DOCK 6.1 Users Manual

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Introduction

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1.1. General Overview

DOCK addresses the problem of "docking" molecules to each other. In general, "docking" is the identification of the low-energy binding modes of a small molecule, or ligand, within the active site of a macromolecule, or receptor, whose structure is known. A compound that interacts strongly with, or binds, a receptor associated with a disease may inhibit its function and thus act as a drug. Solving the docking problem computationally requires an accurate representation of the molecular energetics as well as an efficient algorithm to search the potential binding modes.

Historically, the DOCK algorithm addressed rigid body docking using a geometric matching algorithm to superimpose the ligand onto a negative image of the binding pocket. Important features that improved the algorithm's ability to find the lowest-energy binding mode, including force-field based scoring, on-the-fly optimization, an improved matching algorithm for rigid body docking and an algorithm for flexible ligand docking, have been added over the years. For more information on past versions of DOCK, click here.

With the release of DOCK 6, we continue to improve the algorithm's ability to predict binding poses by adding new features like force-field scoring enhanced by solvation and receptor flexibility. For more information about the current release of DOCK, click here.

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1.2. What Can DOCK Do for You

We and others have used DOCK for the following applications:

- predict binding modes of small molecule-protein complexes
- search databases of ligands for compounds that inhibit enzyme activity
- search databases of ligands for compounds that bind a particular protein
- search databases of ligands for compounds that bind nucleic acid targets
- examine possible binding orientations of protein-protein and protein-DNA complexes
- help guide synthetic efforts by examining small molecules that are computationally derivatized
- many more...

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1.3. Installation

NOTE FOR WINDOWS USERS: DOCK and its accessories must be run using a Linux-like environment like Cygwin (http://www.cygwin.com/). When you install your emulator, make sure to also install compilers, unix shells, and perl (Devel for Cygwin). All steps below should be performed using Cygwin or another Windows-based Linux emulator.

(1) Decompress and extract folders using the following commands:

[user@dock ~] tar -zxvf dock.6.1.tar.gz

(2) Enter the installation directory

[user@dock ~] cd dock6/install

(3) Configure the Makefile for the appropriate operating system

[user@dock ~] ./configure [configuration file]

AUTHOR: Scott Brozell

USAGE: configure [-help] [configuration file]

OPTIONS
-help #emit the usage statement
configuration file #input file containing operating system appropriate variables

Configuration Files	Target
gnu	gnu-style compiler
gnu.parallel	gnu-style compiler with parallel processing library capability
gnu.pbsa	gnu-style compiler with PB/SA (ZAP library) capability
gnu.parallel.pbsa	gnu-style compiler with parallel processing library and PB/SA (ZAP library) capabilities
sgi	sgi-style compiler
sgi.parallel	sgi-style compiler with parallel processing library capability

DESCRIPTION:
Create the DOCK configuration file, config.h, by copying an existing configuration file that is selected using the arguments. When invoked without arguments, print this usage statement and if the configuration file exists then print its creation stamp. Some configuration files require that environment variables be defined; these requirements are listed in the files and emitted by configure.

(4) OPTIONAL: Define environment variables.

(i) DOCK with parallel processing functionality requires a Message Passing Interface (MPI) library. Because of the vagaries of MPI libraries, building parallel DOCK has more pitfalls than installing the serial version. The MPI library must be installed and running on the system if the parallel features of DOCK are to be used.
Currently, the DOCK installation mechanism only directly supports the MPICH2 and MPICH implementations. The MPICH2 library is freely available from

Argonne National Labs (http://www-unix.mcs.anl.gov/mpi/mpich/). Once MPI is installed, define the environment variable MPICH_HOME to the top level MPICH2 directory.

WARNING: The parallel configuration files have been tailored to a typical MPICH2 build. Linking problems, such as undefined references and cannot find libbla_bla, can occur due to idiosyncrasies in the MPI installation. One corrective approach is to use manual linking; add to the LIBS definition in config.h the link flags (-L and -l) from the command: $MPICH_HOME/mpicc -show; in general, the LIBS should contain those link flags in the same order.
(ii) DOCK with PB/SA scoring requires the OpenEye ZAP library. The ZAP library can be obtained from OpenEye (http://www.eyesopen.com/). Once ZAP is installed, define the environment variable ZAP_HOME to the directory that contains the ZAP library.

(5) Build the desired DOCK executable(s) via one of the following commands:

```
[user@dock ~] make all # builds all the DOCK programs
[user@dock ~] make dock # builds only the dock program
[user@dock ~] make utils # builds only the accessory programs
```

(6) Test the built executable(s) via this sequence of commands:

```
[user@dock ~] cd test
[user@dock ~] make clean
[user@dock ~] make test
```

This directory contains the DOCK quality control (QC) suite. It produces pass/fail results via fast regression tests. The suite should complete in less than ten minutes; un-passed tests should be examined to determine their significance.

If failures occur then examine the outputs via the command:

```
[user@dock ~] make check
```

NOTE: Some failures are not significant. For example, differences in the tails of floating point numbers may not be significant. The sources of such differences are frequently platform dependencies from computer hardware, operating systems, and compilers that impact arithmetic precision and random number generators. We are working on increasing DOCK's resilience to these issues. For now, apply common sense and good judgment to determine the significance of a possible failure.

If you have problems with any of the steps above, please contact us at dock_bugs@dock.compbio.ucsf.edu with a full description of your problem.

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1.4. What's New in DOCK 6

Version 6.0

The new features of DOCK 6 include:
additional scoring options during minimization; DOCK 3.5 scoring-including Delphi electrostatics, ligand conformational entropy corrections, ligand desolvation, receptor desolvation; Hawkins-Cramer-Truhlar GB/SA solvation scoring with optional salt screening; PB/SA solvation scoring; AMBER scoring-including receptor flexibility; the full AMBER

molecular mechanics scoring function with implicit solvent; conjugate gradient minimization and molecular dynamics simulation capabilities.

Version 6.1

The newly added features for the incremental release of DOCK 6 include a new pruning algorithm during the anchor-and-grow algorithm, a distance-based movable region and a mildly performance optimized nothing movable region for AMBER score, cleaner output and more complete output files for AMBER score, the ability to perform ranking and/or clustering on ligands between primary and secondary scoring, and more dynamic output when secondary scoring is employed.

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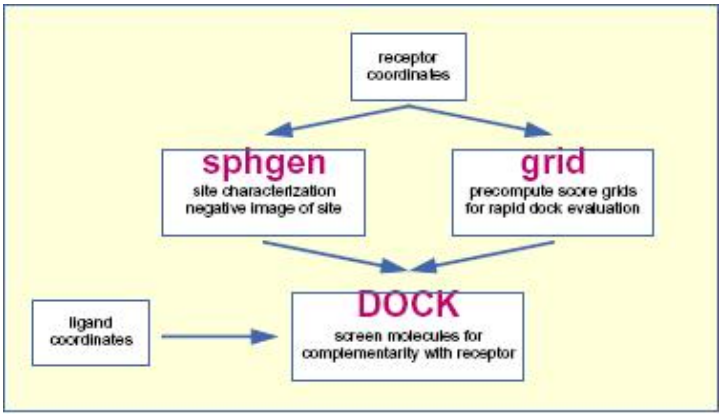
1.5. Overview of the DOCK Suite of Programs

1.5.1. Programs

The relationship between the main programs in the dock suite is depicted in Figure 1. These routines will be described below.



Main programs in DOCK suite

The program sphgen
identifies the active site, and other sites of interest, and generates the sphere centers that fill the site. It has been described in the original paper (Kuntz, et al. *J. Mol. Biol.* 1982). The program grid generates the scoring grids (Shoichet, et al. *J. Comp. Chem.* 1992 and Meng, et al. *J. Comp. Chem.* 1992). Within the DOCK suite of programs, the program DOCK matches spheres (generated by sphgen) with ligand atoms and uses scoring grids (from grid) to evaluate ligand orientations (Kuntz, et al. *J. Mol. Biol.* 1982 and Shoichet, et al. *J. Comp. Chem.* 1992). Program DOCK also minimizes energy based scores (Meng, et al. *Proteins*. 1993).

1.5.2. General Concepts

The DOCK suite of programs is designed to find favorable orientations of a ligand in a "receptor." It can be subdivided into

(i) those programs related directly to docking of ligands and
(ii) accessory programs.

We limit the discussion in this section to only those programs and methods related to docking a ligand in a receptor. A typical receptor might be an enzyme with a well-defined active site, though any macromolecule may be used (e.g. a structural protein, a nucleic acid strand, a

"true" receptor). We'll use an enzyme as an example in the rest of this discussion.

The starting point of all docking calculations is generally the crystal or NMR structure of an enzyme from an enzyme-ligand complex. The ligand structure may be taken from the crystal structure of the enzyme-ligand complex or from a database of compounds, such as the ZINC database (Irwin, et. al. *J. Chem. Inf. Model.* 2005). The primary consideration in the design of our docking programs has been to develop methods which are both rapid and reasonably accurate. These programs can be separated functionally into roughly two parts, each somewhat independent of the other:

(i) Routines which determine the orientation of a ligand relative to the receptor
and
(ii) Routines which evaluate (score) a ligand orientation.

There is a lot of flexibility. You can generate orientations outside of DOCK and score them with the DOCK evaluation functions. Alternatively, you can develop your own scoring routines to replace the functions supplied with DOCK.

The ligand orientation in a receptor site is broken down into a series of steps, in different programs. First, a potential site of interest on the receptor is identified. (Often, the active site is the site of interest and is known a priori.) Within this site, points are identified where ligand atoms may be located. A routine from the DOCK suite of programs identifies these points, called sphere centers, by generating a set of overlapping spheres which fill the site. Rather than using DOCK to generate these sphere centers, important positions within the active site may be identified by some other mechanism and used by DOCK as sphere centers. For example, the positions of atoms from the bound ligand may be used as these sphere centers. Or, a grid may be generated within the site and each grid point may be considered as a sphere center. Our sphere centers, however, attempt to capture shape characteristics of the active site (or site of interest) with a minimum number of points and without the bias of previously known ligand binding modes.

To orient a ligand within the active site, some of the sphere centers are "matched" with ligand atoms. That is, a sphere center is "paired" with an ligand atom. Many sets of these atom-sphere pairs are generated, each set containing only a small number of sphere-atom pairs. In order to limit the number of possible sets of atom-sphere pairs, a longest distance heuristic is used; (long) inter-sphere distances are roughly equal to the corresponding (long) inter-atomic ligand distances. A set of atom-sphere pairs is used to calculate an orientation of the ligand within the site of interest. The set of sphere-atom pairs which are used to generate an orientation is often referred to as a match. The translation vector and rotation matrix which minimizes the rmsd of (transformed) ligand atoms and matching sphere centers of the sphere-atom set are calculated and used to orient the entire ligand within the active site.

The orientation of the ligand is evaluated with a shape scoring function and/or a function approximating the ligand-enzyme binding energy. Most evaluations are done on (scoring) grids in order to minimize the overall computational time. At each grid point, the enzyme contributions to the score are stored. That is, receptor contributions to the score, potentially repetitive and time consuming, are calculated only once; the appropriate terms are then simply fetched from memory.

The ligand-enzyme binding energy is taken to be approximately the sum of the van der Waal attractive, van der Waal dispersive, and Coulombic electrostatic energies. Approximations are made to the usual molecular mechanics attractive and dispersive terms for use on a grid. To generate the energy score, the ligand atom terms are combined with the receptor terms from the nearest grid point, or combined with receptor terms from a "virtual" grid point with interpolated receptor values. The score is the sum of over all ligand atoms for these combined terms. In this case, the energy score is determined by both ligand atom types and

ligand atom positions on the energy grids.

As a final step, in the energy scoring scheme, the orientation of the ligand may be varied slightly to minimize the energy score. That is, after the initial orientation and evaluation (scoring) of the ligand, a simplex minimization is used to locate the nearest local energy minimum. The sphere centers themselves are simply approximations to possible atom locations; the orientations generated by the sphere-atom pairing, although reasonable, may not be minimal in energy.

1.5.3. Specific Concepts

(A) Sphere Centers

Spheres are generated to fill the target site. The sphere centers are putative ligand atom positions. Their use is an attempt to limit the enormous number of possible orientations within the active site. Like ligand atoms, these spheres touch the surface of the molecule and do not intersect the molecule. The spheres are allowed to intersect other spheres; i.e. they have volumes which overlap. Each sphere is represented by the coordinates of its center and its radius. Only the coordinates of the sphere centers are used to orient ligands within the active site (see above). Sphere radii are used in clustering.

The number of orientations of the ligand in free space is vast. The number of orientations possible from all sets of sphere-atom pairings is smaller but still large and cannot be generated and evaluated (scored) in a reasonable length of time. Consequently, various filters are used to eliminate from consideration, before evaluation, sets of sphere-atoms pairs, which will generate poorly scoring orientations. That is, only a small subset of the number of possible ligand orientations are actually generated and scored. The distance tolerance is one filter. Sphere “coloring” and identification of “critical” spheres are other filters.

Sphere-sphere distances are compared to atom-atom distances. Sets of sphere-atom pairs are generated in the following manner: sphere ***i*** is paired with atom ***I*** if and only if for every sphere ***j*** in the set and for every atom ***J*** in the set,

$$\left| d_{ij} - d_{IJ} \right| < \varepsilon$$

where d_{ij} is the distance between sphere *i* and sphere *j*, d_{IJ} is the distance between atom *I* and atom *J*, and *epsilon* is a somewhat small user-defined value.

(B) Chemical Matching

DOCK spheres are generated without regard to the chemical properties of the nearby receptor atoms. Sphere “chemical matching” or “coloring” associates a chemical property to spheres and a sphere of one “color” can only be matched with a ligand atom of complementary color. These chemical properties may be things such as “hydrogen-bond donor,” “hydrogen-bond acceptor,” “hydrophobe,” “electro-positive,” “electro-negative,” “neutral,” etc. Neither the colors themselves, nor the complementarity of the colors, are determined by the DOCK suite of programs; DOCK simply uses these labels. With the inclusion of coloring, only ligand atoms with the appropriate chemical properties are matched to the complementary colored spheres. It is probably more likely, then, that the orientation generated will produce a favorable score. Conversely, by excluding colored spheres from pairing with certain ligand atoms, the number of (probably) unfavorable orientations which are generated and evaluated can be reduced.

Note that requiring complementarity in matching does not mean that all ligand atoms will lie in chemically complementary regions of the enzyme. Rather, only those ligand atoms, when paired with a colored sphere which is part of the sphere-atom match, will be guaranteed to be in the chemically complementary region of the enzyme (provided chirality of the spheres is the same as that of the matching ligand atoms).

(C) Critical Points

The "critical point" filter requires that certain spheres be part of the set of sphere-atom pairs used to orient the ligand (DesJarlais, et al. *J. Comput-Aided Molec. Design.* 1994). Designating spheres as critical points forces the ligand to have at least one atom in that area of the enzyme, where that sphere is located. This filter may be useful, for example, when it is known that a ligand must occupy a particular area of an active site. This filter removes from consideration any orientation that does not guarantee at least one ligand atom in critical areas of the enzyme (provided chirality of the spheres is the same as that of the matching ligand atom).

