

CHEM 6344
Computer Assisted Drug Design, Fundamentals and Application

Class location:	TBD
Lectures, time and location:	TBD
Lab times and location:	TBD
Instructor:	Elfi Kraka, 231 FOOSC, ext 8-2480, ekraka@smu.edu http://smu.edu/catco/
Office Hours:	By appointment
Units:	3
Grading:	ABC Letter Grade
Class number	

1. Rationale:

When a student enters pharmaceutical industry, sooner or later he/she will be involved in drug design. The student will realize that pharmaceutical industry is willing to do anything to cut down and simplify the long and very expensive process of drug design (more than 10 years and hundreds of million dollars costly). Drug development can be best accelerated by computer-assisted approaches. It is a constant (and actually justified) claim of pharmaceutical industry that not enough is done at the universities to prepare students for this work.

The course fills this gap and presents a thorough and in-depth going overview over methods and techniques in computer assisted drug design (CADD) where especially the needs of pharmaceutical industry are considered. Its contents includes topics such as famous examples of drug discovery and drug design, molecular recognition and docking, ligand-receptor interactions, pharmacophore searching, virtual screening, *de novo* design, molecular graphics, chemometrics, etc.

2. Course Recommendations:

The course is designed for all graduate students from chemistry, biochemistry, medicinal chemistry, biology, and engineering who want to obtain a thorough and in-depth overview over methods and techniques applied in computer assisted drug design (CADD). Basic chemical knowledge is required, however no special skills in pharmacy, mathematics or computer science. Since the course addresses a broad audience, it is designed as an interdisciplinary course taking care of the special needs of students with different background.

3. Texts:

- a) Textbook: Molecular Modelling: Principles and Applications (Paperback), by Andrew R. Leach, Pearson Higher Education, USA, 2001 (ISBN 0582382106).
- b) Handouts and notes for the computer labs

4. Course Aims and Objectives:

For a compound to become a drug many factors come into play beyond its fit to a receptor. From hundred thousands of substances tested every year, maybe 40-45 turn out to be a useful drug. Therefore, in order to keep the development costs for a drug at a reasonable level, pharmaceutical industry has to replace more and more costly experiments by modeling chemical properties, especially biological activities of a compound on the computer.

Molecular modeling (MM) has seen in the last years a rapid development which is far beyond its original goal to easily assess conformation and dynamics of larger molecules essentially provided by molecular mechanics and computer graphics. The same holds for computer assisted drug design (CADD). From its infancy in the late 70s it has become a powerful tool ranging now from graphical drug design (De novo design) to application of neural network and artificial intelligence. However, most of these developments have been done at pharmaceutical companies rather than at universities. Therefore, the course will bridge the gap how MM and CADD is performed by industry and used as a money making tool and how it is trained in academics.

The aim of this course is to present the appropriate tools for such a modeling ranging from molecular mechanics, molecular dynamics over computer graphics, data visualization, De Novo Design and chemometrics to computer assisted synthesis design based on artificial intelligence. Among various applications modeling of antigenic complexes, determination of recognition forces in pharmacological processes, computer assisted synthesis of pharmacophors and the design of new anticancer drugs will be discussed. The lectures will be accompanied by computer labs to complete the dedicated knowledge by practical experience

Specific Learning Objectives:

At the end of the course the student

will have an in-depth overview over the state-of-the art methods and techniques nowadays applied in CADD.

will be able to choose the appropriate method (in terms of applicability, accuracy, and economy) for a given problem like, lead optimization, structure based design, investigation of ligand receptor interaction.

will be able to perform, understand, and interpret the results of the calculations and bring them in a publication ready form.

At the end of the course each student will meet the expectations of pharmaceutical industry in this area.

