

# **DOCK 5.4 User Manual**

Irwin D. Kuntz  
Demetri T. Moustakas  
P. Therese Lang

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# General Overview

## Ligand File I/O

Currently, only MOL2 file I/O is supported. 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 (vdw.defn, flex.defn, flex\_table.defn). More information about all of these files can be found in the Appendix. There are several ligand output options, which write molecules to files whose names are formed using the output\_file\_prefix parameter:

DOCK will always write out a scored molecules output file, which contains the best scoring pose for each molecule in the database. This will create a file called outputprefix\_scored.mol2. Beyond this option, there are several other levels of sampling output:

- 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 prior to final optimization. This will create a file called outputprefix\_confs.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 orientations per anchor \* the number of conformers per cycle. This file can grow quite large, so only use it on single poses or small databases.
- 3) Finally, 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, though users can override this and write out the best pose for each molecule as well.

## Rigid Orienting

DOCK 5 uses receptor spheres and ligand heavy atom centers to rigidly orient ligands in the receptor. The spheres are generated using the accessory SPHGEN. Cliques of receptor spheres & ligand centers are identified using the maximum subgraph clique detection algorithm from DOCK 4. All cliques that satisfy the matching parameters are generated in the matching step, and can be sorted or ordered prior to the loop where the program cycles through the orientations.

Both automated and manual matching are available in DOCK5. The sphere/center matches are determined by 2 parameters:

- 1) The distance tolerance is the tolerance in angstroms within which a pair of spheres is considered equivalent to a pair of centers
- 2) The distance minimum is the shortest distance allowed between 2 spheres (any sphere pair with a shorter distance is disregarded)

Manual matching will create as many matches as possible given the specified parameters, and sort the matches according to the RMS error between the spheres and centers in the match. The matches are provided as orientations until either the max\_orients # of orientations are reached, or the end of the match list is reached.

Automated matching will start with the default values for the distance tolerance and distance minimum. A list of matches will be generated, and if the # of matches is less than the # max\_orientations, then the distance tolerance is increased and the matching is repeated until there are at least max\_orientations in the match list. Then the list is sorted, and orientations are generated.

### **Ligand Flexibility**

Ligand flexibility in DOCK 5 uses the anchor-and-grow algorithm, which was introduced in DOCK 4. Rotatable bonds (not contained in rings) are used to partition the molecule into rigid segments, from which all anchors that meet the criteria are selected beginning with the largest anchor segment. All anchor orientations (or the starting orientation only, if no orienting is selected) are used as starting configurations onto which the first flexible layer is appended and conformationally expanded. The total population of conformers is then reduced to the number specified by num\_confs\_per\_cycle, and the process is repeated until the last layer is reached.

The conformer generator class now integrates score optimization in the anchor & grow algorithm. The anchors can be rigidly optimized, the final conformations can be rigidly, torsionally, or completely optimized, and the partially grown conformers can be completely optimized. The anchor & grow steps use whichever scoring function the user selects as the primary scoring function. The final minimization step uses the secondary scoring function.

### **Scoring Functions**

This release of DOCK5 implements a hierarchical scoring function 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 the rigid minimization, and anchor & grow steps, 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. If no secondary scoring function is selected, the primary scoring function is used as the secondary.

This release contains continuous molecular mechanics based scoring (vdw + columbic terms only), grid-based molecular mechanics scoring, contact scoring and bump filtering as implemented in DOCK 4. Scoring grids are created using the GRID program. DOCK also contains GB/SA scoring, as implemented in SDOCK. Scoring grids for the GBSA code are calculated using the accessories nchemgrid\_GB and nchemgrid\_SA.

This release also includes an internal energy scoring function, which is used during the anchor & grow flexible search. This function computes the Lennard-Jones and columbic energy between all ligand atom pairs, excluding all 1-2, 1-3, and 1-4 pairs. This energy is not included in the final reported score.

