Fast and accurate calculation of protein-protein interaction: contribution of surface and interface

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Physical principles
Reliable estimates of the interaction strength of protein-protein interactions (PPIs) are required to construct models of larger regulatory networks, and are vital in designing protein interfaces. Existing approaches, including experimental techniques, prediction from sequence as well as protein-protein docking, all have their specific limitations. Our aim is to build a technique for accurate prediction of PPI strength, based on physical principles using simplified molecular models for computational efficiency.

Interface anatomy

Three groups of residues based on solvent accessible surface:
- Interface core: Buried in the complex.
- Interface rim: Partially buried in the complex.
- Outer rim: Water-exposed residues just outside interface rim.

Coarse-graining without loss of accuracy

- MARTINI CG force field (Marrink et al., 2007)
- Average constraint force as function of distance
- Integration yields PMF
- CG is just as accurate as all-atom

Wild-type MP1-p14

Mutations at interface core disrupt binding

Effect of mutations:
- Interface core
- Interface rim
- Outer rim

TCR-pMHC

BLOSUM62 ‘best’ mutations have no effect

Center of mass separation r [nm]

Conclusions
- Accurate PPI strength at 600-fold speed-up
- Mutations at interface core disrupt interaction
- Mutations at interface rim have minor effects
- Non-interface surface show no effect
- Even at the interface core, BLOSUM62 ‘most likely’ substitutions show no effect on the interaction strength

References