Validation of Symmetric Protein Assemblies Predicted by SymProFold

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SymProFold [1] is a pipeline that predicts symmetric protein assemblies like S-layer lattices and viral capsids from sequence alone, exploiting the capabilities of AlphaFold-Multimer, and geometric and biological constraints inherent to symmetrical assemblies. Here, we present the validation of SymProFold-predicted S-layer structures using X-ray crystallography.

We demonstrate that while the computational models serve as a valuable starting point for construct design and interface hypothesis generation, structural experimentation is critical for confirming interface geometry, quaternary arrangement, and assembly plasticity. Particularly for proteins with high sequence variability and dynamic self-assembly behavior such as S-layer proteins, where experimental data are crucial.

Our results underscore the complementary roles of predictive modeling to other structural biology methods and highlight the need to integrate both approaches to achieve a comprehensive understanding of complex protein architectures.

[1] Buhlheller, C., Sagmeister, T., Grininger, C. et al. *SymProFold: Structural prediction of symmetrical biological assemblies.* Nat Commun 15, 8152 (2024). https://doi.org/10.1038/s41467-024-52138-3