
Preface

Knowledge about protein tertiary structure can guide mutagenesis experiments, help in the understanding of structure–function relationships, and aid the development of new therapeutics for diseases. Homology modeling is an *in silico* method that predicts the tertiary structure of a query amino acid sequence based on a homologous experimentally determined template structure. The method relies on the observation that the tertiary structure of a protein is better conserved than sequence and therefore two proteins that are not fully conserved at the sequence level may still share the same fold. Structures solved by X-ray crystallography and NMR are deposited in the Protein Data Bank (PDB) and form the templates for homology modeling. The human proteome has approximately 20,000 annotated human proteins and only 4,900 human protein fragments and domains can be found in the PDB.

The main steps in a homology modeling experiment are template selection, alignment, backbone and side-chain prediction, and structure optimization, including ligand-guided optimization and evaluation. Errors at the template selection step will result in an incorrect model and so care is needed to identify a template structure that has significant homology with the query sequence. The template sequence is aligned to the query sequence and the alignment is adjusted to ensure optimal correspondence between the homologous regions. The backbone atoms of the model are mapped onto the three-dimensional template structure and nonconserved side-chain orientations are predicted. Optimization of the model in a force field removes steric clashes and improves the hydrogen-bonding network between atoms. Evaluation of the final model highlights regions where there are errors in the model, for example, nonconserved loops, which may need to be modeled independently of the conserved regions. While the ability of models to predict ligand binding is still limited as evaluated recently in a GPCR DOCK 2010 competition, there is noticeable progress.

Energy sampling methods used in the homology modeling optimization step also have application for predicting how ligands bind to the model. Modeling methods are required even when an X-ray or NMR structure is available because the number of possible ligand–receptor combinations is extremely high and experimentally solving all of them is not practical.

In this book, experts in the field describe each homology modeling step from first principles, highlighting the pitfalls to avoid and providing first-hand solutions to common modeling problems. In addition, the book contains chapters from colleagues who model particularly challenging proteins such as membrane proteins where template structures are scarce or large macromolecular assemblies. The book also describes methods that can be applied once the initial model is complete, such as those which can be used to optimize the ligand-binding pocket of the model and predict protein–protein interactions.

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San Diego, CA, USA
La Jolla, CA, USA

Andrew J.W. Orry, Ph.D.
Ruben Abagyan, Ph.D.

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Orry, A.J.W.; Abagyan, R. (Eds.)

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