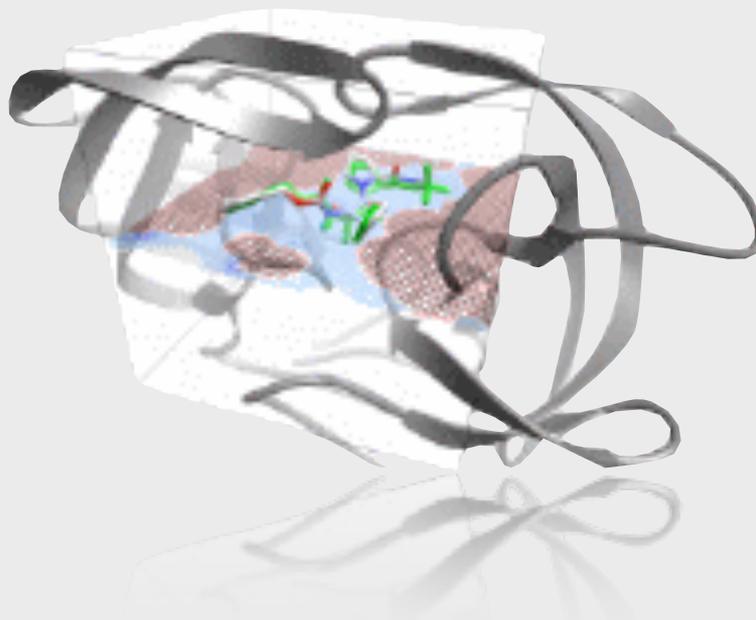


Docking of small molecules. AutoDock.



Marc A. Marti-Renom

<http://bioinfo.cipf.es/squ/>

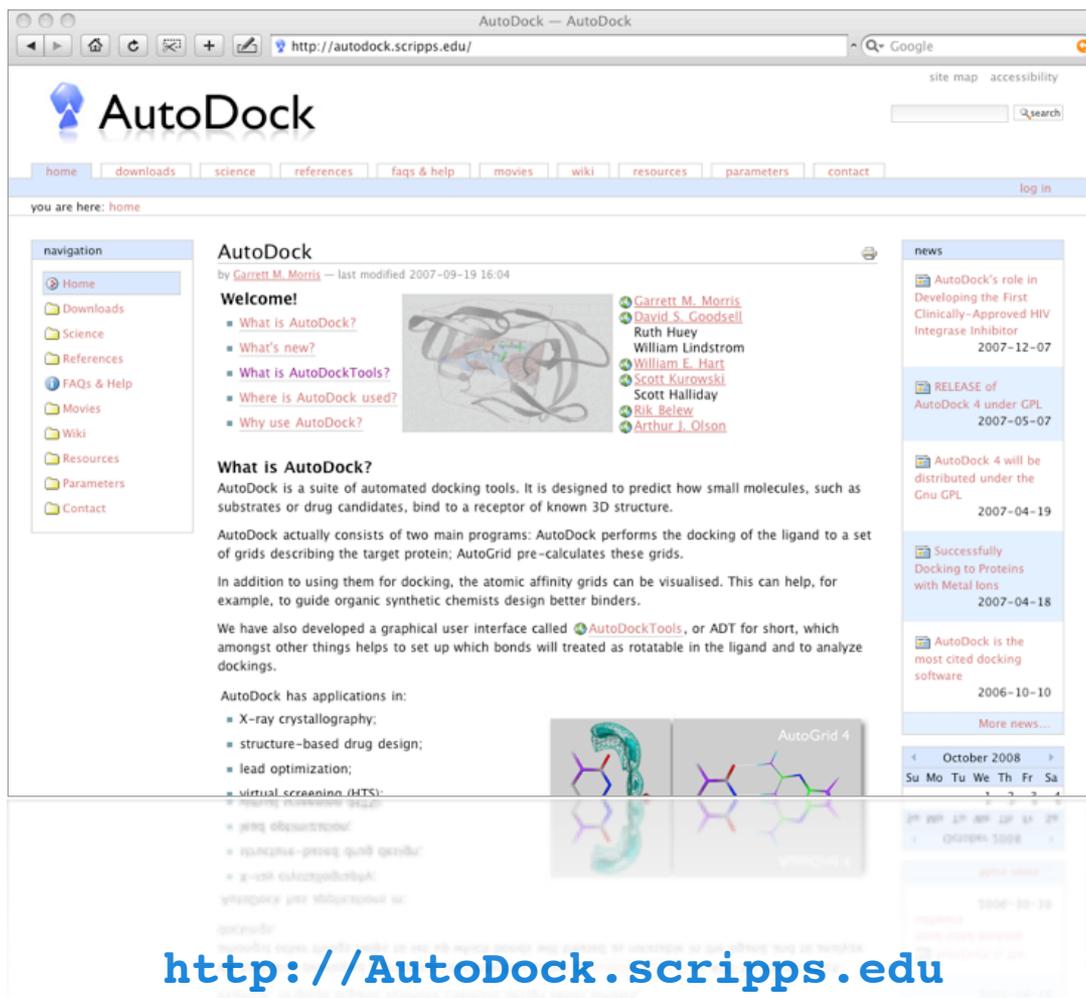
Structural Genomics Unit
Bioinformatics Department

Prince Felipe Research Center (CIPF), Valencia, Spain



DISCLAIMER!

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



The screenshot shows the homepage of the AutoDock website. The browser address bar displays "http://autodock.scripps.edu/". The page features the AutoDock logo, a navigation menu with links like "home", "downloads", "science", "references", "faqs & help", "movies", "wiki", "resources", "parameters", and "contact". A "you are here" breadcrumb shows "home". The main content area includes a "Welcome!" section with a list of links: "What is AutoDock?", "What's new?", "What is AutoDockTools?", "Where is AutoDock used?", and "Why use AutoDock?". Below this is a "What is AutoDock?" section with a paragraph describing the software as a suite of automated docking tools. A list of applications includes X-ray crystallography, structure-based drug design, lead optimization, and virtual screening (HTS). A "news" sidebar on the right lists recent updates, such as "AutoDock's role in Developing the First Clinically-Approved HIV Integrase Inhibitor" and "RELEASE of AutoDock 4 under GPL". At the bottom, a calendar for October 2008 is visible.

<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.

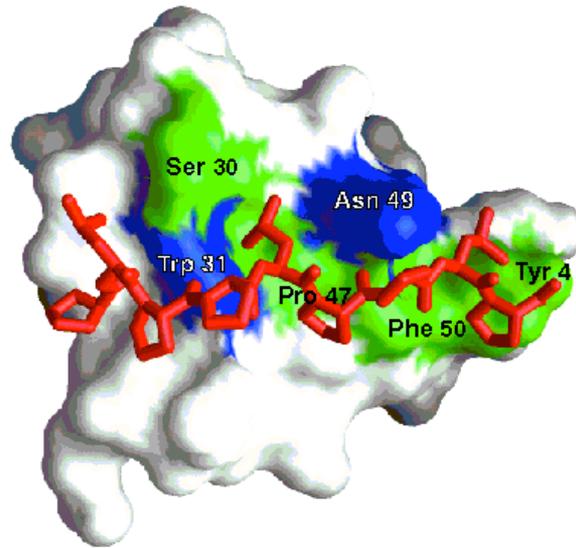
Receptor: Structure (usually a protein) that contains the active binding site.

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

What is docking?

Predicting the best ways two molecules interact.

