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Computational modeling of protein assemblies

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Computational methods to predict the 3D structures of protein interactions fall into 3 categories—template based modeling, protein–protein docking and hybrid/integrative modeling. The two most important considerations for modeling methods are sampling and scoring conformations. Sampling has benefitted from techniques such as fast Fourier transforms (FFT), spherical harmonics and higher order manifolds. Scoring complexes to determine binding free energy is still a challenging problem. Rapid advances have been made in hybrid modeling where experimental data are amalgamated with computations. These methods have received a boost from the popularity of experimental methods such as electron microscopy (EM). While increasingly larger and complicated complexes are now getting elucidated by integrative methods, modeling conformational flexibility remains a challenge. Ongoing improvements to these techniques portend a future where organelles or even cells could be accurately modeled at a molecular level.

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Introduction

Increasingly, the attention in molecular structural biology is being focused on molecular interactions and molecular machines/complexes. The frontiers are being pushed by the solution of larger and more complex assemblies of biomolecules [1,2•,3–5]. These assemblies not only elucidate the functional roles of individual molecules but also uncover complex molecular and cellular phenomena. In the last 2–3 years there has been a large influx of near atomic resolution structures of protein complexes using electron microscopy (EM). This has changed the landscape of structural biology [6,7], and is conceivably only the beginning of a rapidly increasing trend (Figure 1).

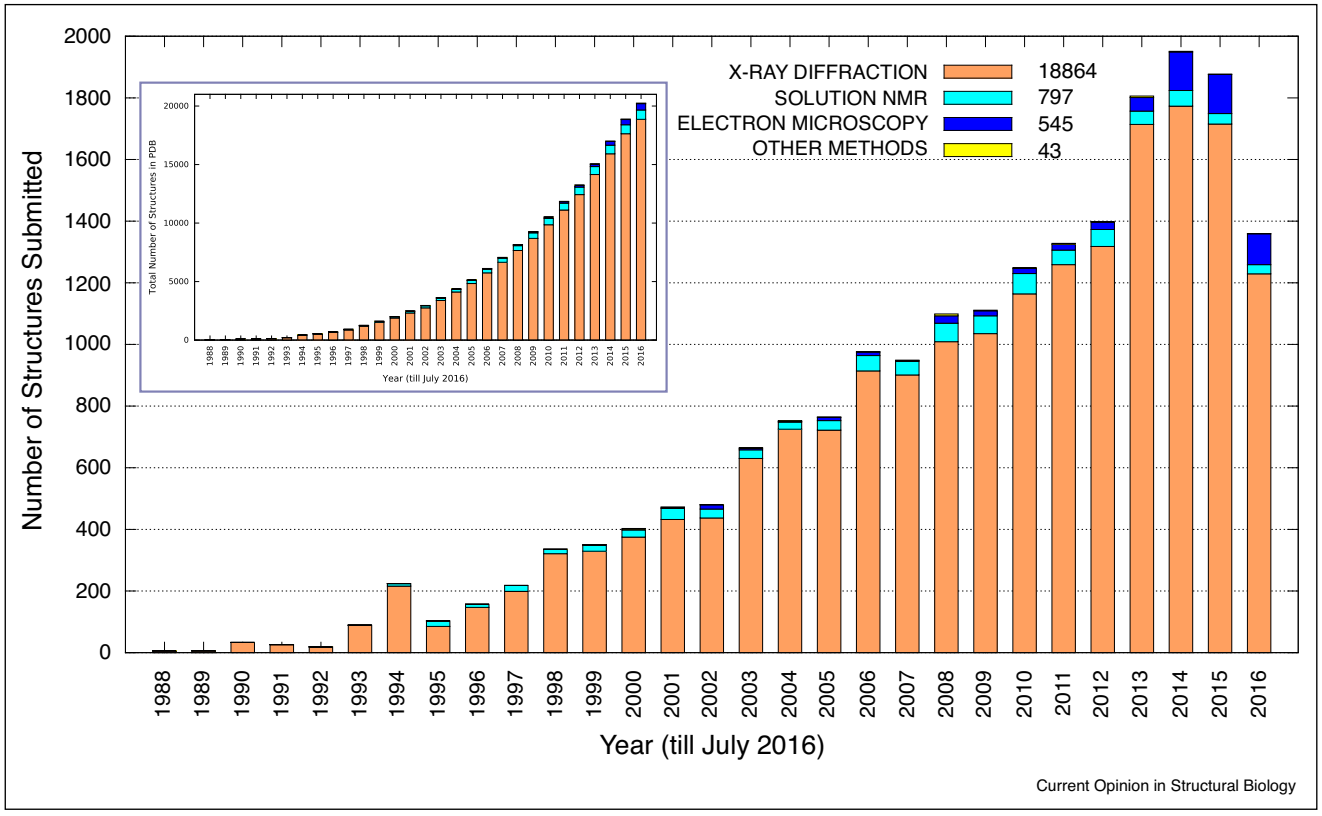
Despite these recent advances vast numbers of interacting complexes are not annotated by experimentally determined 3D structures [8]. In this review we restrict the discussion to only proteins complexes. By various estimates the number of such protein complexes could be in the hundreds of thousands, but limited, just as there are only a few thousands of different protein folds [9,10]. These complexes encompass a wide variety of associations including obligate interactions, transient interactions, interactions restricted to sub-cellular compartments, host–pathogen interactions [11] *etc.* Protein complexes could be homo- or hetero-oligomeric with up to 70% being the former [12]. Though, we now have deeper insights into the dynamics and evolution of the quaternary associations [12,13,14•] in these protein complexes, a significant challenge of modeling them still remains. A large number of curated repositories and databases house information on known protein complexes [15–25]. These data are potential training grounds for computational methods to make predictions of protein–protein interactions. This review deals with the different computational techniques that are used to predict/construct 3D structures of protein complexes.