### **Score Optimization**

Score optimization is implemented using a simplex minimizer based on the DOCK 4 minimizer. 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. The final minimization can be rigid or torsions only, or complete. 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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## **Using DOCK**

### **Installing DOCK**

1. Save file for appropriate operating system to hard drive.
2. Uncompress the archive into a folder called dock5/ in a directory of your choice.
  - a. For windows systems, a Zip file is provided
  - b. For \*nix systems, a gzipped archive is provided
3. All DOCK 5 binaries are installed in dock5/bin/

The dock5 directory contains the following subdirectories:

bin/  
demo/  
installation/

parameters/  
src/  
utilities/  
    accessories/  
    grid/  
    GBSA\_Grids/

### **Compiling DOCK (if required)**

DOCK comes with platform specific compiled binaries. You should not need to compile the code or accessories unless you have made changes to the source code, or are planning to run DOCK on a platform for which we do not distribute binaries.

*Building DOCK:* (all platforms)  
From the dock5 directory:  
cd config/  
./configure gnu  
make

DOCK with mpi function is built upon an mpi library. The MPICH library is provided freely by Argonne National Labs (<http://www-unix.mcs.anl.gov/mpi/mpich/>). The MPI library needs to be installed and running on the system if the MPI features are to be used. Once MPI is installed, you need to define MPICH\_HOME as an environment variable.

*Building MPI-DOCK* (all platforms):  
From the dock5 directory:  
cd config/  
./configure gnu.parallel  
make

NOTE: MPI-DOCK 5.4 has been compiled with MPICH-1.2.7 on all supported platforms (MPICH-1.2.5 for WinXP).

### **Running DOCK**

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 and unix shells ("Devel" for Cygwin).

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

```
dock5/bin/dock5 -i parameter.in [-v1] [-v2] [-o outputfile.txt]
```

If the parameter file does not exist, DOCK will generate one using your responses to the parameter questions. If the parameter file exists, any parameter values found will be read.

DOCK 5 outputs the job parameters to the screen at the start of the job, and prints summary information for each molecule processed. Additional summary information will be included in future releases. The `-v1` flag prints a histogram of sphere matching information. The `-v2` flag prints details about the breakdown of the GB/SA terms.

### **Running DOCK in Parallel**

If you have installed the MPI library, DOCK can be run in parallel using the following command:

```
mpirun -np # dock5.mpi -i parameter.in -o outputfile.txt
```

Note that that parallelization 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.

### **Running the Demo**

DOCK 5.4 includes two demonstration files that are designed to test your installation. These demos must also be run command-line.

*For DOCK:* (all platforms)

From the dock5 directory:

```
cd demo
```

```
./script_clean
```

```
./script_demo
```

*For MPI-DOCK:* (all platforms)

From the dock5 directory:

```
cd demo
```

```
./script_clean
```

```
./script_mpi_demo
```

NOTE: MPI-DOCK will be run on 4 processors for the demo

## DOCK 5 Parameters

The parameters for several common calculations have been optimized using test sets. General recommendations for these parameters can be found in dock5/recommended\_input. Below, all available options for DOCK are described in detail.

The DOCK 5 parameter parser requires that the values entered for a parameter exactly match one of the legal values if any legal values are specified. For example:

```
param_a      [5] ():  
param_b      [5] (0 5 10):
```

param\_a can be assigned any value, however param\_b can only be assigned 0, 5, or 10. If no value is entered, both will default to a value of 5. Below are listed all DOCK 5 parameters, their default values, legal values, and a brief description of each. The parameters are listed in order of function. Also, for questions requiring a yes/no answer, please use the full word (yes or no) as opposed to y or n.