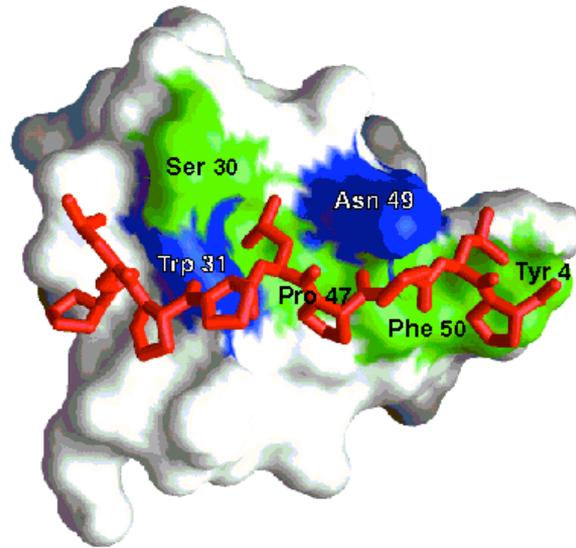
- ◆ Obtain the 3D structures of the two molecules
- ◆ Locate the best binding site (**Remember AnnoLyze?**)
- ◆ Determine the best binding mode.



What is docking?

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

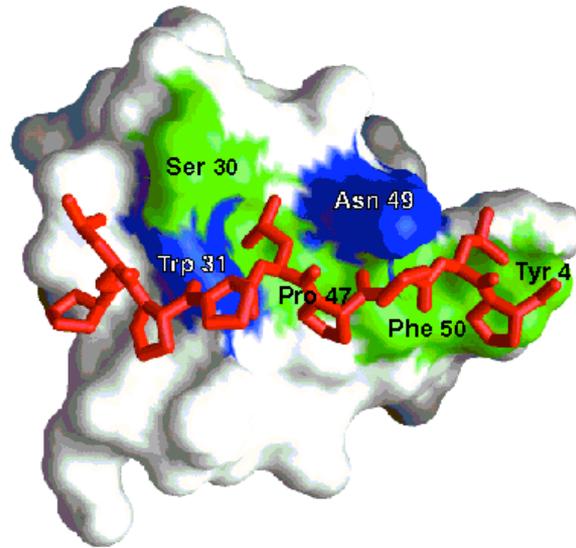
- ◆ We need to quantify or rank solutions
- ◆ We need a good scoring function for such ranking



What is docking?

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

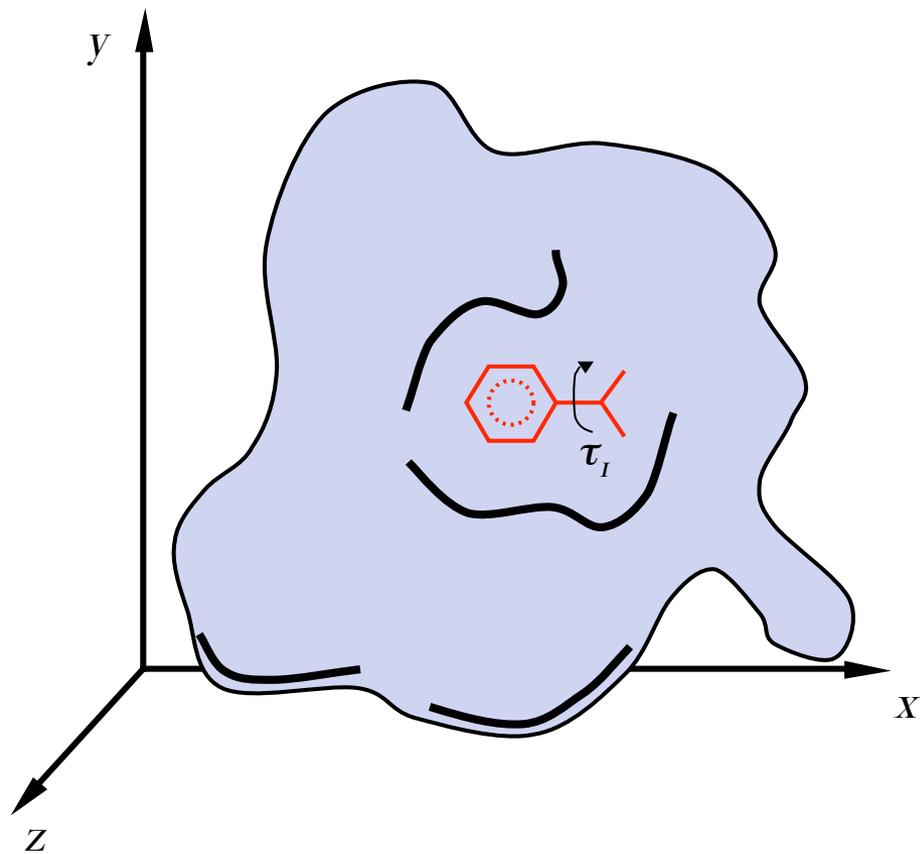
- ◆ X-ray and NMR structures are just ONE of the possible solutions
- ◆ There is a need for a search solution



BIOINFORMATICS (a note)

REPRESENTATION
SCORING
SAMPLING

REPRESENTATION



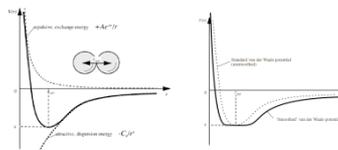
SCORING

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



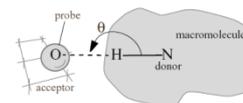
- ΔG_{elec}

Coulombic with Solmajer-dielectric

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

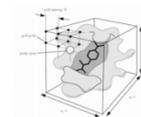
- ΔG_{hbond}

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>

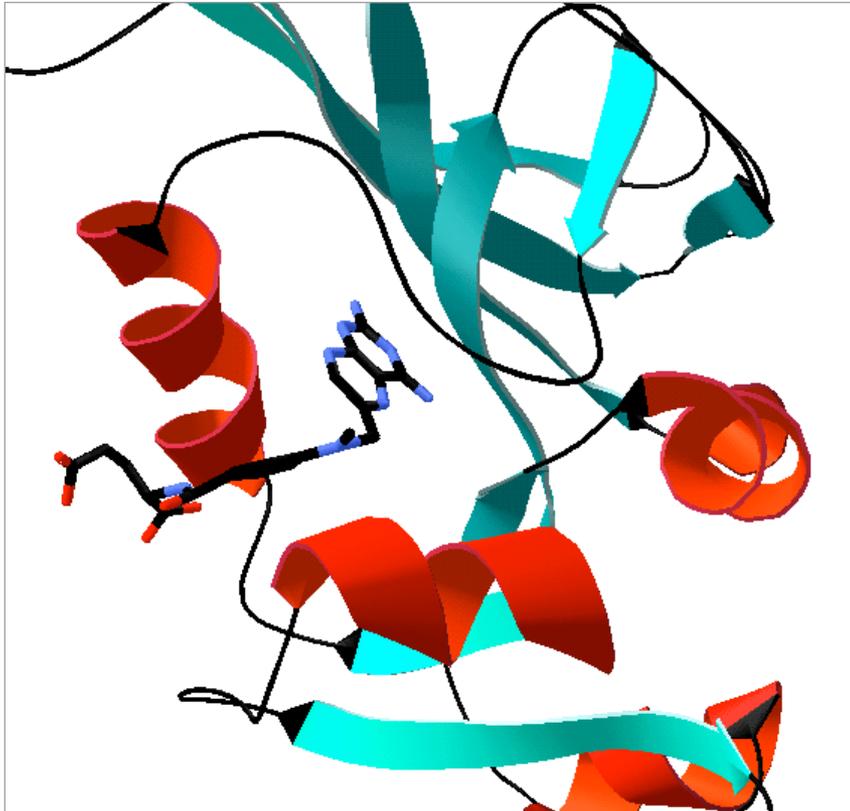
SAMPLING

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...



