PHAR40100 Medicines into Practice

Option 1: *"Advanced methods in the discovery, development and characterisation of small molecule drugs"* (horizontal subunit)

or "Drug DDC" for short…

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Aims of Drug DDC

- To provide students with an understanding of the advanced computational, analytical and synthetic chemistry techniques to produce, optimise and characterise small-molecule drugs.
- To provide students with the opportunity to apply their knowledge of drug discovery concepts to specific disease areas via integrated activities.

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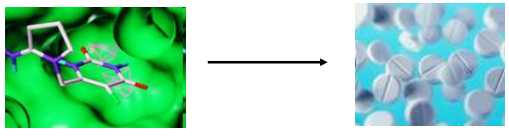
- GPhC 10.1(e) Outcomes: a professional pharmacist should be able to "demonstrate how the science of pharmacy is applied in the design and development of medicines and devices."



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Drug DDC: Lecture outline

Wks1-4, Tues 10-12 in Humanities Bridgeford St Building, G33;
Wks1-4, Wed 10-12 in Kilburn Building, 1.4
Four subsections:

- **Computational Drug Discovery** (Dr Bryce)
  - 6 lectures (weeks 1-2)
- **3D Target Structure Determination** (Dr Bichenkova)
  - 3 lectures (week 2-4)
- **Drug Screening** (Dr Bichenkova)
  - 3 lectures (weeks 2-3)
- **Multi-omics** (Prof Nicolaou)
  - 3 lectures (week 4)

4

Drug DDC LECTURE TIMETABLE
Week 1
Tues 25 Sep
10am - Introduction (RB)
11am - Conformational searching (RB)
Wed 26 Sep
10am - Virtual screening (RB)
11am - Problems in modelling (RB)
Week 2
Tues 2 Oct
10am - De novo design (RB)
11am - 3D QSAR (RB)
Wed 3 Oct
10am - Multidimensional NMR (EB)
11am - X-ray crystallography (EB)

5

Week 3
Tues 9 Oct
10am - Fragment-based approaches in drug discovery (EB)
11am - SAR by NMR (EB)
Wed 10 Oct
10am - Enzyme inhibition assays (EB)
11am - Fragment-based screening by X-ray and NMR: CASE STUDIES (EB)
Week 4
Tues 16 Oct
10am – Multi-omics [1] (AN)
11am - Multi-omics [2] (AN)
Wed 17 Oct
10am – Multi-omics [3] (AN)
11am - Revision session (EB,RB)

6

Computational Drug Discovery

Dr. Bryce, 6 lectures
Room 2.031, r.a.bryce@manchester.ac.uk

Aim

to provide you with an understanding of the role of molecular modelling in the process of rational design of small-molecule drugs, with an appreciation of its strengths and limitations

Objectives

By the end of this subsection, you should be able to:

1. describe briefly the sources from which **drug leads** are obtained

2. outline the concept of structure-based drug design and within this, the role of **molecular modelling**

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3. discuss the key molecular modelling technique of **conformational searching**, which includes the concept of a potential energy surface; the force field method to score geometry through the calculation of energy; and three approaches to exploration of conformation (energy minimisation, Monte Carlo simulation, molecular dynamics)

4. describe **virtual screening** approaches based on molecular docking and/or a pharmacophore; consider the content of compound libraries used for virtual screening; discuss how some common problems in virtual screening are addressed, in regard to scoring function, receptor availability and receptor flexibility.

5. appreciate the principles, strengths and limitations of computer-based **de novo design methods** that use active site analysis and connection methods.

6. Discuss the **3D QSAR** approach to computational design.

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Recommended reading

G.L. Patrick. *An Introduction to Medicinal Chemistry* (Oxford University Press, 5th ed., 2005), Chs. 12, 17 and 18. ISBN 978-0-19-969739-7

J.M.Goodman. *Chemical Applications of Molecular Modelling* (RSC, 1998), ISBN-10: 0854045791

A.R.Leach. *Molecular Modelling: Principles and Applications*, 2nd Ed. (Longman, 2001), ISBN-10: 0582382106

Assessment of Drug DDC

2 hour on-line exam in January:

- 1 hour on Drug DDC (25%)
- 1 hour on Vertical subunit (25%)

2000-word Integrated Analysis, for end of Week 11 (30%)

Group presentation in Week 9 (20%)

(note, Med Chemists will do the exam but instead of the Integrated Analysis and Group presentation, submit a 2000-word Essay for mid-Week 12)

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Integrated drop-in tutorials

Weeks 5,7,8,10-11 Wed 10-12 (Venues will be on Bb; some Tuesdays for "Drug DDC/Cancer" option)

DRUG DDC with Vertical Options…

1: TREATMENT AND PATHOGENESIS OF MICROBIAL DISEASES
- Freeman and Ledder

2: CANCER BIOLOGY AND THERAPY
- Bryce and Demonacos [Integrated Analysis will be in the form of a research proposal]

3: NEUROPSYCHOPHARMACOLOGY
- Bichenkova and Harte

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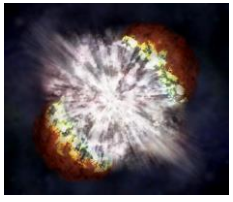

Where do drug leads come from?

1. introduction

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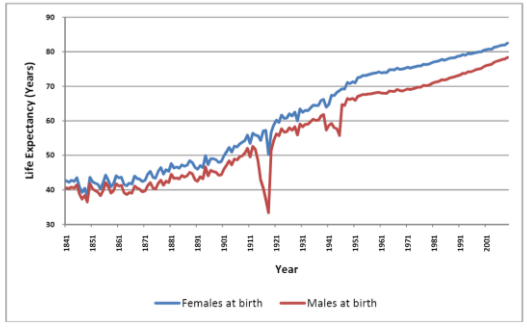
1. Introduction

- Modern medicine - a profound effect on health



Source: England and Wales, Total Population, Life tables (period 1x1), Males and Females. Last modified: 03-Nov-2010, MPv5 (May07).

