

MolShaCS Manual

Alessandro S. Nascimento

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Chapter 1

Introduction

1.1 What is MolShaCS?

MolShaCS (**M**olecular **S**hape and **C**harge **S**imilarity) is a computational tool dedicated to overlay and compute a similarity index among two small molecules. MolShaCS currently can handle only SYBYL MOL2 file format and it is desirable for the molecules to have atomic charges defined, since MolShaCS will use the charge distribution of the molecules together with molecular shape to overlay and compute the similarity index.

For molecular overlay and similarity index computation, MolShaCS uses a Gaussian description of the molecule shape and charge distribution. The overlay is achieved by numerical optimization of the sum of Gaussians that describe molecular shape and charge. Once the overlay is optimized, the similarity index is computed using a Hodgking's like index [5].

MolShaCS can be used as an important tool for small molecule identifications in different contexts, including (i) virtual screening of actives compounds using a "pharmacophore-like" model, i.e., a 3-D model of another compound known to be active; (ii) identification of "off-target" interactions, i.e., the similarities among molecules supposed to have different pharmacological effects or mechanisms of actions.

We provide the software as it is, hoping that it can be useful for the chemoinformatics/medicinal chemistry community, following the terms of the license shown below. Any suggestions, doubts, problems on using the program can be directed to the address below.

Prof. Alessandro S. Nascimento
Sao Carlos Physics Institute - University of Sao Paulo
Av. Trabalhador saocarlense, 400. Centro
Sao Carlos - SP. Brazil
13560-970.
Email: asnascimento@ifsc.usp.br

Chapter 2

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Chapter 3

Theory

MolShaCS uses the concept of overlap of Gaussians for molecular overlay and similarity computation. Here, the volume of each atom is described as a Gaussian function[2, 1, 4, 6]. The pictures below show in one dimension what MolShaCS performs in three dimensions.

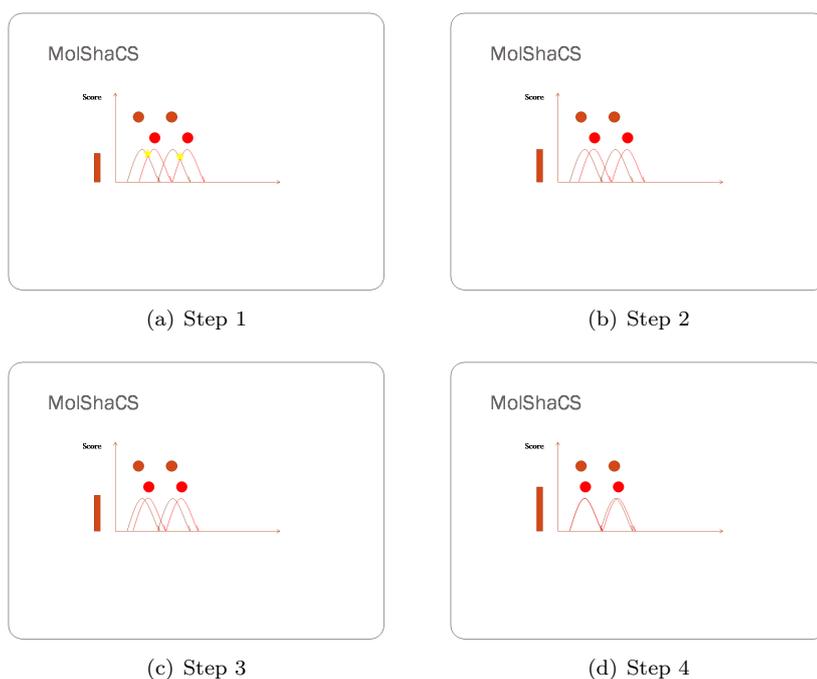


Figure 3.1: A score is computed by summing the overlap of Gaussians that describe atomic shape. A maximal score is obtained when molecules are superposed.

At r , the shape volume is defined as[7]:

$$\rho_i(r) = p_i \exp(-\alpha_i(r - R_i)^2) \quad (3.1)$$

where R_i is the atomic coordinate, p_i is the Gaussian amplitude and α_i is the atomic radius-dependent decay factor:

$$\alpha_i = \pi \left(\frac{3p_i}{4\pi\sigma_i^3} \right) \quad (3.2)$$

The overlap of Gaussians among two molecules named A and B can be given by:

$$V_{AB} = \sum_{i \in A} \sum_{j \in B} \int dr \rho_i(r) \rho_j(r) \quad (3.3)$$

That formulations is the classical description of molecular shape based on Gaussian density and the use of the overlap of Gaussians to estimate the molecular overlap. It has been described since early nineties and is already implemented (with some flavours) in different programs dedicated to molecular similarity identification, such as ROCS[4, 6], ShaEP[7], etc.

