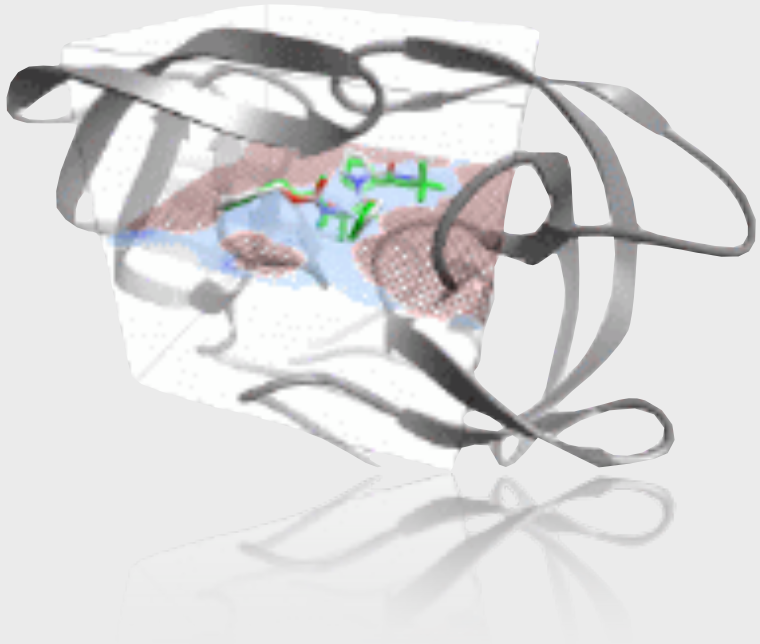
Docking of small molecules. AutoDock.



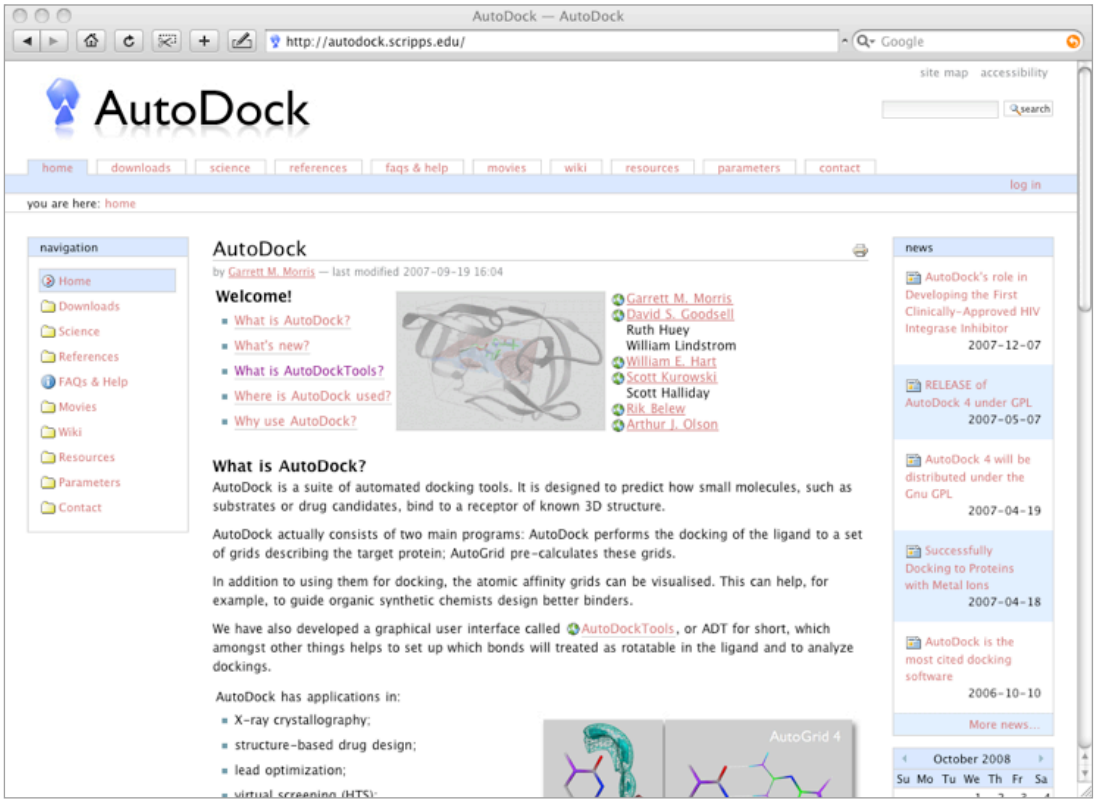
Marc A. Marti-Renom
http://bioinfo.cipf.es/sgu/

Structural Genomics Unit
Bioinformatics Department
Prince Felipe Resarch Center (CIPF), Valencia, Spain

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

DISCLAIMER!

Credit should go to Dr. Ruth Huey and Dr. Garret M. Morris



http://AutoDock.scripps.edu

Summary

- INTRO
- DOCKING
- SEARCH METHODS
- EXAMPLE

- AutoDock 4.0 with ADT

Nomenclature

Ligand: Structure (usually a small molecule) that binds to the binding site.

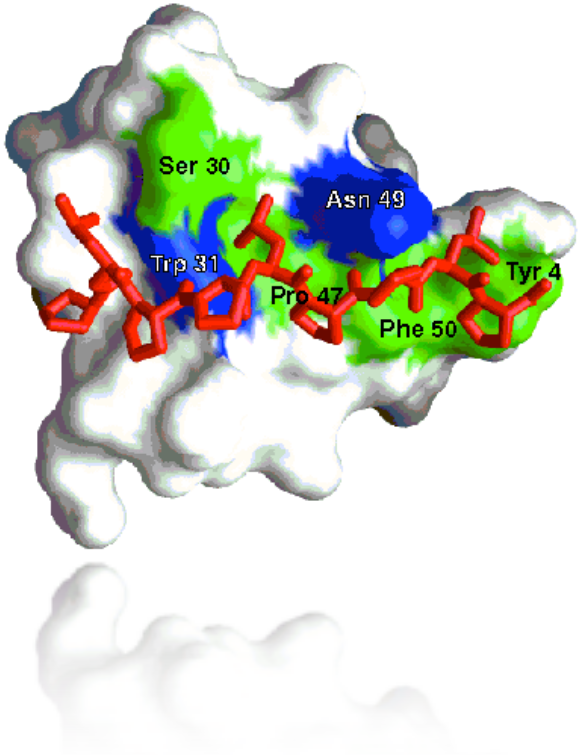
Receptor: Structure (usually a protein) that contains the active binding site.

Binding site: Set of aminoacids (residues) that physically interact with the lingad (usually @ 6 Anstroms).

What is docking?

Predicting the best ways two molecules interact.

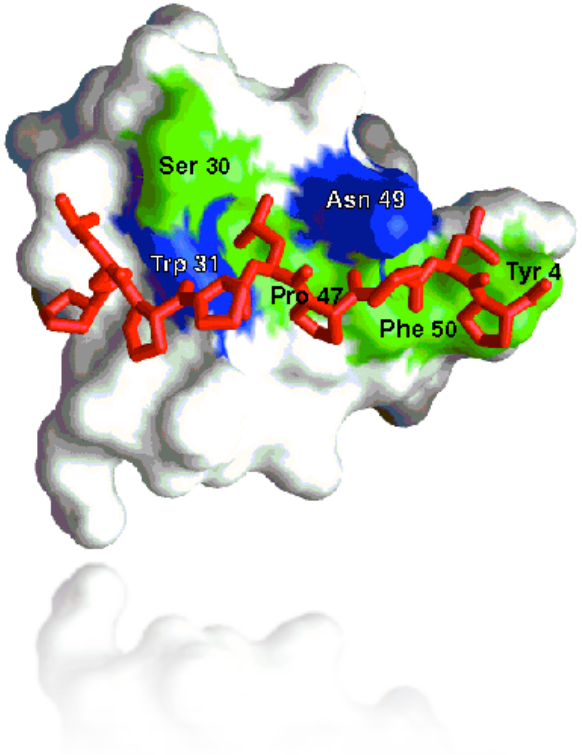
- Obtain the 3D structures of the two molecules
- Locate the best binding site (**Remember AnnoLyze?**)
- Determine the best binding mode.



What is docking?

Predicting the **best** ways two molecules interact.

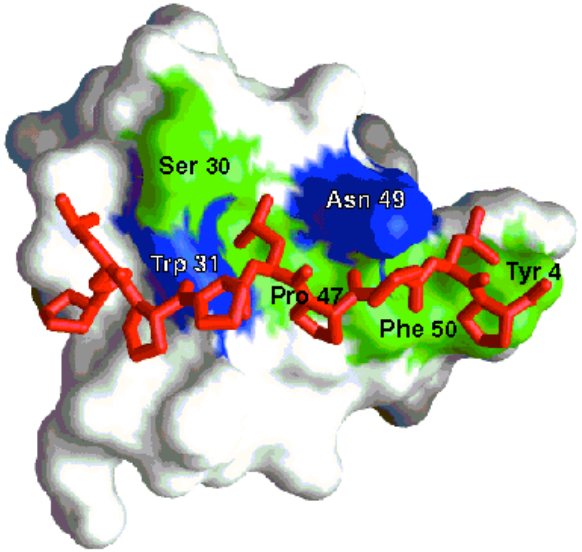
- We need to quantify or rank solutions
- We need a good scoring function for such ranking



What is docking?