Modeling protein complexes

Protein complexes could be as simple as a stable symmetric homo-dimer or as complicated as a multi-component hetero-oligomer whose constituents assemble/disassemble dynamically. *In silico* modeling of protein assemblies can be broadly categorized into 3 types—(a) template based docking [26••,27,28], (b) template-free computational docking and (c) Docking guided by restraints obtained from experimental procedures or Hybrid modeling (see section on hybrid modeling and Figure 2). This section and the ones immediately following it deal primarily with template based and template free modeling methods.

Template based methods could, in principle, be used to model multi-component complexes [29–31]. A pre-requisite for this would be multimeric templates. These are often in short supply and hence the coverage of template-based methods is also mostly limited to pair wise interactions [29,32,33]. Template-based methods have also evolved to not rely on homologous templates alone but to also cover cases where there is interface similarity without sequence homology [26••,34,35]. Despite the fact that interface templates are possibly present to model many interactions [36], template based methods when used as is, generally underperform in comparison to other

Figure 1



Growth of multimeric complexes in PDB.
The number of protein oligomers (with more than 2 subunits) deposited in the PDB [107], as a function of time (spanning the years 1988–2016 (July)). The cumulative growth in these numbers is shown in the inset. Structures solved by X-ray crystallography, NMR spectroscopy, electron microscopy (EM) and other methods are shown in orange, cyan, blue and yellow respectively. The number of 3D structures of the complexes solved by the different methods is shown in the legend. While X-ray crystallography continues to be the largest contributor, the last 2–3 years has seen a spurt in the number of such structures solved by EM. Of the 545 EM structures, 352 (65%) have been solved in the last 2.5 years. Given that EM is a technique amenable to solving the structures of large assemblies with relatively simpler sample preparation, it is set to elucidate the 3D structures of a large number of complexes, both big and small [7,108]. Computational modeling and simulations are integral to the solution and interpretation of the many of the EM structures. It is expected that the accuracy and applicability of these methods would improve with the increase in the number of EM resolved structures.

docking methods [27]. However, with special consideration, these methods could perform on par with the best available docking tools [27,31].