MolShaCS differs from these softwares in the way it includes the molecular charge distribution in the overlap computation. In MolShaCS, two other terms are included in equation 3.3, accounting for the overlap of positive charges and negative charges, respectively. The charge distribution is modeled as a Gaussian similar to equation 3.1, taking σ as proportional to the atomic charge. So, the final objective function in MolShaCS is given by:

$$V_{AB} = \sum_{i \in A} \sum_{j \in B} w_1 \left[\int dr \rho_i(r) \rho_j(r) \right] + w_2 \left[\int dr \phi_i^{pos}(r) \phi_j^{pos}(r) \right] + w_2 \left[\int dr \phi_i^{neg}(r) \phi_j^{neg}(r) \right] \quad (3.4)$$

MolShaCS optimizes this objective function shown in equation 3.4 by changing the molecular atomic coordinates using six parameters for rotation and translations, i.e., the molecule is moved as a rigid body. After a maximal overlap is found, a similarity index (SI) is computed as a Hodgkin's index[5]:

$$SI = \frac{2V_{AB}}{V_{AA} + V_{BB}} \quad (3.5)$$

MolShaCS uses NLOPT library for numerical optimization. Different algorithms provided by NLOPT are available for the user choose:

1. Augmented Lagrangians [3]: `nlopt_ln_auglag` ;
2. Method of Moving Asymptotes[8]: `nlopt_mma`;
3. Improved Stochastic Ranking Evolution Strategy: `nlopt_isres`;
4. Broyden-Fletcher-Goldfarb-Shanno Algorithm: `nlopt_lbfgs2`;
5. Nelder-Mead Simplex method: `nlopt_simplex`;

6. A variant of Nelder-Mead simplex that uses Nelder-Mead on a sequence of subspaces: `nlopt_subplex`;
7. COBYLA: `nlopt_cobyla`;

Chapter 4

Getting and Installing

MolShaCS can be obtained free of charge in the web address <http://www.ifsc.usp.br/biotechmol>. Alternatively, the program can be obtained in the google code repository <http://molshacs.googlecode.com>. The program is distributed as pre-built binaries and source code.

4.1 Compiling MolShaCS

MolShaCS can be compiled from source code in two ways: using Qt libraries to build the GUI, or without the GUI.

4.1.1 Installing necessary libraries

MolShaCS uses a couple of libraries within its engine. GNU Scientific Library (GSL), NLOPT and ZLIB libraries have to be built prior to program compilation.

Building from repositories

On Ubuntu systems, GSL and ZLIB libraries can be built using:

```
sudo apt-get install libgsl0-dev zlib1g-dev
```

Building GSL

Alternatively to the repository install, GSL source code can be downloaded from GSL webpage. The package contains instructions for compilation.

Building NLOPT

NLOPT can be downloaded from NLOPT webpage. The libraries are easily built with the following commands (assuming you have GNU C compiler (gcc) and c++ compiler (g++)):

```
./configure --with-cxx  
make  
sudo make install
```

The libraries are installed by default in `/usr/local/lib`, for linux systems.

Building ZLIB

Alternatively to the repository install, zlib can be obtained from ZLIB webpage. Instructions for library compilation are provided together with the package.

4.1.2 Compiling without the GUI

In MolShaCS `src` folder there is a Makefile named `Makefile.nogui`. Follow the steps described below to compile MolShaCS without GUI:

1. Edit the file `src/Makefile.nogui`. It is important to check the `LDFLAGS` and `CFLAGS`.
2. Build MolShaCS with the command `make`.
3. If compilation succeeds, you will find the binary MolShaCS in the source folder. The program is ready to use in the text mode!

4.1.3 Compiling with GUI

In order to build the Qt GUI, it is necessary to have the program `qmake` and some QT libraries. Again, it can be done with OS repositories, in many cases. In ubuntu, you can use the following command:

```
sudo apt-get install qt4-qmake libqtcore4 libqtgui4 libqt4-dev
```

Alternatively, Qt can be obtained from Nokia webpage and installed. To compile MolShaCS with the GUI, follow the step described below:

1. Edit the file `MolShaCS.pro`. The important keys to look after are `LIBS` and `INCLUDEPATH`. Make sure that the necessary libraries are listed there.
2. Run `qmake` with the command `qmake -recursive MolShaCS.pro`
3. Compile the program with `make`
4. If everything works fine, the binary file named MolShaCS will be built.

4.2 Building MolShaCS for Windows Systems

MolShaCS can be built on MS Windows. However the compilation process can be quite painful. If MS Windows is your operational system of choice, I would recommend to use the pre-built binary provided in the download page. This binary contains the GUI already, so that the user can choose whether or not he wants to use the graphical interface.

