Biomolecular Recognition: Computational Drug Design

Chapter 1: Introduction

1) Principles of Molecular Recognition
2) Molecular Recognition in Biological Systems
3) Drug Design: A Difficult Problem
4) Drug Design: An Expensive Problem
5) Where Computational Techniques are Used

Chapter 2: Properties that Make a Molecule a Good Drug

1) Compound Testing
   Biochemical Assays
   Cell-Based Assays
   Animal Testing
   Human Clinical Trials
2) Molecular Structure
   Activity
   Bioavailability and Toxicity
   Drug Side Effects
   Multiple Drug Interactions
3) Metrics for Drug-Likeness
4) Exceptions to the Rules

Chapter 3: Target Identification

1) Primary Sequence and Metabolic Pathway
2) Crystallography
3) 2D NMR
4) Homology Models
5) Protein Folding

Chapter 4: Target Characterization

1) Analysis of Target Mechanism
   Kinetics and Crystallography
   Automated Crevice Detection
   Transition Structures and Reaction Coordinates
   Molecular Dynamics Simulations
2) Where the Target is Expressed
3) Pharmacophore Identification
4) Choosing an Inhibitor Mechanism

Chapter 5: The Drug Design Process for a Known Protein Target

1) The Structure-Based Design Process,
2) Initial Hits

3) Compound Refinement
4) ADMET,
5) Drug Resistance

Chapter 6: The Drug Design Process for an Unknown Target

1) The Ligand-Based Design Process,
2) Initial Hits,
3) Compound Refinement,
4) ADMET

Chapter 7: Drug Design for Other Targets

1) DNA Binding,
2) RNA as a Target,
3) Allosteric Sites,
4) Receptor Targets,
5) Steroids,
6) Targets inside Cells,
7) Targets within the Central Nervous System
8) Irreversibly Binding Inhibitors,
9) Upregulating Target Activity

Chapter 8: Compound Library Design

1) Targeted Libraries versus Diverse Libraries,
2) From Fragments versus from Reactions,
3) Non-Enumerative Techniques,
4) Drug-Likeness and Synthetic Accessibility,
5) Analyzing Chemical Diversity and Spanning known Chemistries,
6) Compound Selection Techniques

Chapter 9: Homology Model Building

1) How much Similarity is Enough?,
2) Steps for Building a Homology Model,
   Step 1: Template Identification,
   Step 2: Alignment between the Unknown and the Template,
   Step 3: Manual Adjustments to the Alignment,
   Step 4: Replace Template Side Chains with Model Side Chains,
   Step 5: Adjust Model for Insertions and Deletions,
   Step 6: Optimization of the Model,
   Step 7: Model Validation,
   Step 8: If Errors are Found, Iterate Back to Previous Steps,
3) Reliability of Results

Chapter 10: Molecular Mechanics

1) A Really Brief Introduction to Molecular Mechanics,
2) Force Fields for Drug Design

Chapter 11: Protein Folding

1) The Difficulty of the Problem,
2) Algorithms,
3) Reliability of Results,
4) Conformational Analysis

Chapter 12: Docking

1) Introduction,
2) Search Algorithms,
   Searching the Entire Space,
   Grid Potentials versus Full Force Field,
   Flexible Active Sites,
   Ligands Covalently Bound to the Active Site,
   Hierarchical Docking Algorithms,
3) Scoring,
   Energy Expressions and Consensus Scoring,
   Binding Free Energies
   Solvation,
   Ligands Covalently Bound to the Active Site,
   Metrics for Goodness of Fit,
4) Validation of Results,
5) Comparison of Existing Search and Scoring Methods,
6) Special Systems,
7) The Docking Process,
   Protein Preparation,
   Building the Ligand,
   Setting the Bounding Box,
   Docking Options
   Running the Docking Calculation,
   Analysis of Results

Chapter 13: Pharmacophore Models

1) Components of a Pharmacophore Model,
2) Creating a Pharmacophore Model from Active Compounds,
3) Creating a Pharmacophore Model from the Active Site,
4) Searching Compound Databases,
5) Reliability of Results

Chapter 14: QSAR

1) Conventional QSAR versus 3D-QSAR,
2) The QSAR Process,
3) Descriptors,
4) Automated QSAR Programs,
5) QSAR versus Other Fitting Methods

Chapter 15: 3D-QSAR

1) The 3D-QSAR Process,
2) 3D-QSAR Software Packages,
3) Summary

Chapter 16: Quantum Mechanics in Drug Design

1) Quantum Mechanics Algorithms and Software,
2) Modeling Systems with Metal Atoms,
3) Increased Accuracy,
4) Computing Reaction Paths,
5) Computing Spectra

Chapter 17: De novo and Other AI Techniques

1) De novo Building of Compounds,
2) Nonquantitative Predictions,
3) Quantitative Predictions

Chapter 18: Cheminformatics

1) Smiles, SLN, and Other Chemical Structure Representations,
2) Similarity and Substructure Searching,
3) 2D-to-3D Structure Generation,
4) Clustering Algorithms,
5) Screening Results Analysis,
6) Database Systems

Chapter 19: ADMET

1) Oral Bioavailability,
2) Drug Half-Life in the Bloodstream,
3) Blood–Brain Barrier Permeability,
4) Toxicity