

References

- [1] Amélie Barozet, Marc Bianciotto, Marc Vaisset, Thierry Siméon, Hervé Minoux, and Juan Cortés. Protein loops with multiple meta-stable conformations: a challenge for sampling and scoring methods. *Proteins: Structure, Function, and Bioinformatics*, 89(2):218–231, 2021.
- [2] Helen M Berman, John Westbrook, Zukang Feng, Gary Gilliland, Talapady N Bhat, Helge Weissig, Ilya N Shindyalov, and Philip E Bourne. The protein data bank. *Nucleic acids research*, 28(1):235–242, 2000.
- [3] Peter JA Cock, Tiago Antao, Jeffrey T Chang, Brad A Chapman, Cymon J Cox, Andrew Dalke, Iddo Friedberg, Thomas Hamelryck, Frank Kauff, Bartek Wilczynski, et al. Biopython: freely available python tools for computational molecular biology and bioinformatics. *Bioinformatics*, 25(11):1422–1423, 2009.
- [4] Marina Corbella, Gaspar P Pinto, and Shina CL Kamerlin. Loop dynamics and the evolution of enzyme activity. *Nature Reviews Chemistry*, 7(8):536–547, 2023.
- [5] Justas Dauparas, Ivan Anishchenko, Nathaniel Bennett, Hua Bai, Robert J Ragotte, Lukas F Milles, Basile IM Wicky, Alexis Courbet, Rob J de Haas, Neville Bethel, et al. Robust deep learning-based protein sequence design using proteinmpnn. *Science*, 378(6615):49–56, 2022.
- [6] Hongsong Feng, Jeffrey Y. Zhao, and Guo-Wei Wei. Multiscale differential geometry learning for protein flexibility analysis. *Journal of Computational Chemistry*, 46(7):e70073, March 2025. First published: 12 March 2025.
- [7] Jia-Jie Feng, Jia-Nan Chen, Wei Kang, and Yun-Dong Wu. Accurate structure prediction for protein loops based on molecular dynamics simulations with rsff2c. *Journal of Chemical Theory and Computation*, 17(7):4614–4628, 2021.
- [8] András Fiser, Richard Kinh Gian Do, and Andrej Šali. Modeling of loops in protein structures. *Protein science*, 9(9):1753–1773, 2000.
- [9] Thomas Hayes, Roshan Rao, Halil Akin, Nicholas J Sofroniew, Deniz Oktay, Zeming Lin, Robert Verkuil, Vincent Q Tran, Jonathan Deaton, Marius Wiggert, et al. Simulating 500 million years of evolution with a language model. *Science*, page eads0018, 2025.
- [10] Thomas Hrabe, Zhanwen Li, Mayya Sedova, Piotr Rotkiewicz, Lukasz Jaroszewski, and Adam Godzik. Pdbflex: exploring flexibility in protein structures. *Nucleic acids research*, 44(D1):D423–D428, 2016.
- [11] Chloe Hsu, Robert Verkuil, Jason Liu, Zeming Lin, Brian Hie, Tom Sercu, Adam Lerer, and Alexander Rives. Learning inverse folding from millions of predicted structures. In *International conference on machine learning*, pages 8946–8970. PMLR, 2022.
- [12] Xiaozhen Hu, Huanchen Wang, Hengming Ke, and Brian Kuhlman. High-resolution design of a protein loop. *Proceedings of the National Academy of Sciences*, 104(45):17668–17673, 2007.
- [13] Hanlun Jiang, Kevin M Jude, Kejia Wu, Jorge Fallas, George Ueda, TJ Brunette, Derrick R Hicks, Harley Pyles, Aerin Yang, Lauren Carter, et al. De novo design of buttressed loops for sculpting protein functions. *Nature chemical biology*, 20(8):974–980, 2024.