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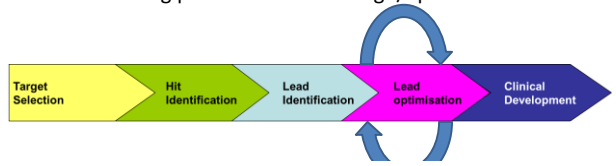
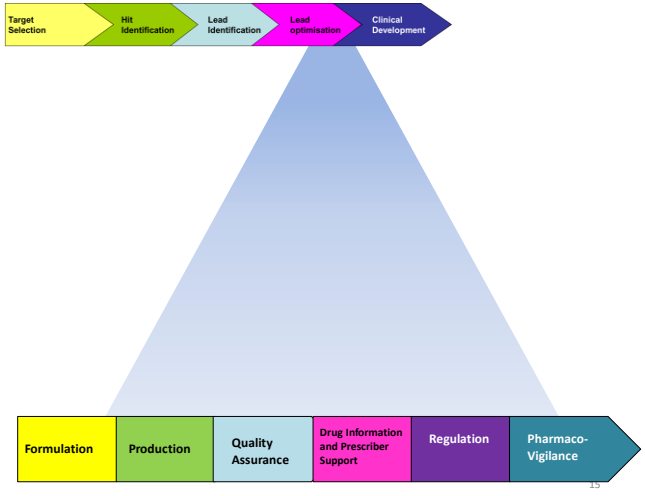
1.1 "Where do drug leads come from?"

lead molecule:

- interacts with target
- therapeutically useful effect
- novel
- patentable
- synthetically accessible
- not a drug (yet)
- suitable starting point for further design/optimisation





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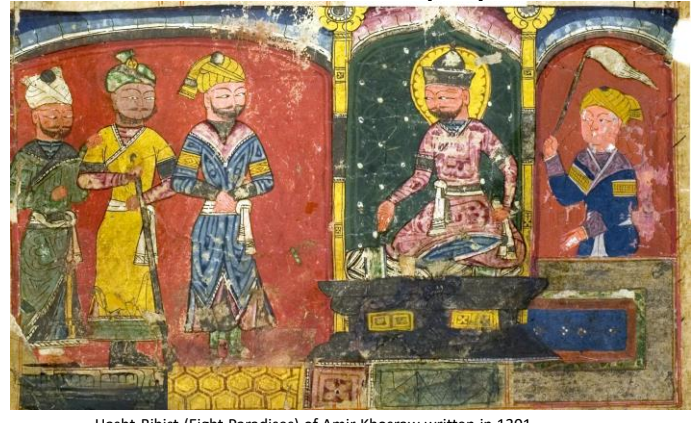
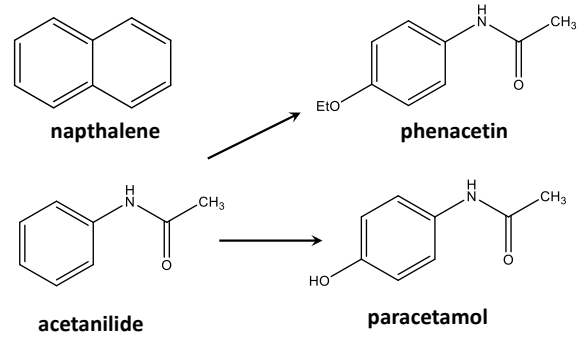
1.1.1. Serendipity



Hasht-Bihist (Eight Paradises) of Amir Khosraw written in 1301

Paracetamol

- Chance and the prepared mind…?



1.1.2. Natural products

Morphine (analgesic)

opium poppy

Quinine (antimalarial)

Cinchona bark

Natural products

Digitoxin (heart disease)

foxglove leaves

Reserpine (blood pressure)

rauwolfia root

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Natural products

Taxol (antitumour)

bark of Pacific yew

Artemesinin (antimalarial)

qinghaosu

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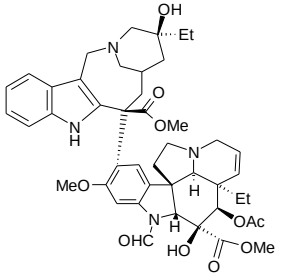
1.1.3. Natural product screening

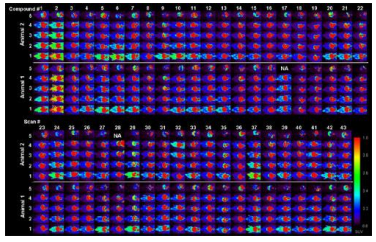


vincristine (anti-cancer)

Vinca plant (periwinkle)

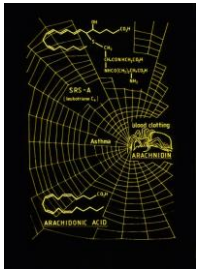
1.1.4. Screening of synthetic libraries

- Large libraries of small-molecule compounds held by pharmaceutical companies
  - can be screened against biological targets rapidly using High-Throughput Screening (HTS) technology



1.1.5. Ethnopharmacology

- examine compounds intuitively considered to resemble (even slightly) a compound with some biological activity



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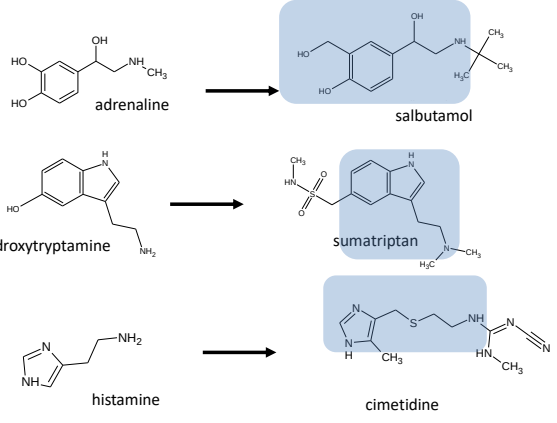
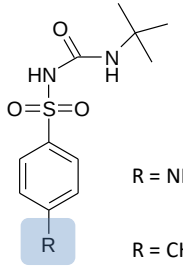
1.1.6. Analogy



1.1.7. Enhance a side-effect

- some molecules known to have more than one pharmacological effect, ie. “side effects”
- design out unwanted activity



R = NH_2 carbutamide

R = CH_3 tolbutamide

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Another way?

Go deeper: **Patrick, Medicinal Chemistry, Ch. 12**

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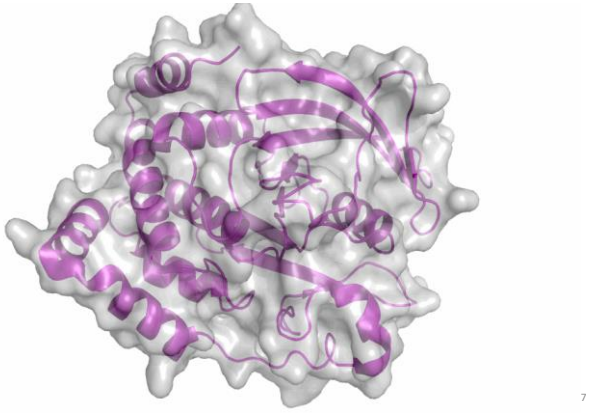
2. Structure-based drug design