(D) Bump Filter

After a ligand is oriented within the active site, the orientation is evaluated. In an attempt to reduce the total computational time, after the ligand is oriented in the site, it is possible to first check whether or not ligand atoms occupy space already occupied by the receptor. If too many of such “bumps” are found, then the ligand is likely to intersect the receptor even after minimization; consequently, the ligand orientation is discarded before evaluation.

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DOCK

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2.1. Overview

This section is intended as a reference manual for the features of the DOCK Suite of Programs. It is intended to give an overview of the ideas which form the basis of the DOCK suite of programs and to detail the available user parameters. It is not intended to be a substitute for all the papers written on DOCK.

In general, this document is geared towards the experienced user and introduces new features and concepts in version 6. If you are new to DOCK, we strongly recommend you look at the tutorials on the DOCK web site at http://dock.compbio.ucsf.edu/DOCK_6/index.htm, which go into much greater practical detail.

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2.2. History

Version 1.0/1.1

Authors: Robert Sheridan, Renee DesJarlais, Irwin Kuntz

The program DOCK is an automatic procedure for docking a molecule into a receptor site. The receptor site is characterized by centers, which may come from SPHGEN or any other source. The molecule being docked is characterized by ligand centers, which may be its non-hydrogen atoms or volume-filling spheres calculated in SPHGEN. The ligand centers and receptor centers are matched based on comparison of ligand-center/ligand-center and receptor-center/receptor-center distances. Sets of ligand centers match sets of receptor centers if all the internal distances match, within a value of distance_tolerance. Ligand-receptor pairs are added to the set until at least nodes_minimum pairs have been found. At least three pairs must be found to uniquely determine a rotation/translation matrix that will orient the ligand in the receptor site. A least-squares fitting procedure is used (Ferro, et al *Act. Cryst. A.* 1977.). Once an orientation has been found, it is evaluated by any of several scoring functions. DOCK may be used to explore the binding modes of an individual molecule, or be used to screen a database of molecules to identify potential ligands.

Version 2.0

Authors: Brian Shoichet, Dale Bodian, Irwin Kuntz

DOCK version 2.0 was written to give the user greater control over the thoroughness of the matching procedure, and thus over the number of orientations found and the CPU time required (Shoichet, et al. *J. Comp. Chem.* 1992). In addition, certain algorithmic shortcomings of earlier versions were overcome. Versions 2.0 and higher are particularly useful for macromolecular docking (Shoichet, et al *J. Mol. Biol.* 1991) and applications which demand detailed exploration of ligand binding modes. In these cases, users are encouraged to run CLUSTER in conjunction with SPHGEN and DOCK.

To allow for greater control over searches of orientation space, the ligand and receptor centers are pre-organized according to their internal distances. Starting with any given center, all the other centers are presorted into “bins” based on their distance to the first center. All centers are tried in turn as “first” positions, and all the points in a bin which has been chosen for matching are tried sequentially. Ligand and receptor bins are chosen for matching when they have the same distance limits from their respective “first” points. The number of centers in each bin determines how many sets of points in the receptor and the ligand will ultimately be compared. In general, the wider the bins, the greater the number of orientations generated. Thus, the thoroughness of the search is under user control.

Version 3.0

Authors: Elaine Meng, Brian Shoichet, Irwin Kuntz

Version 3.0 retained the matching features of version 2.0, and introduced options for scoring (Meng, et al. *J. Comp. Chem.*, 1992). Besides the simple contact scores mentioned above, one can also obtain molecular mechanics interaction energies using grid files calculated by CHEMGRID (which is now superseded by GRID in version 4.0). More information about the ligand and receptor molecules is required to perform these higher-level kinds of scoring. Point charges on the receptor and ligand atoms are needed for electrostatic scoring, and atom-type information is needed for the van der Waals portion of the force field score. Input formats (some of them new in version 3.5) are discussed in various parts of the documentation; one example of a “complete format” (including point charges and atom type information) is SYBYL MOL2 format. Parameterization of the receptor is discussed in the documentation for CHEMGRID. In DOCK, ligand parameters are read in along with the coordinates; input formats are described below. Currently, the options are: contact scoring only, contact scoring plus Delphi electrostatic scoring, and contact scoring plus force field scoring. Atom-type information and point charges are not required for contact scoring only.

Version 3.5

Authors: Mike Connolly, Daniel Gschwend, Andy Good, Connie Oshiro, Irwin Kuntz

Version 3.5 added several features: score optimization, degeneracy checking, chemical matching and critical clustering.

Version 4.0

Authors: Todd Ewing, Irwin Kuntz

Version 4.0 was a major rewrite and update of DOCK. A new matching engine was developed which is more robust, efficient, and easier to use (Ewing, et al. *J. Comput. Chem.* 1997). Orientational sampling can now be controlled directly by specifying the number of desired orientations. Additional features include chemical scoring, chemical screening, and ligand flexibility.

Version 5.0-5.4

Authors: Demetri Moustakas, P. Therese Lang, Scott Pegg, Scott Brozell, Irwin Kuntz

Version 5 was rewritten in C++ in a modular format, which allows for easy implementation of new scoring functions, sampling methods and analysis tools (Moustakas, et al, 2006). Additional new features include MPI parallelization, exhaustive orientation searching, improved conformation searching, GB/SA solvation scoring, and post-screening pose clustering. (Zou, et al. *J. Am. Chem. Soc.*, 1999)

Version 6.0-6.1

DOCK 6 is an extension of the DOCK 5 code base. It includes the implementation of Hawkins-Cramer-Truhlar GB/SA solvation scoring with salt screening and PB/SA solvation scoring through OpenEye's Zap Library. Additional flexibility has been added to scoring options during minimization. The new code also incorporates DOCK version 3.5.54 scoring features like Delphi electrostatics, ligand desolvation, and receptor desolvation. Finally, DOCK 6 introduces new code that allows access to the NAB library of functions such as receptor flexibility, the full AMBER molecular mechanics scoring function with implicit solvent, conjugate gradient minimization, and molecular dynamics simulation capabilities.

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2.3. Command-line Arguments

DOCK must be run command line from a standard unix shell. It reads a parameter file containing field/value pairs using the following command:

USAGE: dock6 -i dock.in [-o dock.out] [-v]

DESCRIPTION:
DOCK may be executed in either interactive or batch mode, depending on whether output is written to a file. In interactive mode, the user is requested only for parameters relevant to the particular run and default values are provided. This mode is recommended for the initial construction of the input file and for short calculations. In batch mode, input parameters are read in from the input file and all output is written to the output file. This mode is recommended for long calculations once an input file has been generated interactively.

OPTIONS
-i dock.in #input file containing user-defined parameters
-help #emit the usage statement.
-v #verbosity flag that prints additional information and warnings for scoring functions

-o dock.out
#output file containing the parameters used in the calculation, summary information for each molecule docked, and all warning messages

Interactive mode

USAGE: dock6 -i dock.in

DESCRIPTION:
When launched this way, DOCK will extract all relevant parameters from dock.in (or any file supplied by the user). If additional parameters are needed (or if the dock.infile is non-existent or empty), DOCK will request them one at a time from the user. Reasonable default values are presented. Any parameters supplied by the user will be automatically appended to the dock.in file. If the user would like to change any previously entered values, the user can edit in the dock.in file using a text editor.

Batch mode

USAGE: dock6 -i dock.in -o dock.out

DESCRIPTION:
When launched in this way, DOCK will run in batch mode, extracting all relevant parameters from dock.in (or any file supplied by the user) and will write out all output to dock.out(or any file supplied by the user). If any parameters are missing or incorrect, then execution will halt and an appropriate error message will be reported in dock.out.

Parallel DOCK

USAGE: mpirun [-machinefile machfile] [-np #_of_proc] dock6.mpi -i dock.in -o dock.out [-v]

DESCRIPTION:
If you have compiled DOCK for parallel processing (see Installation), DOCK can be run in parallel. Parallelzation is set up to have a single Master node with the remaining nodes act as slaves. The Master node performs file processing and input/output, whereas the slaves perform the actual calculations. If np = 1, the code defaults to non-MPI behavior. As a result, there will be minimal difference in performance between 1 and 2 processors. Improved performance will only become evident with more than 2 nodes.

ADDITIONAL OPTIONS
-machinefile
#simple text file containing the names of the computers (nodes) to be used
-np #
specifies the number of processors which typically is the same as the number of lines in the machinefile

PB/SA DOCK

USAGE: dock6.pbsa -i dock.in [-o dock.out] [-v]

DESCRIPTION:
If you have compiled DOCK for use with the ZAP library (see Installation), DOCK can be run using the ZAP PB/SA scoring function.

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2.4. The Parameter Parser

In Interactive Mode, dock will dynamically ask the user to enter the appropriate user parameters. The generic format for the questions is:

parameter_name [default value] (legal values):

The parameter parser requires that the values entered for a parameter exactly match one of the legal values. For example:

Example A: program_location [Hello_World!] ():

Example B: #_red_balloons [99] ():

Example C: glass_status [half_full] (half_full half_empty):

In Example A, the parameter "program_location" can be assigned any string value, and in Example B, the parameter "#_red_balloons" can be assigned any integer value. However, in Example C, the parameter value "glass_status" can only be assigned the strings "half_full" or "half_empty". If no parameter are assigned by the user, the default value--in brackets--will be used.

In Batch Mode, all parameters in the dock.in file, must be:

parameter_name value

Note that the parameter_name and corresponding value need to be separated by white space or a tab.

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2.5. Ligand File Input

Before you can dock a ligand, you will need atom types and charges for every atom in the ligand. Currently, DOCK only reads the Tripos MOL2 format. For a single ligand (or several ligands), you can use Chimera in combination with antechamber to prepare a MOL2 file for the ligand (see Structure Preparation Tutorial) or various other visualization packages. During the docking procedure, ligands are read in from a single MOL2 or multi-MOL2 file. Atom and bond types are assigned using the DOCK 4 atom/bond typing parameter files.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Molecule Library Parameters

- ligand_atom_file [database.mol2] (string):
  # The ligand input filename
- limit_max_ligands [no] (yes, no):
  #Limit the number of ligands to be read in from a library
  - max_ligands[1000]:

#maximum number of ligands that will be read in from a library

- skip_molecule [no] (yes, no):
  #Skip some number of molecules at the beginning of a library
  - initial_skip [0] (int):
    # The number of molecules to skip over at the beginning of a library
- read_mol_solvation [no] (yes, no):
  #Flag to read atomic desolvation information from ligand file
- calculate_rmsd [no] (yes, no):
  #Flag to perform an RMSD calculation between the final molecule pose and its initial #structure.
  - use_rmsd_reference_mol [no] (yes, no):
    #Specify alternative geometric location for reference structure for RMSD #calculation
  - rmsd_reference_filename [ligand_rmsd.mol2] (string):
    #File containing alternative geometric location for reference structure for #RMSD calculation

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2.6. Orienting the Ligand

2.6.1. Sphere Matching

The rigid body orienting code is written as a direct implementation of the isomorphous subgraph matching method of Crippen and Kuhl (Kuhl, et al. *J. Comput. Chem.* 1984). All receptor sphere pairs and atom center pairs are considered for inclusion in a matching clique. This is more computationally demanding than the clique matching algorithm implemented in previous versions that used a distance binning algorithm to restrict the clique search, in which pairs of spheres and atom centers were binned by distance. Only sphere pairs and center pairs that were within the same distance bin were considered as potential matches (Ewing, et al. *J. Comput. Chem.* 1997) .

The clique matching implementation avoids bin boundaries that prevent some receptor sphere and ligand atom pairs from matching, and, as a result, it can find good matches missed by previous versions of DOCK. The rigid body rotation code has also been corrected to avoid a singularity that occurred if the spheres in the match lay within the same plane.

There are two types of ligand orientation currently available:

> (1) Automated Matching —Specify the number of orientations, and DOCK will generate matches until enough orientations passing the bump filter have been formed. Matches are formed best first, with respect to the difference in the ligand and site point internal distances.
> (2) Manual Matching —Specify the distance and node parameters, and DOCK will generate all the matches which satisfy them. The number of orientations scored is equal to the total matches minus the orientations discarded by the user applied filters.

Multiple orientations may be written out for each molecule using the write_orientations parameter (see Ligand File Output), otherwise only the best orientation is recorded.

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2.6.2. Critical Points

The critical_points feature is used to focus the orientation search into a subsite of the receptor active site (DesJarlais, et al. *J. Comput-Aided Molec. Design.* 1994 and Miller, et al *J. Comput. Aided Mol. Design*. 1994). For example, identifying molecules that interact with catalytic residues might be of chief interest. Any number of points may be identified as critical (see Critical Points information on labeling spheres), and any number of groupings of these points may be identified. An alternative to using critical points is to discard all site points that are some distance away from the subsite of interest, while retaining enough site points to define unique ligand orientations. This feature can be highly effective at reducing matching by five-fold or more. It is particularly useful to also assign chemical labels to the critical points to further focus sampling.

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2.6.3. Chemical Matching

The chemical_matching feature is used to incorporate information about the chemical complementarity of a ligand orientation into the matching process. In this feature, chemical labels are assigned to site points (see Chemical Matching for information on labeling spheres) and ligand atoms (see Ligand File Input) (Kuhl, et al. *J. Comput. Chem.* 1984). The site point labels are based on the local receptor environment. The ligand atom labels are based on user-adjustable chemical functionality rules. These labeling rules are identified with the chemical_defn_file parameter and reside in an editable file (see chem.defn). A node in a match will produce an unfavorable interaction if the atom and site point components have labels which violate a chemical match rule. The chemical matching rules are identified with the chemical_match_file parameter and reside in an editable file (see chem_match.tbl). If a match will produce unfavorable interactions, then the match is discarded. The speed-up from this technique depends how extensively site points have been labeled and the stringency of the match rules, but an improvement of two-fold or more can be expected.

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2.6.4. Macromolecular Docking

Although DOCK is typically used to process small ligand molecules, it can be used to study the interactions of macromolecular eigands. The chief difference in protocol is that to use the match_receptor_sites procedure for the orientation search, special ligand centers must be used to represent the ligand. This is signaled by setting the ligand_centers parameter. The ligand centers may be constructed by sphgen and must reside in a file identified with the ligand_center_file parameter. See Shoichet, et al. *J. Mol. Biol.* 1991 for examples and discussion of macromolecular docking.

