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Scoring functions for protein–protein interactions

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The computational evaluation of protein–protein interactions will play an important role in organising the wealth of data being generated by high-throughput initiatives. Here we discuss future applications, report recent developments and identify areas requiring further investigation. Many functions have been developed to quantify the structural and energetic properties of interacting proteins, finding use in interrelated challenges revolving around the relationship between sequence, structure and binding free energy. These include loop modelling, side-chain refinement, docking, multimer assembly, affinity prediction, affinity change upon mutation, hotspots location and interface design. Information derived from models optimised for one of these challenges can be used to benefit the others, and can be unified within the theoretical frameworks of multi-task learning and Pareto-optimal multi-objective learning.

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Introduction

Determining the physical principles and structural elements which allow proteins to bind one another lies at the heart of many different challenging and only partially resolved problems in structural bioinformatics. Below, we highlight some of these challenges, show how their resolution would open up new avenues of exploration, and review recent advances in scoring function development. We argue that, as these problems are united by their reliance on quantifying the relationship between structure and binding free energy, information gained from each of these challenges can be of mutual benefit to all of them, paving the way for general purpose functions and Pareto optimal models capable of simultaneously considering problems that have traditionally been investigated in isolation.

Protein–protein docking

Protein–protein docking aims to determine the native structure of a complex from structures or models of its unbound constituents. Resolution of this problem would allow the generation of structures for approximately 65% of around 45 000 interactions in the known human interactome [1]. Thus, docking scoring functions continue to be an active area of research. Recent themes include the modelling of conformational change [2], coarse-grain models [3–5], and deriving potentials using decoy structures [6,7]. Although many scores are variations on statistical potentials and molecular mechanics functions, novel approaches include an asymmetric potential designed specifically for antibody–antigen docking [8•], a potential which implicitly considers the role of water-mediated interactions in structuring the binding energy funnel [9•], and scores based on machine learning [10–12]. A number of functions have been developed for the inclusion of bioinformatics and experimental information [13,14,15•]. Of particular interest is InterEvScore, which considers evolutionary information beyond sequence conservation [16••]; accounting for interface coevolution via the inclusion of interolog contact energies resulted in a marked improvement in docking performance.

Recently, we benchmarked the docking performance of 115 scoring functions (Moal IH, Torchala M, Bates PA, Fernandez-Recio J: **The scoring of poses in protein–protein docking: current capabilities and future directions**, submitted for publication). Of the highest performing functions, most were designed specifically for docking, although some homology modelling potentials also performed well. The functions were compared to determine whether different functions could identify different complexes. Coarse-grained potentials were more amenable to finding near-natives for flexible complexes, whereas atomic potentials were most suitable for rigid complexes. The comparisons also allowed the identification of a number of scoring approaches, based on the idea of combining scores which can find near-natives for different complexes. These approaches included strategies which have already been applied in the literature. However one method, SPIDER [17•], was capable of correctly identifying near-native solutions which were missed by the others. As SPIDER was the only method tested which explicitly accounts for multi-body interactions, this indicated that accounting for such effects is worthy of further exploration.

Binding affinity estimation

For each known human interaction, there are estimated two unknown interactions [18]. If it were possible to determine not just the lowest energy pose, but also the absolute affinity of the complex, docking could be used to establish whether two proteins interact or not, and structurally annotate true interactions of otherwise questionable veracity [19]. This could be of significance given that the availability of structural data greatly enhances the success of drug development projects [20], and that protein–protein interactions are of increasing interest as drug targets. The earliest ΔG models used molecular mechanics force fields and later statistical potentials, with very high correlations reported. However, benchmark sets were highly biased towards rigid proteins. Energy functions have proven to be less effective when more diverse complexes are considered [21]. The publication of a recent non-redundant binding affinity benchmark [22], cross-referenced to both bound and unbound complexes, has spurred several new affinity models [23–25]. In one study, complexes were found in which affinities had been determined by multiple groups or experimental techniques [23], and were thus known with high confidence. For the intersection of this set with the complexes which undergo small conformational rearrangements, a cross-validated correlation of 0.9 was achieved. However, correlation dropped significantly for the flexible complexes. This highlights conformational energy as challenging aspects of ΔG calculation, represented at the extreme by disorder to order transitions where unbound ensembles sample many configurations.