Predicting the best **ways** two molecules interact.

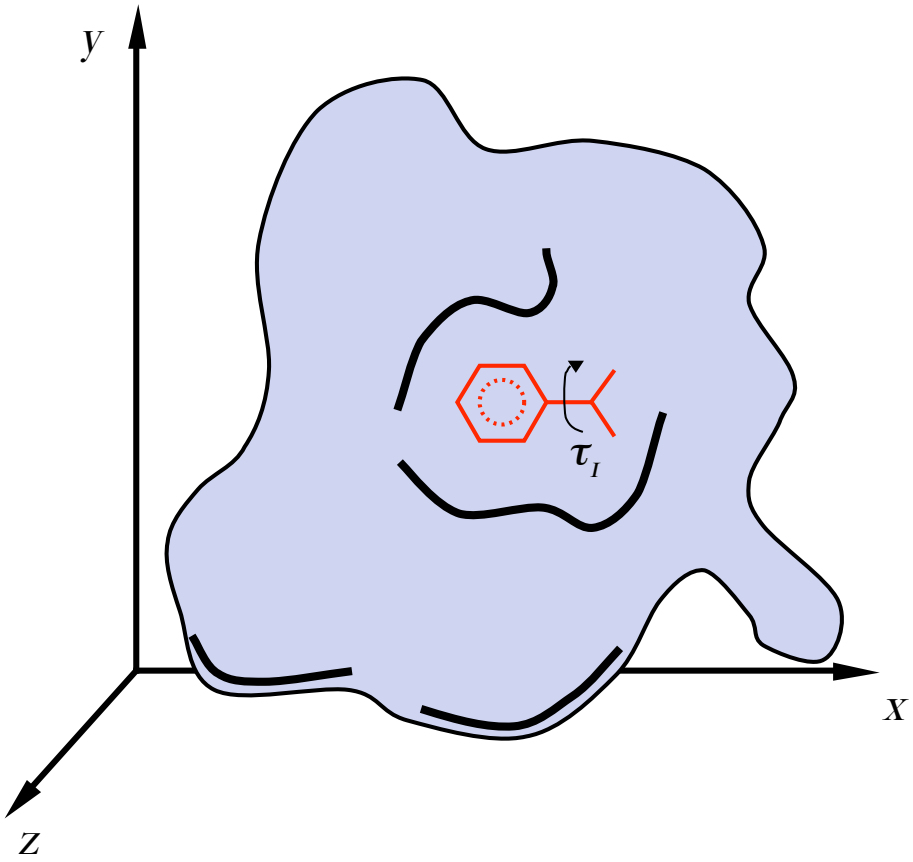
- X-ray and NMR structures are just ONE of the possible solutions
- There is a need for a search solution



BIOINFORMATICS (a note)

REPRESENTATION
SCORING
SAMPLING

REPRESENTATION

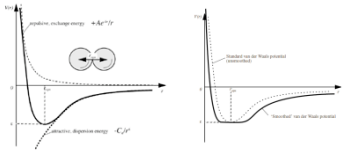


SCORING

AutoDock 4.0

$$\Delta G_{binding} = \Delta G_{vdW} + \Delta G_{elec} + \Delta G_{hbond} + \Delta G_{desolv} + \Delta G_{tors}$$

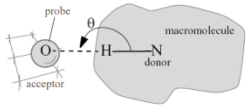
- ΔG_{vdW}
  12-6 Lennard-Jones potential



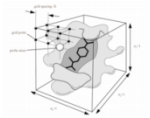
- ΔG_{elec}
  Coulombic with Solmajer-dielectric

$$\varepsilon(r) = A + \frac{B}{1 + ke^{-\lambda Br}}$$

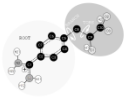
- ΔG_{hbond}
  12-10 Potential with Goodford Directionality



- ΔG_{desolv}
  Stouten Pairwise Atomic Solvation Parameters



- ΔG_{tors}
  Number of rotatable bonds



http://AutoDock.scripps.edu/science/equations

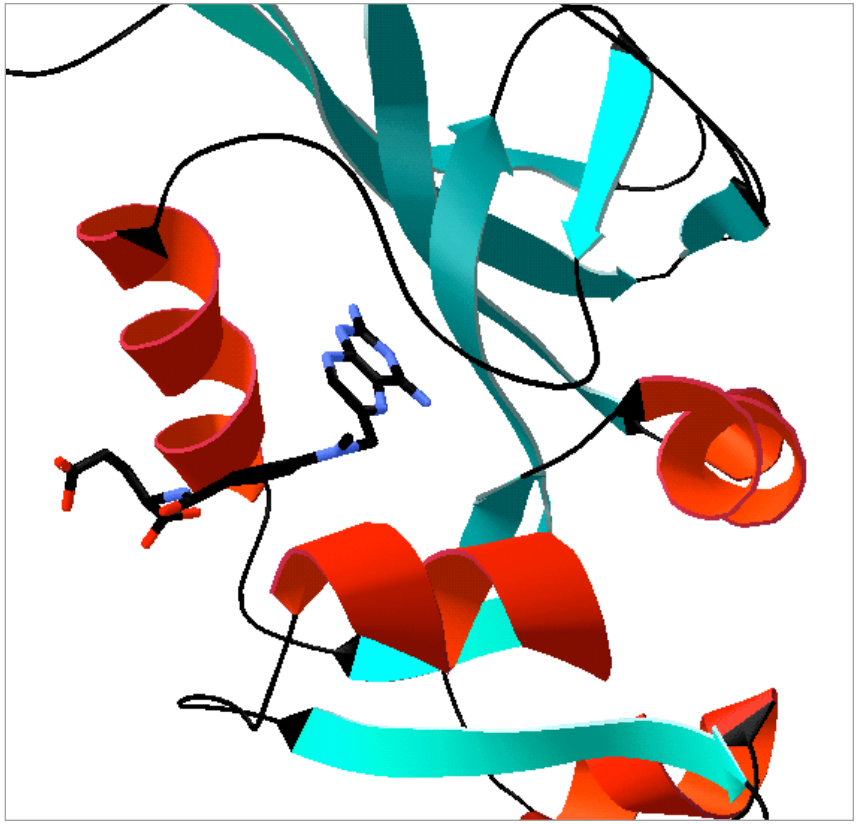
SAMPLING

AutoDock 4.0

- **Global search algorithms**
  - Simulated annealing (Goodsell et al. 1990)
  - Distributed SA (Morris et al. 1996)
  - Genetic Algorithm (Morris et al. 1998)
- **Local search algorithms**
  - Solis & Wets (Morris et al. 1998)
- **Hybrid global-local search**
  - Lamarckian GA (Morris et al. 1998)

PROBLEM!

Very CPU time consuming...



Dihidrofolate reductase with a metotrexate (4dfr.pdb)

$$N=T^{360/i}$$

N: number of conformations

T: number of rotable bonds

I: incremental degrees

Metotrexato

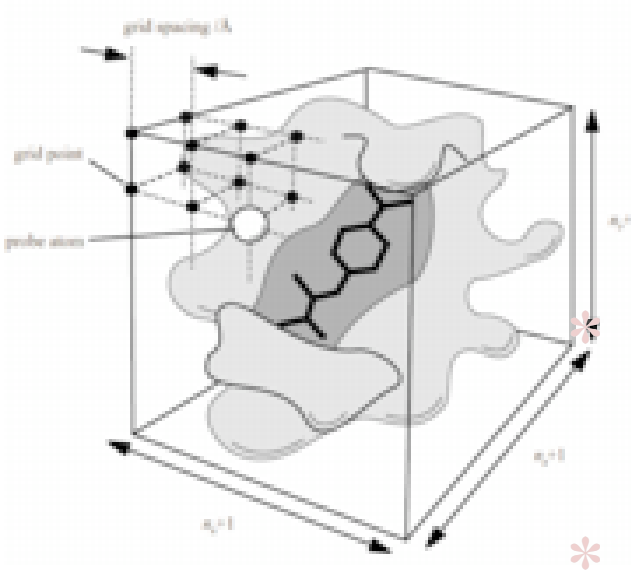
10 rotable bonds

30° increments (discrete)

10^{12} plausible conformations!

SOLUTION

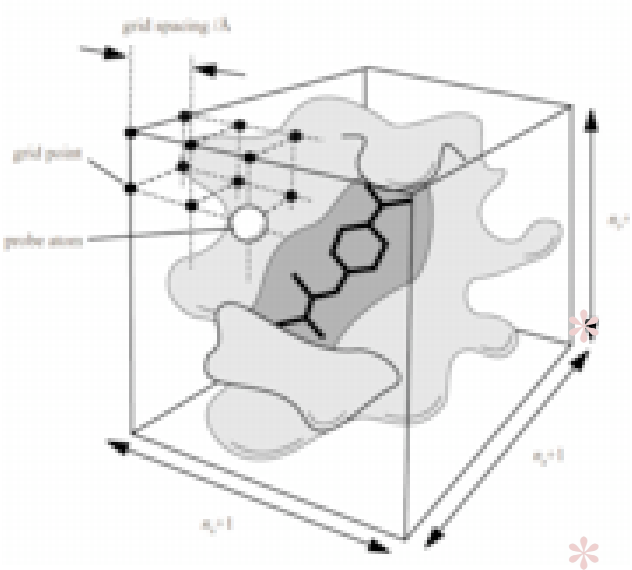
Use of grid maps!