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NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Orient Ligand Parameters

- orient_ligand [yes] (yes, no):
  #Flag to orient ligand to spheres
- automated_matching [yes] (yes, no):
  # Flag to perform automated matching instead of manual matching
  - (If automated_matching = no, then manual_matching is used)
    distance_tolerence [0.25] (float):
    #The tolerance in angstroms within which a pair of spheres is considered equivalent to
    #a pair of centers
  - distance_minimum [2.0] (float):
    #The shortest distance allowed between 2 spheres (any sphere pair with a shorter
    #distance is disregarded)
  - nodes_minimum [3] (int):
    #The minimum number of nodes in a clique
  - nodes_maximum [10] (int):
    #The maximum number of nodes in a clique
- receptor_site_file [receptor.sph] (string):
  # The file containing the receptor spheres
- max_orientations [500] (int):
  # The maximum number of orientations that will be cycled through
- critical_points [no] (yes, no):
  #Flag to use critical point sphere labeling to target orientations to particular spheres
- chemical_matching [no] (yes, no):
  #Flag to use chemical coloring of spheres to match chemical labels on ligand atoms
  - chem_match_tbl [chem_match.tbl] (string):
    #File defining the legal chemical type matches/pairings
- use_ligand_spheres [no] (yes/no):
  #Flag to enable a sphere file representing ligand heavy atoms to be used to orient the ligand
  #Typically used for macromolecular docking
  - ligand_sphere_file [ligand.sph] (string):
    #The file containing the receptor spheres

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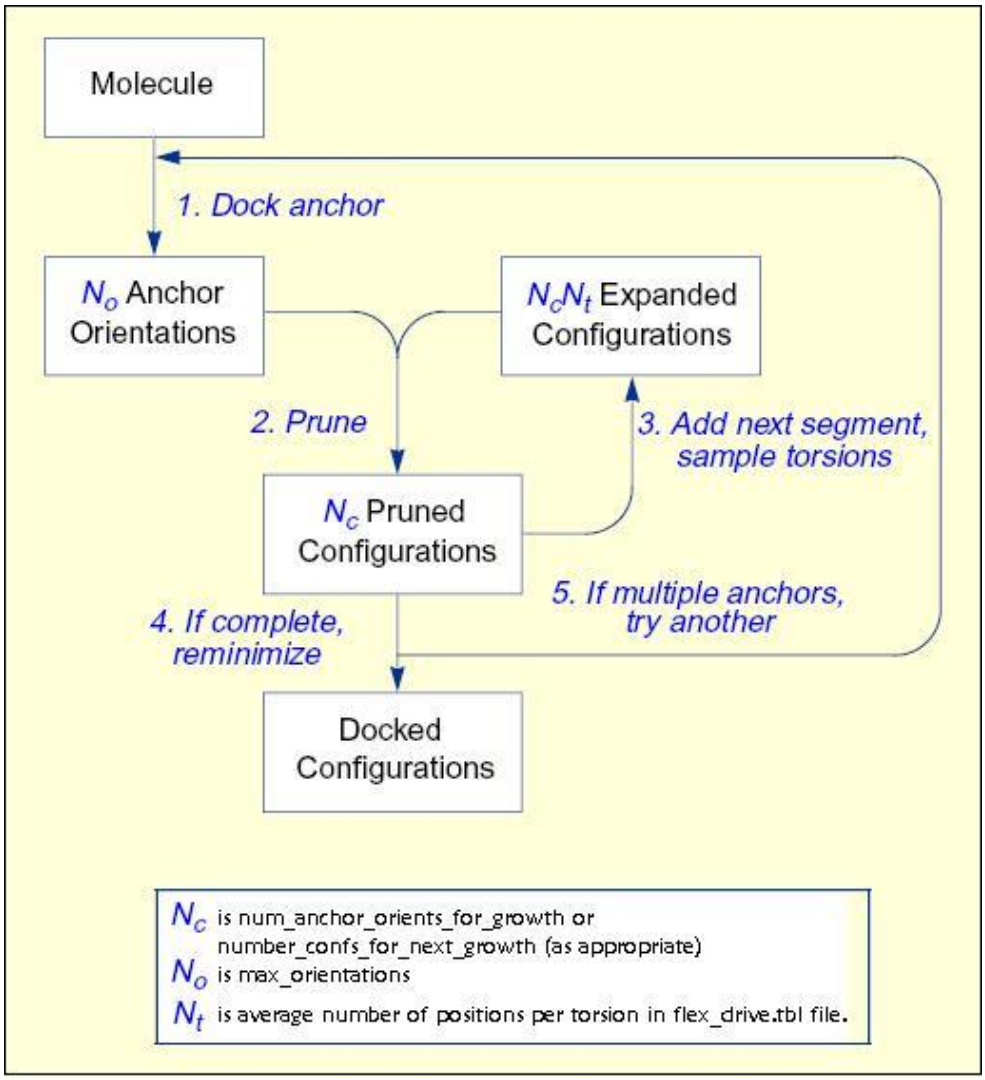
2.7. Ligand Flexibility

2.7.1. Anchor-and-Grow

The process of docking a molecule using the anchor-first strategy is shown in the Workflow for Anchor-and-Grow Algorithm. First, the largest rigid substructure of the ligand (anchor) is identified (see Identification of Rigid Segments) and rigidly oriented in the active site (orientation) by matching its heavy atoms centers to the receptor sphere centers (see Orienting the Ligand). The anchor orientations are evaluated and optimized using the scoring function (see Scoring) and the energy minimizer (see Minimization). The orientations are then ranked according to their score, spatially clustered by heavy atom root mean squared deviation (RMSD), and pruned (see Pruning the Conformation Search Tree). Next, the remaining flexible portion of the ligand (see Identification of Flexible Layers) is built onto the best anchor orientations within the context of the receptor (grow). It is assumed that the shape of the binding site will help restrict the sampling of ligand conformations to those that are most relevant for the receptor geometry.



Workflow for Anchor-and-Grow Algorithm

The conformation of a flexible molecule may be searched or relaxed using the flexible_ligand option. Only the torsion angles are modified, not the bond lengths or angles. Therefore, the input geometry of the molecule needs to be of good quality. A structure generated by ZINC is sufficient.

The torsion angle positions reside in an editable file (see flex_drive.tbl on page 111) which is identified with the flex_drive_file parameter. Internal clashes are detected during the torsion drive search based on the clash_overlap or internal_energy parameters, which are independent of scoring function.

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2.7.2. Identification of Rigid Segments

A flexible molecule is treated as a collection of rigid segments. Each segment contains the largest set of adjacent atoms separated by non-rotatable bonds. Segments are separated by rotatable bonds.

The first step in segmentation is ring identification.All bonds within molecular rings are treated as rigid. This classification scheme is a first-order approximation of

molecular flexibility, since some amount of flexibility can exist in non-aromatic rings. To treat such phenomenon as sugar puckering and chair-boat hexane conformations, the user will need to supply each ring conformation as a separate input molecule. Additional bonds may be specified as rigid by the user (see Manual Specification of Non-rotatable Bonds).

Identification of Rigid Anchor and Flexible Bonds

The second step is flexible bond identification. Each flexible bond is associated with a label defined in an editable file (see flex.defn). The parameter file is identified with the flex_definition_file parameter. Each label in the file contains a definition based on the atom types (and chemical environment) of the bonded atoms. Each label is also flagged as minimizable. Typically, bonds with some degree of double bond character are excluded from minimization so that planarity is preserved. Each label is also associated with a set of preferred torsion positions. The location of each flexible bond is used to partition the molecule into rigid segments. A segment is the largest local set of atoms that contains only non-flexible bonds.

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2.7.3. Manual Specification of Non-rotatable Bonds

The user can specify additional bonds to be non-rotatable, to supplement the ring bonds automatically identified by DOCK. Such a technique would be used to preserve the conformation of part of the molecule and isolate it from the conformation search. Non-rotatable bonds are identified in the Tripos MOL2 format file containing the molecule. The bonds are designated as members of a STATIC BOND SET named RIGID (see Tripos MOL2 Format).

Creation of the RIGID set can be done within Chimera. With the molecule of interest loaded into Chimera, select the portion of the ligand you would like to remain rigid. Then select on File > Save MOL2. Make sure the "Write current selection to @ SETS section of file" is checked and save the file.

Alternatively, the RIGID set can be entered into the MOL2 file by hand. To do this, go to the end of the MOL2 file. If no sets currently exist, then add a SET identifier on a new line. It should contain the text "@<TRIPOS>SET". On a new line add the text "RIGID STATIC BONDS <user> **** Comment". On the next line enter the number of bonds that will be included in the set, followed by the numerical identifier of each bond in the set.

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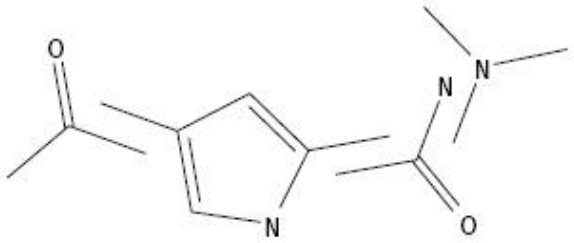
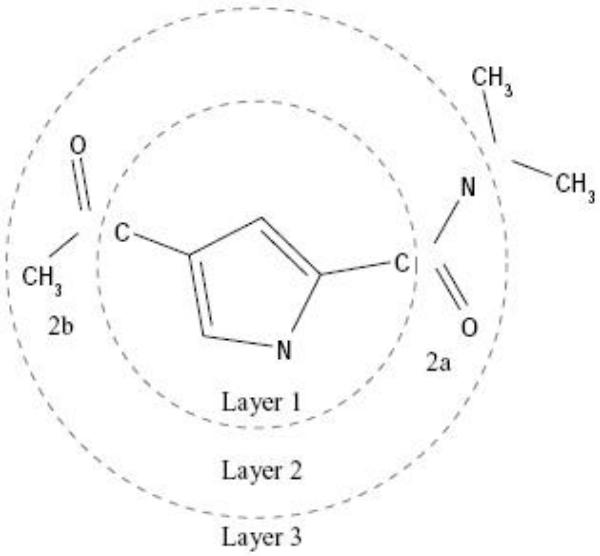
2.7.4. Identification of Flexible Layers

An anchor segment is selected from the rigid segments in an automatic fashion (see see Manual Specification of Non-rotatable Bonds to override this behavior). The molecule is divided into segments that overlap at each rotatable bond. The segment with the largest number of heavy atoms is selected as the anchor. All segments with more heavy atoms then min_anchor_size are tried separately as anchors.



Identification of Overlapping Segments

When an anchor has been selected, then the molecule is redivided into non-overlapping segments, which are then arranged concentrically about the anchor segment. Segments are reattached to the anchor according to the innermost layer first --and within a layer--the largest segment first.



Layered Non-Overlapping Segments

The anchor is processed separately (either oriented, scored, and/or minimized). The remaining segments are subsequently re-attached during the conformation search. The interaction energy between the receptor and the ligand can be optimized with a simplex minimizer (see Minimization).

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2.7.5. Pruning the Conformation Search Tree

There are now two available methods for pruning available. In the first, the pruning attempts to retain the best, most diverse configurations using a top-first pruning method, which proceeds as follows. The configurations are ranked according to score. The top-ranked configuration is set aside and used as a reference configuration for the first round of pruning. All remaining configurations are considered candidates for removal. A root-mean-squared distance (RMSD) between each candidate and the reference configuration is computed. Each candidate is then evaluated for removal based on its rank and RMSD using the inequality shown in Equation 2. If the factor is greater than number_confs_for_next_growth, as appropriate, the candidate is removed.

$$\frac{rank_i}{RMSD(i,\mathbf{0})} > N_C$$

Based on this factor, a configuration with rank 2 and 0.2 Angstroms RMSD is comparable to a configuration with rank 20 and 2.0 Angstroms RMSD. The next best scoring configuration which survives the first pass of removal is then set aside and used as a reference configuration for the second round of pruning, and so on. The pruning method biases its search time towards molecules which sample a more diverse set of binding modes. As the value of num_anchors_orients_for_growth and number_confs_for_next_growth is increased, the anchor-first method approaches an exhaustive search.

In the second method, the goal is to bias the sampling toward conformations that are close to the correct binding mode (as optimized using a test set of experimentally solved structures). Much as the method above, the algorithm ranks the generated poses and conformations. Then, all poses that violate a user-defined score cutoff are removed. To facilitate the speed of the calculation, the remaining list is additionally pared back to a user-defined length. In this technique, the sampling is driven towards molecules that sample closer to the experimentally determined binding site, but results in a significantly less diverse set of final poses.

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2.7.6. Internal Energy Calculation

During the growth phase of the calculation, an internal energy scoring function can be used. This function computes the Lennard-Jones and Coulombic energy between all ligand atom pairs, excluding all 1-2, 1-3, and 1-4 pairs. It reduces the occurrence of internal clashes during the torsional optimization. This energy is not included in the final reported score.

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2.7.7. Time Requirements

The time demand grows linearly with the num_anchors_orients_for_growth, the number_confs_for_next_growth, the number of flexible bonds and the number of torsion positions per bond, as well as the number of anchor segments explored for a given molecule. Using the notation in the Workflow for Anchor-and-Grow Algorithm, the time demand can be expressed as

$$Time \propto N_A(N_O + N_C N_T N_B)$$

where the additional terms are:
N_A is the number of anchor segments tried per molecule.
N_B is the number of rotatable bonds per molecule.

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NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Flexible Ligand Parameters

- flexible_ligand [yes] (yes, no):
  #Flag to perform ligand conformational searching
- min_anchor_size [40] (int):
  #The minimum number of heavy atoms for an anchor segment
- pruning_use_clustering [yes] (yes, no):
  # Flag to enable clustering during pruning (duplicates previous behavior)
  - (if pruning_use_clustering = yes)
    pruning_max_orients [100] (int):
    #The pruning value cutoff for anchor orientations promoted to the conformational
    #search (previously num_anchor_orients_for_growth)
  - pruning_clustering_cutoff [100] (int):
    #The maximum number of conformations carried forward in the anchor & grow search
    #(previous num_confs_for_next_growth)
  - (if pruning_use_clustering = no)
    pruning_max_orients [100] (int):
    #Maximum number of anchor orientations promoted to the conformational
    #search
  - pruning_orient_score_cutoff [25.0] (float):
    #Maximum score for anchor after minimization
  - pruning_max_conformers [75] (int):
    #Maximum number of anchor orientations promoted to the next layer of growth
  - pruning_conformer_score_cutoff [25.0] (float):
    #Maximum score for conformation after minimization
- use_internal_energy [yes] (yes,no):
  #Flag to add an internal energy term to the score during the conformational search
  - internal_energy_att_exp [6] (int):
    # VDW attractive exponent
  - internal_energy_rep_exp [12] (int):
    #VDW repulsive exponent
  - internal_energy_dielectric [4.0] (float):
    #Dielectric used for electrostatic calculation
- use_clash_overlap [no] (yes, no):
  #Flag to check for overlapping atom volumes during anchor and grow
  - clash_overlap [0.5] (float):
    #Percent of overlap allowed before a clash is declared

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2.8. Scoring

DOCK uses several types of scoring functions to discriminate among orientations and molecules. Scoring is requested using the score_molecules parameter. The scoring functions are implemented with a hierarchical strategy. A master score class manages all scoring functions that DOCK uses. Any of the DOCK scoring functions can be selected as the primary and/or the secondary scoring function. The primary scoring function is used during rigid orienting, anchor-and-grow steps, and minimization, which typically make many calls to the scoring function. The secondary scoring function is used in the final minimization, scoring, and ranking of the molecules.

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2.8.1. Bump Filter

Orientations and grow steps may be filtered prior to scoring to discard those in which the molecule significantly overlaps receptor atoms. This feature is enabled with the bump_filter flag. At the time of construction of the bump filter, the amount of atom VDW overlap is defined with the bump_overlap parameter (see Grid). At the time of bump evaluation the number of allowed bumps is defined with the max_bump_anchor and max_bump_growth parameter.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Bump Filter Parameters

- bump_filter [yes] (yes, no):
  #Flag to perform bump filtering
- bump_grid_prefix [grid] (string):
  #The prefix to the grid file containing the desired bump grid
- max_bumps_anchor [12] (int):
  #The maximum allowed number of bumps for a molecule to pass
  #the filter
- max_bumps_growth [12] (int):
  #The maximum allowed number of bumps for a molecule to pass
  #the filter

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2.8.2. Contact Score

The contact score is a simple summation of the number of heavy atom contacts between the ligand and receptor. At the time of construction of the contact scoring grid, the distance threshold defining a contact is set with the contact_cutoff_distance (see Grid). Atom VDW overlaps are penalized by checking the bump filter grid, or with the contact_clash_overlap parameter for the intramolecular score. The amount of penalty is specified with the contact_clash_penalty parameter.

