**Computational Drug Design**

David C. Young PhD, Computational Drug Design: A Guide for Computational and Medicinal Chemists, John Wiley & Sons, 2009.

Weeks and 2:

**Chapter 1:** Introduction

1. A Difﬁcult Problem
2. An Expensive Problem
3. Where Computational Techniques are Used

PART I THE DRUG DESIGN PROCESS

**Chapter 2:** Properties that Make a Molecule a Good Drug

1. Compound Testing

Biochemical Assays

Cell-Based Assays

Animal Testing

Human Clinical Trials

1. Molecular Structure

Activity

Bioavailability and Toxicity

Drug Side Effects

Multiple Drug Interactions

1. Metrics for Drug-Likeness
2. Exceptions to the Rules

Week 3:

**Chapter 3:** Target Identiﬁcation

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

Week 4:

**Chapter 4:** Target Characterization

1. Analysis of Target Mechanism

Kinetics and Crystallography

Automated Crevice Detection

Transition Structures and Reaction Coordinates

Molecular Dynamics Simulations

1. Where the Target is Expressed
2. Pharmacophore Identiﬁcation
3. Choosing an Inhibitor Mechanism

Week 5:

**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

Weeks 6 and 7:

**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

Week 8:

**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

PART II COMPUTATIONAL TOOLS AND TECHNIQUES

Week 9:

**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

1. Reliability of Results

**Chapter 10:** Molecular Mechanics

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

Weeks 10 and 11:

**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

1. Scoring

Energy Expressions and Consensus Scoring

Binding Free Energies

Solvation

Ligands Covalently Bound to the Active Site

Metrics for Goodness of Fit

1. Validation of Results
2. Comparison of Existing Search and Scoring Methods
3. Special Systems
4. The Docking Process

Protein Preparation

Building the Ligand

Setting the Bounding Box

Docking Options5

Running the Docking Calculation

Analysis of Results

Week 12:

**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

Week 13:

**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

Week 14:

**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

Week 15:

**Chapter 17:** De novo and Other AI Techniques

1. De novo Building of Compounds
2. Nonquantitative Predictions, 201 17.3
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

Week 16:

**Chapter 19:** ADMET

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