### *Ligand I/O Parameters*

<b>Parameter Name</b>	<b>Default</b>	<b>Values</b>	<b>Description</b>
ligand_atom_file	database.mol2	string	The ligand input filename
ligand_outfile_prefix	output	string	The prefix that all output files will use
limit_max_ligands	no	bool (yes, no)	The maximum # of ligands that will be read in from a library
write_orientations	no	bool (yes, no)	Flag to write orientations
write_conformations	no	yes, no	Flag to write conformations
initial_skip	0	int	The # of molecules to skip over at the beginning of a library
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 reference structure for RMSD calculation (default is starting structure)
rmsd_reference_filename	ligand_rmsd.mol2	string	File containing RMSD reference structure
rank_ligands	no	yes, no	Flag to enable a ligand top-score list. These ligands will be written to outfile_ranked.mol2, and outfile_scored.mol2 will be

			empty by default
max_ranked_ligands	500	int	The # of ligands to be stored in the top score list
scored_conformer_output_override	no	yes, no	This flag causes all ligands to be written to outfile_scored.mol2, even when rank_ligands is true
num_scored_conformers_written	1	int	The # of scored poses for each ligand printed to output_scored.mol2
cluster_conformations	yes	yes, no	Flag to enable clustering of fully minimized conformations (NOTE: Only available if num_scored_conformers_written > 1)
cluster_rmsd_threshold	2.0	float	The cutoff to determine whether conformations should be clustered

### *Orient Ligand Parameters*

<b>Parameter Name</b>	<b>Default</b>	<b>Values</b>	<b>Description</b>
orient_ligand	yes	bool (yes, no)	Flag to orient ligand to spheres
automated_matching	yes	bool (yes, no)	Flag to perform automated matching instead of manual matching
distance_tolerance	0.25	float	The distance tolerance applied to each edge in a clique
distance_minimum	2.0	float	The minimum size for an edge in a clique
nodes_minimum	3	int	The minimum # of nodes in a clique
nodes_maximum	10	int	The maximum # of nodes in a clique
receptor_site_file	receptor.sph	string	The file containing the receptor spheres
max_orientations	500	int	The maximum # of orientations that will be cycled through
critical_points	no	bool (yes, no)	Flag to use critical point sphere labeling to target orientations to particular spheres
chemical_matching	no	bool (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	bool (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	Ligand spheres

### *Flexible Ligand Parameters*



Parameter Name	Default	Values	Description
flexible_ligand	yes	bool (yes, no)	Flag to perform ligand conformational searching
ag_conf_search	yes	bool (yes, no)	Flag to use the anchor & grow algorithm to search ligand conformations
min_anchor_size	40	int	The minimum # of heavy atoms for an anchor segment
num_anchor_orients_for_growth	100	int	The maximum number of anchor orientations promoted to the conformational search
number_confs_for_next_growth	100	int	The maximum number of conformations carried forward in the anchor & grow search
use_internal_energy	yes	bool (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	bool (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

#### *Ligand Scoring Parameters*

Parameter Name	Default	Values	Description
bump_filter	yes	bool (yes, no)	Flag to perform bump filtering
bump_grid_prefix	grid	string	The prefix to the grid file(s) containing the desired bump grid
max_bumps	2	int	The maximum allowed # of bumps for a molecule to pass the filter
score_molecules	yes	bool (yes, no)	Enables scoring of molecules
contact_score_primary	no	bool (yes, no)	Flag to perform contact scoring as the primary scoring function
contact_score_secondary	no	bool (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	int	The penalty for each contact overlap made
contact_score_grid_prefix	grid	string	The prefix to the grid files