The contact score provides a simple assessment of shape complementarity. It can be useful for evaluating primarily non-polar interactions.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be

asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Contact Score Parameters

- contact_score_primary [no] (yes, no):
  #Flag to perform contact scoring as the primary scoring function
- contact_score_secondary [no] (yes, no):
  #Flag to perform contact scoring as the secondary scoring function
  - contact_score_cutoff_distance [4.5] (float):
    #The distance threshold defining a contact
  - contact_score_clash_overlap [0.75] (float):
    #Contact definition for use with intramolecular scoring
  - contact_score_clash_penalty [50] (float):
    #The penalty for each contact overlap made
  - contact_score_grid_prefix [grid] (string):
    #The prefix to the grid files containing the desired contact
    #grid

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2.8.3. Grid-Based Score

The grid-based score is based on the non-bonded terms of the molecular mechanic force field (see Grid for more background).

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Grid Score Parameters

- grid_score_primary [yes] (yes, no):
  # Flag to perform grid-based energy scoring as the primary scoring
  #function
- grid_score_secondary [yes] (yes, no):
  # Flag to perform grid-based energy scoring as the secondary
  #scoring function
  - grid_score_rep_rad_scale [1] (float):
    #Scalar multiplier of the radii for the repulsive portion of the
    #VDW energy component ONLY
  - grid_score_vdw_scale [1] (float):
    # Scalar multiplier of the VDW energy component
    - (if grid_score_vdw_scale = 0)
      grid_score_turn_off_vdw [yes] (yes, no):
      #Flag to turn of vdw portion of scoring function
  - grid_score_es_scale [1] (float):
    # The prefix to the grid files containing the desired energy
    #grid

        - (if grid_score_es_scale = 0)
          grid_score_turn_off_es [yes] (yes, no):
          #Flag to turn of es portion of scoring function
    - grid_score_grid_prefix [grid] (string):
      #The prefix to the grid files containing the desired nrg grid

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2.8.4. DOCK3.5 Score

DOCK3.5 score is a variant of Grid-based scoring (see Grid). DOCK3.5 score function calculates ligand desolvation in addition to steric and electrostatic interactions between the ligand and receptor. The electrostatic interactions between the ligand and the protein is calculated from a electrostatic potential (ESP) map. The ESP map should be calculated using finite difference Poisson-Boltzmann equation (PBE) as implemented in the program DelPhi. We provide scripts for the calculation, however DelPhi is not distributed by us.

In the DOCK scoring hierarchy DOCK3.5 Score follows GridScore and can be used both as the primary and the secondary scoring function.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

DOCK3.5 Score Parameters

- dock3.5_score_primary [no] (yes, no):
  #Flag to perform dock3.5 scoring as the primary scoring function
- dock3.5_score_secondary [no] #Flag to perform dock3.5 scoring as the secondary scoring
  #function
    - dock3.5_vdw_score [yes] (yes, no):
      #Calculate steric interaction from dock3.5 score
    - dock3.5_grd_prefix [chem52] (string):
      #Default prefix for files containing dock3.5 grids
    - dock3.5_electrostatic_score [yes] (yes, no):
      #Calculate electrostatic interaction from ESP grid calculated using DelPhi
    - dock3.5_ligand_internal_energy [no] (yes, no):
      #Flag to add ligand internal energy to the scoring function
    - dock3.5_ligand_desolvation_score [volume] (volume, total, no):
      #Calculate total or volume based ligand desolvation from solvation
      #grids
        - dock3.5_solvent_occlusion_file [solvmap] (string):
          #Occluded solvent grid of the receptor
        - dock3.5_redistribute_positive_desolvation [no] (yes, no):

#positive partial atomic desolvation penalties are distributed
- dock3.5_write_atomic_energy_contrib[no] (yes, no):
  #write contribution from each atom to total score
- dock3.5_score_vdw_scale [1.0] (float):
  #Scalar multiplier of VDW energy component
- dock3.5_score_es_scale [1.0] (float):
  #Scalar multiplier of electrostatic energy component

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2.8.5. Continuous Score

Continuous scoring may be used to evaluate a ligand:receptor complex without the investment of a grid calculation, or to perform a more detailed calculation without the numerical approximation of the grid. When continuous scoring is requested, then score parameters normally supplied to grid, must also be supplied to DOCK. It is left to the user to make sure consistent values are supplied to both programs.

The distance dependence of the Lennard-Jones function is set with the cont_score_att_exp and cont_score_rep_exp parameters. Typically a 6-12 potential is used, but it can be softened up by using a 6-8 or 6-9 potential. Regardless of the exponent values selected, the same radii and well-depths are used. The distance dependence of the Coulombic function is set with the distance_dielectric parameter. The dielectric constant is adjusted with the cont_score_dielectric parameter.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Continuous Score Parameters

- continuous_score_primary [no] (yes, no):
  #Flag to perform continuous non-grid based scoring as the primary
  #scoring function
- continuous_score_secondary [no] (yes, no):
  #Flag to perform continuous non-grid based scoring as the
  #secondary scoring function
  - cont_score_rec_filename [receptor.mol2] (string):
    #File that contains receptor coordinates
  - cont_score_att_exp [6] (int):
    #VDW Lennard-Jones potential attractive exponent
  - cont_score_rep_ex [12] (int):
    #VDW Lennard-Jones potential repulsive exponent
  - cont_score_dielectric [4.0] (float):
    #Dielectric constant for electrostatic term

- cont_score_vdw_scale [1] (float):
  #Scalar multiplier of vdw energy component
  - (if cont_score_vdw_scale = 0)
    cont_score_turn_off_vdw [yes] (yes, no):
    #Flag to turn of vdw portion of scoring function
- cont_score_es_scale [1] (float):
  #Scalar multiplier of electrostatic energy component
  - (if cont_score_es_scale = 0)
    cont_score_turn_off_es [yes] (yes, no):
    #Flag to turn of es portion of scoring function

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2.8.6. Zou GB/SA Score

The Zou GB/SA scoring function is a fast algorithm, the pairwise free energy model, for ligand binding affinity calculations. Specifically, a pairwise descreening approximation (Hawkins, et al. *Chem. Phys. Lett.* 1995) is used in calculations of the electrostatic energy contribution. The algorithm also includes a procedure to account for the low dielectric region that might form between the ligand and the receptor during docking processes. It has been tested to obtain similar results compared with the grid-based free energy model but with much less computation efforts.

For more information on the scoring function and specifics of the implementation, see Liu, et al *J. Phys. Chem.* B. 2004.

Zou GB/SA Score Parameters

- gbsa_zou_score_primary [no] (yes, no):
  #Flag to perform Zou GB/SA scoring as the primary scoring
  #function
- gbsa_zou_score_secondary [no] (yes, no):
  #Flag to perform Zou GB/SA scoring as the secondary scoring
  #function
  - gbsa_zou_gb_grid_prefix [gb_grid] (string):
    # The path to the pairwise GB grids
  - gbsa_zou_sa_grid_prefix [sa_grid] (string):
    #The path to the SA grids
  - gbsa_zou_vdw_grid_prefix [grid] (string):
    #The path to the nrg grids, used for the vdw portion of the GB/SA calculation
  - gbsa_zou_screen_file [screen.in] (string):
    # GB parameter file for electrostatic screening. Its located in the parameters dir by default
  - gbsa_zou_solvent_dielectric [78.300003] (float):
    # The value for the solvent dielectric

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2.8.7. Hawkins GB/SA Score

The Hawkins GB/SA score is an implementation of the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) method originally described by (Srinivasan, et al. *J. Am. Chem. Soc.* 1998) and

reviewed by (Kollman, et al. *Acc. Chem. Res.* 2000). This particular implementation of MM-GBSA uses the pairwise GB solvation model reported by Hawkins, Cramer and Truhlar (Hawkins, et al. *Chem. Phys. Lett.* 1995 , Hawkins, et al. *J. Phys. Chem.* 1996) with parameters described by Tsui and Case (Tsui, et al. *Biopolymers* 2001). Solvent Accessible Surface Areas (SA) are computed using a C++ implementation of the Amber8 "icosahedra" algorithm.

The total interaction between the ligand and receptor are represented by unscaled Coulombic and Lennard jones energy terms (MM) plus the change (delta) in solvation (GBSA) where *deltaGBSA = GBSA complex - (GBSA receptor + GBSA ligand).* For any given species *GBSA = Gpolar (GB energy) + Gnonpolar (SA*0.00542 + 0.92)*. Note that if inner and outer dielectric constants are set to 1 (gas-phase) and 80 (water-phase), then GBSA terms are formally equivalent to free energies of hydration that can be directly compared with experimental data and useful for evaluating the accuracy of different partial charge models (Rizzo et al. *J. Chem. Theory. Comput.* 2006).

The Hawkins GB/SA score was intended to be used for "single-point" calculations and the current implementation is quite slow if energy minimization is performed at the same time. However, an energy minimization is highly recommended prior to GBSA single-point calculations given that scores can be very sensitive to receptor-ligand geometry. Use of the -v flag will yield separate GBSA terms for each species (complex, receptor, and ligand) and also include raw icosahedra SA values in units of angstroms squared. This scoring method requires that the vdw_AMBER_parm99.defn file be specified which contains GB radii and scale parameters for each atom type.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Hawkins GB/SA Score Parameters

- gbsa_hawkins_score_primary [no] (yes, no):
  #Flag to perform Hawkins GB/SA scoring as the primary scoring
  #function
- gbsa_hawkins_score_secondary [no] (yes, no):
  #Flag to perform Hawkins GB/SA scoring as the secondary scoring
  #function
  - gbsa_hawkins_score_rec_filename [receptor.mol2] (string):

    #File that contains receptor coordinates
  - gbsa_hawkins_score_solvent_dielectric [78.5] (float):
    #Dielectric constant for solvent
  - gbsa_hawkins_score_salt_conc(M) [0.0] (float):
    #Salt concentration for solvent at Molar concentration
  - gbsa_hawkins_score_gb_offset [0.09] (float):

#GB radius offset

- gbsa_hawkins_score_cont_vdw_and_es [yes] (yes, no):
  #Flag to determine whether vdw and es values will be
  #calculated continuously or from a grid
  (if gbsa_hawkins_score_cont_vdw_and_es = yes)
  - gbsa_hawkins_score_vdw_att_exp [6] (int):
    #VDW Lennard-Jones potential attractive exponent
  - gbsa_hawkins_score_vdw_att_exp [12] (int):
    #VDW Lennard-Jones potential repulsive exponent

  (if gbsa_hawkins_score_cont_vdw_and_es = no)

  - gbsa_hawkins_score_vdw_att_exp [6] (int):
    #VDW Lennard-Jones potential attractive exponent
  - gbsa_hawkins_score_vdw_att_exp [12] (int):
    #VDW Lennard-Jones potential repulsive exponent

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2.8.8. PB/SA Score

The PB/SA scoring function is an implementation of the ZAP tool kit from OpenEye. In order to access the PB/SA function, you must have the ZAP tool kit installed and a valid ZAP license. For more information on obtaining the tool kit, licensing, and other OpenEye products, go to the OpenEye web page at www.eyesopen.com

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From the OpenEye Documentation:

"A Smooth Permittivity Function for Poisson-Boltzmann Solvation Methods", J. Andrew Grant, Barry T. Pickup and Anthony Nicholls, J. Comp. Chem, Vol 22, No.6, pgs 608-640, April 2001.

ZAP is, at its heart, a Poisson-Boltzmann (PB) solver. The Poisson equation describes how electrostatic fields change in a medium of varying dielectric, such as an organic molecule in water. The Boltzmann bit adds in the effect of mobile charge, e.g. salt. PB is an effective way to simulate the effects of water in biological systems. It relies on a charge description of a molecule, the designation of low (molecular) and high (solvent) dielectric regions and a description of an ion-accessible volume and produces a grid of electrostatic potentials. From this, transfer energies between different solvents, binding energies, pka shifts, pI's, solvent forces, electrostatic descriptors, solvent dipole moments, surface potentials and dielectric focusing can all be calculated. As electrostatics is one of the two principal components of molecular interaction (the other, of course, being shape), ZAP is OpenEye's attempt to get it right.

ZAP is written in ANSI C and follows a style of object-oriented programming popularized in the chemical information world by Daylight. It encapsulates structures and methods by the use of opaque pointers, or handles. These are integers converted to real pointers in the interior of the object system, hidden from the user.
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ZAP is available to most academic and government institutions free of charge. It comes in the form of a linkable library and a set of prepackaged binaries compiled for SGI, Linux and Cygwin (NT). Commercial use requires a license, available at a very reasonable cost from the nice folks at OpenEye.

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NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

PB/SA Score Parameters

- pbsa_score_primary [yes] (yes, no):
  # Flag to perform pbsa energy scoring as the primary scoring #function
- pbsa_score_secondary [yes] (yes, no):
  # Flag to perform pbsa energy scoring as the secondary #scoring function
  - pbsa_receptor_filename [receptor.mol2] (string):
    # Name of receptor file.
  - pbsa_interior_dielectric [2.0] (float):
    # Value for the dielectric inside the protein
  - pbsa_exterior_dielectric [78.5] (float):
    # Value for the dielectric of the solvent (outside the protein)
  - pbsa_vdw_grid_prefix [grid] (string):
    # The prefix to the grid files containing the VDW values

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2.8.9. AMBER Score

The AMBER score provides a suite of functionality including: AMBER molecular mechanics, implicit solvation, and molecular dynamics simulation, receptor flexibility, and conjugate gradient minimization. The main disadvantages are more complicated input preparation and increased computational expense.

AMBER score implements molecular mechanics implicit solvent simulations with the traditional all-atom AMBER force field (Pearlman, et al. *Comp. Phys. Commun.* 1995) for protein atoms and the general AMBER force field (GAFF, Wang, et al. *J. Comp. Chem.* 2004) for ligand atoms. The interaction between the ligand and the receptor is represented by electrostatic and van der Waals energy terms, and the solvation energy is calculated using a Generalized Born (GB) solvation model. The user has the option to choose one of the following GB models: (i) Hawkins, Cramer and Truhlar pairwise GB model with parameters described by Tsui and Case (gb=1) (Tsui, et al. *Biopolymers* 2001), (ii) Onufriev, Bashford and Case model, GB(OBC) (gb=2) (Onufriev, et al. *Proteins* 2004), and (iii) a modified GB(OBC) (gb=5) (Onufriev, et al. *Proteins* 2004). The surface area term is
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derived using a fast LCPO algorithm (Weiser, et al. *J. Comp Chem* 1999).

The AMBER score is calculated as:
E(Complex) - [E(Receptor) + E(Ligand)],
where E(Complex), E(Receptor), and E(Ligand) represent the energies of the complex, receptor, and ligand, respectively.