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

N: number of conformations

T: number of rotatable bonds

i: incremental degrees

Metotrexato

10 rotatable bonds

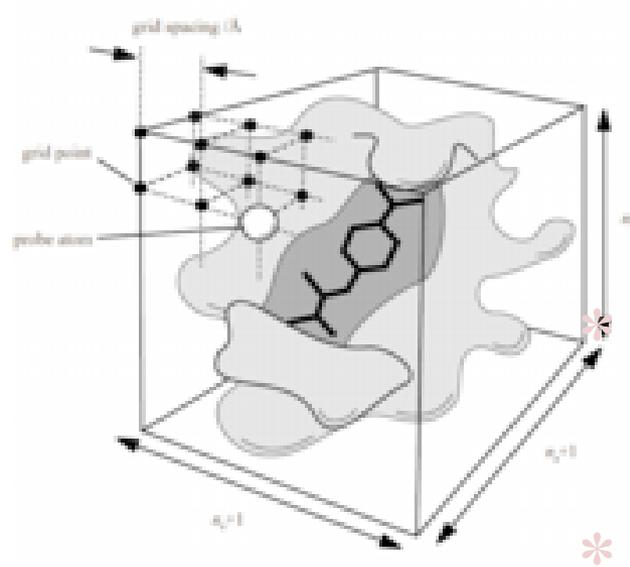
30° increments (discrete)

10¹² plausible conformations!

Dihydrofolate reductase with a metotrexate (4dfr.pdb)

SOLUTION

Use of grid maps!

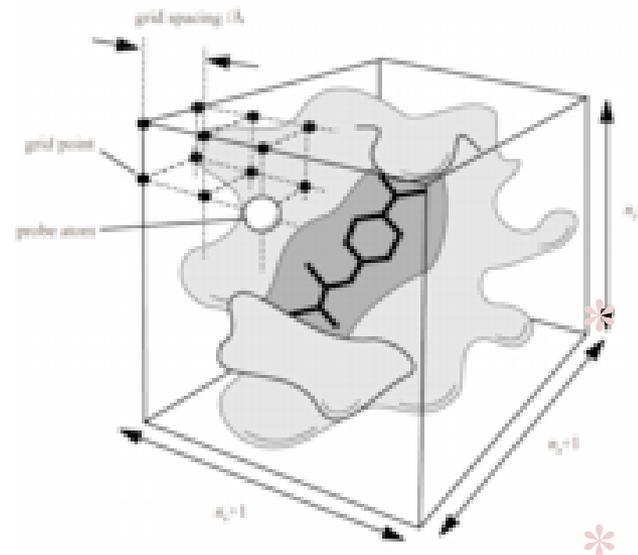


- ◆ Saves lots of time (compared to classical MM/MD)
- ◆ AutoDock uses trilinear interpolation
- ◆ Need to map each atom to a grid point
- ◆ Limits the search space!

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
- ◆ Bond-angle bending
- ◆ Rotational barrier potentials

- ◆ Implicit solvation
- ◆ Polarization

- ◆ What is rigid and what is flexible?

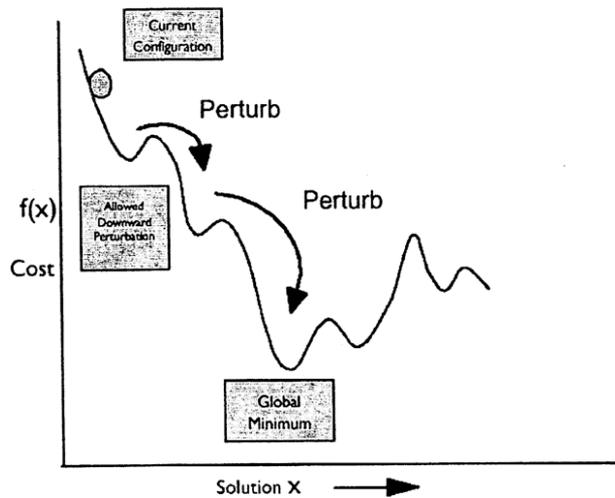
Search algorithms

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

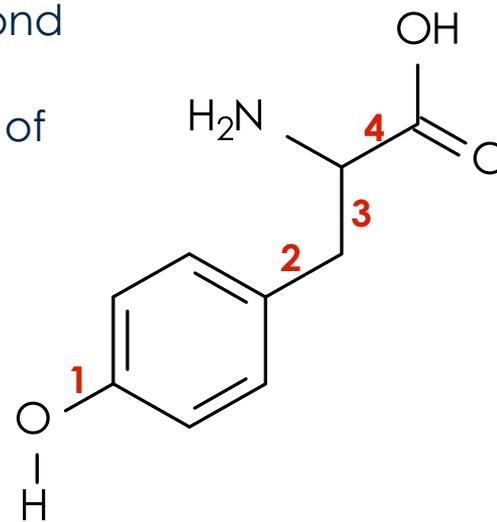
Use of a Genetic Algorithm as a sampling method

- 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

$\underbrace{\hspace{1.5cm}}_{\Phi_1}$ $\underbrace{\hspace{1.5cm}}_{\Phi_2}$...

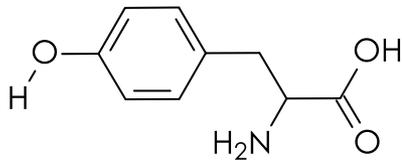
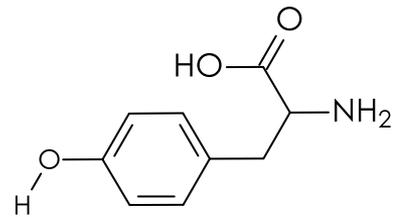
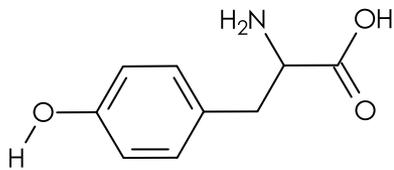
$$\Phi_1 = 1 \times 2^5 + 1 \times 2^4 + 1 \times 2^3 + 0 \times 2^2 + 1 \times 2^1 + 0 \times 2^0 = 58^\circ$$



Search algorithms

Genetic Algorithm

Population (ie, set of chromosomes or configurations)



011010.010110.011010.010111
111010.010110.001011.010010
001010.010101.000101.010001
101001.101110.101010.001000
001010.101000.011101.001011

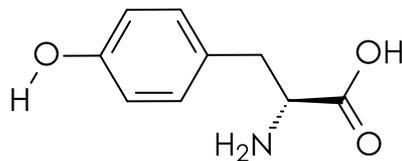
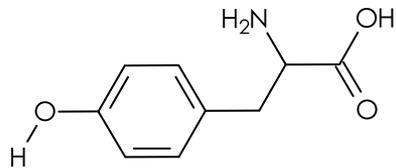
← Chromosome

Gene

Search algorithms

Genetic Algorithm

Genetic operators...



011010.010110.011010.010111



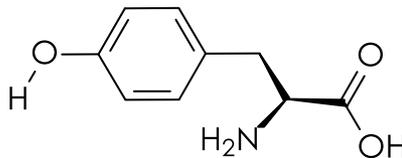
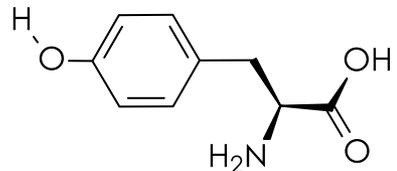
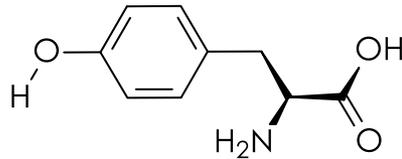
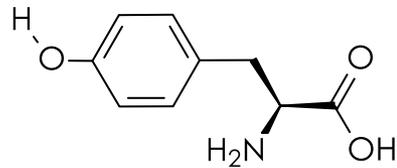
Single
mutation

011010.01**1**110.011**1**10.010111

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...