However, if you really want to build MolShaCS on MS Windows, you can download and install Qt libraries from Nokia webpage. The other libraries (GSL and nlopt) can be built using MINGW. Then you can build MolShaCS and link with the correct libraries. Be careful to use the same compiler to compile the libraries and Qt (some Qt distributions come with GNU compilers that may have different versions of your MINGW compiler).

Chapter 5

Using MolShaCS

MolShaCS can be compiled and used using a Qt graphical user interface or (my preferred method) using command line. For command line, type:

```
MolShaCS Molshacs.inp
```

Where Molshacs.inp is a text file with the following syntax:

```
refmol_mol2      mol1.mol2
output_prefix    MolShaCS
minimizer        nlopt_mma
align_molecules  yes
timeout          60
write_coordinates yes
mol2_aa          no
box_size         30.0 30.0 30.0
multimol         molecules.list
step             1.0E-5
tol              1.0E-4
delta            1.0E-5
```

A file molecules.list should also exist in the directory where MolShaCS is running. This file must be a text file with the path for the comparing molecules, only. For example:

```
$ more molecules.list
../mol2/mol1.mol2
../mol2/mol2.mol2
../mol2/mol3.mol2
../mol2/mol4.mol2
...
```

5.1 Sample Run

As an example on how to use MolShaCS, we will compare aldosterone to a set of FDA approved molecules and take a look at the molecules in the top of the list. First of all, lets get the molecules.

Lets go to ZINC and download the Drugbank list of approved drugs with 1761 representative molecules. The molecules are provided as MOL2 files through script to download in Linux or Windows.

Supposing you already have the mol2 files named fda80.1.mol2, fda80.2.mol2, fda80.3.mol2, etc, in a separate folder named mol2, lets generate a molecules.list file. If you use Linux or Cygwin in Windows, this should be easy (see below). These lines will look for the files in the folder mol2 and put them on the list if the file exists.

```
$ for i in `seq 1 1761`; do if [ -e ../mol2/fda80.$i.mol2 ]; \
then echo ../mol2/fda80.$i.mol2 >> molecules.list ; \
fi; done
```

Lets get aldosterone from ZINC again, using this link.

Now, lets prepare an input file for MolShaCS. This file should have the following instructions (see below). Save the file as input.inp.

```
refmol_mol2      aldo.mol2
output_prefix    MolShaCS
minimizer        nlopt_mma_sog
align_molecules  yes
timeout          60
write_coordinates yes
write_coord_threshold 0.85
mol2_aa          no
box_size         30.0
multimol         molecules.list
step             1.0E-5
tol              1.0E-4
delta            1.0E-5
```

Ok, we are ready to start the computation with the command `$MolShaCS input.inp`.

After a couple of minutes the calculation is done and two files are written: MolShaCS.log and MolShaCS.cc.dat. The latter has the similarities computed for each of the provided molecules. We can rank the results using a bash command again (below) and we will find the top scored molecules:

```
$ more MolShaCS.cc.dat | sort -n -r -k 5 | more
```

Bibliography

- [1] E.E. Hodgkin A.C. Good and W.G. Richards. Similarity screening of molecular-data sets. *Journal of Computer-Aided Molecular Design*, 6:513–520, 1992.
- [2] E.E. Hodgkin A.C. Good and W.G. Richards. Utilization of gaussian functions for the rapid evaluation of molecular similarity. *Journal of Chemical Information and Computer Sciences*, 32:188–191, 1992.
- [3] E.G. Birgin and J.M. Martinez. Improving ultimate convergence of an augmented lagrangian method. *Optimization Methods Software*, 23:177–195, 2008.
- [4] J.A. Grant and B.T. Pickup. A gaussian description of molecular shape. *Journal of Physical Chemistry*, 99:3503–3510, 1995.
- [5] E.E. Hodgkin and W.G. Richards. Molecular similarity based on electrostatic potential and electric-field. *International Journal of Quantum Chemistry*, 1:105–110, 1987.
- [6] M.A. Gallardo J.A. Grant and B.T. Pickup. A fast method of molecular shape comparison: A simple application of a gaussian description of molecular shape. *Journal of Computational Chemistry*, 17:1653–1666, 1996.
- [7] J.S. Puranen M.J. Vainio and M.S. Johnson. Shaep: molecular overlay based on shape and electrostatic potential. *Journal of Chemical Information and Modeling*, 49:492–502, 2009.
- [8] K. Svanberg. A class of globally convergent optimization methods based on conservative convex separable approximations. *Siam Journal on Optimization*, 12:555–573, 2001.

Chapter 6

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