5. Course Outline:

The course is divided into the following 14 chapters:

1.	DRUG DISCOVERY AND DRUG DESIGN	
1.1	What is a drug?	1/1
1.2	The role of drugs in the practice of medicine	1/5
1.3	The role of Pharmaceutical Chemistry	1/8
1.4	The history of Pharmaceutical Chemistry	1/8
1.5	Natural substances as drugs,	1/9
1.6	Modern drug design: What requirements must a drug fulfill?	1/15
1.7	Stages and cost of modern drug design	1/22
1.8	Tools and teams in modern drug design	1/27
1.9	The role of Computational Chemistry in drug design	1/29
1.10	Drug Discovery - Filtering out Failures	1/30
1.11	Rational Molecular Design in Drug Research	1/36

2.	COMPUTER ASSISTED DRUG DESIGN (CADD)	
2.1	What is CADD? - Explanation of some basic terms	2/1
2.2	Pharmacophore, Lock-Key principle and induced fit theory	2/2
2.3	Molecular Recognition and Molecular Docking	2/20
2.4	What makes a compound bioactive?	2/22
2.5	The objects of CADD and Molecular Modeling	2/23
2.6	What are the driving forces of Receptor-Drug interactions?	2/29
2.7	Solvent modeling - the role of water	2/37
2.8	The dynamic aspect of modeling	2/45
2.9	How did CADD develop?	2/46
2.10	What are the techniques and concepts used in CADD and Molecular Modeling?	2/48
3.	MOLECULAR MECHANICS (MM)	3/1
3.1	Basic considerations concerning force fields	3/6
3.2	The concept of the force field in MM: historical development	3/18
3.3	Transferability of force fields	3/20
3.4	The energy expression in MM	3/21
3.5	Nonbonded interaction potential	3/31
3.6	H-bonding	3/53
3.7	Cross term potentials	3/57
3.8	Parametrization of a Force Field	3/60
3.9	Force field energies	3/65
3.10	Determination of energy and geometry	3/73
3.11	Differences between spectroscopic and MM force fields	3/79
3.12	Classification of force fields	3/82
3.13	List of force fields presently in use	3/83
3.14	Generic Force Fields	3/87
3.15	Treatment of long range Coulomb Forces	3/89
3.16	Applicability and limitations of a MM approach	3/91
3.17	Extension of MM: Description of p-conjugated molecules	3/93
3.18	QM/MM methods	3/96
4.	SIMULATION OF MACROSCOPIC PROPERTIES	4/1
4.1	Basic terms from statistical mechanics	4/4
4.2	Searching phase-space and generating an ensemble	4/11
4.3.	Monte Carlo (MC) methods (Random Methods I)	4/13
4.3.6	Metropolis MC method	4/21
4.4	Random methods without V: Distance Geometry and NMR Spectroscopy (Random methods II)	4/23
4.4.1	Nuclear Overhauser Effect (NOE)	4/24
4.4.2	Karplus Curves and NMR spin-spin coupling constants	4/28
4.4.3	Basic considerations concerning DG	4/29
4.5	MD simulation methods	4/39
4.5.1	Basic considerations	4/39
4.5.2	Practical Aspects of a MDS calculation	4/43
4.5.3	Verlet method	4/48
4.5.4	Leapfrog method	4/51
4.5.5	Constrained Verlet: SHAKE method	4/52
4.5.6	Different types of MDS	4/55
4.5.7	Constant-T methods	4/56
4.5.8	Constant-P methods	4/58
4.5.9	Stochastic dynamic simulations	4/60
4.5.10	Boundary conditions	4/61
4.5.11	Quantities calculated	4/65
4.5.12	Radial Distribution function	4/66
4.5.13	Calculation of time-dependent properties	4/67
4.5.14	History of MDS	4/69

