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**Abstract**

The predictive powerhouse of protein structure and function that is protein sequence coevolution analysis has recently matured. The prediction of membrane and disordered protein structures, protein complex architectures,

global statistical models of sequence coevolution. These computational methods, which provide functional and

coevolution analysis to the structure and function of membrane proteins, as well as the promising directions and challenges that lie ahead. Membrane protein biochemists who want to apply sequence coevolution analysis to a

**:** Clustered protocadherin; Sequence coevolution analysis;

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novo protein structure prediction to understanding conformational changes, these examples demonstrate how sequence coevolution can be used to study membrane proteins at multiple levels. We apologize for omitting any studies from this rapidly expanding eld because we were unable to cover all examples. We provide guidelines for using sequence coevolution analysis e ectively based on this survey.

e de novo prediction of protein structure based solely on sequence information was one of the promises made in the initial paper on protein sequence coevolution analysis. e main idea is to use the coevolving residue pairs as distance constraints for structural modeling with NMR methods or computational structure prediction so ware like Rosetta inferring that the paired residues should be close to each other in space in the three-dimensional structure. However, it wasn't until direct methods were developed to distinguish transitively coupled pairs from directly coupled residue pairs that the precision of predicted structural contacts became su cient to infer protein structure. Direct strategies were before long applied to α-helical layer proteins, for certain modi cations explicit for lm proteins. In addition, the model structures were scored based on how well they adhered to secondary structure prediction, coevolution constraints, and models of which residues are exposed to the lipid membrane. Based on a test set of 25 known membrane protein structures, this EV Fold membrane algorithm can produce highly accurate models of -helical membrane proteins [9-10].

ese models are comparable to a reasonable homology model, making them a useful starting point for a membrane protein biochemist lacking other structural information. e RMSD over C atoms for these models and their corresponding experimentally determined structure ranges from 2.8 to 5.1.

is review examines how studies of membrane protein structures and functions can use sequence coevolution analysis to identify functional sites in proteins, understand conformational changes, discover and characterize protein-protein interactions, and integrate with other structural approaches to reveal the structure of large membrane protein complexes. In order to encourage proper usage and increase the likelihood of successful application of this remarkable and cutting-edge method, we have provided guidelines for performing sequence coevolution analysis. When su cient sequence information can be assembled into a high-quality MSA, we anticipate that biochemists will increasingly use sequence coevolution analysis on their own protein families of interest. We nd such analyses to be extremely helpful in generating hypotheses that can be tested experimentally.

e authors declare that they have no competing nancial interests

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None

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implications, source and its prevention

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