- Saves lots of time (compared to classical MM/MD)
- AutoDock uses trilinear interpolation
- Need to map each atom to a grid point
- Limits the search space!

AutoGrid

Use of grid maps!



- Center of grid
  - center of ligand
  - center of receptor
  - a selected atom or coordinate
- Grid resolution (spacing)
  - default 0.375 Angstroms
- Number of grid points (dimension)
  - use ONLY even numbers
- MAKE SURE ALL LIGAND IS INSIDE GRID AND CAN MOVE!

Spectrum of search

Breadth and level of detail

Search breadth

- Local
  - Molecular Mechanics
- Intermediate
  - Monte Carlo Simulated Annealing
  - Brownian dynamics
  - Molecular Dynamics
- Global
  - Docking

Level of detail

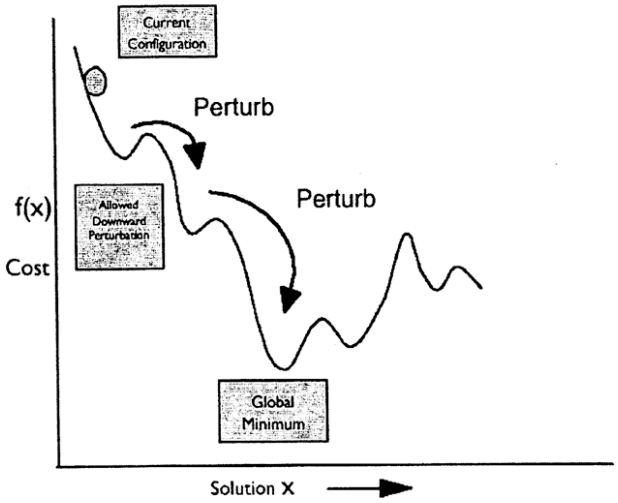
- Atom types
- Bond stretching
- Bon-angle bending
- Rotational barrier poyentials

- Implicit solvation
- Polarization

- What is rigid and what is flexible?

Search algorithms

Simulated Annealing



Ligand starts at initial state (random or user-defined)

The temperature of the system is reduced with time and the moves of the atoms are accepted depending on its energy compared to previous energy (with a probability proportional to the temperature!)

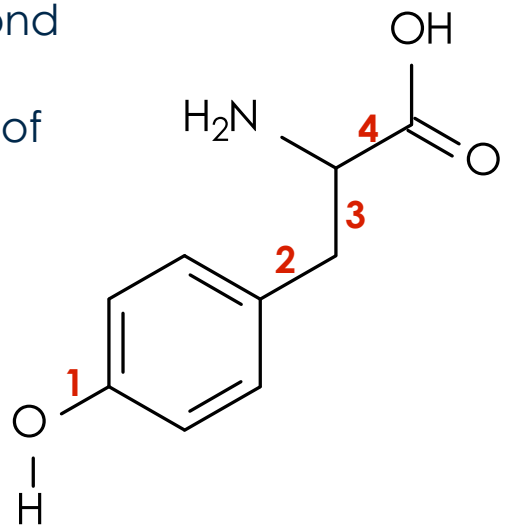
Repeat until reaching final solution.

Search algorithms

Genetic Algorithm

Use of a Genetic Algorithm as a sampling method

- Each conformation is described as a set of rotational angles.
- 64 possible angles are allowed to each of the bond in the ligand.
- Each plausible dihedral angle is codified in a set of binary bits (2^6=64)
- Each conformation is codified by a so called chromosome with 4 × 6 bits (0 or 1)



111010.010110.001011.010010

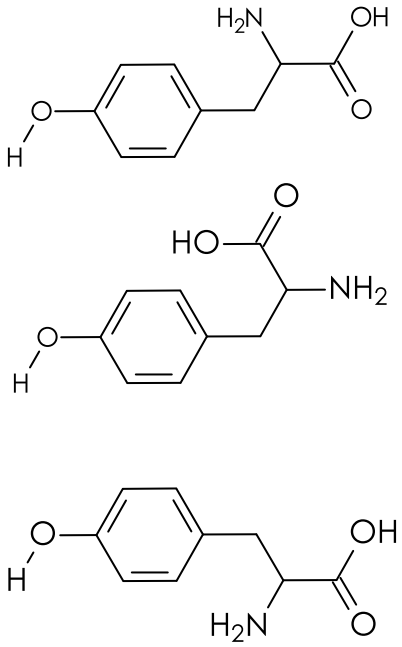
Φ_1 Φ_2 ...

$$\Phi_1 = 1\times2^5 + 1\times2^4 + 1\times2^3 + 0\times2^2 + 1\times2^1 + 0\times2^0 = 58°$$

Search algorithms

Genetic Algorithm

Population (ie, set of chromosomes or configurations)



011010.010110.011010.010111 ← Chromosome

111010.010110.001011.010010

001010.010101.000101.010001

101001.101110.101010.001000

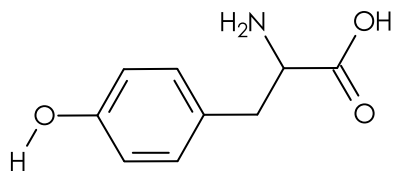
001010.101000.011101.001011

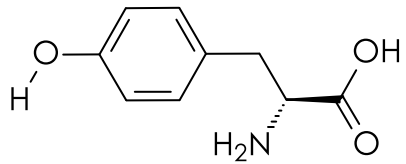
Gene

Search algorithms

Genetic Algorithm

Genetic operators...





011010.010110.011010.010111

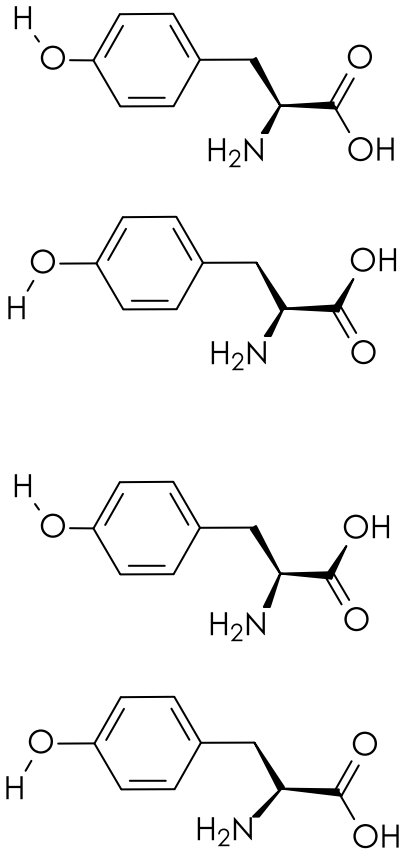
Single mutation

011010.011110.011110.010111

Search algorithms

Genetic Algorithm

Genetic operators...



001010.010101.000101.010001

011010.010110.011010.010111

Recombination

001010.010101.011010.010111

011010.010110. 000101.010001

Search algorithms

Genetic Algorithm

Genetic operators...

Search algorithms

Important to consider in AutoDock

Simulated annealing

- Initial temperature
  - `rt0 = 61600 K`
- Temperature reduction factor
  - `rtrf = 0.95 K/cycle`
- Termination criteria
  - accepted moves (`accs = 25,000`)
  - rejected moves (`rejs = 25,000`)
  - annealing cycles (`cycles = 50`)

Genetic algorithm

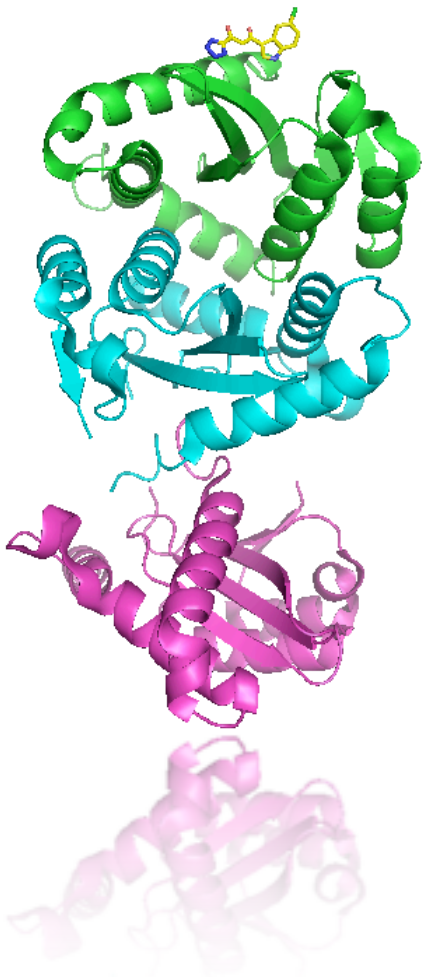
- Population size
  - `ga_pop_size = 300`
- Crossover rate
  - `ga_crossover_rate = 0.8`
- Mutation rate
  - `ga_mutation_rate = 0.02`
- Solis and Wets local search (LGA only)
  - `sw_max_its = 300`
- Termination criteria
  - `ga_num_evals = 25,000 (short)`
  - `ga_num_evals = 250,000 (medium)`
  - `ga_num_evals = 2,500,000 (large)`
  - `ga_num_generations = 27,000`

AutoDock Example

Discovery of a novel binding trench in HIV Integrase

Schames, J.R., R.H. Henchman, J.S. Siegel, C.A. Sotriffer, H. Ni, and J.A. McCammon, Discovery of a novel binding trench in HIV integrase. J Med Chem, 2004. 47(8): 1879-81

ISENTRESS example



- One structure known with 5CITEP
  - Not clear (low resolution)
  - Binding near to DNA interacting site
  - Loop near the binding
- Docking + Molecular Dynamics
  - AMBER snapshots
  - AutoDock flexible torsions thetetrazolering and indole ring.