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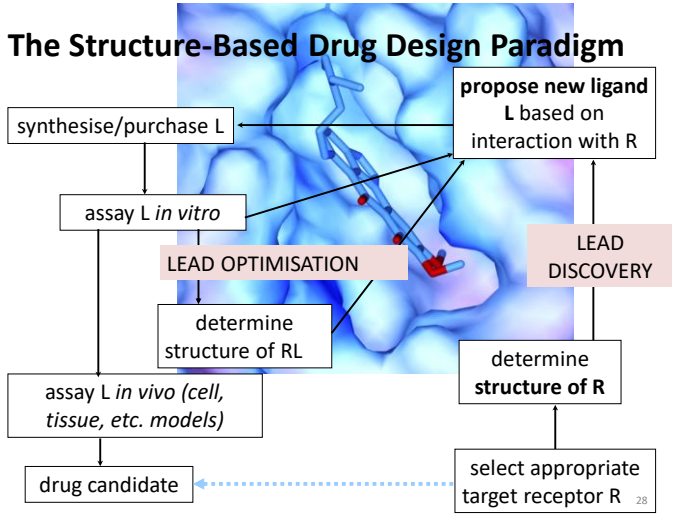

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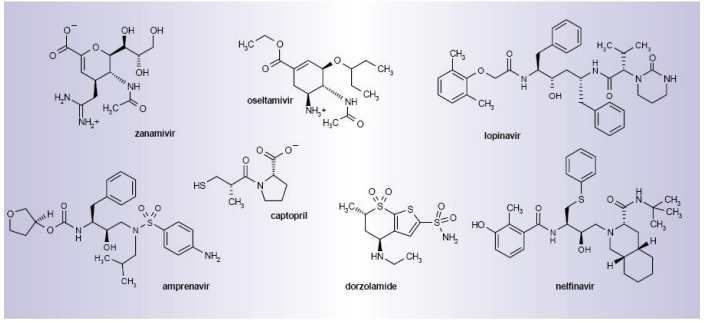
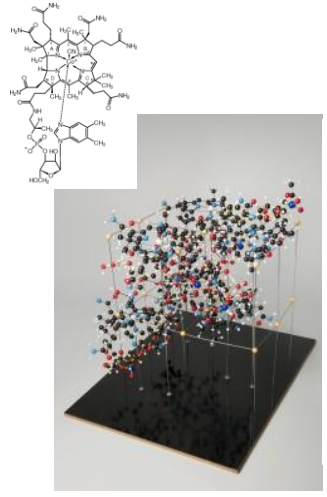
A paradigm that works…



Approved and marketed drugs whose discovery has been aided by 3D structure of the receptor (*Curr Drug Discov*, Dec 2003, p19)



X-ray structure of Vitamin B_{12} (MW = 1355 g/mol)

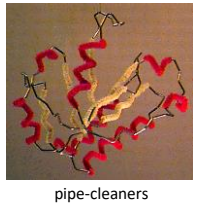
Ribosome (MW = 1404953 g/mol)

Cromemco personal computer (1980s), 4 MHz

Intel Haswell chip, 4000 MHz

2.1. Molecular modelling

- Definition
- Types
- Uses



pipe-cleaners

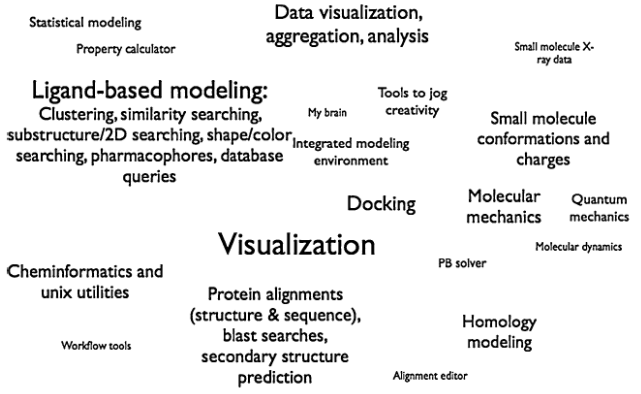
Basmati rice

GSK survey of computational chemists

''What one or two or three programs would cause you to do me *bodily harm* if I were to take that software away from you?''

J Comput Aided Mol Des **26**, 2010, 51

Word cloud of responses…



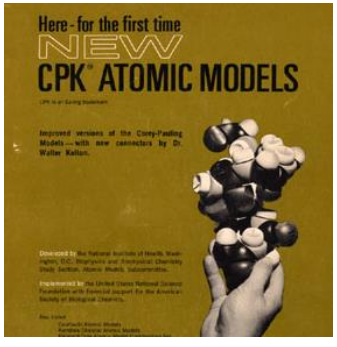
J Comput Aided Mol Des **26**, 2010, 51

2.2. Molecular Graphics

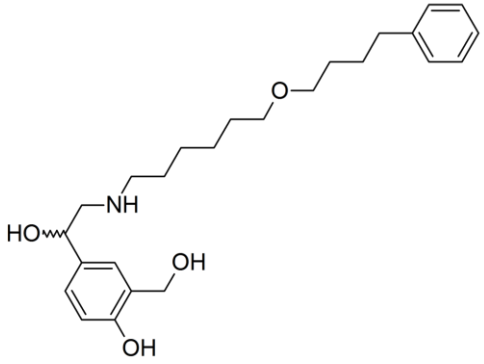
Molecular Graphics and Modelling Society
www.mgms.org

Corey-Pauling-Koltun (CPK) models

- "space-filling" (1960)



Salmeterol



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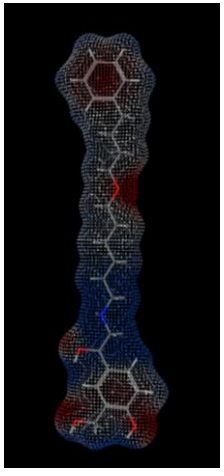
Compute properties



Red = partially negatively charged

Blue = partially positively charged

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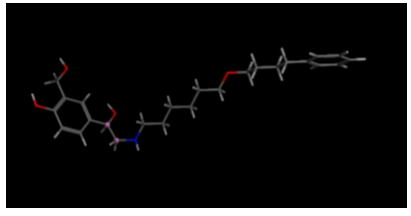
Evaluate different conformations



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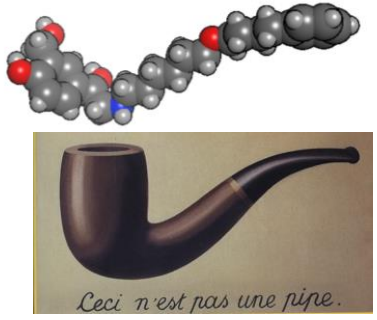

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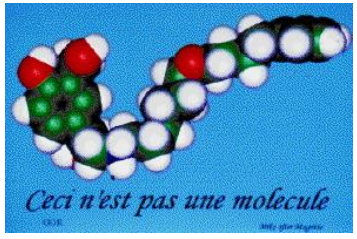

"*Ceci n'est pas une molecule*," writes Mike Hann (1994), "serves to remind us that all of the graphics images presented here are not molecules, not even pictures of molecules, but pictures of icons which we believe represent some aspects of the molecule's properties."