011010.010110.011010.010111
111010.010110.001011.010010
001010.010101.000101.010001
101001.101110.101010.001000
001010.101000.011101.001011

Migration



111110.010010.011110.010101
101010.110110.011011.011010
001010.010101.000101.010001
101101.101010.101011.001100
011010.100000.011001.101011

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

The screenshot shows the Merck website's newsroom page. At the top, there is a navigation bar with the Merck logo and the text "Where patients come first". Below this is a search bar with a "Quick Find" dropdown and a "Search" button. A secondary navigation bar contains links for "HOME", "ABOUT MERCK", "PRODUCTS", "NEWSROOM", "INVESTOR RELATIONS", "CAREERS", "RESEARCH", "LICENSING", and "THE MERCK MANUALS". The main content area is titled "Product News" and features a large image of a hand holding a microphone with "NEWS NEWS" written on it. The primary article is titled "FDA Approves ISENTRESS™ (raltegravir) Tablets, First-in-Class Oral HIV-1 Integrase Inhibitor". The text of the article states that on October 12, 2007, Merck & Co., Inc. announced that the FDA granted accelerated approval for ISENTRESS tablets. The article also includes a section titled "ABOUT ISENTRESS" with links to "Full Prescribing Information" and "Patient Product Information". On the left side of the page, there is a "Newsroom" sidebar with various categories like "Product News", "Research & Development News", "Corporate News", "Financial News", "Corporate Responsibility News", "Fact Sheet", "Executive Speeches", "Webcasts", and "VIOXX® (rofecoxib) Information Center". At the bottom of the sidebar, there are links for "Contact Newsroom", "Podcast", and "RSS".

Where patients come first **MERCK** Patients & Caregivers | Healthcare Professionals | Worldwide Quick Find Search

HOME | ABOUT MERCK | PRODUCTS | NEWSROOM | INVESTOR RELATIONS | CAREERS | RESEARCH | LICENSING | THE MERCK MANUALS

Newsroom

- Product News
- Research & Development News
- Corporate News
- Financial News
- Corporate Responsibility News
- Fact Sheet
- Executive Speeches
- Webcasts
- VIOXX® (rofecoxib) Information Center

Contact Newsroom

Podcast

RSS

Product News

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

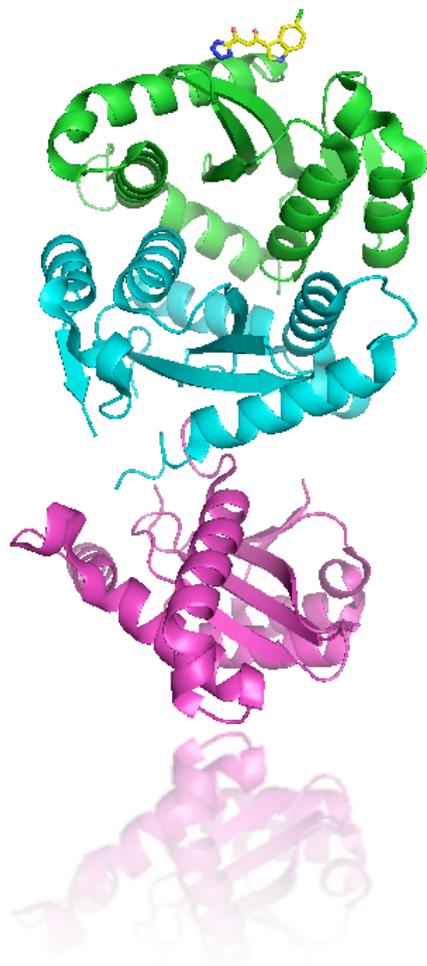
WHITEHOUSE STATION, N.J., Oct. 12, 2007 - Merck & Co., Inc. announced today that the U.S. Food and Drug Administration (FDA) granted ISENTRESS™ (raltegravir) tablets accelerated approval for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced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

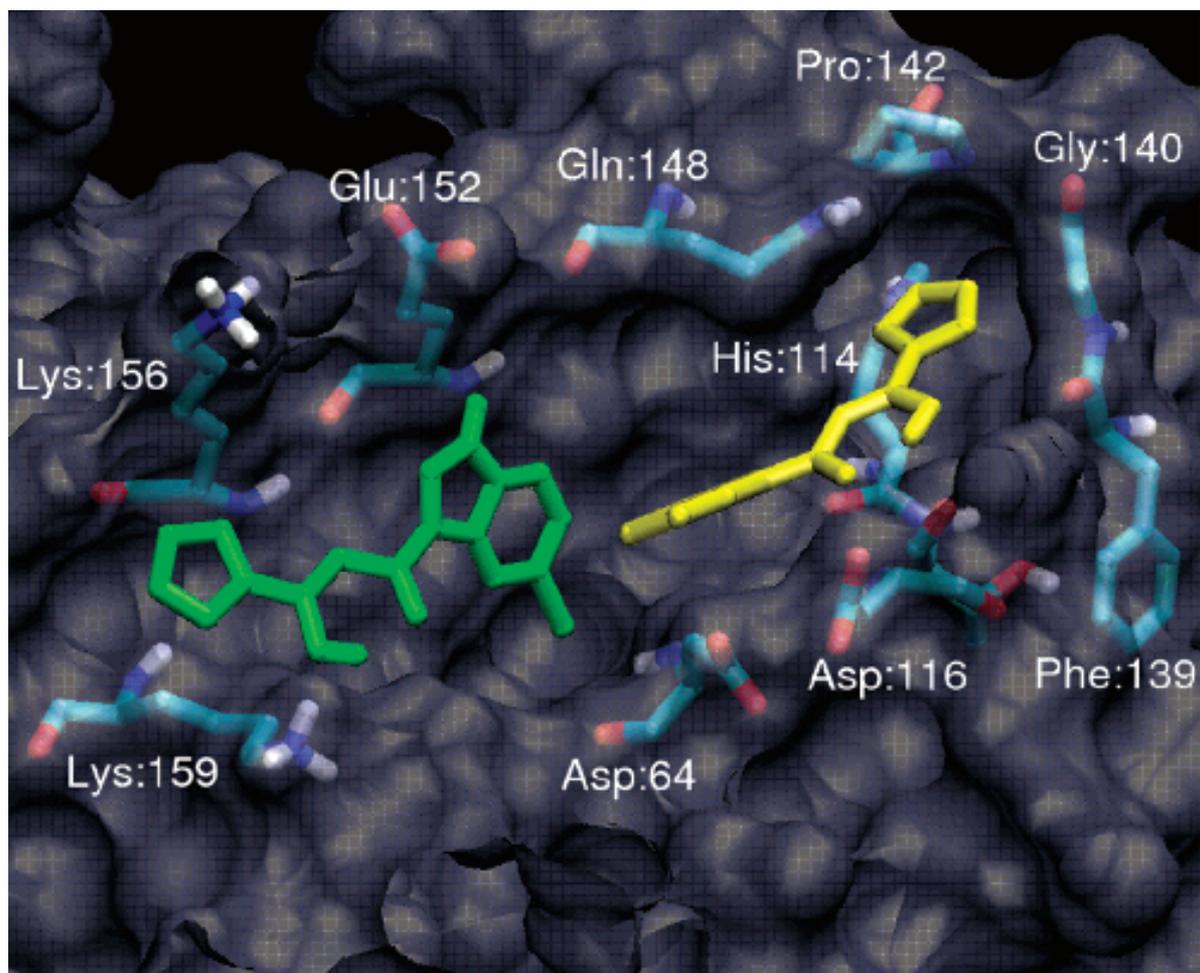
- Full Prescribing Information
- Patient Product Information

