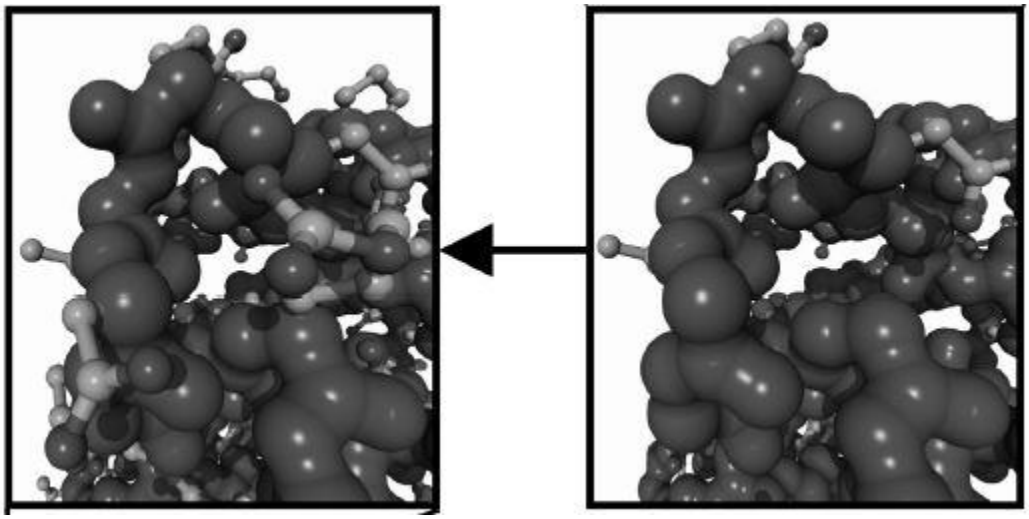
What is Homology Modelling?

Homology modelling allows users to safely use rapidly generated in silico protein models in all the contexts where today only experimental structures provide a solid basis: structure-based drug design, analysis of protein function, interactions, antigenic behavior, and rational design of proteins with increased stability or novel functions. In addition, protein modeling is the only way to obtain structural information if experimental techniques fail. Many proteins are simply too large for NMR analysis and cannot be crystallized for X-ray diffraction.



Among the major approaches to three-dimensional (3D) structure prediction, homology modeling is the easiest one. In the Homology Modelling, structure of a protein is uniquely determined by its amino acid sequence (Epstain, Goldberger, and Anfinsen, 1963). Knowing the sequence should, at least in theory, suffice to obtain the structure. 2. During evolution, the structure is more stable and changes much slower than the associated sequence, so that similar sequences adopt practically identical structures, and distantly related sequences still fold into similar structures. This relationship was first identified by Chothia and Lesk (1986) and later quantified by Sander and Schneider (1991). Thanks to the exponential growth of the Protein Data Bank (PDB), Rost (1999) could recently derive a precise limit for this rule. As long as the length of two sequences and the percentage of identical residues fall in the region marked as “safe,” the two sequences are practically guaranteed to adopt a similar structure.

Homology Modelling or Protein Modelling Example

Imagine that we want to know the structure of sequence A (150 amino acids long,). We compare sequence A to all the sequences of known structures stored in the PDB (using, for example, BLAST), and luckily find a sequence B (300 amino acids long) containing a region of 150 amino acids that match sequence A with 50% identical residues. As this match (alignment) clearly falls in the safe zone (Fig. 25.1), we can simply take the known

structure of sequence B (the template), cut out the fragment corresponding to the aligned region, mutate those amino acids that differ between sequences A and B, and finally arrive at our model for structure A. Structure A is called the target and is of course not known at the time of modeling.

Homology Modelling Steps

In practice, homology modeling is a multistep process that can be summarized in seven steps:
1. Template recognition and initial alignment
2. Alignment correction
3. Backbone generation
4. Loop modeling
5. Side-chain modeling
6. Model optimization
7. Model validation

At almost all the steps choices have to be made. The modeler can never be sure to make the best ones, and thus a large part of the modeling process consists of serious thought about how to gamble between multiple seemingly similar choices. A lot of research has been spent on teaching the computer how to make these decisions, so that homology models can be built fully automatically. Currently, this allows modelers to construct models for about 25% of the amino acids in a genome, thereby supplementing the efforts of structural genomics projects

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