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3D printed models

http://mgl.scripps.edu/

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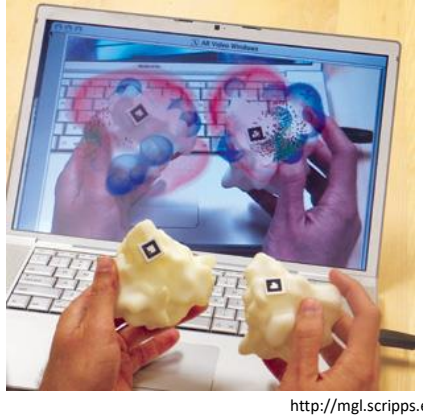
Augmented reality



http://mgl.scripps.edu/

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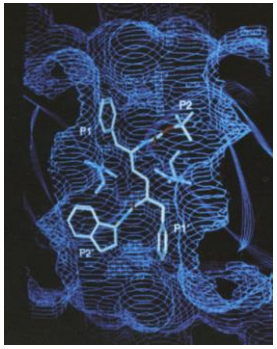
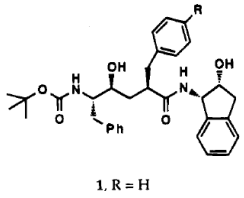
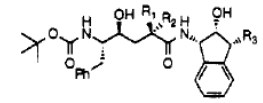
2.3. Graphics for drug design

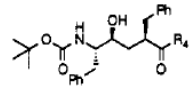
- HIV-1 protease inhibitors (Merck, 1995)

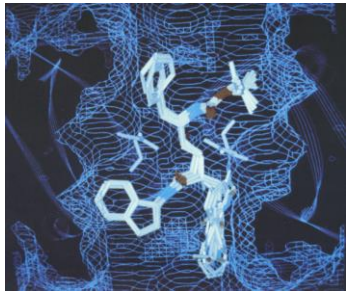


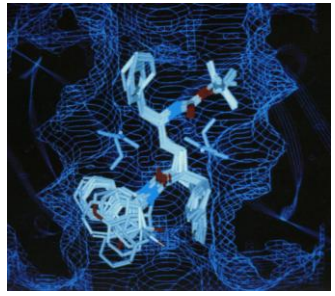


J. Med. Chem. 1995,38, 305-317 55

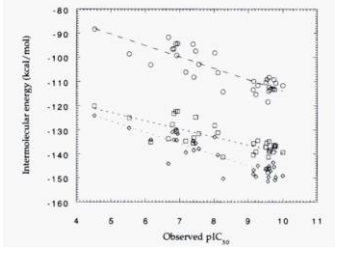


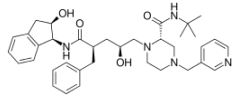






Indinavir





J. Med. Chem. 1995,38, 305-317

Manual docking

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To appreciate how things work…

60

…we need to look at the engine

61

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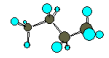
Molecular modelling: under the bonnet

3. conformational analysis

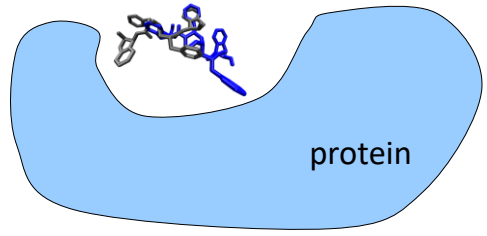
3. Conformational analysis

Identify most likely shape(s) of a molecule or set of molecules

- eg. conformation of a ligand



- eg. orientation of ligand in protein active site



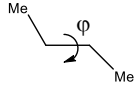
3.1. Most likely shape of a molecule has lowest potential energy

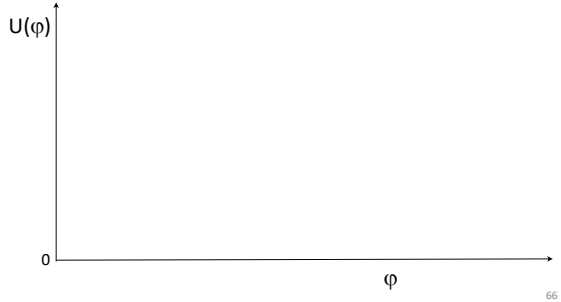
- eg. H_2 molecule geometry

- A plot of potential energy against geometry is called a “potential energy surface”

1D potential energy surface

- eg. butane conformation

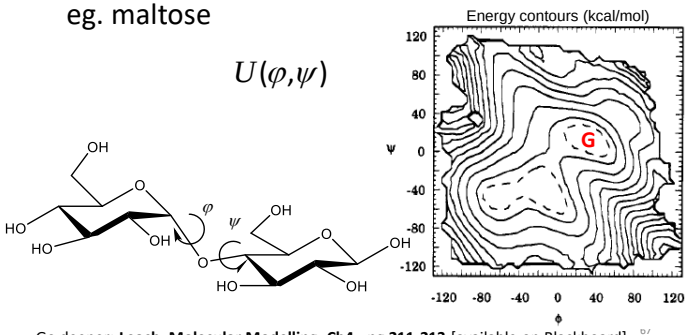




2D potential energy surface

- can study many coordinates simultaneously eg. maltose

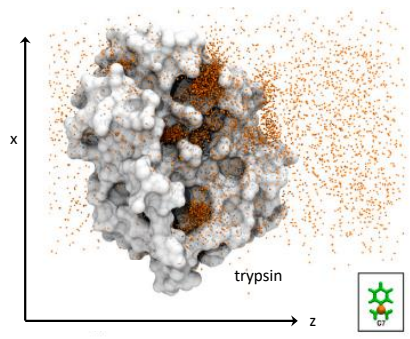
$U(\varphi,\psi)$

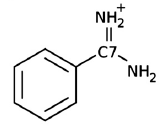


Go deeper: **Leach, Molecular Modelling, Ch4., pg 211-213** [available on Blackboard]

