MS01 MX/Cryo-EM software development

MS1-05

Exploring generality of experimental conformational changes with AlphaFold predictions

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Abstract

Structural predictions (Jumper et al., 2021) have matched the accuracy of experimental structures in the case of close homologues, outperformed docking methods for multimeric complexes and helped sampling the conformational landscape of transporters and receptors. Such successes prompt the question whether predictions can be used to relate experimental structures in the context of available knowledge. LysR-type transcriptional regulators (LTTR) constitute the most common family of bacterial regulators. Intriguingly, their experimental structures are remarkably diverse. The active species, composed of flexible monomers dimerizing through their N- and C-terminal domains in a circular arrangement, differ across LTTR, due to intrinsic sequence differences or because crystals stabilize diverse snapshots of a common dynamic mechanism. We have used AlphaFold2 (AF) to interrogate the experimental AtzR structure in the context of predictions guided towards the different hetero-multimeric conformations known for other LTTR (Castellví et al., 2022). Our approach drives AF prediction with the structure-based selection of the information input through sequence alignment and template conformation, linked to examination of the energy with PISA (Krissinel 2011) and interactions with ALEPH (Medina et al., 2020).

References

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., Back, T., Petersen, S., Reiman, D., Clancy, E., Zielinski, M., Steinegger, M., Pacholska, M., Berghammer, T., Bodenstein, S., Silver, D., Vinyals, O., Senior, A. W., Kavukcuoglu, K., Kohli, P. & Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. Nature, 1–11. https://doi.org/10.1038/s41586-021-03819-2

Castellví, A., Medina, A.,, Petrillo, G.,, Sagmeister, T., Pavkov-Keller T., Govantes, F., Diederichs, K., Sammito, M D. and Usón, I. (2022). Exploring generality of experimental conformational changes with AlphaFold predictions. https://biorxiv.org/cgi/content/short/2022.04.12.488086v1

Medina, A., Triviño, J., Borges, R. J., Millán, C., Usón, I., & Sammito, M. D. (2020). ALEPH: A network-oriented approach for the generation of fragment-based libraries and for structure interpretation. Acta Crystallogr., D76, 193–208. https://doi.org/10.1107/S2059798320001679

Krissinel, E. (2011). Macromolecular complexes in crystals and solutions. Acta Crystallogr., D67(4), 376–385. https://doi.org/10.1107/S0907444911007232