			containing the desired cnt grid
grid_score_primary	yes	bool (yes, no)	Flag to perform grid-based energy scoring as the primary scoring function
grid_score_secondary	yes	bool (yes, no)	Flag to perform grid-based energy scoring as the secondary scoring function
grid_score_vdw_scale	1	float	Scalar multiplier of the vdw energy component
grid_score_es_scale	1	float	Scalar multiplier of the electrostatic energy component
grid_score_grid_prefix	grid	string	The prefix to the grid files containing the desired nrg grid
continuous_score_primary	no	bool (yes, no)	Flag to perform continuous non-grid based scoring
continuous_score_secondary	no	bool (yes, no)	Flag to perform continuous non-grid based scoring
cont_score_rec_filename	receptor.mol2	string	File that contains receptor coordinates
cont_score_att_exp	6	int	VDW L-J potential attractive exponent
cont_score_rep_exp	12	int	VDW L-J 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
cont_score_es_scale	1	float	Scalar multiplier of electrostatic energy component
gbsa_pairwise_score_primary	no	bool (yes, no)	Toggles whether or not to use GB/SA scoring as the primary scoring function
gbsa_pairwise_score_secondary	no	bool (yes, no)	Toggles whether or not to use GB/SA scoring as the secondary scoring function
gbsa_pairwise_gb_grid_prefix	gb_grid	string	The path to the pairwise GB grids
gbsa_pairwise_sa_grid_prefix	sa_grid	string	The path to the SA grids
gbsa_pairwise_vdw_grid_prefix	grid	string	The path to the dock4 nrg grids, used for the vdw portion of the GB/SA calculation
gbsa_pairwise_screen_file	screen.in	string	GB parameter file for electrostatic screening. Its located in the parameters dir by default
gbsa_pairwise_solvent_dielectric	78.300003	float	The value for the solvent

			dielectric
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### Score Optimization Parameters

Parameter Name	Default	Values	Description
minimize_ligand	yes	bool (yes, no)	Flag to perform score optimization
minimize_anchor	yes	bool (yes, no)	Flag to perform rigid optimization of the anchor
minimize_flexible_growth	yes	bool (yes, no)	Flag to perform complete optimization during conformational search
minimize_final_pose	yes	bool (yes, no)	Flag to perform minimization of the final ligand pose
use_advanced_simplex_parameters	no	bool (yes, no)	Flag to use a simplified set of common minimization parameters for each of the minimization steps listed above

### Basic Simplex Minimizer Parameters

Parameter Name	Default	Values	Description
simplex_max_cycles	1	int	Maximum # of minimization cycles
simplex_score_converge	0.1	float	Exit cycle at when energy converges at cutoff
simplex_cycle_converge	1.0	float	Exit minimization when cycles converge at cutoff
simplex_trans_step	1.0	float	Initial translation step size
simplex_rot_step	0.1	float	Initial rotation step size
simplex_tors_step	10.0	float	Initial torsion angle step size
simplex_anchor_max_iterations	500	int	Maximum # of iterations per cycle per anchor
simplex_grow_max_iterations	500	int	Maximum # of iterations per cycle per growth step
simplex_final_max_iterations	0	int	Maximum # of iterations per cycle for entire molecule using secondary scoring function
simplex_random_seed	0	int	Seed for random number generator

### Advanced Simplex Minimizer Parameters

Parameter Name	Default	Values	Description
simplex_anchor_max_iterations	50	int	Maximum # of minimization cycles
simplex_anchor_max_cycles	1	int	Maximum # of minimization cycles
simplex_anchor_score_converge	0.1	float	Exit cycle at when energy converges at cutoff
simplex_anchor_cycle_converge	1.0	float	Exit minimization when cycles

			converge at cutoff
simplex_anchor_trans_step	1.0	float	Initial translation step size
simplex_anchor_rot_step	0.1	float	Initial rotation step size
simplex_anchor_tors_step	10.0	float	Initial torsion angle step size
<i>NOTE: Repeat for minimization of each layer (simplex_grow_xxx) and final minimization (simplex_final_xxx)</i>			

### *Atom & Bond Typing Parameters*

<b>Parameter Name</b>	<b>Default</b>	<b>Legal</b>	<b>Description</b>
atom_model	all	string (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 bond definition parameters
flex_drive_file	flex_drive.tbl	string	File containing conformational search parameters
chem._defn_file	chem.defn	string	File containing chemical label (pharmacophore) definitions

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## **ACCESSORIES**

### **GRID**

Author: Todd Ewing

Based on work by Elaine Meng and Brian Shoichet

#### **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 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 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. 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.

### **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.

### **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:

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

where  $\epsilon$  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:

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

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

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

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

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 0.25 Angstrom.