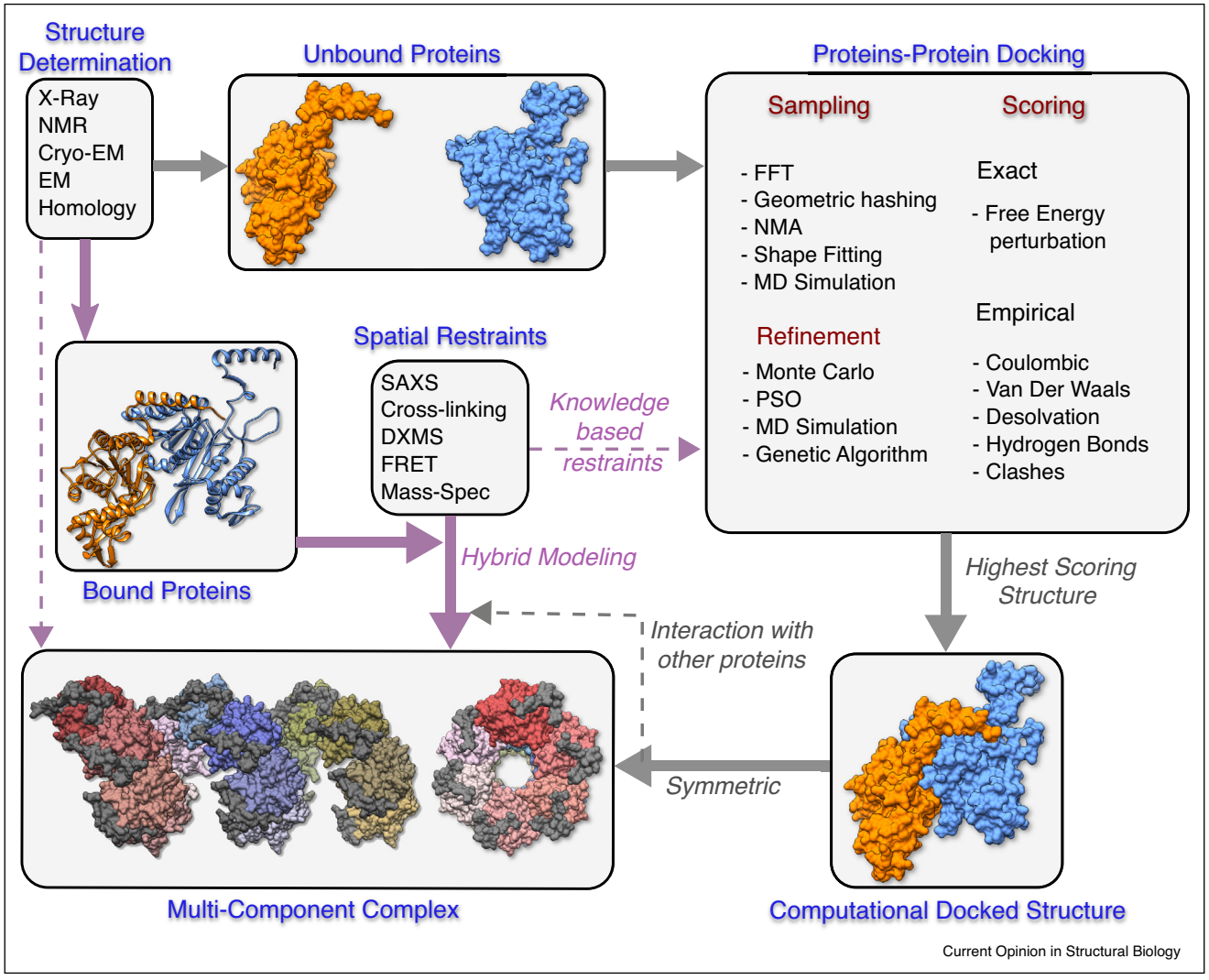
Most (all) protein docking methods assemble pairs of protein structures. A few of the docking software engineer their pair-wise assemblies to account for larger oligomeric complexes. Notable among such methods are RosettaDock [37], CombDock [38,39] and Multi-LZerd [40]

All docking programs face the two significant challenges of scoring and sampling. Template based docking programs do minimal sampling, while template free docking methods invest considerable effort at this stage. The docking software should sample a sufficient number of conformations such that near native conformations of the protein–protein complex are encountered. The programs should also be armed with a scoring scheme to discriminate between native and non-native conformations. Ideally, the scoring scheme should also be sensitive enough to discriminate between native and near native conformations. In the sections below we review recent advances in different sampling and scoring techniques. Though we have treated these two aspects separately, many of the methods integrate scoring and sampling during the docking process.