- [14] Bowen Jing, Bonnie Berger, and Tommi Jaakkola. Alphafold meets flow matching for generating protein ensembles. In *Proceedings of the 41st International Conference on Machine Learning*, pages 22277–22303, 2024.
- [15] Robbie P Joosten, Tim AH Te Beek, Elmar Krieger, Maarten L Hekkelman, Rob WW Hooft, Reinhard Schneider, Chris Sander, and Gert Vriend. A series of pdb related databases for everyday needs. *Nucleic acids research*, 39(suppl_1):D411–D419, 2010.
- [16] John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Židek, Anna Potapenko, et al. Highly accurate protein structure prediction with alphafold. *Nature*, 596(7873):583–589, 2021.
- [17] Martin Karplus and J Andrew McCammon. Molecular dynamics simulations of biomolecules. *Nature structural biology*, 9(9):646–652, 2002.
- [18] James Kirkpatrick, Razvan Pascanu, Neil C. Rabinowitz, Joel Veness, Guillaume Desjardins, Andrei A. Rusu, et al. Overcoming catastrophic forgetting in neural networks. *Proceedings of the National Academy of Sciences*, 114(13):3521–3526, 2017.
- [19] Lucien F. Krapp, Fernando A. Meireles, Luciano A. Abriata, Jean Devillard, Sarah Vacle, Maria J. Marcaida, and Matteo Dal Peraro. Context-aware geometric deep learning for protein sequence design. *Nature Communications*, 15(1):6273, 2024.
- [20] Kale Kundert and Tanja Kortemme. Computational design of structured loops for new protein functions. *Biological chemistry*, 400(3):275–288, 2019.
- [21] Mateusz Kurcinski, Tymoteusz Oleniecki, Maciej Pawel Ciemny, Aleksander Kuriata, Andrzej Kolinski, and Sebastian Kmiecik. Cabs-flex standalone: a simulation environment for fast modeling of protein flexibility. *Bioinformatics*, 35(4):694–695, 2019.
- [22] Aleksander Kuriata, Aleksandra Maria Gierut, Tymoteusz Oleniecki, Maciej Paweł Ciemny, Andrzej Kolinski, Mateusz Kurcinski, and Sebastian Kmiecik. Cabs-flex 2.0: a web server for fast simulations of flexibility of protein structures. *Nucleic Acids Research*, 46(W1):W338–W343, 05 2018.
- [23] Zeming Lin, Robert Verkuil, Alexander Hayes, Joshua Meier, Marc-André Carbonneau, Kevin Gao, and Alexander Rives. Esmdiff: Conditional generation of protein structures from language models. *arXiv preprint arXiv:2410.18403*, 2024.
- [24] Ilya Loshchilov and Frank Hutter. Decoupled weight decay regularization. *arXiv preprint arXiv:1711.05101*, 2017.
- [25] Puyi Ma, Da-Wei Li, and Rafael Brüschweiler. Predicting protein flexibility with alphafold. *Proteins: Structure, Function, and Bioinformatics*, 91(6):847–855, 2023.
- [26] M Merced Malabanan, Tina L Amyes, and John P Richard. A role for flexible loops in enzyme catalysis. *Current opinion in structural biology*, 20(6):702–710, 2010.
- [27] Claire Marks, Jiye Shi, and Charlotte M Deane. Predicting loop conformational ensembles. *Bioinformatics*, 34(6):949–956, 2018.
- [28] Tarun J Narwani, Catherine Etchebest, Pierrick Craveur, Sylvain Léonard, Joseph Rebehmed, Narayanaswamy Srinivasan, Aurélie Bornot, Jean-Christophe Gelly, and Alexandre G de Brevern. In silico prediction of protein flexibility with local structure approach. *Biochimie*, 165:150–155, 2019.

