] M. V. Uppuladinne, U. B. Sonavane, R. C. Deka, and R. R. Joshi, "Structural insight into antisense gapmer-RNA oligomer duplexes through molecular dynamics simulations," *Journal of Biomolecular Structure and Dynamics*, vol. 37, no. 11, pp. 2823–2836, 2019.
- [25] Z. Zhang, J. Vogele, K. Mrazikov´a, H. Kruse, X. Cang, J. Wohnert, M. Krepl, and J. Sponer, "Phos-´ phorothioate substitutions in RNA structure studied by molecular dynamics simulations, QM/MM calculations, and NMR experiments," *The Journal of Physical Chemistry B*, vol. 125, no. 3, pp. 825–840, 2021.
- [26] R. Galvelis, S. Doerr, J. M. Damas, M. J. Harvey, and G. De Fabritiis, "A scalable molecular force field parameterization method based on density functional theory and quantum-level machine learning," *Journal of Chemical Information and Modeling*, vol. 59, no. 8, pp. 3485–3493, 2019.
- [27] Y. Wang, J. Fass, and J. D. Chodera, "End-to-end differentiable molecular mechanics force field construction," arXiv preprint arXiv:2010.01196, 2020.

- [28] B. A. Anderson, G. C. Freestone, A. Low, C. L. De-Hoyos, W. J. D. Iii, M. E. Østergaard, M. T. Migawa, M. Fazio, W. B. Wan, A. Berdeja, et al., "Towards next generation antisense oligonucleotides: mesylphosphoramidate modification improves therapeutic index and duration of effect of gapmer antisense oligonucleotides," Nucleic Acids Research, vol. 49, no. 16, pp. 9026–9041, 2021.
- [29] X. Yang, X. Han, C. Cross, S. Bare, Y. Sanghvi, and X. Gao, "NMR structure of an antisense dna:rna hybrid duplex containing a 3'-ch2n (ch3)-o-5 'or an MMI backbone linker," *Biochemistry*, vol. 38, no. 39, pp. 12586–12596, 1999.
- [30] K. M. E. Nielsen, M. Petersen, A. E. Hakansson, J. Wengel, and J. P. Jacobsen, "° α-L-LNA (α-l-ribo configured locked nucleic acid) recognition of DNA: An NMR spectroscopic study," *Chemistry–A European Journal*, vol. 8, no. 13, pp. 3001–3009, 2002.
- [31] B. Diop-Frimpong, T. P. Prakash, K. G. Rajeev, M. Manoharan, and M. Egli, "Stabilizing contributions of sulfur-modified nucleotides: Crystal structure of a DNA duplex with 2'o[2(methoxy) ethyl]2thiothymidines," *Nucleic Acids Research*, vol. 33, no. 16, pp. 5297–5307, 2005.
- [32] R. Aduri, B. T. Psciuk, P. Saro, H. Taniga, H. B. Schlegel, and J. SantaLucia, "Amber force field parameters for the naturally occurring modified nucleosides in RNA," *Journal of Chemical Theory and Computation*, vol. 3, no. 4, pp. 1464–1475, 2007.
- [33] G. H. Zerze, F. H. Stillinger, and P. G. Debenedetti, "Thermodynamics of dna hybridization from atomistic simulations," *The Journal of Physical Chemistry B*, vol. 125, no. 3, pp. 771–779, 2021.
- [34] S. Agrawal, "Importance of nucleotide sequence and chemical modifications of antisense oligonucleotides," *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, vol. 1489, no. 1, pp. 53–67, 1999.
- [35] M. Nowotny, S. A. Gaidamakov, R. Ghirlando, S. M. Cerritelli, R. J. Crouch, and W. Yang, "Structure of human RNase H1 complexed with an RNA/DNA hybrid: insight into HIV reverse transcription," *Molecular Cell*, vol. 28, no. 2, pp. 264–276, 2007.
- [36] Y. Cho and D. Butler, "Crystal structure of rnase h/rna/ps-aso complex at an atomic level." https://www.rcsb.org/structure/6VRD.
- [37] J. A. Martin, P. Robustelli, and A. G. Palmer III, "Quantifying the relationship between conformational dynamics and enzymatic activity in ribonuclease HI homologues," *Biochemistry*, vol. 59, no. 35, pp. 3201–3205, 2020.
- [38] Ł. J. Kiełpinski, E. D. Funder, S. Schmidt, and P. H. Hagedorn, "Characterization of escherichia coli' RNase H discrimination of DNA phosphorothioate stereoisomers," nucleic acid therapeutics, 2021.
- [39] M. Lindow, H.-P. Vornlocher, D. Riley, D. J. Kornbrust, J. Burchard, L. O. Whiteley, J. Kamens, J. D. Thompson, S. Nochur, H. Younis, *et al.*, "Assessing unintended hybridization-induced biological effects of oligonucleotides," *Nature biotechnology*, vol. 30, no. 10, pp. 920–923, 2012.
- [40] T. Yoshida, Y. Naito, H. Yasuhara, K. Sasaki, H. Kawaji, J. Kawai, M. Naito, H. Okuda, S. Obika, and

- T. Inoue, "Evaluation of off-target effects of gapmer antisense oligonucleotides using human cells," *Genes to Cells*, vol. 24, no. 12, pp. 827–835, 2019.
- [41] C. Stein, J. B. Hansen, J. Lai, S. Wu, A. Voskresenskiy, A. Ho g, J. Worm, M. Hedtjarn, N. Souleimanian, P. Miller, *et al.*, "Efficient gene silencing by delivery of locked nucleic acid antisense oligonucleotides, unassisted by transfection reagents," *Nucleic acids research*, vol. 38, no. 1, pp. e3– e3, 2010.
- [42] E. M. Holgersen, S. Gandhi, Y. Zhou, J. Kim, B. Vaz, J. Bogojeski, M. Bugno, Z. Shalev, K. CheungOng, J. Gonc, alves, *et al.*, "Transcriptome-wide off-target effects of steric-blocking oligonucleotides," *nucleic acid therapeutics*, vol. 31, no. 6, pp. 392–403, 2021.
- [43] S. Michel, K. Schirduan, Y. Shen, R. Klar, J. Tost, and F. Jaschinski, "Using RNA-seq to assess offtarget effects of antisense oligonucleotides in human cell lines," *Molecular Diagnosis & Therapy*, vol. 25, no. 1, pp. 77–85, 2021.
- [44] D. H. Mathews, M. E. Burkard, S. M. Freier, J. R. Wyatt, and D. H. Turner, "Predicting oligonucleotide affinity to nucleic acid targets," *Rna*, vol. 5, no. 11, pp. 1458–1469, 1999.
- [45] D. Banerjee, H. Tateishi-Karimata, T. Ohyama, S. Ghosh, T. Endoh, S. Takahashi, and N. Sugimoto, "Improved nearest-neighbor parameters for the stability of RNA/DNA hybrids under a physiological condition," *Nucleic acids research*, vol. 48, no. 21, pp. 12042–12054, 2020.
- [46] R. Barrett and A. D. White, "Investigating active learning and meta-learning for iterative peptide design," *Journal of chemical information and modeling*, vol. 61, no. 1, pp. 95–105, 2020.
- [47] L. Koch, "Exploring human genomic diversity with gnomAD," *Nature Reviews Genetics*, vol. 21, no. 8, pp. 448–448, 2020.