Sampling conformational space

An exhaustive search of all possible conformations of protein–protein interfaces including conformation flexibility is practically intractable. Prior knowledge of the (approximate) location of interactions sites could reduce sampling complexity and time. In the absence of such knowledge, many docking programs consider proteins as rigid bodies. Even with this approximation most methods do not exhaustively scan the entire molecular surface of the interactors. Methods such as the FFT correlation

Figure 2



A general schema for computationally assembling a multi-protein complex.
Computational techniques are necessary when the structures of multi-oligomeric complexes cannot be obtained experimentally. The individual components of an assembly could either be obtained from the PDB or computationally modeled. The whole complex or sub-complexes could be obtained by protein–protein docking. Mostly these docking exercises deal with pairs of proteins and employ a myriad of sampling and scoring techniques to produce an optimal docked structure. Whole or sub-complexes could also be obtained by assimilating data from different experiments that provide restraints to the docking exercise. The experiments could be any one of many (a partial list is shown) whose readout directly or indirectly leads to some spatial inference. The 32-mer complex structure represented in the multi-component complex panel is a homology/template-based model of the inactive human Rad51 filament (16mer) complexed with the 16 BRC4 fragments. The modeled structure, together with the EM structure of the active filament, helps elucidate the mechanism of interaction between Rad51 and the tumor suppressor BRCA2 [104•,105].

approach [41,42•] and Geometric Hashing [43] are exceptions to this trend and systematically cover the entire accessible interacting surface. Most current methods initially perform rigid body docking and then select the top few conformations as filtered by their scoring functions. These conformations are further optimized by incorporating the surface flexibility of the interacting partners [44]. Numerous algorithms are employed to model the dynamics/flexibility of the interacting surfaces such as normal mode analysis [45], molecular dynamic simulations [46,47] and sampling the torsion angle space from available rotamer libraries [48–51].

To efficiently sample near native conformations, sampling algorithms have evolved by combining different features and techniques. The programs CLUSPRO [52], GRAMM-X [53], DOT [54], HEX [55], FTDOCK [56], ZDOCK [57,58••,59], M-ZDOCK [60], PIPER [61] and MEGADOCK4.0 [62] all use FFT based sampling that implement shape complementarity along with other

improvements. For instance, DOT and HEX incorporate electrostatic complementarity whereas FTDOCK, ZDOCK, MEGADOCK 4.0 and M-ZDOCK combine electrostatic and desolvation free energy. PIPER incorporates pairwise knowledge-based interaction potentials. Among the methods that do not take recourse to FFT, PATCHDOCK [63,64] and SYMMDOCK [63,64] work by dividing the surface into concave, convex and flat patches. This ensures better shape complementarity and fewer atomic clashes while maximizing interface area. Another non-FFT method, RosettaDock [65,66•], attempts to achieve atomic level accuracy by searching backbone and side chain conformational space using Monte Carlo in combination with various biochemical and pairwise residue propensities. FRODOCK2.0, an improved version of FRODOCK [67••,68], uses a combination of grid based potentials, spherical harmonics (to deal with rotational degrees of freedom) and a knowledge based potential for docking.

Scoring schemes for evaluating protein–protein interfaces

Increasing computational power should alleviate some difficulties associated with conformational sampling. The main issue would then be to distinguish the native, or near-native structure from among the sampled decoys. Many aspects of protein interactions confound scoring schemes. For instance, analyses of protein–protein interfaces show that native conformations do not necessarily have the most hydrogen bonds or the largest buried solvent accessible surface area [69–71]. Induced fit conformations on the interface and the role of molecular crowding [1,72] and solvent (water and ions) in mediating interactions further complicate scoring schemas.