Schames, J.R., R.H. Henchman, J.S. Siegel, C.A. Sotriffer, H. Ni, and J.A. McCammon, Discovery of a novel binding trench in HIV integrase. J Med Chem, 2004. 47(8): 1879-81

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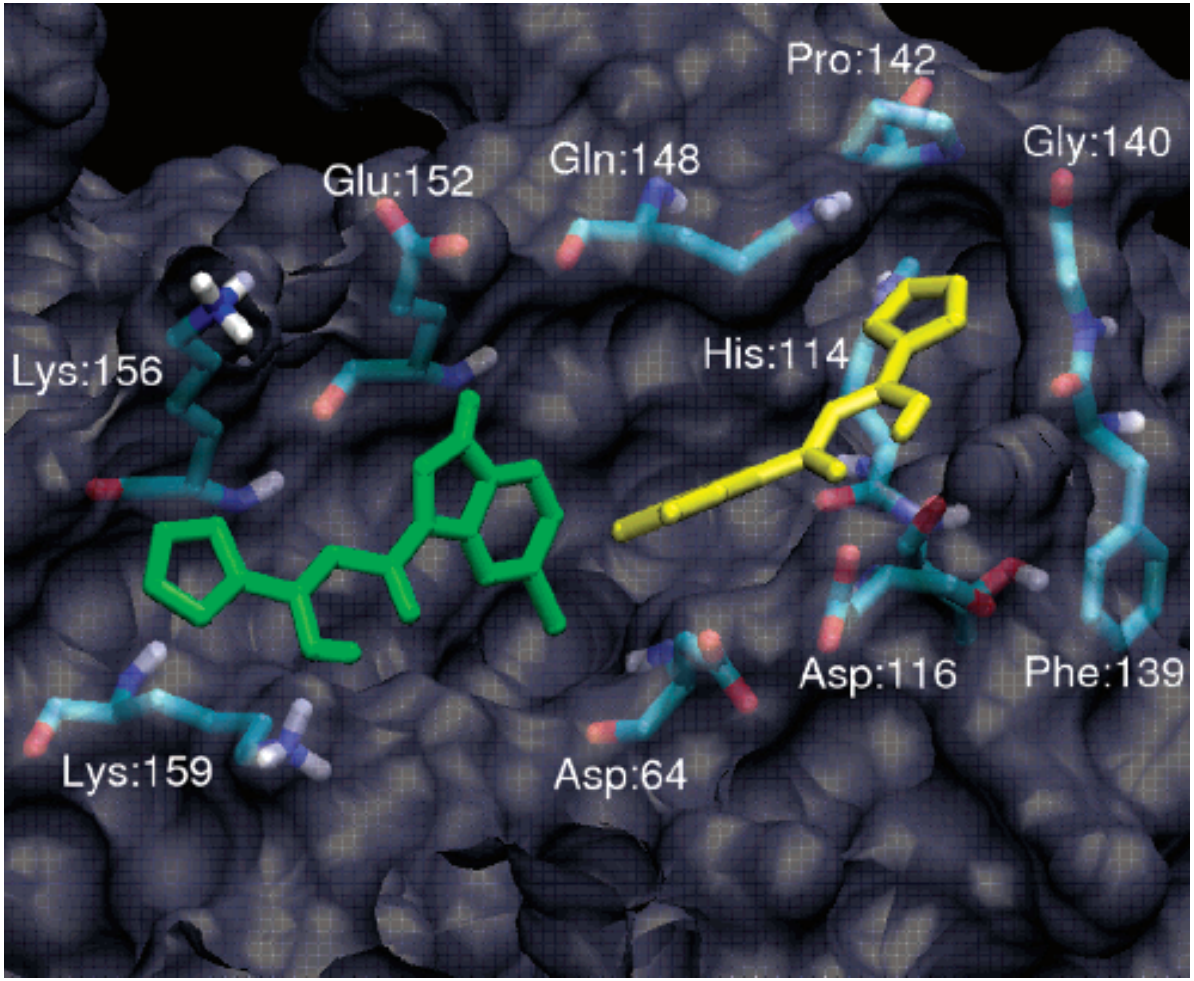

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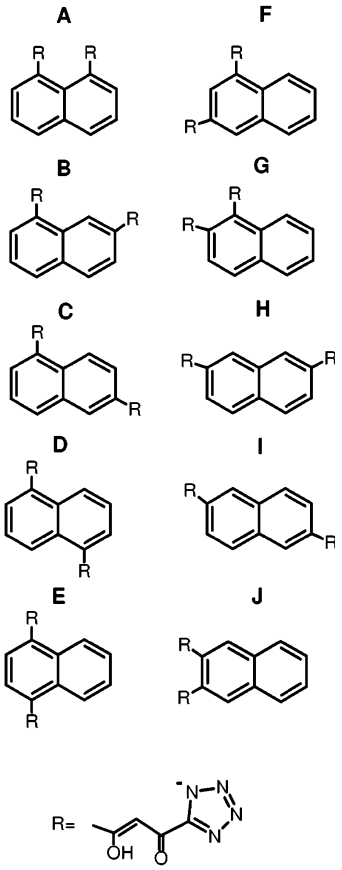

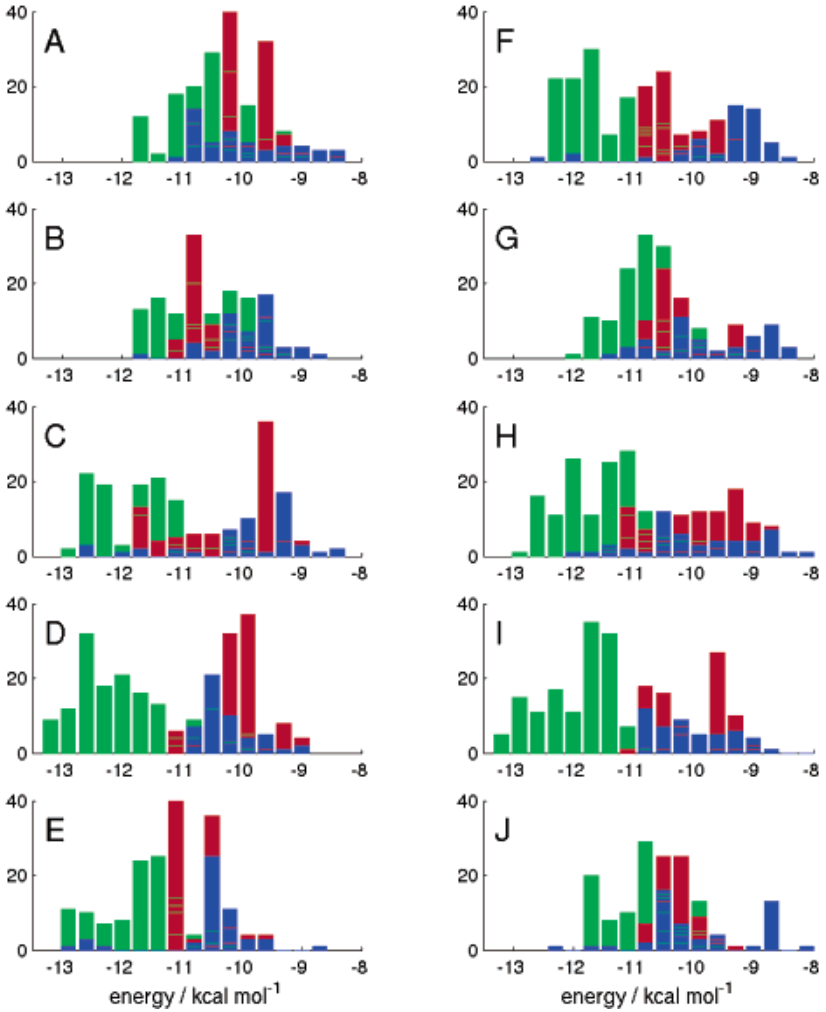

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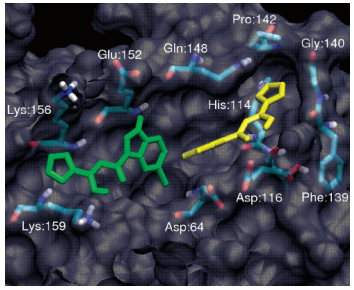