The calculation of each of these three energies uses the same protocol: minimization with a conjugate gradient method is followed by MD simulation (Langevin molecular dynamics at constant temperature), another minimization, and a final energy evaluation. The user can specify the number of pre-MD-minimization cycles, the number of MD simulation steps, and the number of post-MD-minimization cycles in the dock input file. During the final energy evaluation, a surface area term is included. The receptor energy is determined once. The AMBER score energy protocol is performed for every ligand and its corresponding complex.

AMBER score enables all or a part of the receptor to be flexible, in order to reproduce the so-called "induced-fit". The Cartesian coordinates of atoms that are flexible can be altered during the AMBER score energy protocol. The Cartesian coordinates of atoms that are not flexible cannot be altered during the AMBER score energy protocol. The flexible parts of the receptor-ligand complex are specified with a movable region dock input file parameter. The movable region options are ligand, everything, nothing, distance, and NAB atom expression. For the ligand option, only the ligand is allowed to move during minimization and MD simulation. For the everything option, all the atoms in the receptor and the ligand are allowed to move. No minimization or MD simulation occurs for the nothing option. This is the only movable region option for which the ligand is not flexible during the AMBER score energy protocol. Consequently, close contacts can produce very large energies because the AMBER force field can be sensitive to the receptor-ligand geometry. However, the nothing option is the fastest type of AMBER scoring.

The distance movable region option selects residues that are allowed to move by receptor-ligand distance. If any atom in a receptor residue is within the dock input file parameter distance cutoff Angstroms of the ligand then the whole residue is selected. The ligand is represented by the active site sphere list, and thus the movable receptor residues are well defined and independent of any particular ligand molecule. The ligand is always movable. The selected residues are emitted with the -v verbose flag as a NAB atom expression.

The NAB atom expression movable region option is based on the program Nucleic Acid Builder (NAB). Every atom in a NAB molecule has a unique name. This name is composed of the strand name, the residue number and the atom name. A NAB atom expression is a character string that contains one or more patterns that match a set of atom names in a molecule. The dock input file parameter associated with this option specifies the set of atoms in the receptor that are movable. All atoms of the ligand are movable. In DOCK a strand name is in fact a strand sequence number, and in a receptor-ligand complex, the ligand is always last in the sequence. Thus, a receptor molecule

with two strands has strand names of "1" and "2"; in a corresponding receptor-ligand complex the ligand (which is almost certainly single stranded) has strand name "3".

NAB atom expressions contain three subexpressions separated by colons. They represent the strand, residue and atom parts of the atom expression. Not all three parts are required. An empty part selects all strands, residues or atoms depending on which parts are empty. Each subexpression consists of a comma separated list of patterns, or for the residue part, patterns and/or number ranges. Several atom expressions may be placed in a single character string by separating them with the vertical bar. Patterns in atom expressions are similar to Unix shell expressions. Each pattern is a sequence of one or more single character patterns and/or stars. The star matches zero or more occurrences of any single character. Each part of an atom expression is composed of a comma separated list of limited regular expressions, or in the case of the residue part, limited regular expressions and/or ranges. A range is a number or a pair of numbers separated by a dash. The NAB manual contains more information on atom expressions.

Here are some examples of NAB atom expressions:

- :SER:
  #Select all atoms in any residue named SER. All three parts are present but both the strand and atom parts are empty. The atom expression :SER selects the same set of atoms.
- ::C,CA,N,O
  #Select all atoms with names C, CA, N or O in all residues in all strands (typically the peptide backbone).
- 1:1-10,13:CA,C,N
  #Select all atoms named CA,C,N in residues 1-10 and 13 in strand 1.
- ::C*[^1]
  #The [^1] is an example of a negated character class. It matches any character in the last position except 1. In this case, it will match all the atoms starting with C, such as CA, CB, CG2, but not those ending with 1, such as CD1, CE1.
- 2::|1:50,100:O*,N*
  #Select all atoms in strand 2. Select all atoms whose name starts with O and N in residue 50, 100 in strand 1. Note that the vertical bar separates the two strands
- 4::|2::|1::
  #Select strand 4, 2 and 1.
- :: or :
  #Select all atoms in the molecule.

All the input files, such as the prmtop, frcmod, amber.pdb, etc. should be generated prior to running the AMBER score. A perl script, prepare_amber.pl, has been provided for this purpose. The usage of prepare_amber.pl is
prepare_amber.pl ligand_mol2_file receptor_PDB_file
For example, if lig.mol2 is ligand_mol2_file, and rec.pdb is receptor_PDB_file, then use: prepare_amber.pl lig.mol2 rec.pdb
The script, prepare_amber.pl, also has the ability to read in a mol2 file

containing multiple ligands (usually the output from a previous DOCK run), and generate AMBER score readable input files. prepare_amber.pl calls other scripts and programs, such as antechamber to calculate the AM1-BCC charges for the ligands, and tleap to assign the parm94 parameter set for protein atoms and the GAFF parameter set for ligand atoms. See the tutorials for information on how to use the script to generate the input files. With knowledge of and experience using AMBER one could create the input files manually; see the amberize scipts for the gory details. Note that the ligand_atom_file, which has the extension ".amber_score.mol2", must have a TRIPOS AMBER_SCORE_ID section.

The AMBER score output in the DOCK output contains energy terms for each species (complex, receptor, and ligand) such that the sum of the terms is equal to the score. Use of the DOCK -v verbose flag will produce detailed energy breakdowns; the formats and definitions of this information are discussed in the the NAB manual: Nucleic Acid Builder (NAB). The verbose output is best captured via UNIX shell file redirection as opposed to the DOCK -o flag.

The AMBER score output in the ligand_outfile_prefix_scored.mol2 file contains the ligand coordinates extracted from the final structure of the complex (i.e., the structure after the AMBER score energy protocol is performed). The ligand charges are from the ligand prmtop file. The ligand atom types are the normal ones from DOCK and are not the GAFF atom types used by AMBER score.

The AMBER score uses the following method for emitting all the final structures in their entirety. The AMBER score will create a file with the extension ".final_pose.amber.pdb" for every species (receptor, ligands, and complexes) that contains any movable region (regardless of whether that region actually exists or actually does move). Thus, for the distance, everything, and NAB atom expression options of the movable region, a file for the receptor (amber_score_receptor_file_prefix.final_pose.amber.pdb) and two for each ligand,complex pair (AMBER_SCORE_ID.final_pose.amber.pdb, amber_score_receptor_file_prefix.AMBER_SCORE_ID.final_pose.amber.pdb) will be created; for the nothing option of the movable region, no files will be created. In addition, if the -v verbose flag is present then the AMBER score will create an AMBER restart file with the extension ".final_pose.amber.restart" for every species (receptor, ligands, and complexes) that contains any movable region (regardless of whether that region actually exists or actually does move).

Here is some general advice on the AMBER score. Since it is slower and more complicated than the other scoring functions, one should proceed carefully when using the AMBER score as the sole primary score. The most obvious use is to rescore, with the default amber_score input parameters, the ligands that have been already scored using one of the faster scoring functions. In general, the input preparation for AMBER score is more involved than for the other scores. Effectively, one needs to generate input files for AMBER. In particular, examine the amberize*.out and *.log files for warnings and errors. Experience using AMBER will help in understanding and judging the impact of the messages in these files. Correcting problems

may involve substantial effort. See the DOCK Fans mailing list for specific examples.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

AMBER Score Parameters

- amber_score_primary [no] (yes, no):
  #Flag to perform amber scoring as the primary scoring function.
- amber_score_secondary [no] (yes, no):
  #Flag to perform amber scoring as the secondary scoring function. This is temporarily deprecated, and using input parameter amber_score_secondary causes program termination. The recommended protocol is to perform two DOCK runs with the second run specifying amber_score as the primary_score.
  - amber_score_receptor_file_prefix[rec] (string):
    #Prefix of the Receptor. Use the prefix that was used in the prepare_amber.pl input file preparation step.
  - amber_score_movable_region [ligand] (distance, everything, ligand, nab_atom_expression, nothing):
    #The region that will be flexible during the scoring protocol.
    - amber_score_movable_distance_cutoff [3.0] (float):
      #All receptor residues within this cutoff in Angstroms of the ligand will be movable. This is active only for amber_score_movable_region=distance.
    - receptor_site_file [receptor.sph] (string):
      #The file containing the receptor spheres that define the active site. This is not specific to amber_score. This is active for amber_score_movable_region=distance.
    - amber_score_movable_atom_expression [::] (string):
      #NAB atom expression defining the movable receptor region. This is active only for amber_score_movable_region=nab_atom_expression.
  - amber_score_before_md_minimization_cycles [100] (int):
    #Number of conjugate gradient minimization cycles to be performed before MD.
  - amber_score_md_steps [3000] (int):
    #Number of Molecular Dynamics (MD) steps to be performed.
  - amber_score_after_md_minimization_cycles [100] (int):
    #Number of conjugate gradient minimization cycles to be performed after MD.
  - amber_score_gb_model [5] (int):
    #GB model to be used.
  - amber_score_nonbonded_cutoff [18.0] (float):
    #Non-bonded cutoff in Angstroms for the energy

calculation.
- amber_score_temperature [300.0] (float):
  #Temperature at which MD should be performed.

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2.9. Minimization

Score optimization allows the conformation and orientation of a molecule to be adjusted to improve the score. Although the calculation is expensive, it makes the conformation and orientation search more efficient because less sampling becomes necessary. Optimization is activated with the
minimize_ligand parameter. The optimizer currently uses the simplex algorithm, which does not require evaluation of derivatives (Nelder et al, *ComputerJournal*, 1964). It does however depend on a random number generator which makes it sensitive to the initial seed provided with random_seed parameter. The amount of variance should be small, though. For detailed calculations, it is recommended that the optimization be repeated with different random number seeds to check convergence.

The initial step size of the minimizer is specified with the initial_translation, initial_rotation, and
initial_torsion parameters. The length of minimization may be controlled with the maximum_iterations parameter. Users can choose to minimize the rigid anchors, minimize during flexible growth, and minimize the final conformation. The anchor minimization is always done rigidly; also, if no flexible growth is being done, this step will minimize the entire molecule. The minimization during the flexible growth is a complete (torsions + rigid) minimization. When the simplex shrinks enough so that the highest and lowest points are within the scoring tolerance or if the number of requested minimizer steps is reached, the minimizer terminates.

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NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Score Optimization Parameters

- minimize_ligand [yes] (yes, no):
  #Flag to perform score optimization

  (if flexible_ligand = no)

  simplex_max_iterations [50] (int):
  #Maximum number of minimization cycles

  (if flexible_ligand = yes)

  - minimize_anchor [yes] (yes, no):
    # Flag to perform rigid optimization of the anchor
    - simplex_anchor_max_iterations [500] (int):
      #Maximum number of iterations per cycle per anchor

- minimize_flexible_growth [yes] (yes, no):
  # Flag to perform complete optimization during conformational search
  - simplex_grow_max_iterations [500] (int):
    #Maximum number of iterations per cycle per growth step
- use_advanced_simplex_parameters [no] (yes, no):
  #Flag to use a simplified set of common minimization parameters for each of the
  #minimization steps listed above (see below for list of these options)

  (if minimize_ligand = yes)

- simplex_final_min [no] (yes, no):
  #Flag to perform one more cycle of minimization on each fully grown pose
- simplex_final_max_iterations [0] (int):
  # Maximum number of iterations for final cycle
- simplex_final_min_rep_rad_scale [1] (float):
  #Scalar multiplier of the radii for the repulsive portion of the
  #VDW energy component ONLY
- simplex_final_min_add_internal [no] (yes, no):
  #Flag to add ligand internal energy to primary scoring function

  (if secondary_score = yes)

- simplex_secondary_minimize_pose [yes] (yes, no):
  #Flag to perform an additional cycle of minimization using the secondary scoring
  #function
- use_advanced_secondary_simplex_parameters [no] (yes,no):
  #Flag to use a simplified set of common minimization parameters for each of the
  #minimization steps listed above (see below for list of these options)
- secondary_min_add_internal [no] (yes,no):
  #Flag to add ligand internal energy to secondary scoring function

  (if minimize = yes)

- simplex_random_seed [0] (int):
  #Seed for random number generator

Generic Minimizer Parameters

1. if flexible_ligand = no OR use_advanced_simplex_parameters = no, XXX = simplex
2. if use_advanced_simplex_parameters = no AND minimize_anchor = yes, XXX = simplex_anchor
3. if use_advanced_simplex_parameters = no AND minimize_flexible_growth = yes, XXX = simplex_growth
4. if use_advanced_simplex_parameters = no AND simplex_final_min = yes, XXX = simplex_final
5. if simplex_secondary_minimize_pose AND use_advanced_secondary_simplex_parameters, XXX = simplex_secondary

   - XXX_max_cycles [1] (int):
     #Maximum number of minimization cycles
   - XXX_score_converge [0.1] (float):
     #Exit cycle at when energy converges at cutoff
   - XXX_cycle_converge [1.0] (float):
     # Exit minimization when cycles converge at cutoff
   - XXX_trans_step [1.0] (float):
     #Initial translation step size

- XXX_rot_step [0.1] (float):
  #Initial rotation step size
- XXX_tors_step [10.0] (float):
  #Initial torsion angle step size

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2.10. Parameter Files

The parameter files contain atom and bond data needed during DOCK calculations. The definition (*. defn) files contain atom and bond labeling data. The table (*. tbl) files contain additional data for chemical interactions and flexible bond torsion positions. They may be edited by the user. All the parameter files described below can be found in the "parameter" directory in the DOCK distribution.

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2.10.1. Atom Definition Rules

The definition files use a consistent atom labeling convention for which an atom in virtually any chemical environment can be identified. The specification of adjacent atoms is nested using the elements listed below:

- Each element must be separated by a space.
- If more than one adjacent atom is specified, then ALL must be present (i.e. a boolean AND for rules within a line).
- If a label can have multiple definition lines, then any ONE of them must be satisfied for inclusion (i.e. a boolean OR for rules on different lines).

Atom Definition Elements

Element	Function
atom type	Specifies partial or complete atom type. A partial specification is more general (i.e. "C" versus "C.3"). An asterisk (*) specifies ANY atom type.
( )	Specifies atoms that must be bonded to parent atom.
[ ]	Specifies atoms that must NOT be bonded to parent atom.
integer	Specifies the number of an atom that must be bonded.

Example Definitions

Example	Explanation

C.2 (2 O.co2)	A carboxylate carbon.
.3 [3 H]	Any sp3 hybridized atom that is not attached to three hydrogens .
C. [O .] [N . [2 O.2] [2 C.]]	Any carbon not attached to an oxygen or a nitrogen (unless the nitrogen is a nitro or tertiary nitrogen).

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2.10.2. vdw.defn

This file contains atom labels and definitions for van der Waals (VDW) atom typing. The following data types are associated with each atom: VDW radius, VDW well-depth, flag for heavy atom, and valence. The VDW radius and VDW well-depth values are used in molecular mechanics-scoring functions (see Grid). The valence is the value for the maximum number of atoms that can be attached. The definition is the Sybyl atom types that should be associated with the atom name. A label may have multiple definitions.

In the vdw_AMBER_parm99.defn file, there are additional parameters needed for use with the Hawkins GB/SA scoring function (see Hawkins GB/SA). Each entry has an additional gbraii and gbscale parameter.

WARNING: The last entry in the vdw.defn file MUST be Dummy.