Just as in sampling techniques, scoring techniques have evolved by combining various features and properties. Methods such as GRAMM-X [53], ATTRACT [73,74], 3D-DOCK [50,75], LZERD [76] *etc.* use different combinations of solvation energy, dielectric constants, electrostatics, van der Waals interaction, hydrogen bonds, clashes, clustering using pairwise RMSD *etc.* Of these methods, HADDOCK [77–79], CLUSPRO [52] and SWARMDOCK [72,80] have demonstrably outperformed other methods [27]. HADDOCK scoring works synergistically with sampling to refine docked structures using explicit water, buried surface area, interaction restraint energy and desolvation energy. Similarly, CLUSPRO uses electrostatics and desolvation free energy for filtering models. SWARMDOCK uses particle swarm optimization along with van der Waals, electrostatics, hydrogen bonding and desolvation energy terms.

While this review mainly concerns itself with methods that bundle model building and assessment into a single package, one must be aware of the development of stand-alone assessment methods. These assessments make use of interaction energy and sequence conservation to deduce binding affinity [81]. Methods such as KFC [82], MINERVA [83], HotPoint [84], *etc.* (not an exhaustive list), also make predictions of hotspot residues. For a recent comparison of the performance of these methods refer to [85]. These methods could be used in conjunction with any of the packages mentioned above as an independent assessment of the predicted complexes. Recent advances have also seen the growth of machine learning methods to predict interaction interfaces (for a review see [86]).