4.6	Calculation of the Free energy	4/70
4.6.1	Why is it difficult to calculate A, G, and S?	4/71
4.6.2	The coupling parameter approach	4/74
4.6.3	The Thermodynamic perturbation method	4/78
4.6.4	The Thermodynamic integration method	4/81
4.6.5	The potential of mean force	4/82
4.6.6	Free energy differences and the thermodynamic cycle	4/83
4.6.7	Beyond the free energy: Entropy and enthalpy	4/86
4.6.8	Practical considerations	4/87
4.6.9	Recommendations	4/90
5.	MOLECULAR MODELING AND MOLECULAR GRAPHICS	
5.1	Historical overview	5/2
5.2	Development of computer graphics	5/3
5.3	Graphical representation of molecules: Standard models	5/6
5.4	Graphical representation technologies	5/7
5.5	Simplified molecular representations	5/8
5.6	Molecular surfaces	5/9
5.6.1	Corey-Pauling-Koltun (CPK) or van der Waals surface	5/9
5.6.2	The Solvent accessible surface (SAS)	5/11
5.6.3	Solvent excluded surface - Conolly surface	5/13
5.6.4	Surfaces of macromolecules	5/14
5.6.5	The electron density surface	5/14a
5.7	Molecular volume	5/15
5.8	Molecular superposition and molecular similarity	5/18
5.9	Molecular skin	5/21
5.10	Mapping of information on molecular surfaces	5/22
5.10.1	The lipophilicity potential	5/22
5.10.2	The electrostatic potential	5/22
5.11	Molecular shape descriptors	5/24
6.	CONFORMATIONAL SEARCHING	6/1
6.1	Conformations of biomacromolecules	6/3
6.2	Systematic search methods	6/14
6.3	Random search methods	6/18
6.3.1	Genetic algorithms	6/19
6.3.2	Distance geometry	6/22
6.3.3	Metropolis Monte Carlo	6/22
6.4	MDS-based methods	6/23
6.4.1	Simulated annealing (SA)	6/23
6.4.2	Structure refinement by simulated annealing	6/25
6.4.3	Crystallographic refinement	6/25
6.4.4	NMR structure refinements	6/29
7.	CHEMOMETRICS	7/1
7.1	Origin and current status	7/1
7.2	Multivariate Data	7/3
7.2.1	Definitions	7/3
7.2.2	Organization and classification of data	7/4
7.2.3	Preprocessing	7/5
7.2.4	Distances between objects	7/6
7.2.5	Latent variables	7/8
7.3	Linear Methods	7/8
7.3.1	Projection of multivariate data	7/8
7.3.2	Principal component analysis (PCA)	7/11
7.3.3	Multiple linear regression (MLR) and principle component regression (PCR)	7/12
7.3.4	Partial least squares method (PLS)	7/14

7.4	Non-linear methods	7/16
7.4.1	An example for non-linear models	7/17
7.5	Modeling methods	7/18
7.5.1	SIMCA principle component modeling	7/19
7.5.2	Classification methods	7/21
7.5.3	Factor analysis	7/23
7.5.4	Cluster analysis	7/25
7.5.5	Linear discriminant analysis (LDA)	7/29
7.6	Validation tools	7/30
7.6.1	Cross-validation	7/30
7.6.2	Bootstrapping	7/31
7.6.3	Frequently used statistical indices	7/32
7.6.4	Cross-validation in PLS	7/34
7.6.5	Chance effects and chance correlation	7/35
8.	ARTIFICIAL NEURAL NETWORKS (ANN)	8/1
8.1	Background and basics of ANN	8/1
8.2	What can neural networks do?	8/1
8.2.1	Artificial neuron	8/4
8.2.2	Net input, net and weight	8/5
8.2.3	How to get the best weights?	8/6
8.2.4	Transfer functions in neurons	8/8
8.2.5	Bias	8/9
8.2.6	Linking neurons to networks	8/10
8.3	Architecture	8/12
8.4	The Kohonen network	8/13
8.4.1	Special characteristics	8/13
8.4.2	Competitive learning	8/14
8.4.3	An example: mapping from 3 to 2 dimensions	8/16
8.5	Counterpropagation	8/20
8.5.1	Supervised competitive learning	8/20
8.6	Error-backpropagation learning	8/23
8.7	When is the training finished?	8/30
8.7.1	Overtraining	8/30
8.8	Applications of ANNs in Drug design	8/31
8.8.1	ANN in Quantitive structure activity relationships	8/32
8.8.2	ANN to determine the secondary structure of proteins	8/37
8.8.3	Kohonen maps of the electrostatic potential	8/43
9.	LIPHILICITY AND PARTITION COEFFICIENT (LOG P)	
9.1	Factorization of molecular lipophilicity	9/4
9.2	1D-approaches for calculating partition coefficients	9/6
9.2.1	Substituent constants of Hansch and Fujita	9/6
9.3	2D-approaches for calculating partition coefficients	9/7
9.3.1	Methods based on fragmental constants and correction factors	9/8
9.3.2	Method of Leo and Hansch (CLOGP)	9/11
9.3.3	Klopman's method (CASE)	9/14
9.3.4	Methods based on fragmental constants only	9/15
9.3.5	Methods based on global two-dimensional structural properties	9/17
9.4	3D- approaches for calculating partition coefficients	9/20
9.4.1	Solvent-accessible surface areas (SASA)	9/21
9.4.2	MO calculations and Bodor's method (BLOGP)	9/24
9.4.3	Methods based on molecular fields: the lipophilicity potential (MLP)	9/26
9.5	4D- approaches for calculating partition coefficients	9/28
9.5.1	Methods based on an ensemble of conformers	9/28
9.5.2	Methods based on direct computation	9/29
9.5.3	Methods based on a continuum solvation model	9/30

