all methods try to optimize a function that models to some extent the free energy of binding.

3.1.3.1 Geometric/Combinatorial Search Strategies. Most of the early docking methods were entirely based on the concept of shape complementarity. Until today this is the fundamental idea in most protein-protein docking programs. The observation that protein–ligand complexes frequently show a remarkable shape fit of both binding partners has stimulated the conception of surface or descriptor matching as docking search technique. The molecules are represented by geometric and/or physicochemical descriptors and various alignment procedures are applied to match complementary parts of ligand and protein. An example is the original DOCK method, where the ligand is superimposed onto a negative sphere image of the binding pocket, using a distance matching algorithm followed by least-squares fitting (106, 132). Other examples are the least-squares fitting procedure described by Bacon and Moult to achieve matches between complementary surface patterns (133), or the hierarchical search of geometrically compatible triplets of surface normals on the molecules to be docked, as proposed by Wallqvist and Covell (134). The program ADAM performs a complete combinatorial search over all possible matches between hydrogen bond patterns (135). Recently, a new matching algorithm based on so-called quadratic shape descriptors has been described (QSDock); along with the presentation of their method, the authors also provide an extensive discussion of shape-based docking algorithms (136).

Another recent example of descriptor matching is SLIDE, developed as a tool for ligand database screening by docking (111). The binding site is represented by a template of favorable interaction points onto which ligand atoms are matched during the search. Instead of serving as a purely geometric description, these points address four different types of interactions (hydrogen-bond donor, acceptor, donor/acceptor, or hydrophobic interaction center). The search is then performed such that all triangles of appropriate atoms in the ligand are exhaustively mapped onto triangles of template points with compatible geometry and chemistry. This mapping is used to generate initial placements of molecules in the binding site and followed by a series of steps that refine the initial position, resolve collisions, and consider flexibility of both the ligand and the protein side chains (cf. note on hybrid approaches below). Similarly, the rapid docking approach for library prioritization developed by Diller and Merz (112) is based on rigid-body triplet matching of ligand atoms onto precalculated hot spots; subsequently, pruning is performed to remove any positions with significant steric clash, and the remaining matches are subjected to energy minimization.

Pure descriptor matching is efficient for rigid-body docking only. Flexible docking, in fact, is always faced with the additional problem of a combinatorial explosion of possible conformers depending on the number of rotatable bonds. Systematic searches or explicit consideration of each possible conformation would therefore require enormous computing resources. A popular way to address this problem within the class of geometric/combinatorial docking methods is incremental construction (110, 130, 131, 137). The ligand is dissected into fragments and incrementally reconstructed in the binding site starting from a suitably docked base fragment. To avoid dead-end solutions during construction, multiple placements of the base fragment have to be considered. In addition, it can be useful to perform different fragmentations and hence to use different base fragments as starting points, especially for long and highly flexible molecules. The docking itself, that is, the placement of the base fragment and the attachment of remaining portions, is guided by some descriptor matching procedure.

An example of an incremental construction method is the program FlexX (110, 130, 138, 139). Conformational flexibility is considered using a discrete set of preferred torsion angles about acyclic single bonds, together with multiple conformations for ring systems. These torsion angle preferences are taken from a library compiled from torsional fragments extracted from the Cambridge Structural Database (140). The model of molecular interactions is based on similar rules as implemented in LUDI, originating from a composite crystal-