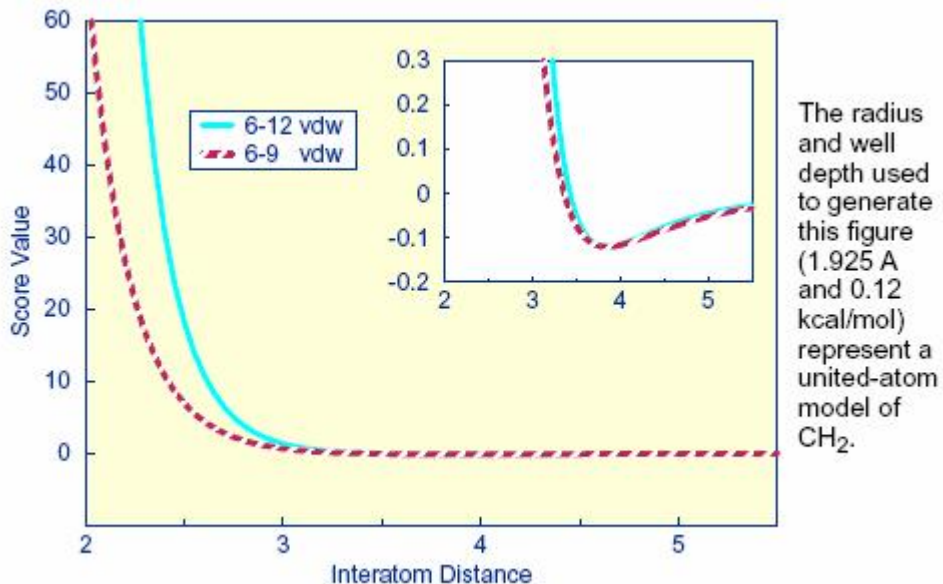


Figure 1: Distance dependence of the Lennard-Jones Function

### ***Precomputing potentials on a grid***

By inspection of the above equations, the repulsion and attraction parameters ( $A_{ij}$  and  $B_{ij}$ ) for the interactions of identical atoms can be derived from the van der Waals radius,  $R$ , and the well depth,  $\epsilon$ .

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

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

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:

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

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

Using this approximation, the first equation can be rewritten:

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

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**. 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.

### **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. The distance dependence of the contact score is represented in **Figure 2**.



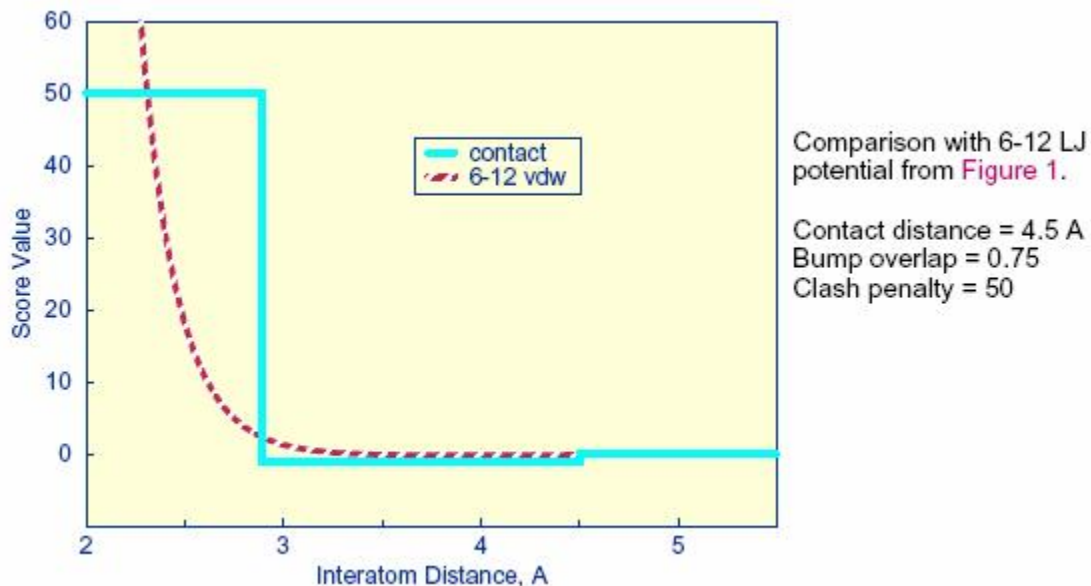


Figure 2. Distance dependence of contact score function

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.