- [29] Bettina M Nestl and Bernhard Hauer. Engineering of flexible loops in enzymes. *Acs Catalysis*, 4(9):3201–3211, 2014.
- [30] Chandran Nithin, Rocco Peter Fornari, Smita P Pilla, Karol Wroblewski, Mateusz Zalewski, Rafał Madaj, Andrzej Kolinski, Joanna M Macnar, and Sebastian Kmiecik. Exploring protein functions from structural flexibility using cabs-flex modeling. *Protein Science*, 33(9):e5090, 2024.
- [31] Razvan Pascanu, Tomas Mikolov, and Yoshua Bengio. On the difficulty of training recurrent neural networks. In *International conference on machine learning*, pages 1310–1318. PMLR, 2013.
- [32] Samuel Schmitz, Moritz Ertelt, Rainer Merkl, and Jens Meiler. Rosetta design with co-evolutionary information retains protein function. *PLoS Computational Biology*, 17(1):e1008568, 2021.
- [33] Andrew Shrake and John A Rupley. Environment and exposure to solvent of protein atoms. lysozyme and insulin. *Journal of molecular biology*, 79(2):351–371, 1973.
- [34] Xintao Song, Lei Bao, Chenjie Feng, Qiang Huang, Fa Zhang, Xin Gao, and Renmin Han. Accurate prediction of protein structural flexibility by deep learning integrating intricate atomic structures and cryo-em density information. *Nature Communications*, 15(1):5538, 2024.
- [35] Amy O Stevens and Yi He. Benchmarking the accuracy of alphafold 2 in loop structure prediction. *Biomolecules*, 12(7):985, 2022.
- [36] Zhoutong Sun, Qian Liu, Ge Qu, Yan Feng, and Manfred T Reetz. Utility of b-factors in protein science: interpreting rigidity, flexibility, and internal motion and engineering thermostability. *Chemical reviews*, 119(3):1626–1665, 2019.
- [37] William Hedley Thompson and Peter Fransson. On stabilizing the variance of dynamic functional brain connectivity time series. *arXiv preprint arXiv:1603.00201*, 2016.
- [38] Yann Vander Meersche, Gabriel Cretin, Aria Gheeraert, Jean-Christophe Gelly, and Tatiana Galochkina. Atlas: protein flexibility description from atomistic molecular dynamics simulations. *Nucleic acids research*, 52(D1):D384–D392, 2024.
- [39] Mihaly Varadi, John Berrisford, Mandar Deshpande, Sreenath S Nair, Aleksandras Gutmanas, David Armstrong, Lukas Pravda, Bissan Al-Lazikani, Stephen Anyango, Geoffrey J Barton, et al. Pdb-e-kb: a community-driven resource for structural and functional annotations. *Nucleic Acids Research*, 48(D1):D344–D353, 2020.
- [40] Ashish Vaswani, Noam Shazeer, Niki Parmar, Jakob Uszkoreit, Llion Jones, Aidan N. Gomez, Łukasz Kaiser, and Illia Polosukhin. Attention is all you need. In *Advances in Neural Information Processing Systems 30 (NeurIPS)*, pages 5998–6008, 2017.
- [41] Junlin Wang, Wenbo Wang, and Yi Shang. Protein loop modeling using alphafold2. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 20(5):3306–3313, 2023.
- [42] Tianyue Wang, Langcheng Wang, Xujun Zhang, Chao Shen, Odin Zhang, Jike Wang, Jialu Wu, Ruofan Jin, Donghao Zhou, Shicheng Chen, et al. Comprehensive assessment of protein loop modeling programs on large-scale datasets: prediction accuracy and efficiency. *Briefings in Bioinformatics*, 25(1):bbad486, 2024.
- [43] Tianyue Wang, Xujun Zhang, Odin Zhang, Guangyong Chen, Peichen Pan, Ercheng Wang, Jike Wang, Jialu Wu, Donghao Zhou, Langcheng Wang, et al. Highly accurate and efficient deep learning paradigm for full-atom protein loop modeling with karmaloop. *Research*, 7:0408, 2024.

- [44] Yuan Xie, Jiao An, Guangyu Yang, Geng Wu, Yong Zhang, Li Cui, and Yan Feng. Enhanced enzyme kinetic stability by increasing rigidity within the active site. *Journal of Biological Chemistry*, 289(11):7994–8006, 2014.
- [45] Haoran Yu, Yihan Yan, Cheng Zhang, and Paul A Dalby. Two strategies to engineer flexible loops for improved enzyme thermostability. *Scientific reports*, 7(1):41212, 2017.
- [46] Xinyu Yuan, Zichen Wang, Marcus Collins, and Huzefa Rangwala. Protein structure tokenization: Benchmarking and new recipe. *arXiv preprint arXiv:2503.00089*, 2025.