Challenges for sampling and scoring techniques

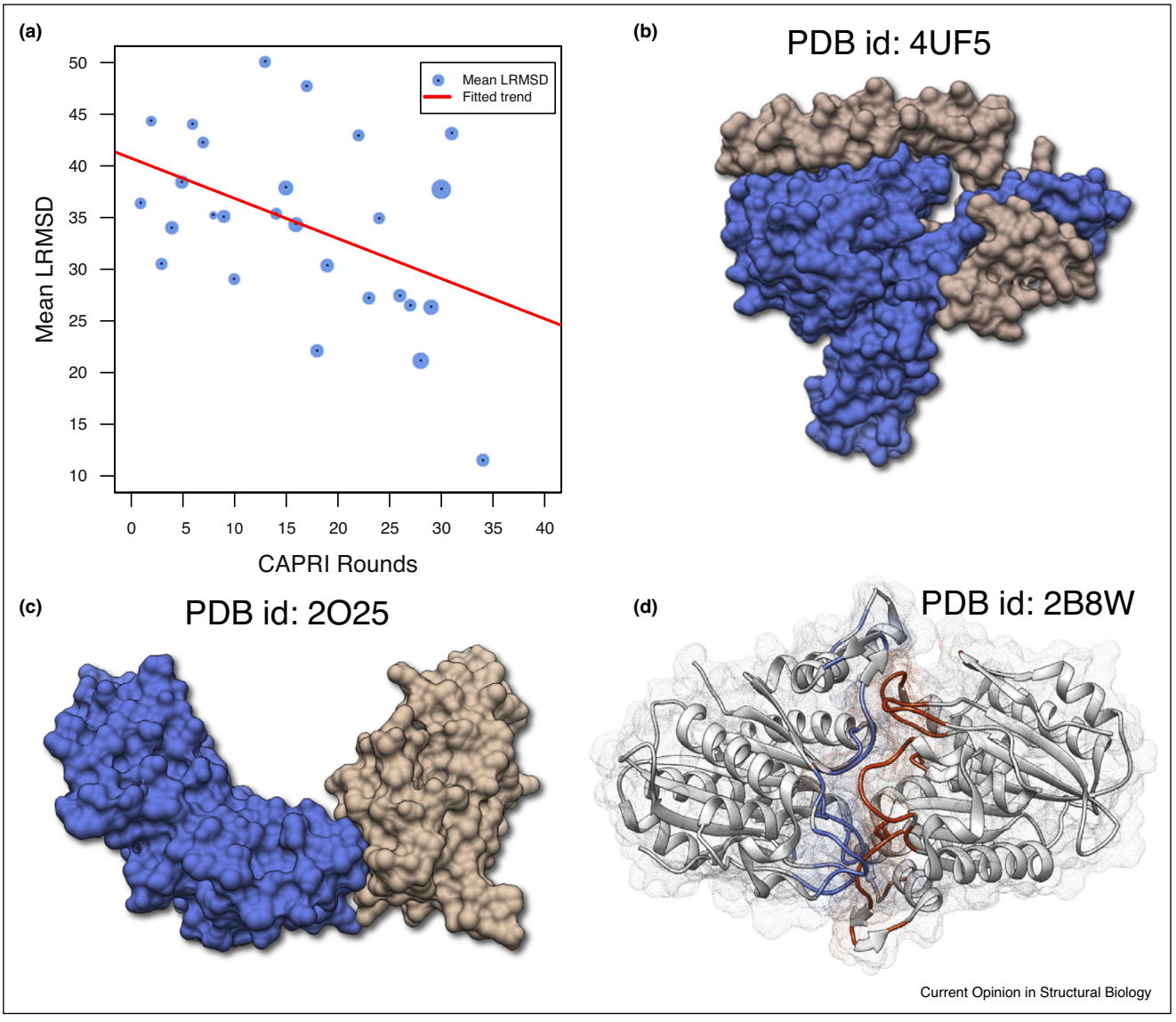
There are two major sampling challenges to protein–protein docking—speed and conformational flexibility. Docking methods should be able to sift through billions of possible configurations. Many methods hence use FFT based sampling as it is swifter than Monte Carlo and geometric fitting based methods. Recent advances such as the fast manifold Fourier transform [42•] and GPU implementations (as in MEGADOCK4.0) have significantly enhanced FFT sampling speed even further. Programs such as FRODOCK and HADDOCK have further improved sampling speed with parallel implementation of their algorithms. In all these methods, the increase in speed does not compromise on accuracy. The problem with conformational flexibility, however, still remains. Methods such as HADDOCK, that take some flexibility into consideration, albeit at a refinement stage, tend to perform better than methods that treat interactors as rigid bodies. Note that in methods that account for flexibility, only small conformational changes are sampled. Extensive conformational variations, such as those observed in some induced fit interactions remain computationally illusive.