### Running GRID

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

```
grid -i grid.in [-stv] [-o grid.out]
-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
```

### General Parameters

Parameter Name	Default	Value	Description
compute_grids	no	bool (yes, no)	Flag to compute scoring grids
grid_spacing	0.3	float	The distance between grid points along each axis.
output_molecule	no	bool (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. Terminal SYBYL capping groups are

			merged with the terminal residues.
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### Scoring Parameters

Parameter Name	Default	Value	Description
contact_score	no	bool (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
chemical_score	no	bool (yes, no)	Flag to construct chemical grid
energy_score	no	bool (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	string (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	Exponent of repulsive Lennard-Jones term for VDW potential
distance_dielectric	yes	bool (yes, no)	Flag to make the dielectric depend linearly on the distance
dielectric_factor	4.0	float	Coefficient of the dielectric
bump_filter	no	bool (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

### File Input

Parameter Name	Default	Value	Description
receptor_file	receptor.mol2	bool (yes, no)	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.

### *File Output*

Parameter Name	Default	Value	Description
score_grid_prefix	grid	string	Core file name of grids (file extension will be appended automatically)
receptor_out_file	receptor_out.mol2	string	File for cleaned-up receptor when output_molecule set

## NCHEMGRID\_GB and NCHEMGRID\_SA

Author: Xiaoqin Zou

### **Overview**

The NCHEMGRID\_GB and NCHEMGRID\_SA programs create the GB and SA receptor grids for use with DOCK 5's GB/SA scoring function.

### **Input**

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.ambcrq.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

### **SPHGEN**

Author: Irwin D. Kuntz

Modified by: Renee DesJarlais, Brian Shoichet

#### **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 ([www.cgl.ucsf.edu](http://www.cgl.ucsf.edu)). 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.

#### **Input**

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

NOTES:

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).

### 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. The color table contains color names (format A30) 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 (I5, 3F10.5, F8.3, I5, I2, I3) where the values correspond to, respectively,

- 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 all of 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 [demo](#).

### **SHOWBOX**

Author: Elaine Meng

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.

### **SHOWSPHERE**

Authors: Stuart Oatley, Elaine Meng, Daniel Gschwend

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. 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.

### **SPHERE\_SELECTOR**

Author: P. Therese Lang

SPHERE\_SELECTOR will take the output from SPHGEN and select all spheres with a user-defined radius of a target molecule. The target molecule can be anything (ie known ligand, receptor residue, ect) as long as it is in proper MOL2 format. The required input for sphere\_selector is:

USAGE: sphere\_selector <sphere\_cluster\_file.sph> <set\_of\_atoms.mol2>  
<radius>

Please note that above order of input files must be maintained for the program to work.

---

## APPENDIX 1: Parameter File Formats

### Overview

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.

### 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 sp <sup>3</sup> 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).
-------------------------------------	---

### ***vdw.defn***

This file contains atom labels and definitions for van der Waals atom typing.

- The following data types are associated with each atom: VDW radius, VDW well-depth, flag for heavy atom, number of attached atoms.
- Some labels are used only for the united-atom model, some for only the all-atom model, and some for either.
- A label may have multiple definitions.

#### *Sample Entries from vdw.defn*

---

```
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
```

```
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 )
```

---

### ***chem.defn***

This file contains labels and definitions for chemical labeling.

- Nothing in addition to a label is assigned to an atom.
- A label may have multiple definition lines.