9.5.4	Methods based on free energy perturbation methods	9/31
9.6	Comparison of the accuracy of different methods	9/32
9.7	Examples from drug design	9/35
9.8	Summary of computer programs	9/37
9.9	Concluding remarks	9/39
10.	2D-QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS (2D-QSAR)	
10.1	Definition	10/1
10.2	QSAR methodology	10/2
10.2.1	Historical background	10/2
10.3	Basic concepts of QSAR	10/6
10.3.1	Hansch analysis	10/7
10.3.2	Free-Wilson analysis	10/8
10.3.3	An example: Adrenergic activities of N,N-di-methyl-a bromophenethylamines	10/8
10.4	Molecular descriptors	10/11
10.4.1	Electronic parameters	10/11
10.4.2	Polar interactions	10/11
10.4.3	Steric parameters	10/11
10.4.4	Topological parameters	10/12
10.4.5	Quantum-chemical descriptors	10/13
10.5	Biological parameters	10/16
10.6	2D-QSAR in drug design	10/17
10.6.1	Transport and distribution of drugs in biological systems	10/17
10.6.2	Enzyme inhibition	10/20
10.6.3	Model system for cysteine protease	10/21
10.6.4	Prediction of mutagenic potencies	10/22
10.6.5	QSAR for antimalarial compounds	10/22
10.6.6	β_1 - and β_2 - antagonist activities	10/23
10.6.7	Activity-activity relationships	10/24
10.7	Validation of QSAR models	10/25
10.8	Conclusions	10/26
11	3D-QSAR; COMPARATIVE MOLECULAR FIELD ANALYSIS (CoMFA) and - SIMILARITY ANALYSIS (CoMSIA)	
11.1	3-QSAR	11/1
11.2	Assumptions in 3D-QSAR	11/2
11.3	CoMFA methodology	11/3
11.4	Steps of a CoMFA analysis	11/4
11.4.1	Pharmacophore hypothesis and alignment	11/6
11.4.2	Superposition of all molecules	11/7
11.4.3	Box, Grid size and 3D field calculations	11/8
11.4.4	Derivation of the CoMFA model	11/9
11.4.5	CoMFA coefficient maps	11/10
11.4.6	Validation of results	11/11
11.5	An example: CBG and TBG binding affinities of steroids	11/12
11.6	CoMFA application in drug design, overview	11/14
11.7	Conclusions on CoMFA	11/15
11.8	Comparative molecular similarity analysis (CoMSIA)	11/17
11.8.1	Definition of similarity indices	11/19
11.8.2	Similarity fields	11/19
11.9	An example: benzamidine inhibitors binding to trypsin, thrombin, and factor Xa	11/20
12.	CADD: METHODS and STRATEGIES	
12.1	Lead discovery	12/4
12.2	Irrational drug design and combinatorial chemistry	12/7