To identify a binding event, a fast and accurate scoring function should complement an exhaustive sampling algorithm. Ideally, the scoring scheme should compute the free energy of binding. Such computations are hard to accomplish and none of the current methods consistently make accurate estimates of the binding free energy [87]. Most scoring functions discriminate between binding and non-binding events, while being unable to consistently rank order binding partners by affinity [88].

Another aspect of scoring that needs improving, in the face of the increasing number of multi-component complexes being modeled, is determining the relative stoichiometry of binding partners. In other words we need to determine how many concurrent binding partners a particular protein is likely to have. The scoring scheme should be able to determine if the free energy of the complex would decrease with/without additional interactors. In general, the environment of the interaction could influence the strength of binding. A recent method makes use of explicit water in the docking protocol to account for this environment [89•]

The CAPRI experiment serves as an ideal testing platform for new docking methods. It is also a barometer of the progress we have made in protein–protein docking over the years. Prediction difficulties are usually associated with interfaces that are made of more than 1 surface patch, or with interfaces that are flexible (Figure 3).

Figure 3



The progress made in protein assembly modeling as gauged from the CAPRI experiments.
LRMSD is the root mean square deviation (RMSD) of the backbone atoms of amino acids in protein complexes when modeled structures are compared to the native. The smaller the LRMSD, the better is the prediction, with the most accurate prediction having a value of 0. Starting from July 2001, 35 rounds of the CAPRI experiment has elicited predictions for 107 different target complexes from several different research groups [27,109–115]. The average LRMSD is computed for all qualified models of a particular CAPRI round. The size of the points are indicative of number of structures deposited in a particular round. The average LRMSD is decreasing over time indicating that computational techniques are improving with time (Panel A). However, the absolute value of the average LRMSD remains high (currently ~20 Å). The LRMSD improvement is not monotonic, as for different rounds the criteria for acceptability of models differ. Another contributing factor could be that, unlike the homology modeling part of CASP experiments, there is no measure such as sequence identity or e-value that gauges the difficulty level of targets. The CAPRI predictors, automated servers and humans alike, faced difficulties when sub units contacted one another in several non-contiguous patches (Panel B, CAPRI target 101, Complex of ubiquitin carboxyl-terminal hydrolase isozyme L5 (blue) and nuclear factor related to Kappa-B binding protein (grey); pdb code: 4uf5 [116]), or when the interface regions were small (crystal contact like) (Panel C, CAPRI target 27, Ubiquitin-conjugating enzyme E2 (blue) and SUMO-1-conjugating enzyme UBC9 (grey); pdb code: 2o25) or when the interface residue were predominantly from non-secondary structure regions (Panel D, CAPRI target 23, homodimer of Inteferon induced guanylate binding protein; pdb code: 2b8w [117]).

However, on average, the overall accuracy with which the 3D structures of protein complexes have been modeled has continuously improved over the years.

Hybrid modeling

From the state of the art in protein–protein docking, it is clear that the accuracy of predicted/modeled 3D structure improves with some prior knowledge. For instance, knowledge of the binding site regions vastly reduces the search space. A more generic implementation of this idea is to complement computational docking/modeling efforts with experimental data [90]. These data should be of the kind that could directly or indirectly lead to inference of spatial features such as distances, angles, torsion angles, volumes *etc.* [91]. Advances in technology, such as EM and Mass spectrometry, make it possible to attempt to solve 3D structures of large and complex molecular machines [6,7,92–94]. However, a key aspect of these new technologies is the flexibility to combine experimental data with computations [94,95]. For instance, knowing the overall shape (obtained from EM studies) does not necessarily inform one about sub unit packing [96]. This leads to the requirement of new and improved algorithms to 'dock' subunits with restraints [97,98]. Depending on the restraints, different types of docking solutions are possible, including fitting/refining structures and/or models to EM density maps. For flexible fitting and refinement, molecular dynamics simulations and other methods are utilized [99–101].

There are many protein complexes that have been solved using experimental data integrated with computations (Table 1, and schematically represented by the purple arrowhead path in Figure 2). Sometimes, none of the experimental techniques are able to determine the

Table 1

Examples of structures elucidated by hybrid modeling. This list includes only those complexes that have used at least two different experimental methods in addition to computational technique(s) to construct the 3D structure