Apply same idea to ligand-protein geometry

- consider 2D binding energy surface for binding

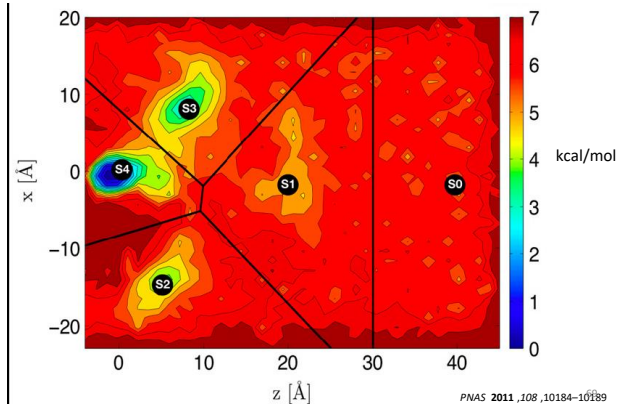




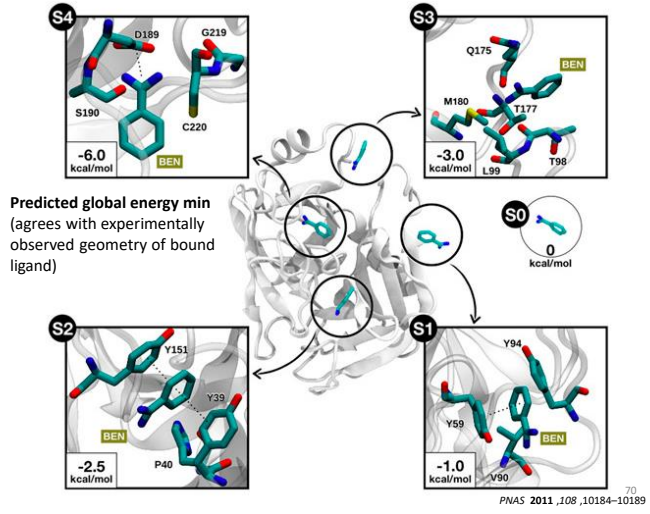
benzamidine

PNAS **2011** ,*108* ,10184–10189

2D binding energy surface



PNAS **2011** ,*108* ,10184–10189



Predicted global energy min (agrees with experimentally observed geometry of bound ligand)

PNAS **2011** ,*108* ,10184–10189

Conformational analysis

- require two ingredients:
- (a) *searching*: a strategy to generate/explore different conformations

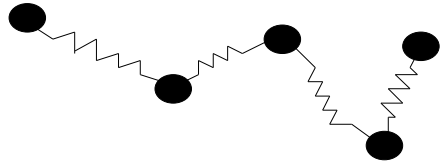
- (b) *scoring*: an ability to evaluate the potential energy U for a given conformation

3.2. Scoring: calculation of energy, U

Modelling methods often use *molecular mechanics* (MM) to calculate a molecule's potential energy

- otherwise known as a "force field"

• treat nuclei and electrons as atoms, connected by springs



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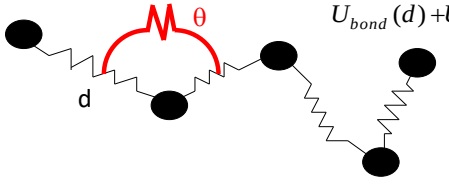
A molecule modelled by MM

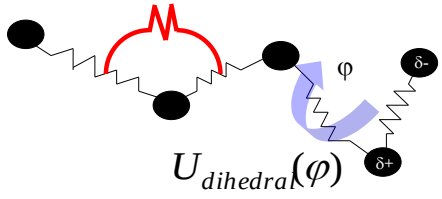
"bonded terms" – for atoms up to 3 covalent bonds apart: *(1) bond length and angle stretching*



75

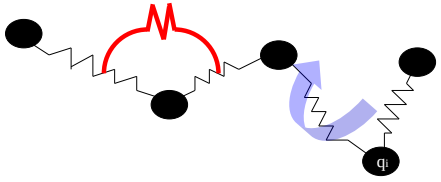
A molecule modelled by MM

"bonded terms" – atoms up to 3 covalent bonds apart *(2) rotations about single bonds*



76

A molecule modelled by MM



- can place partial charges **q**ᵢ on all atoms to mimic distribution of charge in the molecule

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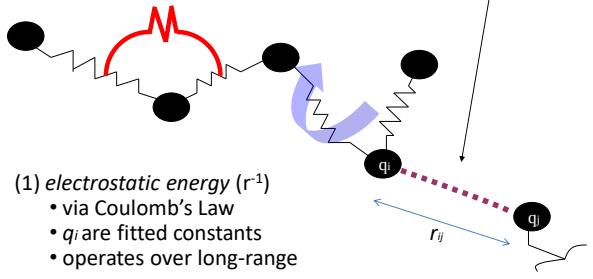
Then two (or more) molecules can interact electrostatically:

"nonbonded interactions"
- for atoms > 3 bonds apart

$$U_{elec}(r_{ij}) = \sum_{i,j}^{atoms} \frac{q_i q_j}{r_{ij}}$$



(1) *electrostatic energy* (r^{-1})
- via Coulomb's Law
- q_i are fitted constants
- operates over long-range

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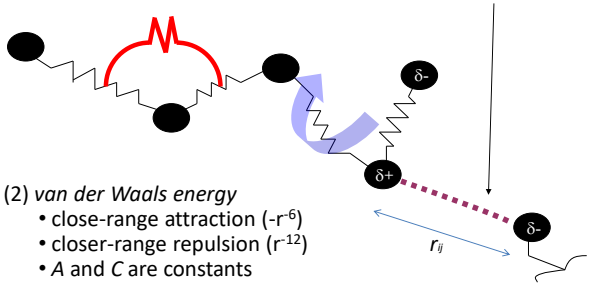
- can also add a short-range van der Waals interaction:

"nonbonded interactions"

$$U_{vdw}(r_{ij}) = \sum_{i,j}^{atoms} \left(\frac{A}{r_{ij}^{12}} - \frac{C}{r_{ij}^{6}} \right)$$



(2) *van der Waals energy*
- close-range attraction ($-r^{-6}$)
- closer-range repulsion (r^{-12})
- *A* and *C* are constants

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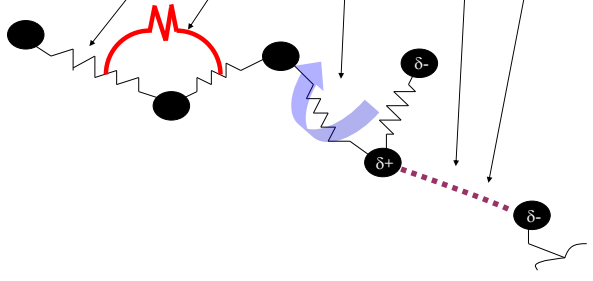
Using MM, total potential energy of a molecule or molecules:

$$U_{total} = U_{bond}(d) + U_{angle}(\theta) + U_{dihedral}(\varphi) + U_{vdw}(r_{ij}) + U_{elec}(r_{ij})$$



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Molecular mechanics force field