12.3	Virtual screening	12/16
12.4	Structure-based ligand design: Pharmacophore generation	12/27
12.4.1	Structure-based ligand design	12/28
12.4.2	Determination of a pharmacophore	12/28
12.4.3	The active analog approach (AAA)	12/31
12.4.4	Ensemble distance geometry	12/33
12.4.5	Ensemble molecular dynamics	12/35
12.4.6	Pharmacophores by clique detection	12/37
12.4.7	Pharmacophore representation	12/39
12.5	Molecular recognition	12/41
12.6	Molecular docking	12/43
12.7	De Novo design of ligands	12/45
12.7.1	Analysis of the receptor: Generation of a constraints model	12/47
12.7.2	Structure generation methods	12/50
12.7.3	Structure evaluation	12/54
12.7.4	When does one use de Novo design?	12/55
12.8	Peptides and peptide analogs as drugs: Peptidomimetics	12/58
13.	PROTEIN MODELING	13/1
13.1	The Protein Data Bank (PDB)	13/2
13.2	Relationship between sequence and 3D structure of a protein	13/4
13.3	Alignment of protein sequences	13/6
13.3.1	Needleman-Wunsch alignment method	13/7
13.3.2	Multiple sequence alignments (MSA)	13/9
13.4	Homology modeling of proteins	13/10
13.4.1	Construction of the core	13/10
13.4.2	Construction of loops and turns	13/11
13.4.3	Construction of the Side chains	13/12
13.4.4	Refinement of the homology model	13/12
13.5	Prediction of protein structures by threading	13/14
13.6	Comparison of various strategies in homology modeling	13/15
13.7	Protein folding	13/17
13.7.1	Thermodynamics of protein folding	13/16
13.7.2	Levinthal's paradox and the kinetics of protein folding	13/17
14.	PRESENT and FUTURE PERSPECTIVES OF DRUG DESIGN	
14.1	Successes of CADD	14/1
14.2	Genetechnology and drug design	
14.3	Bioinformatics	
14.4	Future developments	

The lectures are complemented by a series of computer labs using the TRIPOS-SYBYL software, the state-of-the-art-modeling software used in pharmaceutical industry.

6. Student Responsibilities:

We are planning to have a quiz after every second chapter. Therefore, it is recommended that each student actively participate in the lectures. The student has to hand in a lab report for each computer lab along the lines described in the lab instructions. Each quiz and lab report will count toward the final grade. Questions regarding grades should be brought to the instructor's attention within one week after receiving back the exam.

7. Final Examination: TBD**8. Grading Procedures:**

Final grades will be calculated according to the following scheme:

Final exam 40%

Quizzes 30%

Lab reports 30%

Grading Table	A	100 – 90 %
	B	89 – 80 %
	C	79 – 70 %
	D	69 - 60 %
	F	59% and below

9. Statement of Honor Code:

All SMU Dedman College students are bound by the honor code. The applicable section of the code reads: "All academic work undertaken at the University shall be subject to the guidelines of the Honor Code. Any giving or receiving of aid on academic work submitted for evaluation, without the express consent of the instructor, or the toleration of such action shall constitute a breach of the Honor Code." A violation of the Code can result in an F for the course and an Honor Code Violation recorded on a student's transcript. Academic dishonesty includes plagiarism, cheating, academic sabotage, facilitating academic dishonesty and fabrication. Plagiarism is prohibited in all papers, projects, take-home exams or any other assignments in which the student submits another's work as being his or her own. Cheating is defined as intentionally using or attempting to use unauthorized materials, information or study aids in any academic exercise. Academic sabotage is defined as intentionally taking any action, which negatively affects the academic work of another student. Facilitating academic dishonesty is defined as intentionally or knowingly helping or attempting to help another to violate any provision of the Honor Code. Fabrication is defined as intentional and unauthorized falsification or invention of any information or citation in an academic exercise.

10. Disability Accommodations:

Students needing academic accommodations for a disability must first contact Ms. Rebecca Marin, Director, Services for Students with Disabilities (214-768-4557) to verify the disability and establish eligibility for accommodations. They should then schedule an appointment with the professor to make appropriate arrangements.

11. Religious Observance:

Religiously observant students wishing to be absent on holidays that require missing class should notify their professors in writing at the beginning of the semester, and should discuss with them, in advance, acceptable ways of making up any work missed because of the absence.

12. Excused Absences for University Extracurricular Activities:

Students participating in an officially sanctioned, scheduled University extracurricular activity should be given the opportunity to make up class assignments or other graded assignments missed as a result of their participation. It is the responsibility of the student to make arrangements with the instructor prior to any missed scheduled examination or other missed assignment for making up the work.

13. Assessment:

In accordance with University regulations copies of student work may be retained to assess how the learning objectives of the course are being met.

14. Course Schedule:

Will be discussed in the first meeting worked out to accommodate best to the student needs.