Sample Entries

```
_____________________________________________
name Carbon_sp/sp2
atom_model either
radius 1.850
well_depth 0.120
heavy_flag 1
valence 4

definition C
_____________________________________________
name Carbon_All_sp3
atom_model all
radius 1.800
well_depth 0.060
heavy_flag 1
valence 4
gbradii 1.70
gbscale 0.72

definition C.3
_____________________________________________
```

```
name Carbon_United_CH3
atom_model united
radius 2.000
well_depth 0.150
heavy_flag 1
valence 4

definition C. ( 3 H )
```

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2.10.3. chem.defn

This file contains labels and definitions for chemical labeling. Nothing outside of addition to a label needs to be assigned to an atom. A label may have multiple definition lines but the names must match the rules in the chem_match.tbl file.

Sample Entries

```
name hydrophobic
definition C. [ O. ] [ N . [ 2 O.2 ] [ 2 C. ] ] ( * )
definition N.pl3 ( 3 C. )
definition Cl ( C. )
definition Br ( C. )
definition I ( C. )
definition C.3 [ * ]
```

```
name donor
definition N. ( H )
definition N.4 [ * ]
```

```
name acceptor
definition O. [ H ] [ N. ] ( * )
definition O.3 ( 1 * ) [ N. ]
definition O.co2 ( C.2 ( O.co2 ) )
definition N. [ H ] [ N. ] [ O . ] [ 3 . ] ( * )
definition O.2 [ * ]
```

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2.10.4. chem_match.tbl

This file contains the interaction matrix for which chemical labels can form an interaction in matching. The labels must be identical to labels in chem.defn. The table flag indicates the beginning of the interaction table. Compatible labels are identified with a one, otherwise a zero.

Sample File

```
label null
label hydrophobic
label donor
label acceptor
label polar
table
1
1 1
1 0 1
1 0 0 1
1 0 1 1 1
```

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2.10.5. flex.defn

This file contains labels and definitions for flexible bond identification. The drive_id field corresponds to a torsion type in the flex_drive.tbl file. The minimize field is a flag for whether the bond may be minimized. Two definition lines must be present. Each definition corresponds to an atom at either end of the bond.

Sample Entries

```
_____________________________________________
name sp3-sp3
drive_id 3
minimize 1
definition .3 [ 3 H ] [ 3 O.co2 ]
definition .3 [ 3 H ] [ 3 O.co2 ]

_____________________________________________
name sp3-sp2
drive_id 4
minimize 1
definition .3 [ 3 H ] [ 3 O.co2 ]
definition .2 [ 2 H ] [ 2 O.co2 ]

_____________________________________________
name sp2-sp2
drive_id 2
minimize 0
definition .2 [ 2 H ] [ 2 O.co2 ]
definition .2 [ 2 H ] [ 2 O.co2 ]

_____________________________________________
```

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2.10.6. flex_drive.tbl

This file contains torsion positions assigned to each rotatable bond when the flexible docking parameter is used in DOCK. The drive_id field corresponds to each torsion type in the flex.defn file. The positions field specifies the number of torsion angles to sample. The torsions field specifies the angles that are sampled.

Sample Entries

```
_____________________________________________
drive_id 2
positions 2
torsions 0 180
_____________________________________________
drive_id 3
positions 3
torsions -60 60 180
_____________________________________________
drive_id 4
positions 4
torsions -90 0 90 180
_____________________________________________
```

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NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Atom Typing Parameters

- atom_model [all] (all, united):
  #Choice of all atom or united atom models
- vdw_defn_file [vdw.defn] (string):
  #File containing VDW parameters for atom types
- flex_defn_file [flex.defn] (string):
  # File containing conformational search parameters
- chem_defn_file [chem.defn] (string):
  # File containing chemical label definitions
- chem_match_tbl [chem_match.tbl] (string):
  # File containing rules for chemical matching

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2.11. Ligand File Output

DOCK reports several kinds of information as output which is either written to screen in interactive mode or written to file in batch mode (see Installation). All input parameters are echoed into the output. If a parameter is not needed it is not reported in the output. At the completion of each DOCK run, the number of molecules that were processed and the total time of the calculation is reported.

The results of each molecule are printed in the outfile as well. Depending on the combination of user parameters, each molecule entry will contain the number of anchors used (see Identification of Rigid Segments), the number of orientations that passed pruning (see Orienting the Ligand), the number of fully grown conformations that passed pruning (see Pruning the Conformation Search Tree), and a breakdown of the interaction energy between the ligand and receptor (see Scoring).

Example Molecule Section of Output

```
_____________________________________________________
Molecule: C1
Anchors: 1
Orientations: 1
Conformations: 1

Grid Score: -29.223606

    vdw: -26.868692
    es: -2.254913
```

In addition to the information printed to the output files, there are several structural output options. Each structural file name is formed using the ligand_outfile_prefix parameter. In a typical run, the best scoring pose of each ligand in the library will be written to a file called outputprefix_scored.mol2. In addition, there are several more advanced output options:

(1) Users can choose to write out orientations. This will create a file called outputprefix_orients.mol2. This will write out the molecules after they have been rigidly oriented and optimized. If anchor & grow is being used, this option will write out only the anchor fragment. All orientations generated will be written out, so be careful that the output does not get too huge.

(2) Users can also write out conformers after the final level of optimization. This will create a file called outputprefix_conformers.mol2. Again, be aware that the number of molecules in the output file will be equal to the database size * the # of anchors per molecule * the number of confomations that pass the final pruning stage * the number of conformers per cycle. This file can grow quite large, so only use it on single poses or small databases. (NOTE: If clustering is enabled, all conformations will be written to the outputprefix_conformers.mol2 file while the clusterheads will be written to the outputprefix_scored.mol2 file. This seemingly redundant writing is to ensure that no portion of the analysis is lost if a failure of some kind occurs).

(3) Users can write molecules ranked by score. This will create a file called outputprefix_ranked.mol2, which writes out the top N molecules from the database. This option disables the scored molecule output file by default.

If secondary scoring is enabled, all of the above files will be generated for both primary and secondary scoring. The secondary scoring files will contain both the original primary score as well as the new secondary score.

NOTE: The following parameter definitions will use the format below:

```
parameter_name [default] (value):
#description
```

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Ligand File Output

- ligand_outfile_prefix [output] (string):
  #The prefix that all output files will use
- write_orientations [no] (yes, no):

#Flag to write all anchor orientations

(if secondary_score = yes)

- num_primary_scored_conformers_rescored [1] (int):
  #The number of conformations scored and ranked using the primary score
  #to be rescored by the secondary score. Conformations written to
  #ligand_outfile_prefix_primary_conformers.mol2
  - (if num_primary_scored_conformers_rescored > 1):
    cluster_primary_conformations [yes] (yes, no):
    #Flag to enable clustering of fully minimized conformations from
    #primary score
    - (if cluster_primary_conformations = yes)
      cluster_rmsd_threshold [2.0] (float):
      #The cutoff to determine whether conformations should be
      #included in a particular cluster
    - num_clusterheads_for_rescore [5] (int):
      #The number of clusterheads scored using the primary score
      #to be rescored by the secondary score. Clusterheads
      # written to
      ligand_outfile_prefix_primary_scored.mol2

- num_secondary_scored_conformers_written [1] (int):
  #The number of conformations scored and ranked using the
  # secondary score. Conformations written to
  #ligand_outfile_prefix_secondary_conformers.mol2
- rank_primary_ligands [no] (yes, no):
  #Flag to enable ranking by primary score over all ligands:
  #the set of best scoring poses, one pose per ligand, will be sorted by
  #primary score into descending order. The top poses will be written to
  #file ligand_outfile_prefix_primary_ranked.mol2.
  - max_primary_ranked [500] (int):
    #The maximum number of ligands to be stored in this _ranked file.
- rank_secondary_ligands [no] (yes, no):
  #Flag to enable ranking by secondary score over all ligands:
  #the set of best scoring poses, one pose per ligand, will be sorted by
  #secondary score into descending order. The top poses will be written to
  #file ligand_outfile_prefix_secondary_ranked.mol2.
  - max_secondary_ranked [500] (int):
    #The maximum number of ligands to be stored in this _ranked file.

(if secondary_score = no)

- num_scored_conformers_written [1] (int):

#The number of conformations scored and ranked using the primary score.
#Conformations written to
#ligand_outfile_prefix_conformers.mol2
    - (if num_scored_conformers_written > 1):
      cluster_conformations [yes] (yes, no):
      #Flag to enable clustering of fully minimized conformations from
      #primary score
    - (if cluster_conformations = yes)
      cluster_rmsd_threshold [2.0] (float):
      #The cutoff to determine whether conformations should be
      #included in a particular cluster
- rank_ligands [no] (yes, no):
  #Flag to enable ranking by score over all ligands:
  #the set of best scoring poses, one pose per ligand, will be sorted by
  #score into descending order. The top poses will be written to
  #file ligand_outfile_prefix_ranked.mol2.
    - max_ranked_ligands [500] (int):
      #The maximum number of ligands to be stored in this _ranked file.

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2.12. Parallel Processing

Parallel processing is fully integrated into the DOCK program. It is set up to have a single Master node, while the remaining nodes act as slaves. The Master node performs file processing and input/output, whereas the slaves perform the actual calculations. If the number of processors (np) is 1 then the code defaults to the non-MPI behavior. As a result, there will be a minimal difference in performance between 1 and 2 processors. Improved performance will only become evident with more than 2 processors. It should be emphasized that the primary benefit in using DOCK6 in parallel mode is to reduce bookkeeping tasks associated with manually splitting up a database into multiple chunks which then must be submitted to different processors individually. DOCK6 automatically partitions out subsets of a database to various processors, collates and ranks the final results, and takes care of all intermediate bookkeeping. Parallel jobs simply require that the user specify the location of the MPI program used to compile DOCK6, a machine file listing the names of the nodes, and the total number of processors to be used. For parallel docking three additional parameters must be specified: (1) the path of the MPICH2 installation (i.e /usr/local/mpich2-1.0.4/bin/mpirun), (2) a machine file containing the names of the computers (nodes) to be used, and (3) the number of processors which typically is the same as the number of lines in the machine file. See Commandline Arguments for usage information on how to run DOCK with parallel processing functionality.

Accessories

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3.1. Grid

AUTHOR: Todd Ewing (based on work by Elaine Meng and Brian Shoichet)

USAGE: grid -i grid.in [-stv] [-o grid.out]

OPTIONS:
- i input_file #Input parameters extracted from input_file, or grid.in if not specified
-o output_file #Output written to output_file, or grid.out if not specified
-s Input parameters entered interactively
-t Reduced output level
-v Increased output level

DESCRIPTION:

3.1.1. Overview

Grid creates the grid files necessary for rapid score evaluation in DOCK. Two types of scoring are available: contact and energy scoring. The scoring grids are stored in binary files ending in *.cnt and *.nrg respectively. When docking, each scoring function is applied independent of the others and the results are written to separate output files. Grid also computes a bump grid which identifies whether a ligand atom is in severe steric overlap with a receptor atom. The bump grid is identified with a *.bmp file extension. The binary file containing the bump grid also stores the size, position and grid spacing of all the grids.

The grid calculation must be performed prior to docking. The calculation can take up to 45 minutes, but needs to be done only once for each receptor site. Grid generation and docking should be performed on the same platform; because the grid files have a binary format, copying grid files between machines may produce incorrect results. Furthermore, binary files should not be modified with text editors. Since DOCK can perform continuum scoring without a grid, the grid calculation is not always required. However, for most docking tasks, such as when multiple binding modes for a molecule or multiple molecules are considered, it will become more time efficient to precompute the scoring grids.

NOTE: The following parameter definitions will use the format below:

> parameter_name [default] (value):
> #description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

General Grid Parameters

- compute_grids [no] (yes, no):

#Flag to compute scoring grids
    - grid_spacing [0.3] (float):
      # The distance between grid points along each axis.
- output_molecule [no] (yes, no):
  #Flag to write out the coordinates of the receptor into a new, cleaned-up file. Atoms are
  #resorted to put all residue atoms together
    - receptor_out_file [receptor_out.mol2] (string):
      #File for cleaned-up receptor when output_molecule set
- receptor_file [receptor.mol2] (string):
  #Receptor coordinate file. Partial charges and atom types need to be present.
- box_file [site_box.pdb] (float):
  #File containing SHOWBOX output file which specifies boundaries of grid
- vdw_definition_file [vdw.defn] (string):
  #VDW parameter file (see vdw.defn)
- score_grid_prefix [grid] (string):
  #Prefix for file name of grids. File extension will be appended automatically.

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3.1.2. Bump Checking

Prior to scoring, each orientation can be processed with the bump filter to reject ones that penetrate deep into the receptor. Orientations that pass the bump filter are then scored and/or minimized with any of the available scoring functions. A bump is based on the sum of the van der Waals radii of the two interacting atoms. The user specifies what fraction of the sum is considered a bump. For example, the default definition of a bump is if any two atoms approach closer than 0.75 of the sum of their radii. Grid stores an atomic radius which corresponds to smallest radius of ligand atom at the grid position which would still trigger a bump. During docking, for a given orientation, the position of each atom is checked with the bump grid. If the radius of the atom is greater than or equal to the radius stored in the bump grid, then the atom triggers a bump. To conserve disk space, the atom radius is multiplied by 10 and converted to a short unsigned integer.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Bump Grid Parameters

- bump_filter [no] (yes, no):
  #Flag to screen each orientation for clashes with receptor prior to scoring and minimizing
- bump_overlap [0.75] (float):
  #Amount of VDW overlap allowed. If the probe atom and the

receptor heavy atom approach
#closer than this fraction of the sum of their VDW radii, then the position is flagged as a
#bump

0 = Complete overlap allowed
1 = No overlap allowed

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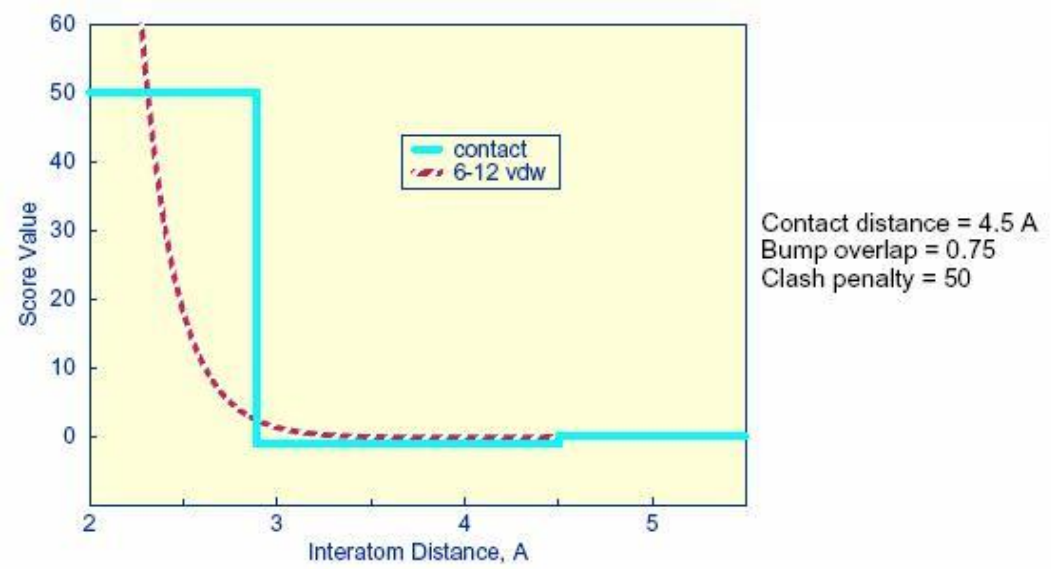
3.1.3. Contact Scoring

Contact scoring in grid incorporates the scoring performed with the DISTMAP program (developed by Shoichet and Bodian). The score is a summation of the heavy atom contacts (every atom except hydrogen) between the ligand and receptor. A contact is defined as an approach of two atoms within some cutoff distance (usually 4.5 Angstroms). If the two atoms approach close enough to bump (as identified with the bump grid) then the interaction can be penalized by an amount specified by the user.