ISENTRESS example

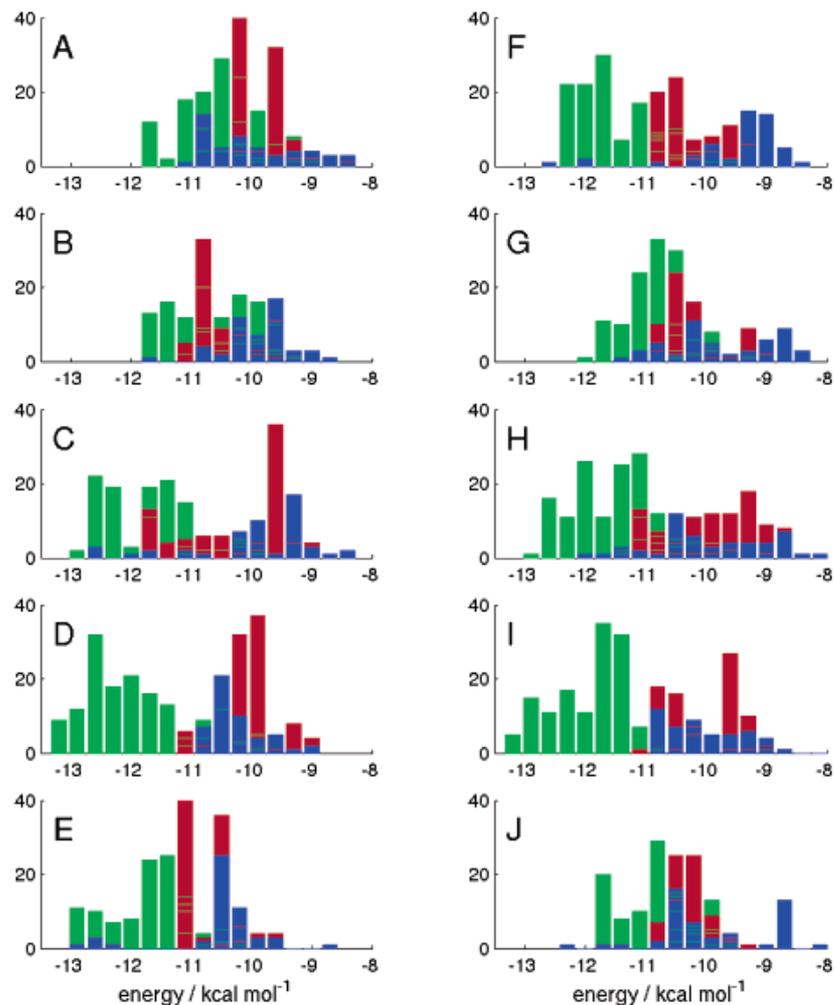
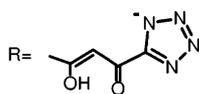
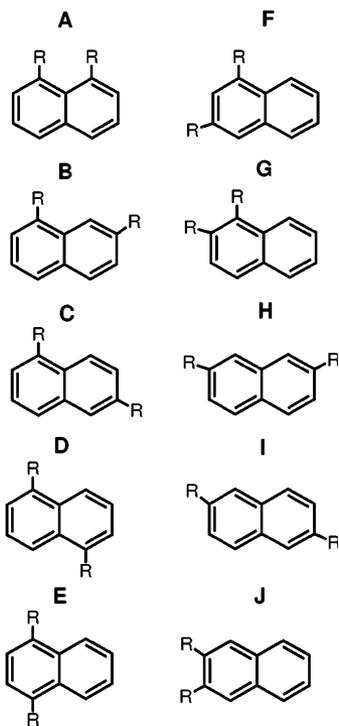


- ◆ One structure known with 5CITEP
 - ◆ Not clear (low resolution)
 - ◆ Binding near to DNA interacting site
 - ◆ Loop near the binding
- ◆ Docking + Molecular Dynamics
 - ◆ AMBER snapshots
 - ◆ AutoDock flexible torsions thetetrazolering and indole ring.

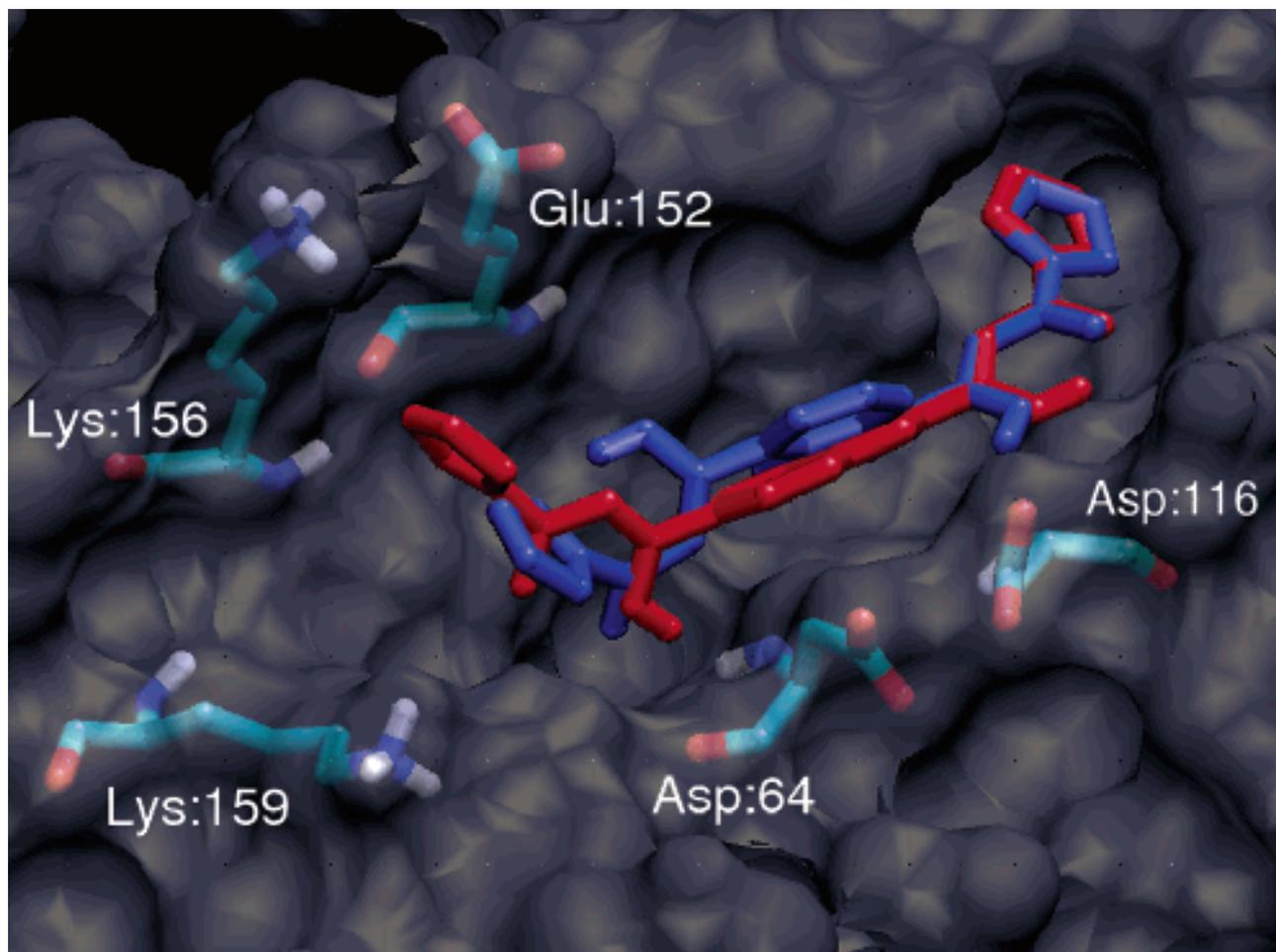
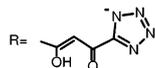
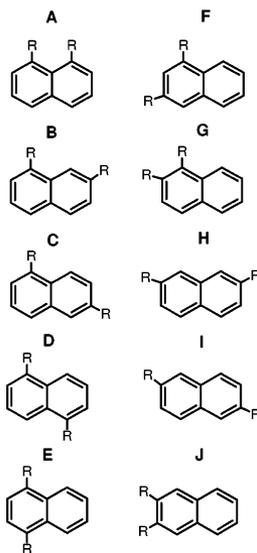
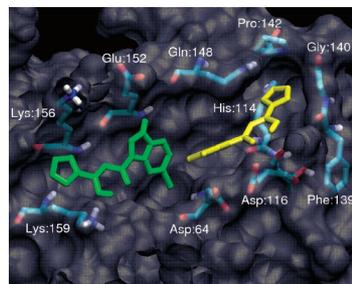
ISENTRESS example