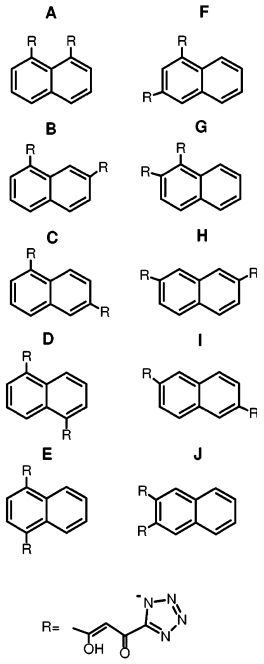

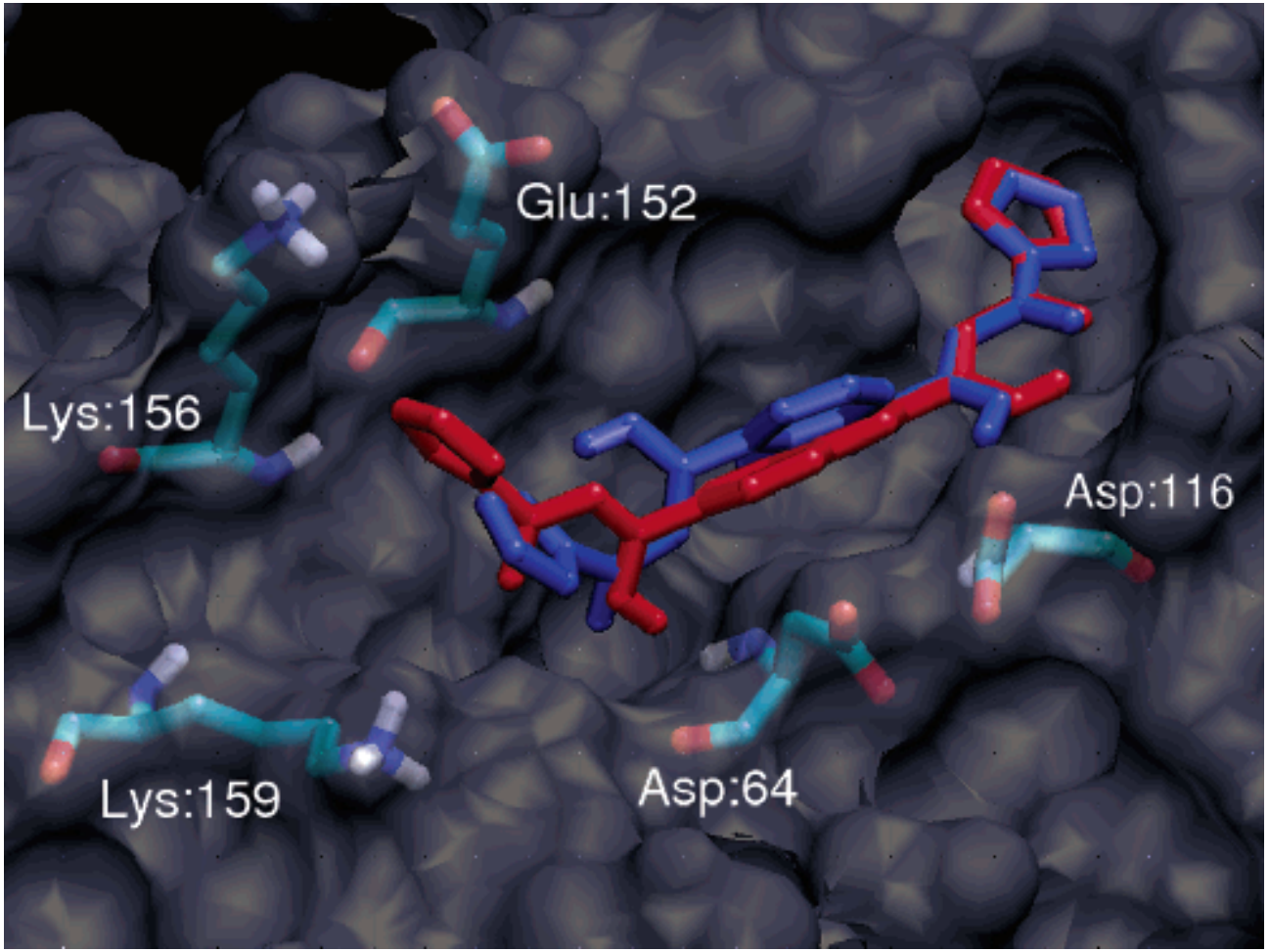

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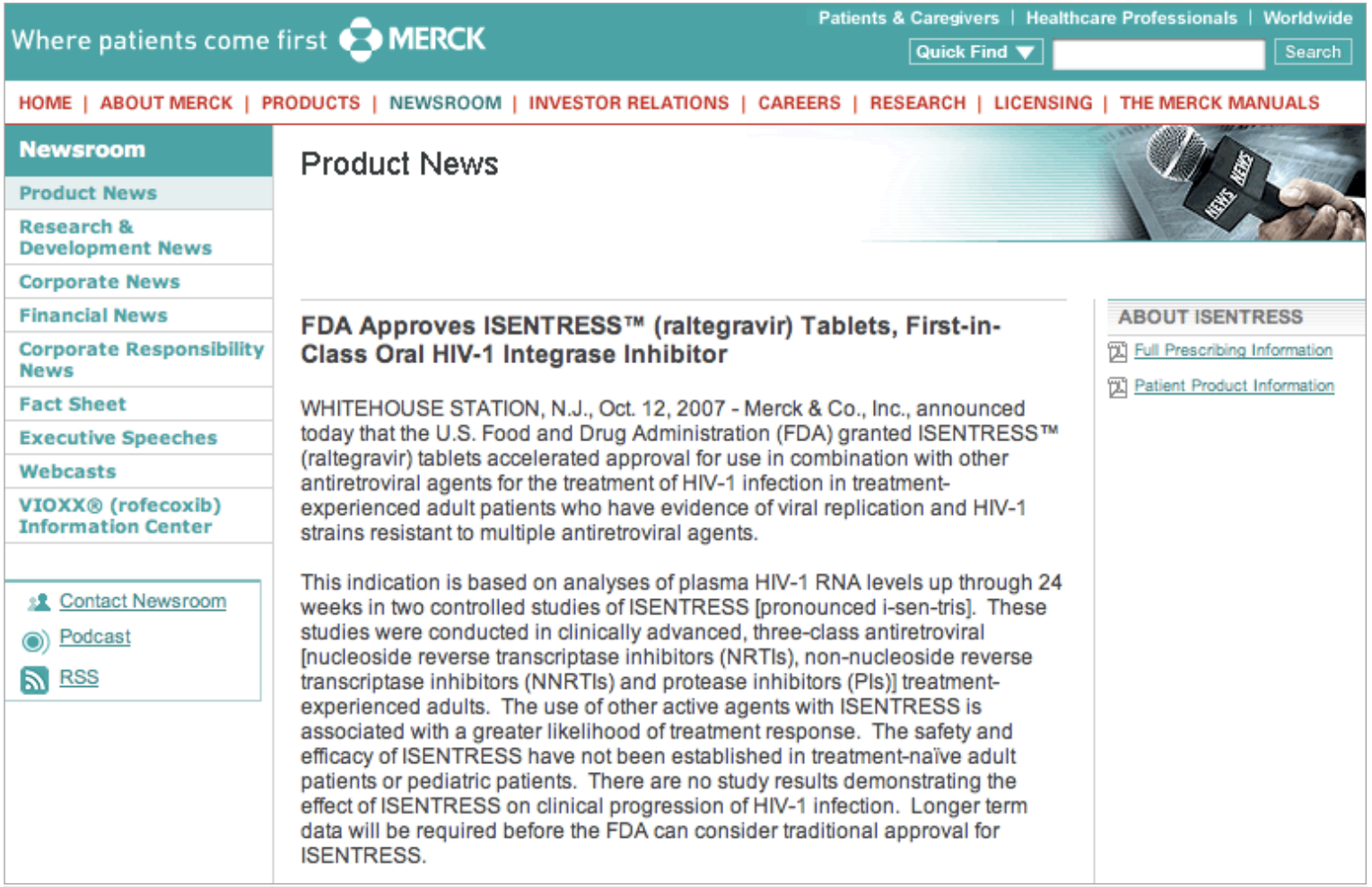

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FDA Approves ISENTRESS™ (raltegravir) Tablets, First-in-Class Oral HIV-1 Integrase Inhibitor

WHITEHOUSE STATION, N.J., Oct. 12, 2007 - Merck & Co., Inc., announced today that the U.S. Food and Drug Administration (FDA) granted ISENTRESS™ (raltegravir) tablets accelerated approval for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in two controlled studies of ISENTRESS [pronounced i-sen-tris]. These studies were conducted in clinically advanced, three-class antiretroviral [nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)] treatment-experienced adults. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response. The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients. There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection. Longer term data will be required before the FDA can consider traditional approval for ISENTRESS.

ABOUT ISENTRESS

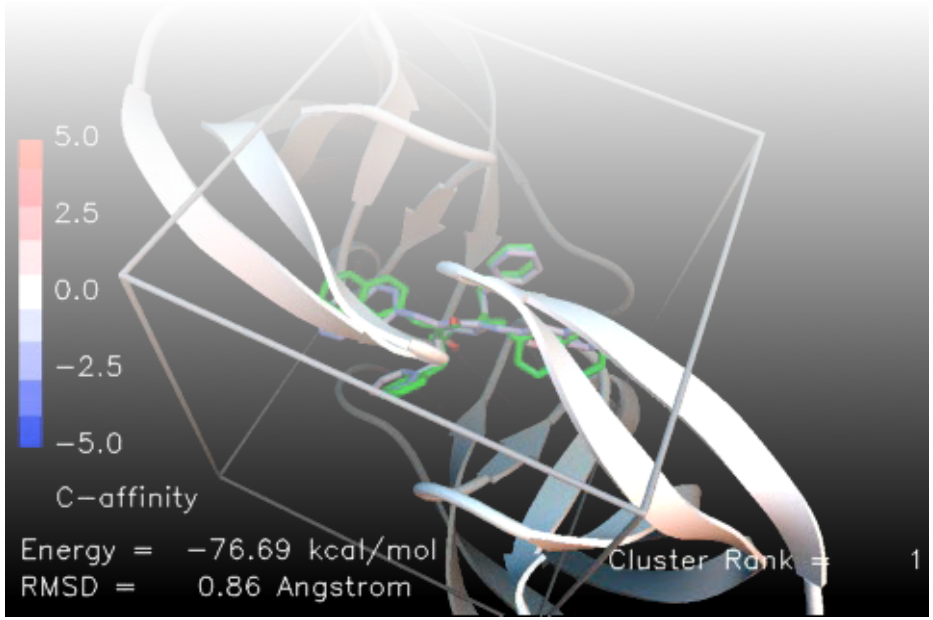
Full Prescribing Information

Patient Product Information

AutoDock

Goodsell, D. S. and Olson, A. J. (1990), Automated Docking of Substrates to Proteins by Simulated Annealing Proteins:Structure, Function and Genetics., 8: 195-202.
Morris, G. M., et al. (1996), Distributed automated docking of flexible ligands to proteins: Parallel applications of AutoDock 2.4 J. Computer-Aided Molecular Design, 10: 293-304.
Morris, G. M., et al. (1998), Automated Docking Using a Lamarckian Genetic Algorithm and and Empirical Binding Free Energy Function J. Computational Chemistry, 19: 1639-1662.
Huey, R., et al. (2007), A Semiempirical Free Energy Force Field with Charge-Based Desolvation J. Computational Chemistry, 28: 1145-1152.