Total MM potential energy is sum of parts:

$$U_{tot}(d,\theta,\varphi,r_{ij}) = U_{bond}(d) + U_{angle}(\theta) + U_{torsion}(\varphi)$$
$$+ \sum_{i,j}^{atoms}\left(\frac{A}{r_{ij}^{12}} - \frac{C}{r_{ij}^{6}}\right) + \sum_{i,j}^{atoms}\frac{q_i q_j}{r_{ij}}$$

eg. most widely used are the AMBER, CHARMM and GROMOS force fields

Molecular Mechanics

approximations
- considers atoms, not electrons and nuclei
- relies heavily on parameters eg. *A*, *C*, q_i

limitations
- need new parameters for new types of molecule
- cannot treat chemical reactions

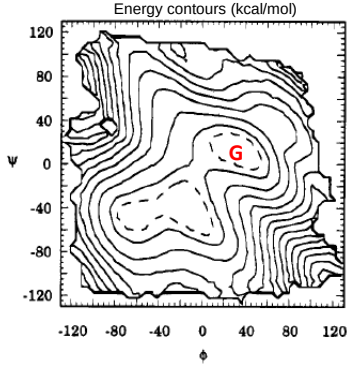
advantages
- can treat very large systems, up to 10^6 atoms
- can be accurate if used in right context (i.e. appropriate to parametrization)

Go deeper: **Goodman, Chemical Applications of Molecular Modelling, Ch. 2** [available on Blackboard]

3.3. Searching molecular conformation

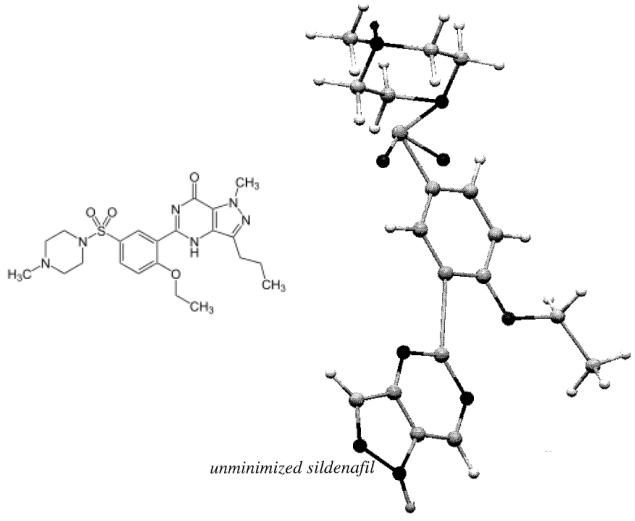
– e.g. of a molecule from 2D sketch/database

– having defined a potential energy U, we can *explore the potential energy surface* to find the lowest energy point **G** which corresponds to the most likely structure of the molecule(s)



3.3.1. Energy minimisation

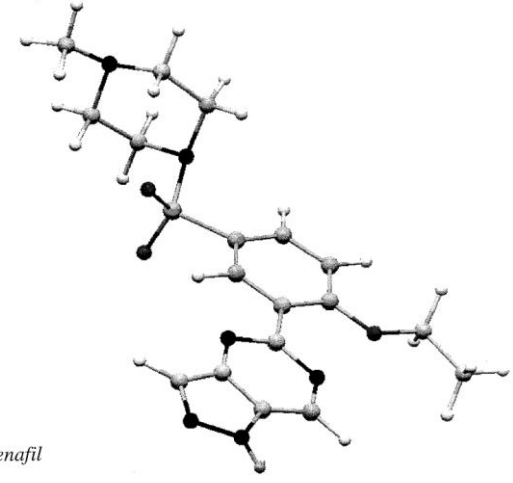
- will find the nearest minimum on PES by using the gradient of U for direction (use –g)
  – gradient, g = first derivative of U with respect to geometric coordinate, x = dU/dx



unminimized sildenafil

```
min.mi       Fri Mar 16 14:36:33 2001      1
 STRT  001 BatchMin V7.0.0  dynamic  16-Mar-2001 09:50:44
 STRT  002 Reading [illegible]...
 STRT  003 Generating interactions...
 STRT  004 Loading parameters from force field...
 FFLD  002 WARNING - Conformational Energies May Not Be Accurate
 FFLD  001 Low quality force field parameters in use:
 FFLD  001 Number of low quality stretches, bends & torsions =   2  11  45
 STRT  005 Simulation initiated...
 MINI  010                 Total Energy = 0.113468E+05 kJ/mol
 MINI  011                      Stretch = 0.3405812E+04 kJ/mol
 MINI  012                         Bend = 0.2596178E+04 kJ/mol
 MINI  013                      Torsion =-0.2216741E+02 kJ/mol
 MINI  014           Improper Torsion = 0.6215879E-09 kJ/mol
 MINI  015                          VDW = 0.5499671E+04 kJ/mol
 MINI  016               Electrostatic =-0.9666096E+02 kJ/mol
 MINI  017 Explicit Hydrogen Bonds = 0.0000005E+00 kJ/mol
 MINI  021                 Cross Terms =-0.1593749E+03 kJ/mol
 MINI  040  No more updates
 MINI  003 Iter    10  Movt 1.528310A  Energy    1859.826 kJ/mol
 MINI  006 Regenerating nonbonded interactions
 MINI  003 Iter    20  Movt 1.081557A  Energy    1008.906 kJ/mol
 MINI  006 Regenerating nonbonded interactions
 MINI  003 Iter    30  Movt 1.193944A  Energy     644.992 kJ/mol
 MINI  006 Regenerating nonbonded interactions
 MINI  003 Iter    40  Movt 0.207961A  Energy     589.751 kJ/mol
 MINI  003 Iter    50  Movt 0.224374A  Energy     537.660 kJ/mol
 MINI  003 Iter    60  Movt 0.208284A  Energy     495.205 kJ/mol
 MINI  003 Iter    70  Movt 0.186165A  Energy     461.357 kJ/mol
 MINI  003 Iter    80  Movt 0.168210A  Energy     433.742 kJ/mol
 MINI  006 Regenerating nonbonded interactions
 MINI  003 Iter    90  Movt 0.153031A  Energy     406.079 kJ/mol
 MINI  003 Iter   100  Movt 0.139698A  Energy     387.055 kJ/mol
 MINI  003 Iter   110  Movt 0.127642A  Energy     371.186 kJ/mol
 MINI  003 Iter   120  Movt 0.116667A  Energy     357.937 kJ/mol
 MINI  003 Iter   130  Movt 0.106614A  Energy     346.879 kJ/mol
 MINI  003 Iter   140  Movt 0.097427A  Energy     337.647 kJ/mol
 MINI  003 Iter   150  Movt 0.089063A  Energy     329.930 kJ/mol
 MINI  003 Iter   160  Movt 0.081482A  Energy     323.468 kJ/mol
 ...
 MINI  003 Iter   480  Movt 0.020594A  Energy     276.978 kJ/mol
 MINI  003 Iter   490  Movt 0.020358A  Energy     276.568 kJ/mol
 MINI  003 Iter   500  Movt 0.020135A  Energy     276.168 kJ/mol
 MINI  005 Minimization terminated
 MINI  008 Computing final energy, standby...
 MINI  009 Final Gradient =  0.235E+01 kJ/A-mol     CPU Time =      2.1 sec
 MINI  010                 Total Energy = 0.276033E+03 kJ/mol
 MINI  011                      Stretch = 0.2544936E+02 kJ/mol
 MINI  012                         Bend = 0.7826538E+02 kJ/mol
 MINI  013                      Torsion =-0.3003627E+02 kJ/mol
 MINI  014           Improper Torsion = 0.3454479E+00 kJ/mol
 MINI  015                          VDW = 0.2250946E+03 kJ/mol
 MINI  016               Electrostatic =-0.2798023E+02 kJ/mol
 MINI  017 Explicit Hydrogen Bonds = 0.0000000E+00 kJ/mol
 MINI  021                 Cross Terms = 0.4894449E+01 kJ/mol
 MINI  040  No more updates
 DONE  001
```