ISENTRESS example



ISENTRESS example



ISENTRESS example

Where patients come first  **MERCK** Patients & Caregivers | Healthcare Professionals | Worldwide

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Newsroom

- [Product News](#)
- [Research & Development News](#)
- [Corporate News](#)
- [Financial News](#)
- [Corporate Responsibility News](#)
- [Fact Sheet](#)
- [Executive Speeches](#)
- [Webcasts](#)
- [VIOXX® \(rofecoxib\) Information Center](#)

 [Contact Newsroom](#)

 [Podcast](#)

 [RSS](#)

Product News



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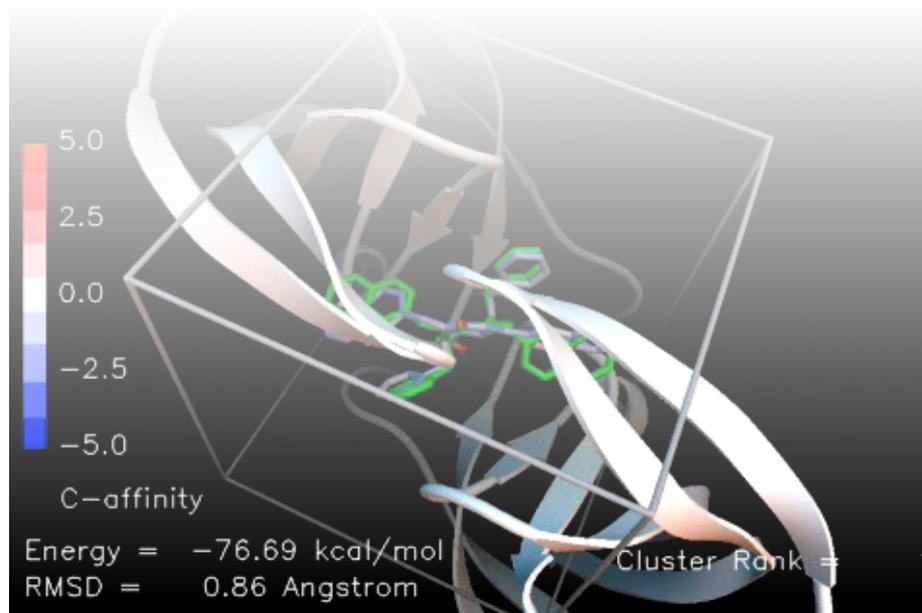
-  [Full Prescribing Information](#)
-  [Patient Product Information](#)

ISENTRESS™
data will be required before the FDA can consider traditional approval for
effect of ISENTRESS on clinical progression of HIV-1 infection. Longer term

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 an 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...

The screenshot shows a web browser window with the URL <http://autodock.scripps.edu/faqs-help/how-to>. The page features the AutoDock logo and a navigation menu with links for home, downloads, science, references, faqs & help, movies, wiki, resources, parameters, and contact. A breadcrumb trail indicates the current location: home → faqs & help → how-tos. On the left, a navigation sidebar lists various resources, with 'How-tos' highlighted. The main content area is titled 'How-tos' and includes an introduction, a 'User' section with a 'General' subsection, and a 'How To Get Help' section. The 'General' subsection lists links for 'How to use this resource', 'Positioning the ligand with ADT', and 'Setting up AutoDockTools utility scripts'. The 'How To Get Help' section lists links for 'How to Subscribe to ADL' and 'How to Unsubscribe from ADL'. The 'How To Get Started' section lists a link for 'How to prepare a ligand file for AutoDock 4'.

