

NEWLEAD

Introduction

NEWLEAD [1] is a software application that connects chemical fragments with spacers. The NEWLEAD project was started at Novartis by Vincenzo Tschinke and Nissim Claude Cohen. In 1999 NEWLEAD was released into the public domain. It is currently maintained by Vincenzo Tschinke.

The software is written in ANSI C. It runs under SGI/Irix, Linux, Mac OS X, and Windows.

The present document covers the use of NEWLEAD from its MOE GUI. The MOE GUI has been written in SVL and runs on any platform suitable for both the MOE and the NEWLEAD executables.

For further information on the command line operations, the customization options, and other available GUIs, please visit the website.

Installation

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If you have NEWLEAD already installed please skip to paragraph "SVL GUI".

As of 2009, NEWLEAD distributions for various operating systems contain the following folders/directories

`bin`

`data`

`svl`

`demos`

In general

- the files in the `bin` folder should be included in the operating system's "path"
- the location of the `data` folder should be registered as an environment variable
- the folder `svl` contains files to be handled according to MOE's standard procedures
- the folder `demos` contains NEWLEAD run examples.

[1] Tschinke, V.; Cohen, N.C. The NEWLEAD Program: A New Method for the Design of Candidate Structures from Pharmacophoric Hypotheses. *J. Med. Chem.* **1993**, *36*, 3863-3870

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Detailed and up-to-date informations on how to handle the above-mentioned components are given in the "README" files of each distribution. Below, you find some general instructions for the various operating systems.

Windows

Define the environment variable NEWLEAD_ROOT as the location of the NEWLEAD data files, and add the location of the NEWLEAD binary files to the "Path" system variable, see Fig. 1.

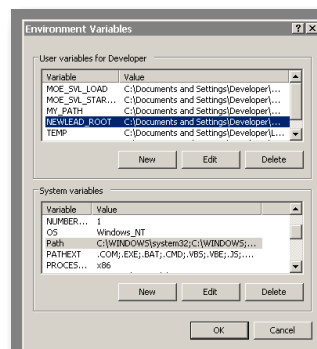


Fig. 1

Linux/Mac OS X/Unix

Define the environment variable NEWLEAD_ROOT and add the NEWLEAD binary file directory to the "PATH", according to your local installation. E.g., add the following lines to the ".bashrc" file

```
export NEWLEAD_ROOT=  
$HOME/newlead/data  
export PATH=$PATH:$HOME/  
newlead/bin
```

Ensure that all files in the bin folder possess UNIX "executable" permissions.

SVL GUI

If you have a Linux/UNIX/Mac OS X distribution prior to 2009, please add the files "newlead.sh" and "nld2moë" to a directory included in your "PATH". If you have a distribution from 2009 or later for any OS, go to the next paragraph.

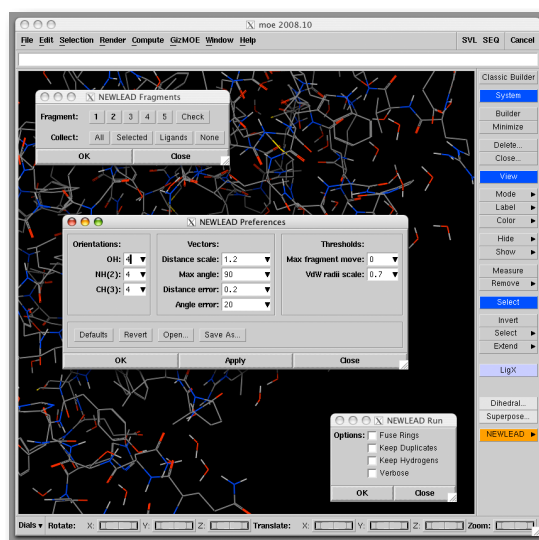


Fig. 2

Install the file "newlead.svl" in your chosen location for SVL scripts. Modify the local menu definitions as described on the SVL distribution.

GUI elements

NEWLEAD functions can be accessed by the submenu "NEWLEAD" at the bottom-right of the MOE main window, see Fig.2. Three dialog boxes are used: "Fragments", "Preferences", and "Run".

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Input (Fragments)

The input for NEWLEAD consists of two or more fragments. In addition, other molecular structures, that are not used for the connections, could be present near and/or around the fragments. For example, the fragments could be docked inside a protein binding site.

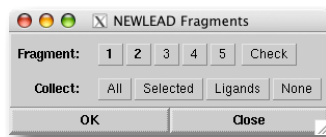


Fig. 3

To define the fragments, use the Fragments dialog box from the NEWLEAD menu, see Fig. 3.

There are two sets of buttons, the “Fragment” and the “Collect” set. The first set is used to pick individual fragments as well as to visualize how the fragments have been defined. The second set is used for groups of structures, and to clear the selections. In additions, there are the two standard buttons “OK” and “Cancel”. “OK” stores the input for NEWLEAD on disk, while “Cancel” leaves the system unchanged. In the simplest case, you wish to connect all structures in the MOE window. Simply click the “All” and the “OK” buttons. The input is ready for further processing.