86



minimized sildenafil

Energy Minimization (EM)

method to find local minimum on PES
(equivalent to quenching a "hot" molecule to 0 K)

approximations
quality of structure depends on quality of U

limitations
will only find the nearest energy minimum, which may not be the global minimum

advantages
fast
can treat very large systems

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3.3.2. Monte Carlo (MC) simulation

- random walk over PES
  - make random change of size Δx to geometry x to give new structure $x+\Delta x$
  - assume lowest energy structure found is the global minimum

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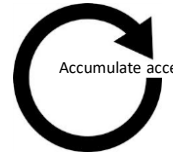
MC Method

#1) make random change in geometry x to give new structure $x+\Delta x$

#2) compare energies U of old and new structures

- **accept** new structure if its energy is lower than that of the old structure: $U(x+\Delta x) < U(x)$
- **accept** new structure if $U(x+\Delta x) > U(x)$ but uphill step in energy is not too large [see next slide]
- **reject** otherwise

#3) go to #1



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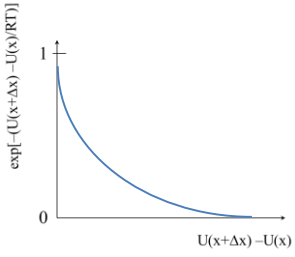
Uphill steps

- At temperature T, there is a finite (Boltzmann) probability that molecule(s) will have sufficient kinetic energy to move uphill in potential energy from U(x) to $U(x+\Delta x)$

  $= \exp[-\{U(x+\Delta x)-U(x)\}/RT]$



Therefore, in the MC method:

accept uphill step if:

Boltzmann factor $\exp[-\{U(x+\Delta x) - U(x)\}/RT]$ > random number between 0 and 1

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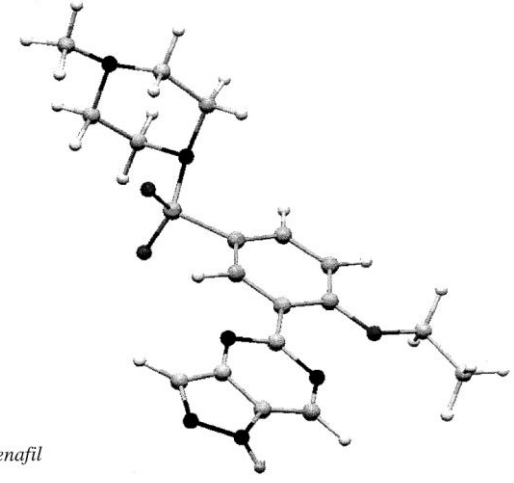

minimized sildenafil

```
mcsrch.ml       Fri Mar 16 14:37:38 2001      1

STRT  001 BatchMin V7.0.0  dynamic  16-Mar-2001 10:05:28
STRT  002 Reading force field...
STRT  003 Generating interactions...
STRT  004 Loading coordinates from force field...
STRT  005 Simulation initiated...
MCMM  001 Step     1 New global minimum.  E (kJ/mol) =       237.83
MCMM  002 Step     1 Unique conf. E(kJ/mol),Grad =      237.83        0.29
MCMM  005 Read  1 structures from the .dat file
MCMM  005 Now starting conf search
MCMM  005    1 unique conformations found so far
MCMM  005    0 minimized with good convergence
MCMM  005 Found     1 confs within  1.00 kcal/mol ( 4.18 kJ/mol) of glob. min.
MCMM  005 Global minimum E =   237.83 found     1 times.
MCMM  005    1 steps performed so far, out of  1000
MCMM  005  E of low-energy structures above global min (kJ/mol),  and no. times found:
MCMM  005    E:  0.00
MCMM  005  No.:    1
MCMM  001 Step     2 New global minimum.  E (kJ/mol) =       237.59
MCMM  007 Step     2 Duplicate conformation
MCMM  002 Step     3 Unique conf. E(kJ/mol),Grad =      263.37        0.49
MCMM  001 Step     4 New global minimum.  E (kJ/mol) =       234.31
MCMM  002 Step     4 Unique conf. E(kJ/mol),Grad =      234.31        0.42
MCMM  002 Step     5 Unique conf. E(kJ/mol),Grad =      260.29        0.17
MCMM  002 Step     6 Unique conf. E(kJ/mol),Grad =      238.74        0.30
MCMM  007 Step     7 Duplicate conformation
MCMM  001 Step     8 New global minimum.  E (kJ/mol) =       234.24
MCMM  007 Step     8 Duplicate conformation
MCMM  002 Step     9 Unique conf. E(kJ/mol),Grad =      253.86        0.13
MCMM  002 Step    10 Unique conf. E(kJ/mol),Grad =      248.70        0.27
MCMM  002 Step    11 Unique conf. E(kJ/mol),Grad =      256.34        0.04
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MCMM  007 Step    13 Duplicate conformation
MCMM  002 Step    14 Unique conf. E(kJ/mol),Grad =      262.96        0.19
MCMM  002 Step    15 Unique conf. E(kJ/mol),Grad =      249.74        0.17
MCMM  002 Step    16 Unique conf. E(kJ/mol),Grad =      239.87        0.43
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MCMM  002 Step    18 Unique conf. E(kJ/mol),Grad =      250.86        2.10
MCMM  002 Step    19 Unique conf. E(kJ/mol),Grad =      247.78        2.27
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MCMM  002 Step    21 Unique conf. E(kJ/mol),Grad =      247.44        0.44
MCMM  007 Step    22 Duplicate conformation
MCMM  002 Step    23 Unique conf. E(kJ/mol),Grad =      253.47        2.63
MCMM  002 Step    24 Unique conf. E(kJ/mol),Grad =      250.13        0.69
......
MCMM  002 Step   995 Unique conf. E(kJ/mol),Grad =      247.21        0.16
MCMM  007 Step   996 Duplicate conformation
MCMM  002 Step   997 Unique conf. E(kJ/mol),Grad =      250.12        1.82
MCMM  007 Step   998 Duplicate conformation
MCMM  002 Step   999 Unique conf. E(kJ/mol),Grad =      237.50        3.28
MCMM  007 Step  1000 Duplicate conformation
MCMM  999 Conformational search complete
MCMM  005
MCMM  005 Final report:
MCMM  005   367 unique conformations found
MCMM  005    22 minimized with good convergence
MCMM  005 Found     7 confs within  1.00 kcal/mol ( 4.18 kJ/mol) of glob. min.
MCMM  005 Found    18 confs within  2.00 kcal/mol ( 8.37 kJ/mol) of glob. min.
MCMM  005 Found    57 confs within  3.00 kcal/mol (12.55 kJ/mol) of glob. min.
MCMM  005 Found   227 confs within  5.00 kcal/mol (20.92 kJ/mol) of glob. min.
MCMM  005 Found   366 confs within 10.00 kcal/mol (41.84 kJ/mol) of glob. min.
MCMM  005 Global minimum E =   237.66 found     1 times.
MCMM  005 Global minimum E =   237.83 found     1 times.
MCMM  990 Total number of conformers found =   367
```