AutoDock



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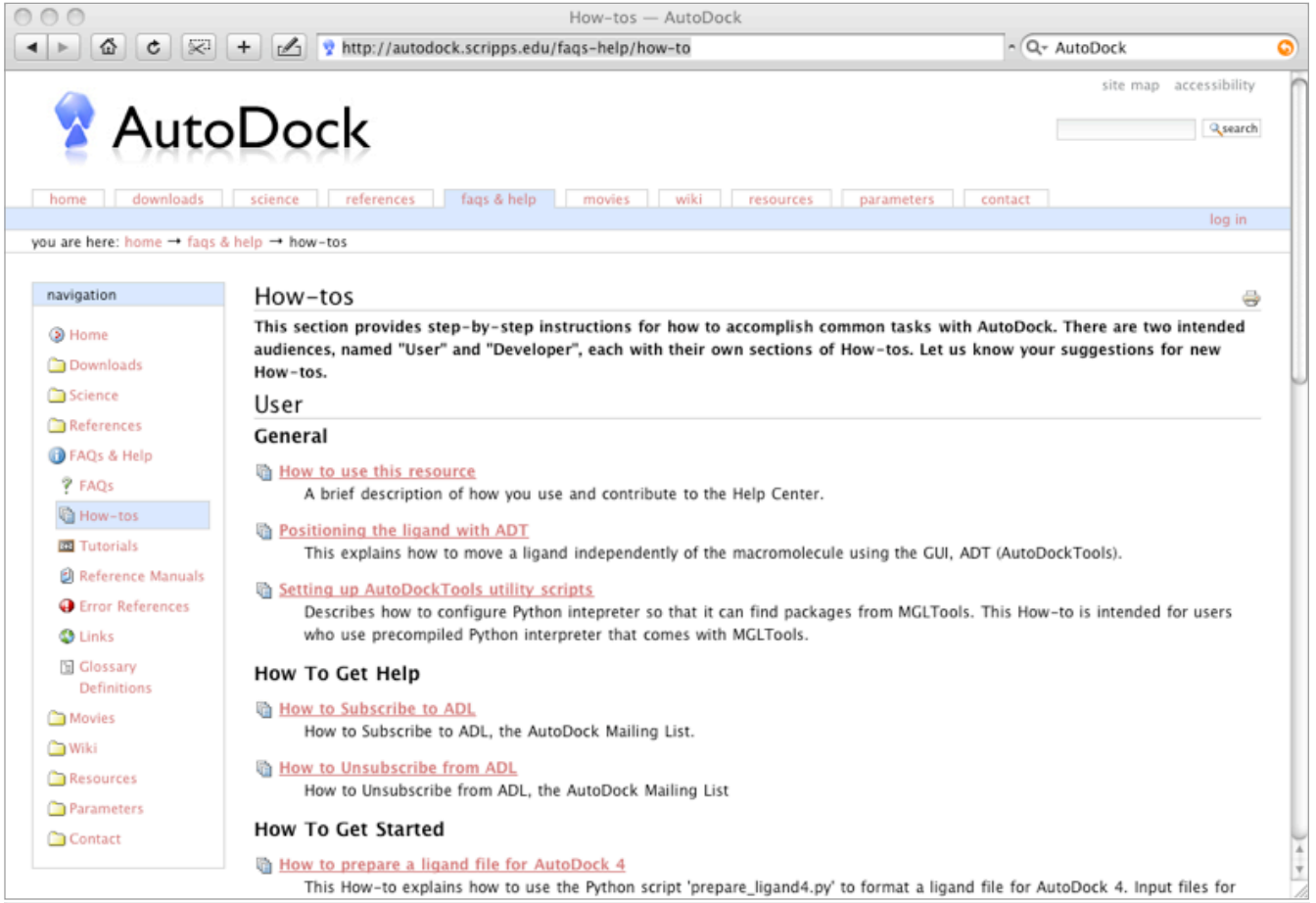
AutoDock 4.0

Where to get help...