#### *Sample Entries from chem.defn*

---

```
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 [ * ]
```

---

### ***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 of chem\_match.tbl*

```
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
```

### ***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 from flex.defn*

---

```
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 ]
```

---

### ***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.
- The positions field specifies the number of torsion angles to sample.
- The torsions field specifies the angles that are sampled.

#### *Sample Entries from flex\_drive.defn*

---

```
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
```

---

## **APPENDIX 2: Molecular File Formats**

### **Tripos MOL2 format**

#### ***Overview***

This format is used for general molecule input and output of DOCK. 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.

### Specification

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 the user wants to define the anchor for flexible docking.

Please refer to Sybyl documentation for additional information.

### Example

This example file illustrates all the elements of the MOL2 file read and written by dock. It includes optional SET records which are used by the ligand flexibility routines.

```
@<TRIPOS>MOLECULE
```

```
example
```

```
23 23 1 0 2
```

```
GAST_HUCK
```

```
@<TRIPOS>ATOM
```

```
1 C 1.2300 0.7100 0.0000 C.ar 1 ABC -
0.0529
2 H 2.1620 1.2490 0.0000 H 1 ABC
0.0571
3 C 0.0000 1.4200 0.0000 C.ar 1 ABC -
0.0242
4 C 0.0000 2.9060 0.0000 C.3 1 ABC
0.0319
5 H -0.5150 3.2700 0.8920 H 1 ABC
0.0598
6 H -0.5150 3.2700 -0.8920 H 1 ABC
0.0598
7 N 1.3680 3.3900 0.0000 N.3 1 ABC -
0.3075
8 H 1.8480 3.0500 0.8320 H 1 ABC
0.1243
9 C 1.3680 4.8410 0.0000 C.3 1 ABC -
0.0136
10 H 0.8530 5.2050 0.8920 H 1 ABC
0.0390
11 H 0.8530 5.2050 -0.8920 H 1 ABC
0.0390
12 H 2.3990 5.2050 0.0000 H 1 ABC
0.0390
13 C -1.2300 0.7100 0.0000 C.ar 1 ABC -
0.0529
14 H -2.1620 1.2490 0.0000 H 1 ABC
0.0571
```

15 C	-1.2300	-0.7100	0.0000	C.ar	1 ABC	-
0.0471						
16 H	-2.1620	-1.2490	0.0000	H	1 ABC	
0.0655						
17 C	-0.0000	-1.4200	0.0000	C.ar	1 ABC	
0.0547						
18 C	1.2300	-0.7100	0.0000	C.ar	1 ABC	-
0.0471						
19 H	2.1620	-1.2490	0.0000	H	1 ABC	
0.0655						
20 C	-0.0000	-2.7800	0.0000	C.2	1 ABC	
0.2555						
21 O	-0.0850	-3.5030	0.9750	O.2	1 ABC	-
0.3604						
22 O	0.1090	-3.2660	-1.2480	O.3	1 ABC	-
0.2944						
23 H	0.1010	-4.2400	-1.1490	H	1 ABC	
0.2522						

@<TRIPOS>BOND

1	1	2	1
2	1	18	ar
3	1	3	ar
4	3	13	ar
5	3	4	1
6	4	6	1
7	4	5	1
8	4	7	1
9	7	8	1
10	7	9	1
11	9	12	1
12	9	11	1
13	9	10	1
14	13	14	1
15	13	15	ar
16	15	16	1
17	15	17	ar
18	17	20	1
19	17	18	ar
20	18	19	1
21	20	21	2
22	20	22	1
23	22	23	1

@<TRIPOS>SUBSTRUCTURE

1 ABC	1 GROUP	0 A	****	0 ROOT
-------	---------	-----	------	--------

@<TRIPOS>SET

ANCHOR	STATIC	ATOMS	<user>	**** Anchor atom set
6 1 3 13 15 17 18				
RIGID	STATIC	BONDS	<user>	**** Rigid bond set
6 2 3 4 15 17 19				