Model system	Structural data used	Reference
Phosphoinositide 3-Kinase p85α Homodimer	SAXS, Cross-linking	[118]
Yeast Mediator complex	Cross-linking, Mass spectrometry, X-ray crystallography, homology modeling, Cryo-EM	[119]
Chromatin	Mass spectrometry, Cryo-EM	[120–123]
Human and Yeast TFIIH	Cross-linking, Mass spectrometry, biochemical analysis, Electron microscopy	[124]
Bilitranslocase Transmembrane Domain	Bioinformatics, NMR, FRET	[125]
Yeast eIF3:eIF5 complex	Cross-linking, Mass spectrometry	[126]
DNA Repair Complex of Human Rad9-Hus1-Rad1/FEN1/DN	X-ray crystallography, Single particle EM	[127,128]
Ubiquitin-modified PCNA	SAXS	[127,129]
Photoreceptor phosphodiesterase PDE6 catalytic dimer (αβ)	Cross-linking and Mass spectrometry	[130]
Actin-scruin complex	X-ray crystallography, Cross-linking	[131]
SEA complex	Affinity purification, Cross-linking	[132]
40S·eIF1·eIF3 Translation Initiation Complex	Electron microscopy, Cross-linking, Mass spectrometry	[133]
26S proteosome	X-ray crystallography, Cross-linking, Mass spectrometry, Cryo-EM	[134]
Nucleo-pore Complex, Nup84 complex	Ultracentrifugation, Quantitative immunoblotting, Affinity purification, overlay assay, Electron microscopy, Immuno-EM, Bio-informatics, Membrane fractionation, Cross-linking, Mass spectrometry, X-ray crystallography, homology modeling	[135–137]
Proteasomal lid (back calculate)	Mass Spectrometry, Proteomics, ion mobility-MS, Cross-linking	[138]
Proteasome interacting proteins (PIPs)(back calculate)	Mass Spectrometry, Proteomics, ion mobility-MS, Cross-linking	[138]
Chaperone involved in formation proteasomal base complex (back calculate)	Mass Spectrometry, Proteomics, ion mobility-MS, Cross-linking	[138]
Collicin-immunity protein and dnase complex (back calculate)	X-ray crystallography, Mas spectrometry	[5]
Eukaryotic Ribosome	Cryo-EM, Homology Modeling	[139]
Mammalian Ribosome	Cryo-EM, Homology Modeling	[140]
Exosome on polyribonucleotide phosphorylase (PNPase)	Homology modeling, Electron microscopy	[33]
RNA polymerase II with RPB4/7	X-ray crystallography, Homology modeling, Electron microscopy	[33]
Chaperonin CCT and phophoducin 2(PLP2) and G protein homolog VID27	X-ray crystallography, Electron microscopy	[33]
Ski complex	Homology modeling, Electron microscopy	[33]
RNase P (POP) complex	Electron microscopy	[33]
Bacterial type II pilus	Cryo-EM, EM, NMR, Cross-linking	[141,142]
Ryanodine receptor channel	Cryo-EM, Homology Modeling	[143]
TriC/CCT chaperonin	Cryo-EM, Homology Modeling	[144]
γ-tubulin small complex	Cryo-EM, Cross-linking, Homology Modeling	[145]
Triprptidyl peptidase II	Cryo-EM, Homology Modeling, molecular dynamics fitting, Single particle analysis	[146]
Dam1 kinetochore complex	Cross-linking	[147]

spatial restraints enough for hybrid modeling (purple color dashed line in Figure 2). In such cases protein-protein docking and knowledge-based restraints contribute significantly in determining the 3D structure of the complex (gray arrow heads in Figure 2). Recent successes of hybrid modeling include the NUP82 complex of the Nucleopore [102••] and the Ferrodoxin-FusA complex [103••]. A more comprehensive list is given in Table 1.

What is in store for the future of computational modeling of complexes

Template (homology) based docking methods, despite their limitations, are still effective when dealing with protein complexes whose related homologues have been characterized experimentally. These methods are particularly powerful in furthering biological hypothesis, for instance, in determining the 3D structures of active and inactive states of complexes [104•,105]. Many large scale interactome studies have been carried out using such template based studies alone [1,29,32]. The lack of adequate templates, and the fact that 'off the shelf' homology solutions are unreliable, means that protein–protein docking is widely used. Over the years, the CAPRI experiments have shown that docking methods have continually improved. Docking sampling techniques have made many advances, mostly in processing speed, using methods such as FFT. Scoring the complexes remains a significant problem and is driving the evolution of new and improved methods. Our analyses of the results over several rounds of CAPRI show that pairwise binding when mediated by more than one surface patch leads to difficulties. Somewhat related to this is the fact that docking is mostly restricted to assembling pairs of proteins or sub-complexes. There appears to be no clear method for an *a priori* determination of the number of components of the complex during the docking procedure.

Docking, despite some limitations, is instrumental in providing experimentally testable hypothesis. Successful experimental confirmations of the predictions not only validate the hypothesis but also validate the 3D models. In this light, the last few years have seen the emergence of integrated modeling or hybrid modeling. Philosophically, experiments and computations are treated as complementary approaches. Hybrid modeling techniques use many experimental and computational methods to resolve the structure of interacting complexes. The advent of EM has been a fillip to the development of such methods. Conformational flexibility is taken care of by modeling and molecular dynamics [106] and soon ambitiously large systems of complexes now modeled by packages such as CellPack [2•] could be within the reach of such methods.

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- •• of outstanding interest

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