http://autodock.scripps.edu/faqs-help/how-to

AutoDock 4.0

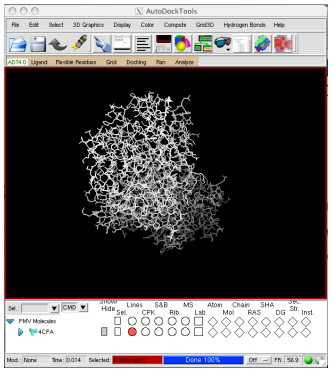
AutoDock and ADT

AutoDock

- 1990
- Number crunching (CPU expensive)
- Command-line!
- C& C++ compiled

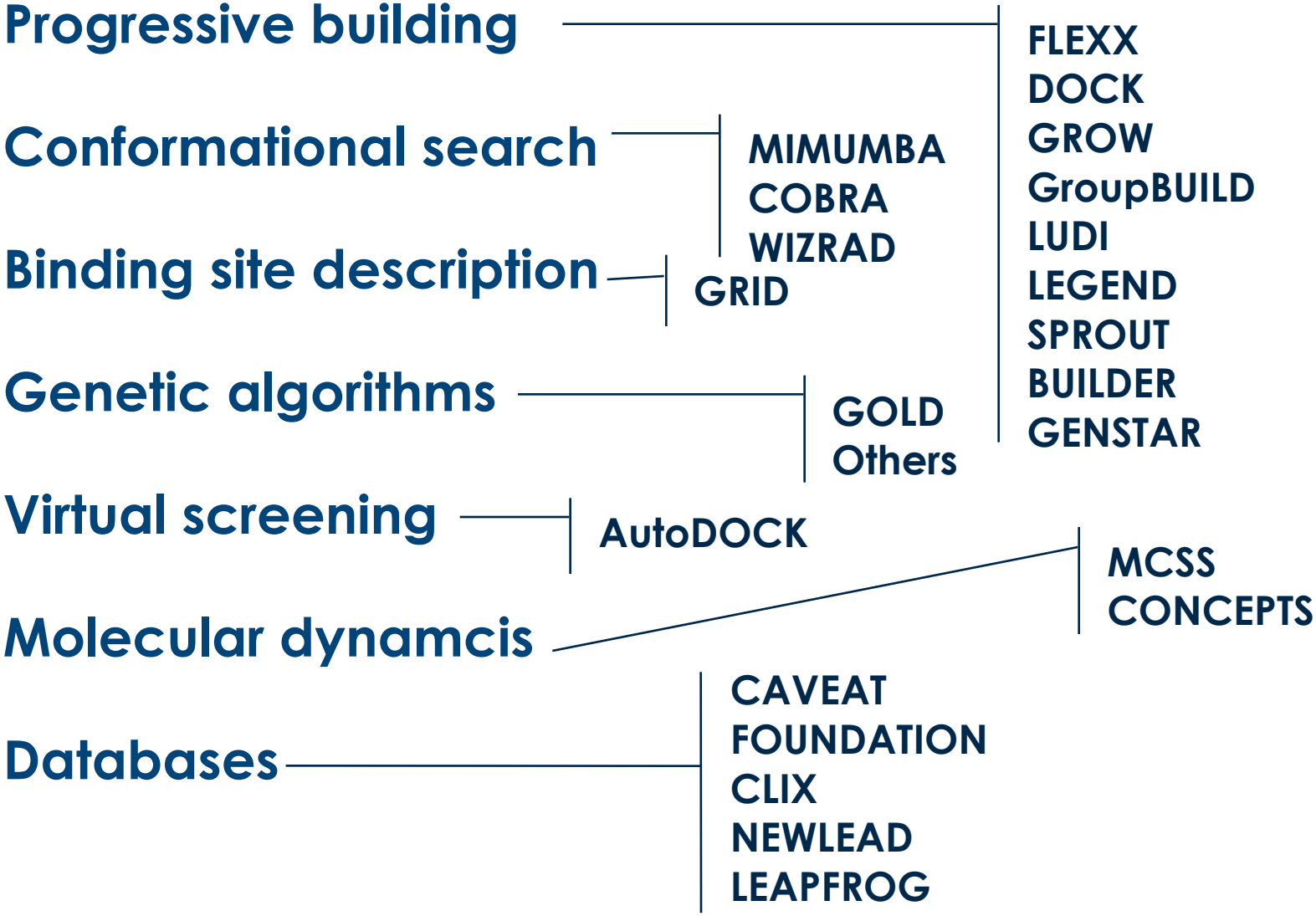
AutoDock Tools

- 2000
- Visualizing set-up
- Graphical user interphase
- Python interpreter



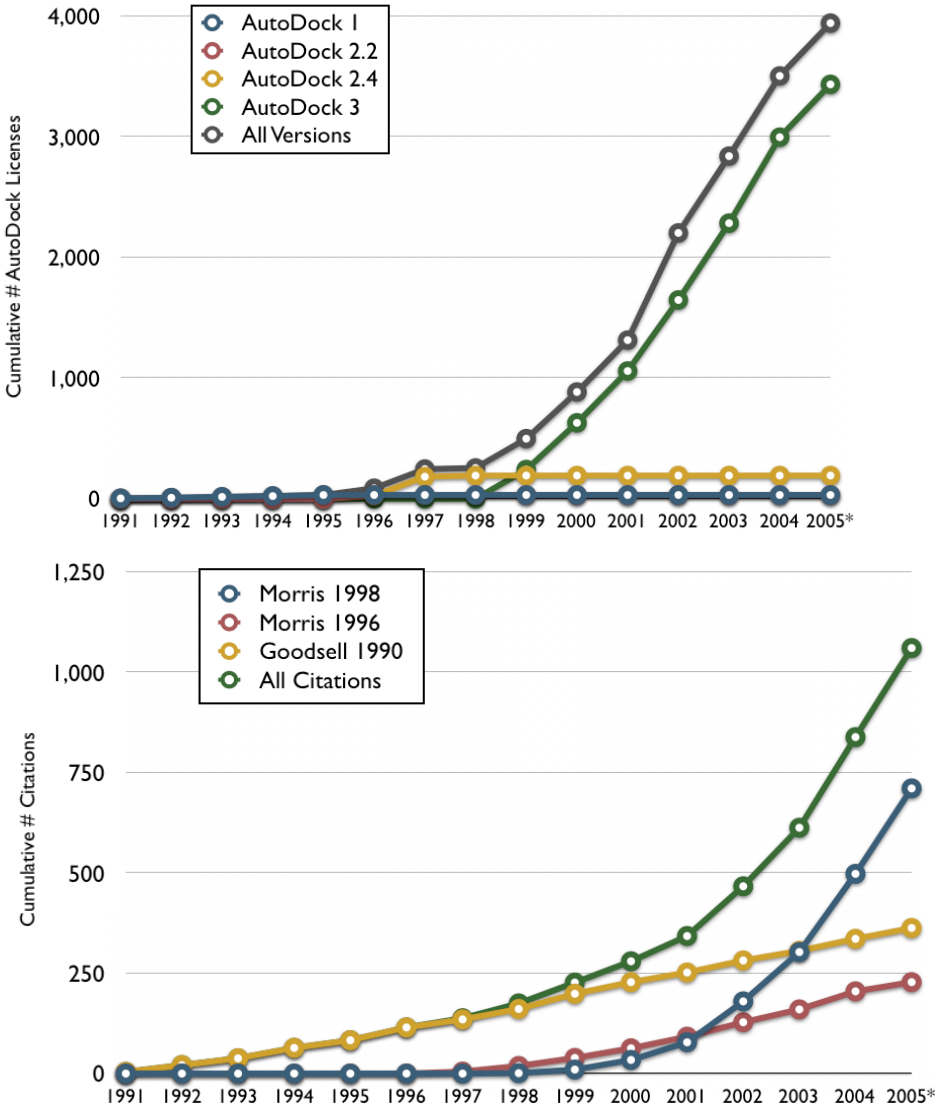
AutoDock 4.0

Alternatives



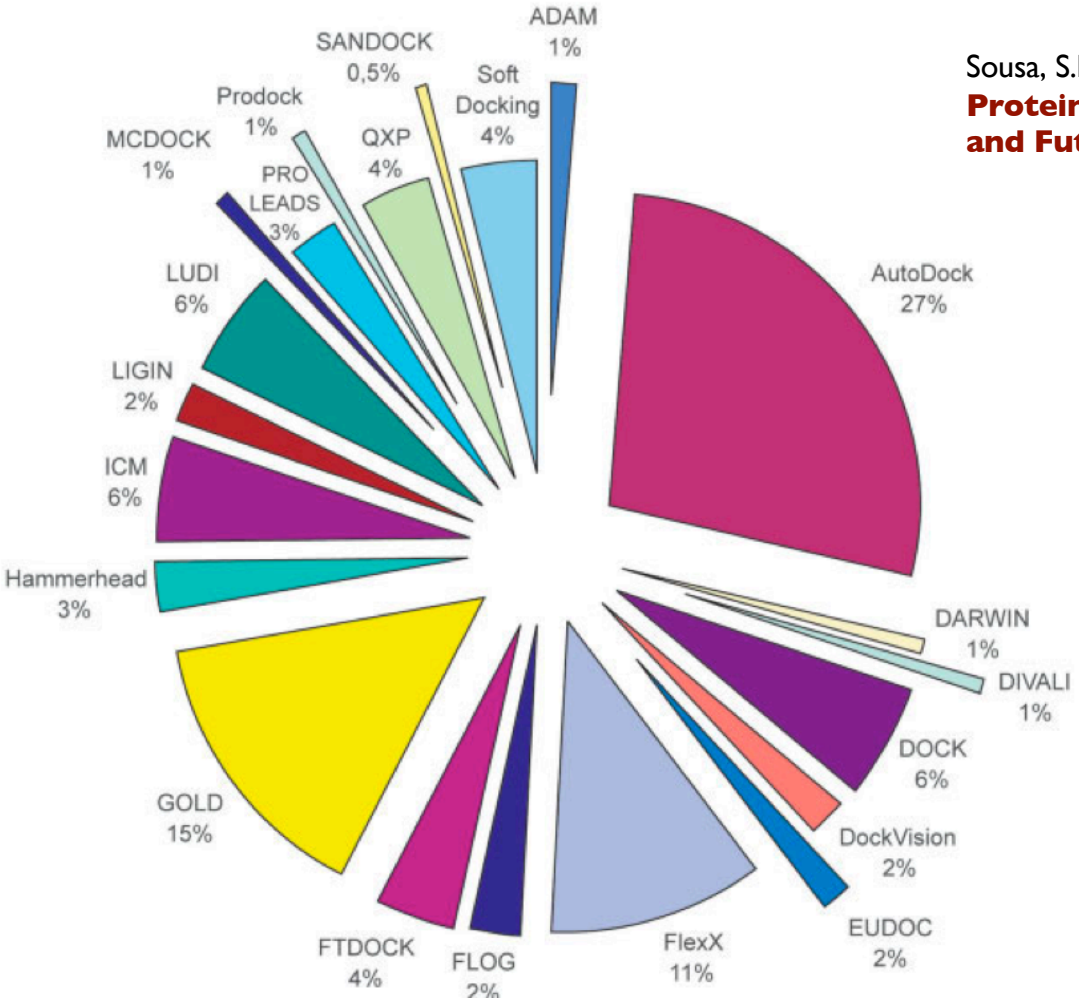
AutoDock 4.0

Why AutoDock over others



AutoDock 4.0

Why AutoDock over others



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Protein-Ligand Docking: Current Status and Future Challenges *Proteins*, **65**:15-26

AutoDock 4.0

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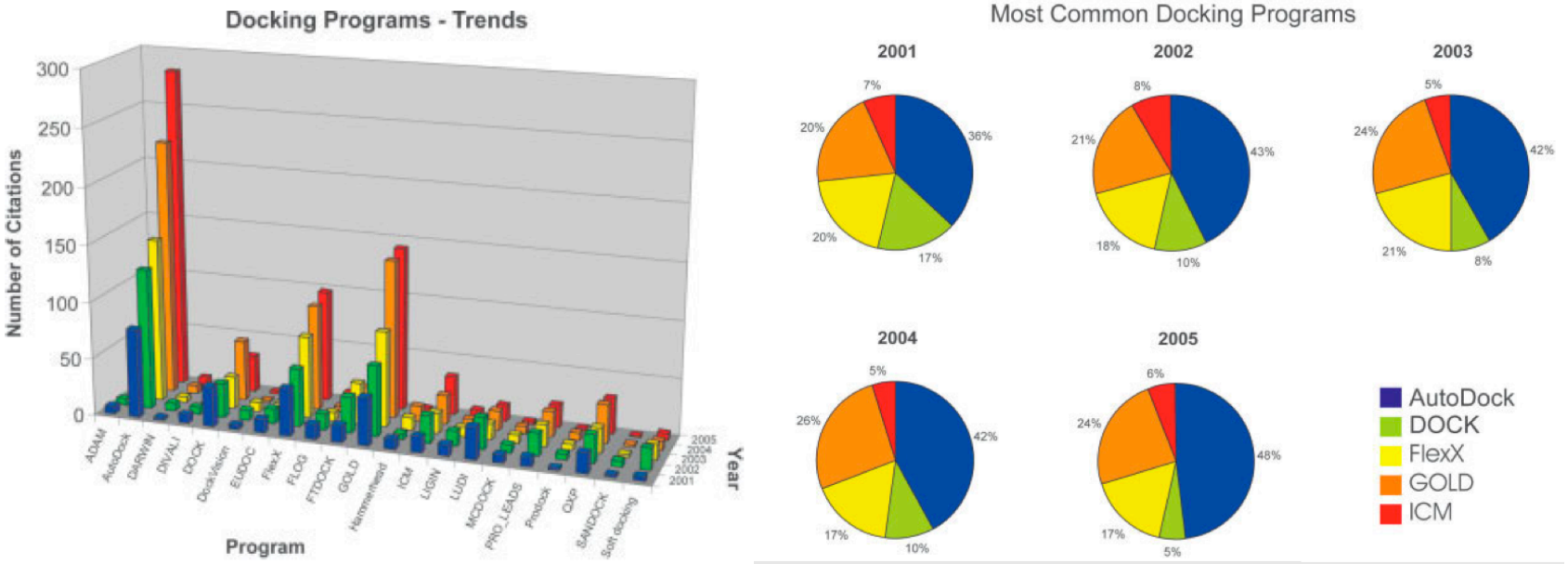