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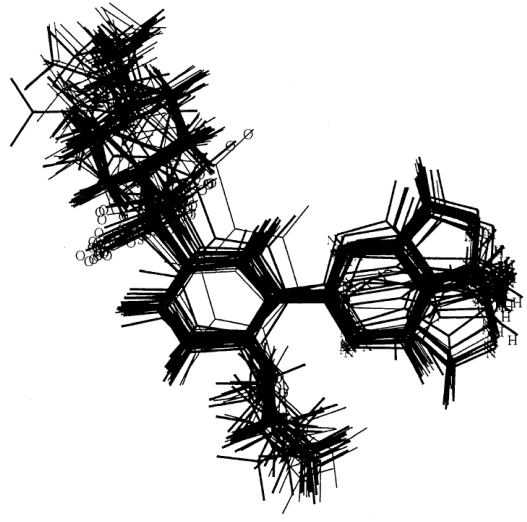
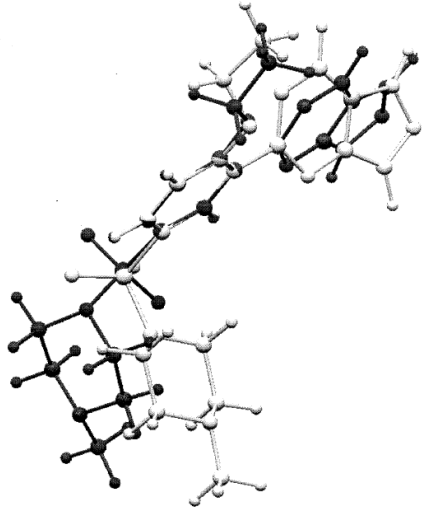


94



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Monte Carlo (MC) searching

random walk over PES using MC simulation at a given temperature

approximations

number of steps of MC

quality of structure depends on quality of U

limitations

cannot easily treat fully flexible polymers (rejection rate for random moves is too large)

bonds and angles of molecules are usually treated as rigid

advantages

can go uphill and through energy barriers to escape from local energy minima

fast (does not require gradients for MC simulation, only for energy minimization part)

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3.3.3. Molecular dynamics (MD)

- use kinetic energy to push molecule(s) over potential energy barriers (total energy is constant)

  total energy = potential energy + kinetic energy

  – e.g. 1-dimensional case

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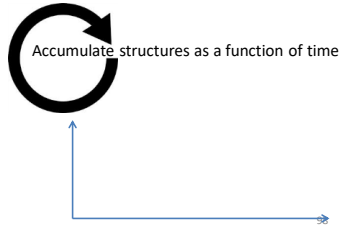
Molecular dynamics

need to solve Newton's equations of motion

$$f = ma$$

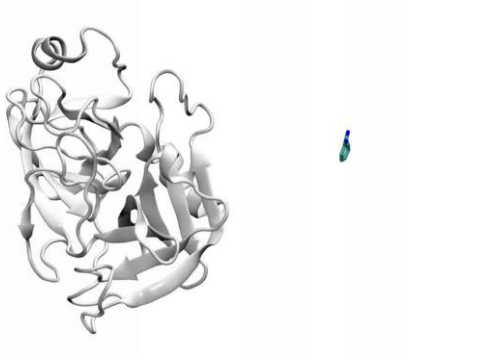
f = force = −gradient = −dU/dx (1-D case)
m = mass
a = acceleration = d^2x/dt^2



$$a = f/m$$

$$\frac{d^2x}{dt^2} = -\frac{1}{m}\frac{dU}{dx}$$

benzamide binding to trypsin…



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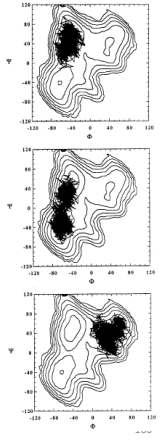
problem:

How efficient is MD at exploring the PES?

- tends to only explore local minima (may never get to the global minimum)
- need to simulate for a long time to see transitions between minima (1 ns - 1 μs)



a solution:

- can accelerate process by performing MD simulation at high temperature (500-2000 K)

Molecular dynamics

perform dynamics of system at a given T

approximations
number of time steps of MD (length of simulation)
quality of structure depends on quality of U

limitations
each MD step is slow compared to MC - need to calculate forces (negative of gradients)
also explores PES slowly

advantages
all atoms can move together
can handle large systems eg. proteins
can abstract dynamic information (eg. protein domain movement)

Further reading: **Section 2** only of "Locally Enhanced Sampling Pathways in Globins", Methods in Enzymology, Volume 437,459-475 [on Blackboard]

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3.4. Summary

- Many molecular modelling methods need to predict most likely structure of molecule(s)
  - to do this, need to find lowest energy structure on potential energy surface
  - to search the potential energy surface, we need:
    - a *search* method to *generate* conformations (eg. EM, MC, MD)
    - a *scoring* method to *evaluate* the energies of the conformations (eg. force field)