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

AutoDock 4.0

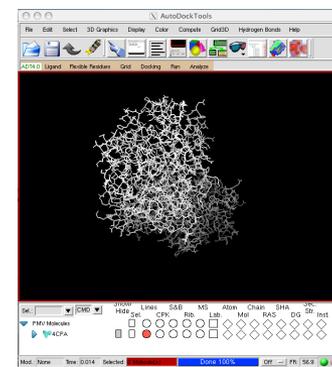
AutoDock and ADT

AutoDock

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

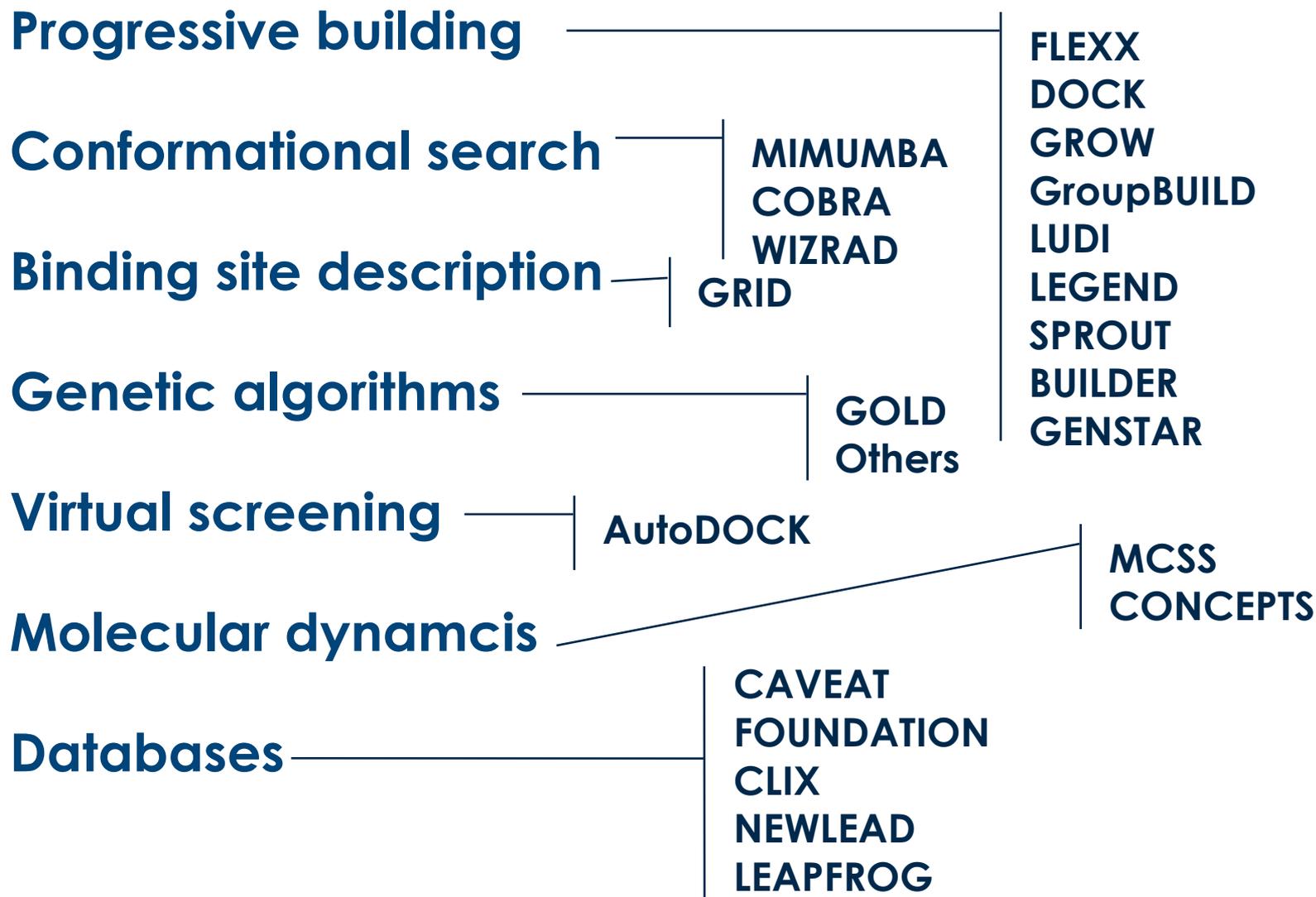
AutoDock Tools

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



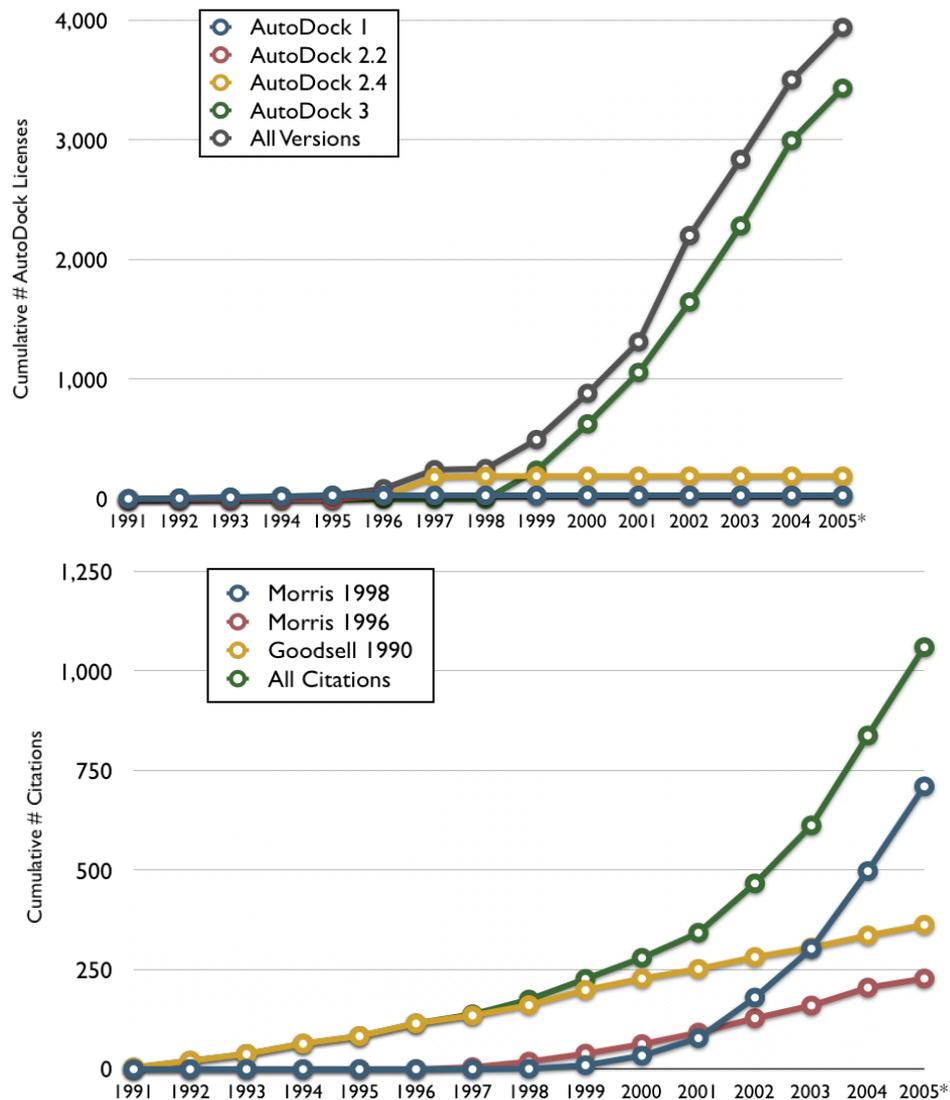
AutoDock 4.0

Alternatives



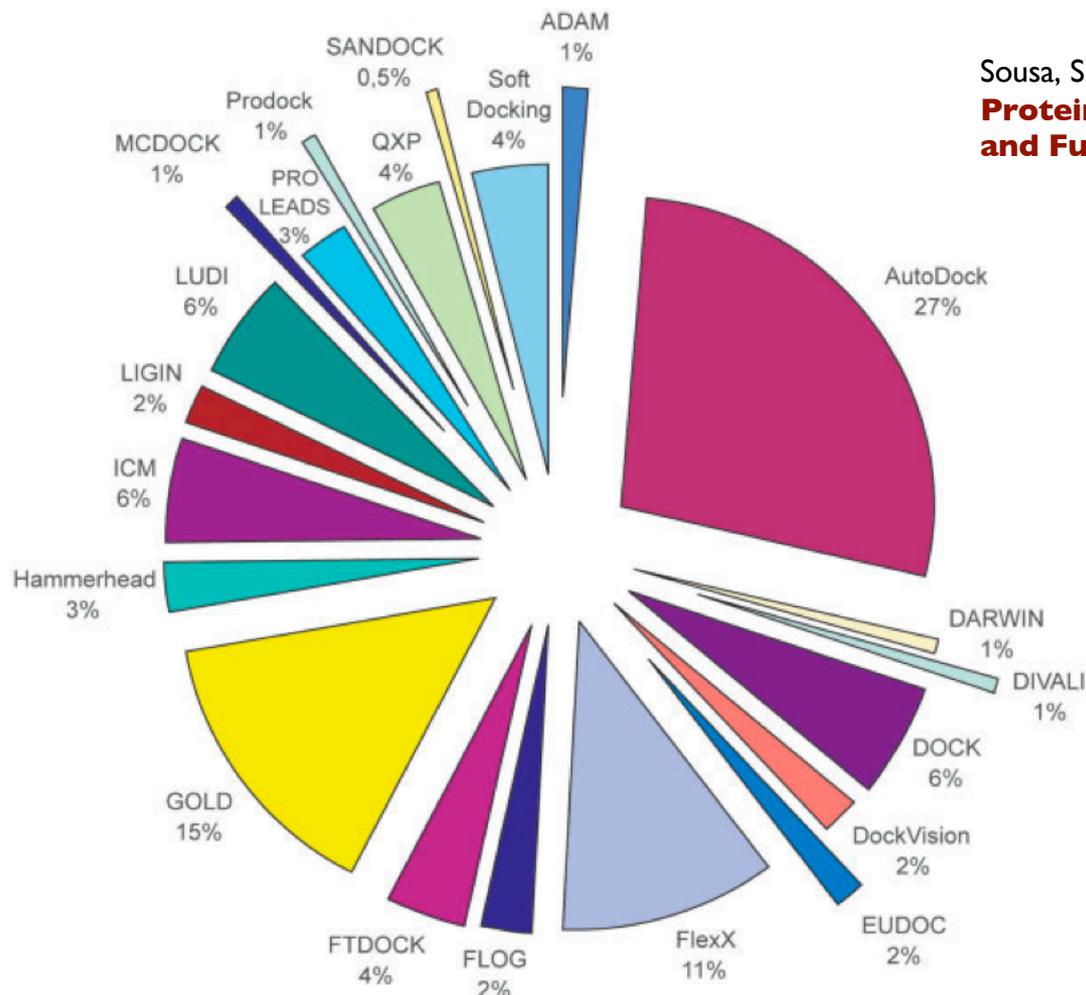
AutoDock 4.0

Why AutoDock over others



AutoDock 4.0

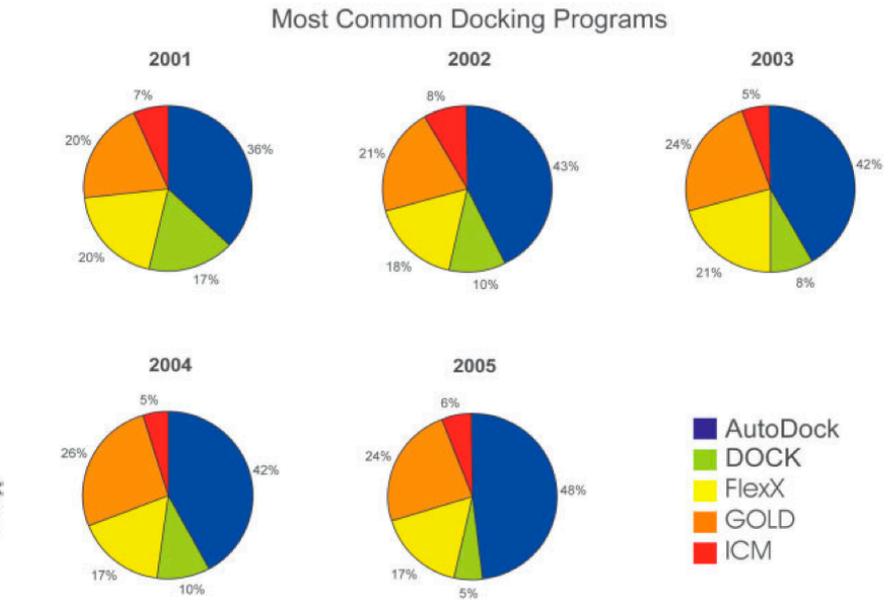
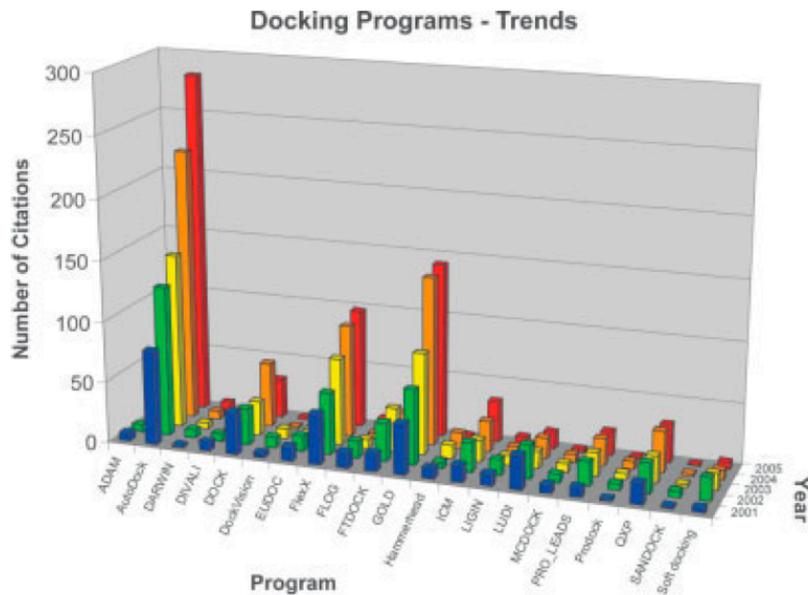
Why AutoDock over others



Sousa, S.F., Fernandes, P.A. & Ramos, M.J. (2006)
**Protein-Ligand Docking: Current Status
and Future Challenges** *Proteins*, **65**:15-26