Distance dependence of contact score function

The attractive score in grid is negative and a repulsive score is positive. This switch of sign is necessary to allow the same minimization protocol to be used for contact scoring as implemented for energy scoring.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Contact Grid Parameters

- contact_score [no] (yes, no):
  #Flag to construct contact grid
- contact_cutoff_distance [4.5] (float):
  #Maximum distance between heavy atoms for the interaction to be counted as a contact

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3.1.4. Energy scoring

The energy scoring component of DOCK is based on the implementation of force field scoring. Force field scores are approximate molecular mechanics interaction energies, consisting of van der Waals and electrostatic components:

$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

where each term is a double sum over ligand atoms i and receptor atoms j, which include the quantities listed below.

Generalization of the VDW component

The van der Waals component of the scoring function has been generalized to handle any combination of repulsive and attractive exponents (providing that a> b). The user may choose to "soften" the potential by using a 6-9 Lennard -Jones function. The general form of the van der Waals interaction between two identical atoms is presented:

$$E_{vdw} = C\varepsilon \left(\frac{2R}{r} \right)^{a} - D\varepsilon \left(\frac{2R}{r} \right)^{b}$$

where e is the well depth of the interaction energy, R is the van der Waals radius of the atoms, and coefficients C and D can be determined given the two following boundary conditions:

$$\frac{dE}{dr} vdw = 0 \text{ at } r = 2R$$

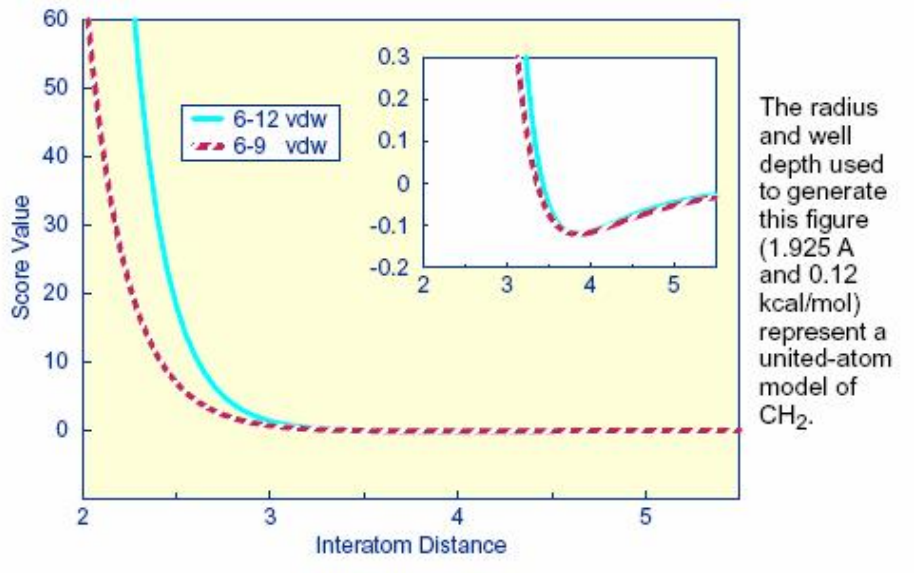
$$E_{vdw} = -\varepsilon \text{ at } r = 2R$$

Application of these boundary conditions to the above equation yields an expression of the van der Waals interaction with a generalized Lennard -Jones potential.

$$E_{vdw} = \varepsilon \left(\frac{b}{a-b} \right) \left(\frac{2R}{r} \right)^{a} - \varepsilon \left(\frac{a}{a-b} \right) \left(\frac{2R}{r} \right)^{b}$$

The consequence of using a different exponent for the repulsive term

is illustrated in Figure 1 . Notice that the well position and depth are unchanged, but that the repulsive barrier has shrunk by about a 0.25 Angstrom.



The radius and well depth used to generate this figure (1.925 A and 0.12 kcal/mol) represent a united-atom model of CH_2.

Distance dependence of the Lennard -Jones Function

Precomputing potentials on a grid

By inspection of the above equations , the repulsion and attraction parameters (Aij and Bij) for the interactions of identical atoms can be derived from the van der Waals radius, R, and the well depth, e.

$$A_{ii} = \varepsilon\left(\frac{b}{a-b}\right)(2R)^a$$

$$B_{ii} = \varepsilon\left(\frac{a}{a-b}\right)(2R)^b$$

In order to evaluate the interaction energy quickly, the van der Waals and electrostatic potentials are precomputed for the receptor and stored on a grid of points containing the docking site. Precomputing the van der Waals potential requires the use of a geometric mean approximation for the A and B terms, as shown:

$$Aij = \sqrt{A_{ii}}\sqrt{A_{jj}}$$

$$Bij = \sqrt{B_{ii}}\sqrt{B_{jj}}$$

Using this approximation, the first equation can be rewritten:

$$E = \sum_{i=1}^{lig} \left(\sqrt{A_{ii}} \sum_{j=1}^{rec} \frac{\sqrt{A_{jj}}}{r_{ij}^{a}} - \sqrt{B_{ii}} \sum_{j=1}^{rec} \frac{\sqrt{B_{jj}}}{r_{ij}^{b}} + 332 q_i \sum_{j=1}^{rec} \frac{q_j}{Dr_{ij}} \right)$$

Three values are stored for every grid point k ,each a sum over receptor atoms that are within a user defined cutoff distance of the point:

$$A_{rec} = \sum_{j=1}^{rec} \frac{\sqrt{A_{jj}}}{r_{ij}^{a}}$$

$$B_{rec} = \sum_{j=1}^{rec} \frac{\sqrt{B_{jj}}}{r_{ij}^{b}}$$

$$Q_{rec} = 332 \sum_{j=1}^{rec} \frac{q_j}{Dr_{ij}}$$

These values, with trilinear interpolation, are multiplied by the appropriate ligand values to give the interaction energy. Grid calculates the grid values and stores them in files. The values are read in during a DOCK run and used for force field scoring.

The user determines the location and dimensions of the grid box using the program showbox (see showbox). It is not necessary for the whole receptor to be enclosed; only the regions where ligand atoms may be placed need to be included. The box merely delimits the space where grid points are located, and does not cause receptor atoms to be excluded from the calculation. Besides a direct specification of coordinates, there is an option to center the grid at a sphere cluster center of mass. Any combination of spacing and x, y, and z extents may be used.

NOTE: The following parameter definitions will use the format below:

parameter_name [default] (value):
#description

In some cases, parameters are only needed (questions will only be asked) if the parameter above is enforced. These parameters are indicated below by additional indentation.

Energy Grid Parameters

- energy_score [no] (yes, no):
  #Flag to perform energy scoring
- energy_cutoff_distance [10] (float):
  #Maximum distance between two atoms for their contribution to the energy score to be
  #computed

- atom_model [u] (u, a):
  # Flag for how to model of nonpolar hydrogens

  u = United atom model. Hydrogens attached to carbons are assigned a zero VDW well-depth and the partial charge is transferred to the carbon.
  a = All atom model. Hydrogens attached to carbons have regular VDW well-depth and partial charge is not modified.

- attractive_exponent [6] (int):
  # Exponent of attractive Lennard - Jones term for VDW potential
- repulsive_exponent [12] (int):
  # Repulsive of attractive Lennard - Jones term for VDW potential
- distance_dielectric [yes] (yes, no):
  # Flag to make the dielectric depend linearly on the distance
- dielectric_factor[4.0] (float):
  #Coefficient of the dielectric

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3.2. Docktools

Docktools is a suite of programs that are available to create grids used by Dock3.5 score function in DOCK 6 which is an implementation of the scoring function available in the older version of DOCK i.e., dock3.5.54. These programs can be used to generate steric, electrostatic and ligand and receptor desolvation grids. Dock3.5 scoring functionality in DOCK 6 is an alternate scoring approach to electrostatic interaction energy and also includes different grid-based methods for calculating ligand and receptor desolvation. Docktools consists of chemgrid, solvmap, solvgrid, grid-convert and grid-convrds. This section will briefly review the theory behind each of the programs and the describe the usage.

3.2.1. CHEMGRID

AUTHOR: Brian K. Shoichet

DESCRIPTION:

This program chemgrid produces values for computing force field scores and bump checking. The force field scores, or molecular mechanics interaction energies are calculated as van der Waals and electrostatic components and stored on grids. The calculations are based on the theory presented in the Grid section above. However only the steric interaction energy grids are used in DOCK 6 as a part of Dock3.5 Score. The electrostatic interaction calculation differs from Energy Scoring in the following aspects. For calculating the electrostatic interaction, the electrostatic potential of the receptor calculated using the linearized form of Poisson-Boltzmann equation:

$$\nabla \cdot [\varepsilon(\mathbf{x})\nabla\phi(\mathbf{x})] - \kappa(\mathbf{x})^2\phi(\mathbf{x}) = -4\pi\rho(\mathbf{x})$$

Where phi(x) the potential is determined by the dielectric function epsilon(x), a modified Debye-Huckel parameter kappa(x), and the charge density of the receptor rho(x). The electrostatic potential map (or phimap) is calculated using DelPhi and then is used by DOCK 6 to calculate the electrostatic interaction energy as:

$$E_{\text{elec}} = \sum_{i \in L}^{L} q_i \phi_i$$

Where, q_i the partial charge of every atom *i*, is multiplied by the electrostatic potential of the receptor phi at the respective atomic position. Trilinear interpolation method is used for interpolating the electrostatic potential from the phimap on to the ligand position.

USAGE: chemgrid

INPUT FILE:

This programs require that an INCHEM file be created in the working directory, which contains the parameters to control the program. The INCHEM parameters for chemgrid are detailed below:

receptor.pdb ; receptor pdb file
parameters/ prot.table.ambcrg.ambH ; charge parameter file
parameters/ vdw.parms.amb.mindock ; VDW parameter file

box.pdb ; box pdb file
0.33 ; grid spacing in angstroms
1 ; es type: distance-dependent dielectric; 2: constant dielectric
1 ; es scale for ff scoring
2.3 2.8 ; bumping distances for polar and non-polar receptor atoms
output_prefix ; output grid prefix name

OUTPUT FILES

- OUTCHEM #restatement of input parameters; messages pertaining to calculation of the grids
- OUTPARM #messages pertaining to parameterization of receptor atoms; net charge on the receptor molecule including any ions or waters in the receptor pdb file
- PDBPARM #shows which parameters have been associated with each atom in the receptor pdb file
- output_prefix.bmp #bump grid
- output_prefix.vdw #vdw values for receptor
- output_prefix.es #electrostatic values for receptor

3.2.2 SOLVMAP

AUTHOR: Brian K. Shoichet

DESCRIPTION:

The solvmap program calculates the grid that is used by DOCK6 for calculating ligand desolvation. Ligand desolvation is calculated as a sum of the atomic desolvation multiplied by a normalization factor that accounts for the extent to which the ligand atom is buried by the binding site. The atomic desolvation for each ligand atom can be calculated by AMSOL (AMSOL is not distributed by us, please follow the link
for more information) and is stored in the input file (see file formats). The cost of desolvating each atom, or the normalization factor, is the distance weighted high dielectric volume displaced by the protein that is stored for each grid element in the active site. Thus the volume based ligand desolvation energy is calculated as:

$$E_{desolv} = \sum_{i} L \frac{dV}{4\pi} \sum_{k}^{V} \frac{1}{r_{ik}^{4}}$$

Here *L* is the ligand atom desolvation, volume summed over *k* volume elements, *V*. This method is only an approximation to GB solvation and works within the limits of complete burial from the solvent and complete exposure to the solvent on the protein surface. However, being grid-based it is fast and can be used during conformational search and final scoring.

USAGE: solvmap

INPUT FILE:

This programs require that an INSOLV file be created in the working directory, which contains the parameters to control the program. The INSOLV parameters for chemgrid are detailed below:

receptor.pdb; receptor file
solvmap ; output grid file
1.4,1.3,1.7,2.2,2.2,1.8 ; radii of oxygen, nitrogen, carbon, sulfur, phosphorus, and "other" atoms.
1.4 ; radius of probe
1 ; grid resolution
box.pdb ; box file

OUTPUT FILES:

- OUTSOLV #restatement of input parameters; messages pertaining to calculation of the grids
- solvmap #ligand desolvation grids

3.2.3 SOLVGRID

AUTHOR Kaushik Raha

DESCRIPTION:

The solvgrid program creates bulk (or receptor) and explicit (or ligand)

desolvation grids using the occupancy desolvation method (Luty et. al., *J. Comp. Chem,* 1995; Verkhiver et. al., *J. Mol. Recog.*, 1999). The occupancy desolvation method is phenomenonlogical in nature where desolvation energy can be described pairwise additively. The desolvation energy due to interaction between a ligand atom and receptor atom can be calculated as the solvent affinity of a ligand atom weighted by the volume of the solvent displaced from the receptor atom due to binding and vice versa. Thus,

$$E_{dsol} = S_i \, ø^{\mathrm{DES,EXPL}}(x_i) + f_i \, ø^{\mathrm{DES,BULK}}(x_i)$$

Where the mobile atom i, has a solvation affinity of S_i and a fragmental volume of f_i. The solvent affinity of the ligand atom is calculated as:

$$S_i = \alpha q_i^2 + \beta$$

Where q_i is the charge on the ligand atom i, and alpha and beta are constants set at alpha = 0.25 kcal/mol and beta = -0.005 kcal/mol. f_i is the volume of ligand atom i, calculated from the amber radius of the ligand atom. For the receptor, these can be precalculated and stored on a grid. $ø^{\mathrm{DES,BULK}}(x_i)$ and $ø^{\mathrm{DES,EXPL}}(x_i)$ are interpolated from grids calculated using the solvgrid program during docking. It requires the calculation of two separate grids:

$$\phi^{DES,EXPL}(p) = \sum_{j \in rigid\_atoms} f_i \exp\left(\frac{-r_{jp}^2}{2\sigma^2}\right) / \sigma^3$$

$$\phi^{DES,BULK}(p) = \sum_{j \in rigid\_atoms} S_i \exp\left(\frac{-r_{jp}^2}{2\sigma^2}\right) / \sigma^3$$

where j is a rigid receptor atom, and S_j and f_j are the solvent affinity and the fragmental volume of the receptor atom respectively. Bulk and explicit desolvation grids are calculated from f_j and S_j at grid points p, distance r_{jp} from the receptor atom multiplied by gaussian weighting of the distance. The solvgrid program calculates these grids from the charge and the volume of the receptor atoms.