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AutoDock 4.0

Practical considerations

- What problem does AutoDock solve?
  - *Flexible* ligands (4.0 *flexible* protein).
- What range of problems is feasible?
  - Depends on the search method:
    - LGA > GA >> SA >> LS
    - SA : can output trajectories, D < about 8 torsions.
    - LGA : D < about 8-32 torsions.
- When is AutoDock not suitable?
  - No 3D-structures are available;
  - Modelled structure of poor quality;
  - Too many (32 torsions, 2048 atoms, 22 atom types);
  - Target protein too flexible.

AutoDock 4.0

Using AutoDock step-by-step

- Set up ligand PDBQT—using ADT's "Ligand" menu
- *OPTIONAL:* Set up flexible receptor PDBQT—using ADT's "Flexible Residues" menu
- Set up macromolecule & grid maps—using ADT's "Grid" menu
- Pre-compute AutoGrid maps for all atom types in your set of ligands—using "`autogrid4`"
- Perform dockings of ligand to target—using "`autodock4`", and in parallel if possible.
- Visualize AutoDock results—using ADT's "Analyze" menu
- Cluster dockings—using "analysis" DPF command in "autodock4" or ADT's "Analyze" menu for parallel docking results.

AutoDock 4.0

AutoDock 4.0 file formats

Prepare the Following Input Files

- Ligand PDBQT file
- Rigid Macromolecule PDBQT file
- Flexible Macromolecule PDBQT file ("Flexres")
- AutoGrid Parameter File (GPF)
  - GPF depends on atom types in:
    - Ligand PDBQT file
    - *Optional* flexible residue PDBQT files)
- AutoDock Parameter File (DPF)

Run AutoGrid 4

- Macromolecule PDBQT + GPF → Grid Maps, GLG

Run AutoDock 4

- Grid Maps + Ligand PDBQT + [Flexres PDBQT +] DPF → DLG (dockings & clustering)

Run ADT to Analyze DLG

AutoDock 4.0

Things to know before using AutoDock

Ligand:

- Add all hydrogens, compute Gasteiger charges, and merge non-polar H; also assign AutoDock 4 atom types
- Ensure total charge corresponds to tautomeric state
- Choose torsion tree root & rotatable bonds

Macromolecule:

- Add all hydrogens, compute Gasteiger charges, and merge non-polar H; also assign AutoDock 4 atom types
- Assign Stouten atomic solvation parameters
- Optionally, create a flexible residues PDBQT in addition to the rigid PDBQT file
- Compute AutoGrid maps

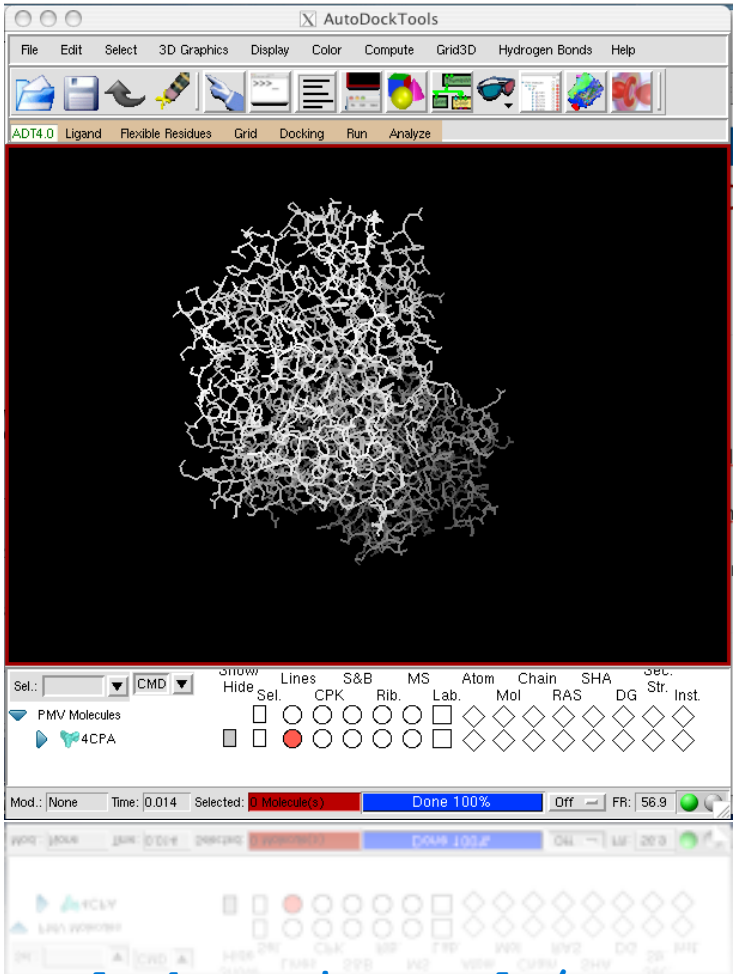
AutoDock 4.0

Preparing ligands and receptors

- AutoDock uses 'United Atom' model
  - Reduces number of atoms, speeds up docking
- Need to:
  - Add polar Hs. Remove non-polar Hs.
    - Both Ligand & Macromolecule
  - Replace missing atoms (disorder).
  - Fix hydrogens at chain breaks.
- Need to consider pH:
  - Acidic & Basic residues, Histidines.
  - http://molprobity.biochem.duke.edu/
- Other molecules in receptor:
    - Waters; Cofactors; Metal ions.
- Molecular Modelling elsewhere.

AutoDock 4.0

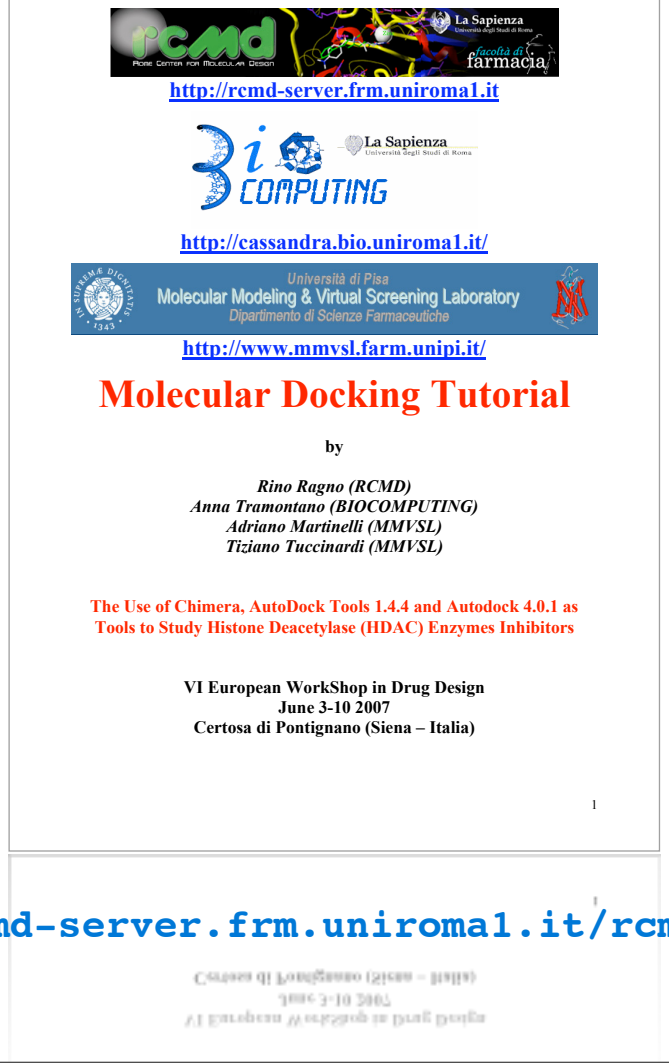
Good we have AutoDock Tools (ATD)



http://autodock.scripps.edu/resources/adt/

AutoDock 4.0

Good we have a nice tutorial



http://rcmd-server.frm.uniroma1.it

http://cassandra.bio.uniroma1.it/

http://www.mmvsl.farm.unipi.it/

Molecular Docking Tutorial

by

Rino Ragno (RCMD)
Anna Tramontano (BIOCOMPUTING)
Adriano Martinelli (MMVSL)
Tiziano Tuccinardi (MMVSL)

The Use of Chimera, AutoDock Tools 1.4.4 and Autodock 4.0.1 as Tools to Study Histone Deacetylase (HDAC) Enzymes Inhibitors

VI European WorkShop in Drug Design
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1

http://rcmd-server.frm.uniroma1.it/rcmd-portal/

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