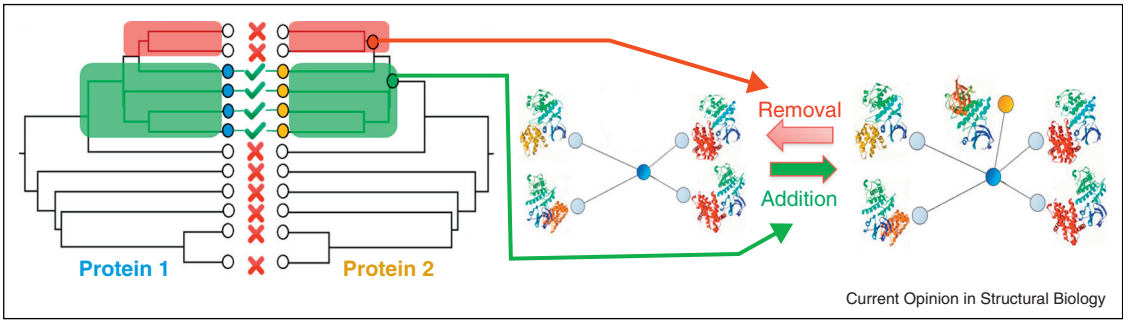
Hotspot identification and $\Delta\Delta G$ prediction

The modulation of protein–protein interactions can be aided by identifying interaction hotspots, the residues through which affinity is mostly facilitated, and are amenable to targeting with peptides and other small molecule [26,27]. Hotspot prediction is inherently a classification problem, commonly approached with machine learning tools. However, as hotspots are residues for which mutation to alanine strongly attenuates binding, their identification constitutes a special case of determining $\Delta\Delta G$, the change in binding energy upon mutation. The ability to accurately calculate how affinity changes with sequence would open up applications including large-scale determination of the functional consequences of pathological mutations. Further, clinical mutation data could be used in conjunction with structural interaction networks for personalised diagnostics. Were it possible to map larger regions of sequence-binding landscapes, one could map the affinity of homologous binding partners to phylogenetic trees. Mapping orthologous binding partners would permit investigations into how organisms adapted to their niches through speciation events in terms network rewiring, illustrated in Figure 1. Similarly, mapping affinities of paralogous pairs of binding partners onto phylogenetic trees would allow investigation of neofunctionalisation and subfunctionalisation events. Such studies could provide a critical evaluation of network evolution models. However, much groundwork remains before they become viable. Although a recent database of 3047 structurally cross-referenced experimental $\Delta\Delta G$ values will aid in the construction of empirical models [28], modelling of structural changes is also required. Although for interface point mutations these changes are often minor, a recent survey of structural interologs shows that the accumulation of mutations can result in remarkable plasticity [29].

Interaction design

A further area which can be facilitated by mapping sequence-function landscapes is the design of

Figure 1



Mapping binding affinities onto phylogenetic trees can be used to investigate interaction network rewiring over evolutionary time-scales. The phylogenetic trees for two proteins are shown on the left, with leaves corresponding to extant species and nodes representing speciation events. Pairs with very low affinity cannot form specific interactions, indicated by red crosses, whereas pairs with high affinity correspond to interologs, marked with green ticks. Assuming that interactions result from *de novo* evolution events rather than convergent evolution, the most recent known common ancestor which possessed the interaction, and in which the interaction may have evolved, corresponds to the root node of the smallest subtree which encompasses the interologs, as shown by the green dot. If any leaves in this subtree correspond to non-binders, then the root of the subtrees that encompasses non-binders, but not interologs, corresponds to the common ancestor in which the interaction was destroyed by loss-of-function mutations, as shown by the red dot. This information can then be mapped onto interactions networks to yield information regarding their rewiring; *de novo* evolution events correspond to the addition of an edge in the network, while loss of function events correspond to edge removal.

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