
Preface

Peptide-mediated interactions play prominent roles in many cellular processes: their weak, transient character, and their easy manipulation by targeted changes such as post-translational modifications, makes them especially amenable to versatile regulation.

The structure of a peptide-protein complex allows its detailed characterization and fine-tuned manipulation and provides important leads for targeted inhibitor design. It is therefore not surprising that much effort has been put into the development of tailored tools for the modeling of peptide-protein complex structures. However, until not long ago, such approaches were significantly limited, mainly due to challenges of sampling (peptides predominantly do not adopt a defined conformation prior to binding, so that peptide docking may be seen as a “fold-and-dock” challenge), but also scoring (peptide-protein interactions are often transient and weak, and modeling of solvation can be particularly challenging for these small interfaces).

The last few years have witnessed an unprecedented interest, and consequently advance, in our abilities to model and manipulate peptide-mediated interactions. This started with the development of dedicated protocols for local peptide-protein docking that apply a range of different algorithms to tackle the sampling problem. These now generate on a regular basis accurate, near-atom resolution models. It did not take long for the development of a second wave of approaches that extend and complement these tools towards full blind docking, without prior knowledge of the binding site, or an approximate starting conformation for the peptide. Such global docking may be accomplished either by combining binding site prediction with subsequent peptide docking or, alternatively, by performing both together.

Another area of fruitful advance has been our improved ability to predict not only the structure but also the binding affinity and specificity of peptide-protein interactions. These come together with dramatic improvement in the design of inhibitory peptides for the fine-tuned manipulation of protein interactions. Such advances bring us closer to be able to perform peptide-protein modeling on proteomic scale.

It is truly impressive how, in a short time, peptide-protein modeling has risen from a challenged side topic to an ever improving, buzzing field! Key to this improvement has been benchmarks, in the form of curated datasets of peptide-protein complex structures (such as PeptiDB), and last but not least, the CAPRI challenge for the assessment of the modeling of protein interactions: CAPRI has enthusiastically embraced peptide docking and included several peptide-protein docking targets over the past few years. This has further spurred the development of peptide docking protocols; many of them have been discussed in detail at the latest CAPRI evaluation meeting in 2016 in Tel Aviv (www.cs.tau.ac.il/conferences/CAPRI2016/).

In this book we have collected a series of chapters from the leading figures in the field of peptide-protein docking. The chapters are bundled into four inter-related parts, including (1) peptide binding site prediction; (2) peptide-protein docking; (3) prediction and

design of peptide binding specificity; and (4) the design of inhibitory peptides. In their combination in this book, the chapters provide a diverse and unified state-of-the-art overview of this rapidly advancing field of major interest and applicability.

We look forward to seeing the many applications that will result from applying the methodologies described in this book.

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