USAGE: solvgrid

INPUT

This programs require that an INRDSL file be created in the working directory, which contains the parameters to control the program. The INRDSL parameters for solvgrid are detailed below:

```
receptor.pdb ; receptor pdb file
parameters/ prot.table.ambcrg.ambH ; charge parameter
file
```

parameters/ vdw.parms.amb.mindock ; VDW parameter file

box.pdb ; box pdb file
0.33 ; grid spacing in angstroms
1 ; es type: distance-dependent dielectric; 2: constant dielectric
4 ; es scale for ff scoring
2.3 2.8 ; bumping distances for polar and non-polar receptor atoms
output_prefix ; output grid prefix name
sol_op ; method for calculating desolvation grid
solE_recep; solvation free energy of receptor

OUTPUT FILES

- OUTRDSL #restatement of input parameters; messages pertaining to calculation of the grids
- OUTPARM #messages pertaining to parameterization of receptor atoms; net charge on the receptor molecule including any ions or waters in the receptor pdb file
- PDBPARM #shows which parameters have been associated with each atom in the receptor pdb file
- output_prefix.bmp #bump grid
- output_prefix.vdw #vdw values for receptor
- output_prefix.es #electrostatic values for receptor
- output_prefix.dsl #bulk and explicit desolvation grid for receptor

3.2.4 GRID-CONVERT

AUTHOR: Kaushik Raha, John J. Irwin (Derived from Todd Ewing's GRID Program)

DESCRIPTION:

This consists of programs grid-convert and grid-convrds that convert grids generated by chemgrid, solvgrid and DelPhi into DOCK6 readable grids.

USAGE: grid-convert -i gconv.in >& gconv.out

INPUT FILES:

- gconv.in; input file with parameters
- vdw.defn; vdw parameters file
- conv.defn; atomtype definition file

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3.3. Nchemgrids

AUTHOR: Xiaoqin Zou

USAGE: nchemgrid_GB *or* nchemgrid_SA

INPUT FILE:

Both programs require that an INCHEM file be created in the working directory, which contains the parameters to control the program. The INCHEM parameters for both the nchemgrid_GB and nchemgrid_SA programs are detailed below:

For nchemgrid_GB:

receptor.pdb ; receptor pdb file
cavity.pdb ; cavity pdb file
parameters/ prot.table.ambcrg.ambH ; charge parameter file
parameters/ vdw.parms.amb ; VDW parameter file
box.pdb ; box pdb file
0.4 ; grid spacing in angstroms
2 ; es type: GB
1 ; es scale for ff scoring
8.0 8.0 ; cutoff for es and outer box
78.3 78.3 ; dielectric of solvent ,cavity
2.3 2.8 ; bumping distances
output_prefix ; output grid prefix name
1 ; pairwise calculation

NOTE: The cavity.pdb file should be an empty file. This feature is not frequently used. However, the parameter must still be passed. The pairwise calculation value must also always be 1.

For nchemgrid_SA:

receptor.pdb ; receptor pdb file
parameters/prot.table.ambcrg.ambH ; charge parameter file
parameters/ vdw.parms.amb ; VDW parameter file
box.pdb ; box pdb file
0.4 ; grid spacing in angstroms
1.4 ; probe radius for SA
2 ; scoring type: SA
8.0 ; cutoff for SA calculations
output_prefix ; output grid prefix name

DESCRIPTION:

The nchemgrid_gb and nchemgrid_sa programs create the GB and SA receptor grids for use with the Zou GB/SA scoring function (see Zou GB/SA Scoring).

OUTPUT FILES

For nchemgrid_gb

- inva #debugging file with inverse Born radius for receptor atoms
- NEG_INVA #error file listing embedded receptor atoms
- OUTCHEM #restatement of input parameters; messages pertaining to calculation of the grids
- OUTPARM #messages pertaining to parameterization of

receptor atoms; net charge on the receptor molecule including any ions or waters in the receptor pdb file
- PDBPARM #shows which parameters have been associated with each atom in the receptor pdb file
screen.para #file that contains descreening parameters
- zou_grid.bmp #bump grid
- zou_grid.rec #xyz coordinates, effective charge, effective vdw radii, inverse Born radii, and descreening parameters for receptor
- zou_grid.sol #flags for whether receptor atoms are solvated
- zou_grid.vdw #vdw values for receptor

For nchemgrid_sa:

- OUTCHEM #restatement of input parameters; messages pertaining to calculation of the grids
- OUTPARM #messages pertaining to parameterization of receptor atoms; net charge on the receptor molecule including any ions or waters in the receptor pdb file
- PDBPARM #shows which parameters have been associated with each atom in the receptor pdb file
- zou_grid.bmp #bump grid
- zou_grid.sas #xyz coordinates, effective vdw radii, vdw type, number of spherical grid points, and polarity type for each receptor atom
- zou_grid.sasmark #information about grid spacing, coordinates, dimensions, etc

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3.4. Sphgen

AUTHOR: Irwin D. Kuntz (modified by Renee DesJarlais and Brian Shoichet)

USAGE: sphgen

INPUT FILE*:
rec.ms #molecular surface file
R #sphere outside of surface (R) or inside surface (L)
X #specifies subset of surface points to be used (X=all points)
0.0 #prevents generation of large spheres with close surface contacts (default=0.0)
4.0 #maximum sphere radius in Angstroms (default=4.0)
1.4 #minimum sphere radius in Angstroms (default=radius of probe)
rec.sph #clustered spheres file

*WARNINGS:
(1) The input file names and parameters are read from a file called INSPH, which should not contain any blank lines or the comments (denoted by #) from above.
(2) The molecular surface file must include surface normals . SPHGEN expects the Fortran format

A3, I5, X, A4, X, 2F8.3, F9.3, X, A3, 7X, 3F7.3

DESCRIPTION:

3.4.1. Overview

Sphgen generates sets of overlapping spheres to describe the shape of a molecule or molecular surface. For receptors, a negative image of the surface invaginations is created; for a ligand , the program creates a positive image of the entire molecule. Spheres are constructed using the molecular surface described by Richards (1977) calculated with the program dms . Each sphere touches the molecular surface at two points and has its radius along the surface normal of one of the points. For the receptor, each sphere center is outside the surface, and lies in the direction of a surface normal vector. For a ligand, each sphere center is inside the surface, and lies in the direction of a reversed surface normal vector.

Spheres are calculated over the entire surface, producing approximately one sphere per surface point. This very dense representation is then filtered to keep only the largest sphere associated with each receptor surface atom. The filtered set is then clustered on the basis of radial overlap between the spheres using a single linkage algorithm. This creates a negative image of the receptor surface, where each invagination is characterized by a set of overlapping spheres. These sets, or clusters, are sorted according to numbers of constituent spheres, and written out in order of descending size. The largest cluster is typically the ligand binding site of the receptor molecule. The program showsphere writes out sphere center coordinates in PDB format and may be helpful for visualizing the clusters (see showsphere).

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3.4.2. Critical Points

The process of labeling site points for critical matching must currently be done by hand (see Critical Points for use in DOCK). The user should load the site points and the receptor coordinates into a graphic program to determine the spheres closest to the target area. Once a sphere or group of spheres has been determined to be critical, the sphere(s) should be labeled by changing the second to last column of the final sphere file to the critical cluster number (see Output).

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3.3.3. Chemical Matching

The process of labeling site points for chemical matching must also be done by hand (see Chemical Matching for use in DOCK). The user should load the site points and the receptor coordinates into a graphic program and study the local environment of each point. Labeled site points may be input as either a SPH format or SYBYL MOL2 format coordinate file. To store labeled site points in a MOL2 file, select an atom type for each label of interest. Then edit the

chem.defn file to include the selected atom types (see chem.defn). Site point definitions can be distinguished from ligand atom definitions by explicitly requiring that no bonded atoms can be attached (ie. followed by [*]). Using the convention in that example file, site points should be labeled as follows: hydrophobic, "C.3"; donor, "N.4"; acceptor, "O.2"; polar, "F".

Example of chemical labels in SPH format

```
DOCK 3.5 receptor_spheres
color hydrophobic 1
color acceptor 2
color donor 3
cluster 1 number of spheres in
cluster 49
7 2.34500 36.49000 16.93500 1.500
0 0 1
8 -0.05200 42.29900 14.18800
1.500 0 0 1
9 -0.67000 41.20600 11.59800
1.500 0 0 1
17 -6.00000 34.00000 17.00000
1.500 0 0 3
18 -5.00000 29.00000 22.00000
1.500 0 1 3
...
```

Caveats on Chemical Matching

It can take a significant amount of effort to chemically label a large site and to verify that the docking results are what were expected. If you use this chemical matching, plan to spend some time in preparation and validation BEFORE running an entire database of molecules.

It must be pointed out that the ultimate arbiter of which orientations of a ligand are saved is actually the scoring function. If the scoring function is unable to discriminate what the user feels are bad chemical interactions, then any improvement with chemical matching will probably be obscured. In addition, if score optimization is used, then the orientation will be perturbed from the original chemically-matched position to a new score-preferred positions.

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3.4.4. Output

Some informative messages are written to a file called OUTSPH. This includes the parameters and files used in the calculation. The spheres themselves are written to the clustered spheres file. They are arranged in clusters with the cluster having the largest number of spheres appearing first. The sphere cluster file consists of a header followed

by a series of sphere clusters. The header is the line DOCK 3.5 receptor_spheres followed by a color table (see Chemical Matching). The color table contains color names each on a separate line. As sphgen produces no colors, the color table is simply absent.

The sphere clusters themselves follow, each of which starts with the line

cluster n number of spheres in cluster i

where n is the cluster number for that sphere cluster, and i is the number of spheres in that cluster. Next, all spheres in that cluster are listed in the format below:

FORMAT: (I5, 3F10.5, F8.3, I5, I2, I3)
I: Integer F: Float
01234501234567890123456789012345678901234567890123456789012345678 9
63 5.58405 50.91005 59.97029 1.411 92 0 0
64 9.00378 52.46159 62.30926 1.400 321 0 0
66 11.43685 56.49715 61.79008 1.984 493 0 0
I5: Column 0~4 (the first 5 columns) were used to put integer data.
F10.5: Column 5~14 (total 10 columns,and 5 digits for mantissa) were used to put float data.

The values in the sphere file correspond to:

- The number of the atom with which surface point i (used to generate the sphere) is associated.
- The x, y ,and z coordinates of the sphere center.
- The sphere radius.
- The number of the atom with which surface point j (second point used to generate the sphere) is associated.
- The critical cluster to which this sphere belongs.
- The sphere color. The color is simply an index into the color table that was specified in the header. Therefore, 1 corresponds to the first color in the header, 2 for the second, etc. 0 corresponds to unlabeled.

The clusters are listed in numerical order from largest cluster found to the smallest. At the end of the clusters is cluster number 0. This is not an actual sphere cluster, but a list of allof the spheres generated whose radii were larger than the minimum radius, before the filtering heuristics (i.e . allowing only one sphere per atom and using a maximum radius cutoff) and clustering were performed. Cluster 0 may be useful as a starting point for users who want to explore a wider range of possible clusters than is provided by the standard SPHGEN clustering routine. The program creates three temporary files: temp1.ms, temp2.sph, and temp3.atc. These are used internally by SPHGEN, and are deleted upon completion of the computation. For more information on sphere generation and selection, go to the Sphere Generation and Selection demo.

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3.5. Showbox

AUTHOR: Elaine Meng

USAGE: showbox [< input.in]

DESCRIPTION:

Showbox is an interactive program that allows visualization of the location and size of the grids that will be calculated by the program grid , using any graphics program that can display PDB format. The user is asked whether the box should be automatically constructed to enclose all of the spheres in a cluster. If so, the user must also enter a value for how closely the box faces may approach a sphere center (how large a cushion of space is desired) and the sphere cluster filename and number. If not, the user is asked whether the box will be centered on manually entered coordinates or a sphere cluster center of mass. Depending on the response, the coordinates of the center or the sphere cluster filename and number are requested. Finally, the user must enter the desired box dimensions (if not automatic) and a name for the output PDB-format box file. If the input parameters are known, they can be listed in an input file and piped into the program.

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3.6. Showsphere

AUTHORS: Stuart Oatley , Elaine Meng , Daniel Gschwend

USAGE: showsphere [< input.in]

DESCRIPTION:

Showsphere is an interactive program; it produces a PDB-format file of sphere centers and an MS-like file of sphere surfaces, given the sphere cluster file and cluster number. The surface file generation is optional. The user may specify one cluster or all, and multiple output files will be generated, with the cluster number appended to the end of the name of each file. The input cluster file is created using sphgen (see sphgen). Showsphere requests the name of the sphere cluster file, the number of the cluster of interest, and names for the output files. Information is sent to the screen while the spheres are being read in, and while the surface points are being calculated. If the input parameters are known, they can be listed in an input file and piped into the program.

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3.7. Sphere Selector

AUTHOR: P. Therese Lang

USAGE: sphere_selector < sphere_cluster_file.sph >
<set_of_atoms.mol2> <radius>

Sphere_selector will take the ouput from spghen and select all spheres with a user-defined radius of a target molecule (see sphgen). The target molecule can be anything (ie known ligand, receptor residue, etc) as long as it is in proper MOL2 format. WARNING: Please note that above order of input files must be maintained for the program to work.

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3.8. Antechamber

Antechamber is an accessory program originally developed to prepare small molecules on the fly to use in AMBER. With permission, we have included a distribution of the code to facilitate preparing small molecules for Amber_Score. For more information on the use of the antechamber accessory, please visit the source web site at amber.scripps.edu/antechamber/antechamber.html.

From the web site:

"Antechamber is a set of auxiliary programs for molecular mechanic (MM) studies. This software package is devoted to solve the following problems during the MM calculations: (1) recognizing the atom type; (2) recognizing bond type; (2) judging the atomic equivalence; (3) generating residue topology file; (4) finding missing force field parameters and supplying reasonable and similar substitutes. As an accessory module..., antechamber can generate input automatically for most organic molecules in a database...."

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Molecular File Formats

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4.1. Tripos MOL2 Format

This format is used for general molecule input and output of DOCK. Although previous versions of DOCK supported an extended PDB format to store molecule information, the current version now uses MOL2 as the molecule format. This format has the advantage of storing all the necessary information for atom features, position, and connectivity. It is also a standardized format that other modeling programs can read. For more information on how to generate MOL2 files from PDB files, go to the Structure Preparation demo.

Of the many record types in a MOL2 file, DOCK recognizes the

following: MOLECULE, ATOM, BOND, SUBSTRUCTURE and SET. In the MOLECULE record, DOCK utilizes information about the molecule name and number of atoms, bonds, substructures and sets. In the ATOM record DOCK utilizes information about the atom names, types, coordinates, and partial charges. In the BOND record, DOCK utilizes the atom identifiers for the bond. In the SUBSTRUCTURE record, DOCK records the fields, but does not utilize them. The SET records are entirely optional. They are used only in special circumstances, like when ligand flexibility is considered. In DOCK 6, an additional record type has been introduced. This is the SOLVATION record, that has the atomic desolvation information for the ligand atoms. The parameter read_mol_solvation can be used to read in this record.

For extensive details on the MOL2 format, as well as example files, please refer to the Tripos web site documentation (http://www.tripos.com/data/support/mol2.pdf).

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4.2. PDB Format

This format is used for several of the DOCK accessories and the AMBER score function. For extensive details on the PDB format, as well as example files, please refer to the Protein Databank File Format Documentation (http://www.pdb.org/pdb/static.do?p=file_formats/pdb/index.html).

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