A more complex situation arises when some of the structures in MOE are *not* to be connected. In such cases, you select the fragments to be connected, and the software processes the remaining structures appropriately. To select two or more fragments in a set of many, a few options are available. The first option is to use the buttons labeled “1”, “2”, etc.

- select one or more atoms on the first fragment, then click the button labeled “1”
- select one or more atoms on the second fragment, then click the button labeled “2”
- repeat if needed for a third fragment, and so on

The second option consists in selecting one or more atoms on each target fragment, then clicking the “Selected” button.

The third option consists in clicking the “Ligands” button. This procedure uses the internal definition of ligand(s) in MOE. It is to be used with caution because it may lead to the selection of structures not involved in biologically relevant binding, or by contrast to neglecting such structures. To check that the selected fragments are the desired ones, click the “Check” button. The selected structures are briefly highlighted as “ball-and-stick” models, while the remaining structures are unchanged.

To clear the selection, use the “None” button.

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As mentioned above, click the “OK” button to store the fragments for further processing, or the “Cancel” button to leave the system unchanged.

Preferences

NEWLEAD uses geometrical rules to build its results. After creating the input as described above, you can start a run using the built-in parameters. In addition, you can influence the outcome of a run with the help of the “Preferences” dialog box, see Fig. 4.

The parameters are ordered in the three groups “Orientations”, “Vectors”, and “Thresholds”. In addition, the dialog box carries the buttons “Defaults”, “Revert”, “Open...”, and “Save As...”, and finally, the standard buttons “OK”, “Apply”, and “Cancel”.

The preference parameters are described below.

Orientations

The number of times a single-atom spacer (see Ref. 1, Fig. 2) is rotated with respect to the fragment to which it is added. The rotations span 360° by constant increments. Higher value \Rightarrow more solutions.

The single atoms spacers are OH, NH₂, and CH₃

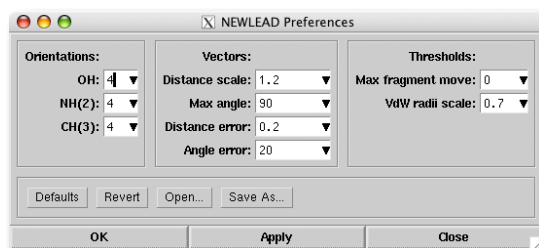


Fig. 4

Vectors

- Scaling factor for the maximum distance d in a vector pair (see Ref. 1, Fig. 5). To avoid connecting atoms that are far apart on two fragments. The value is a scaling factor which multiplied by the shortest distance between two fragments gives the maximum distance searched for in the spacer library. Lower value \Rightarrow shorter spacers
- Maximum value for either of the angles a_1 , a_2 in a vector pair (see Ref. 1, Fig. 5). Higher value \Rightarrow more solutions; distorted structures possible
- Error threshold for vector-pair distances (see Ref. 1, Fig. 5). Higher value \Rightarrow more solutions; distorted structures possible
- Error threshold for vector-pair angles (see Ref. 1, Fig. 5). Higher value \Rightarrow more solutions; distorted structures possible

Thresholds

- Maximum movement of a fragment: maximum displacement of any atom on a fragment after a movement. Higher value \Rightarrow more solutions

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- **Scaling factor for the Van der Waals radii sums.**
When the distances between pairs of atoms are compared with the Van der Waals radii sums, the latter values are scaled (see Ref. 1, p 3865). Lower value \Rightarrow more solutions; higher energy structures.



Fig. 5

The use of the buttons is described below.

- **Default** to load the default values
- **Revert** to re-load the previous values
- **Open...** to load a set of parameters from a file (recommended prefix “.prf”)
- **Save...** to save the current set (recommended prefix “.prf”)
- **OK** to save the set for the current session, and close the dialog box
- **Apply** so save the set as above, without closing the dialog box
- **Cancel** to exit without saving changes.

Run

The “Run” dialog box is used to perform the actual NEWLEAD calculation. A set of options are presented to the user, see Fig. 5, and described below.

- **Fuse Rings** to fuse rings in the first pass of the run. The rings are used as attachment points for further spacers
- **Keep Duplicates** to retain geometrically similar results
- **Keep Hydrogens** to retain all Hydrogen atoms in the results
- **Verbose** to produce an extensive log file.

To start the run, click the “OK” button, or the “Cancel” button to exit.

Output

The results are stored in a standard MOE database, that is automatically opened for viewing, see Fig. 6, as soon as the calculation is completed.

Each entry in the database contains

- the result in 3D
- its number in the output sequence
- its name indicating the spacers used to build it.


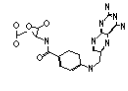
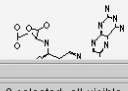
	mol	result	name
32		32/75	cyclohexene_1 propane+M
33		33/75	pyrazine aniline+M
34		34/75	pyrazine quinoline+0

Fig. 6

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The database is stored in the current directory under the filename "nld.mdb". Because the file is over-written at each further NEWLEAD run, you should save any output set or individual result of interest, as you consider fit.