AutoDock 4.0

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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

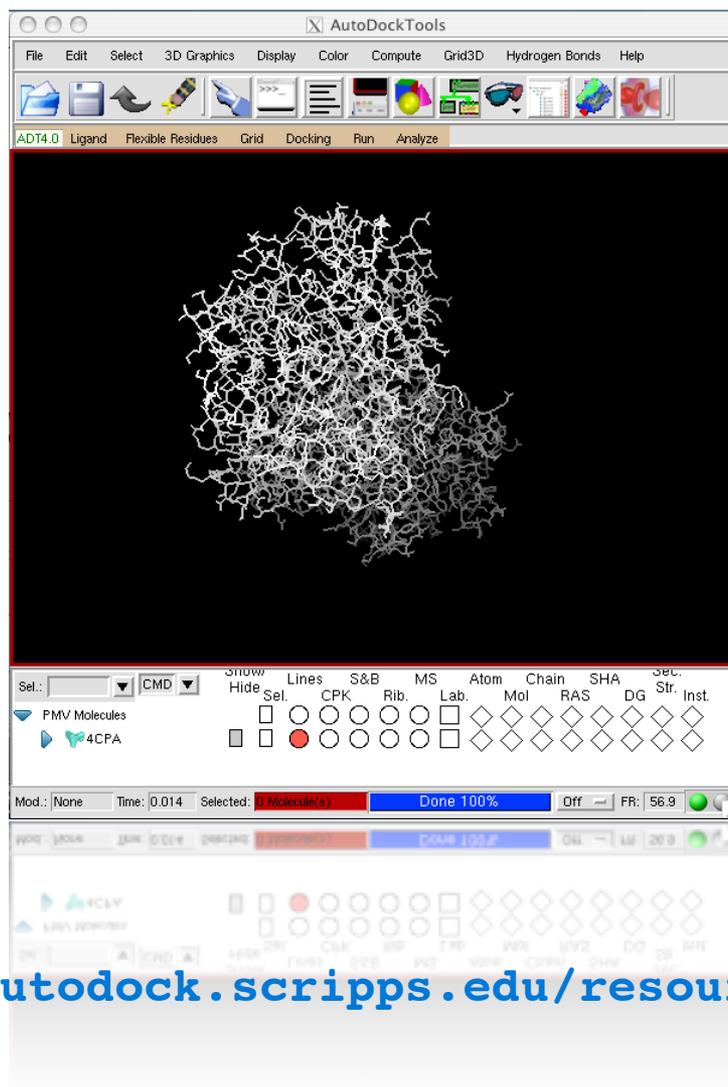
AutoDock 4.0

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://molprobioty.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/>



Università di Pisa
Molecular Modeling & Virtual Screening Laboratory
Dipartimento di Scienze Farmaceutiche

<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
June 3-10 2007
Certosa di Pontignano (Siena – Italia)

1

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

Acknowledgements

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“**Using AutoDock 4 with ADT. A tutorial**”
by Dr. Ruth Huey and Dr. Garret M. Morris

