



Fragment & Structure-Based Design Suite

Team-Building Tools for MedChems & CompChems

User Reference
Release 2.1.0



Today, *LeadIT* embeds FlexX (FlexSIS in Japan) and ReCore.

Development of *FlexX/FlexSIS* has originally been initiated by Matthias Rarey (now Hamburg Univ.) in Thomas Lengauer's group at the SCAI Fraunhofer Institute. For comprehensive information about FlexX and FlexSIS please see the separate documents in the `doc` folder of your installation, or contact BioSolveIT at leadit@biosolveit.de.

Development of *ReCore* has been initiated by Tanja Schulz-Gasch, Martin Stahl (Hoffmann LaRoche AG, Basel, Switzerland), Patrick Maass, and Matthias Rarey (ZBH, Univ. Hamburg, Germany). ReCore is now available solely through BioSolveIT, St. Augustin, Germany. For comprehensive information on *ReCore* usage, please see the separate documentation in your `doc` folder, or contact BioSolveIT at the above-mentioned address.

The integrated FBDD and SBDD platform *LeadIT* has been developed by BioSolveIT.

This document contains proprietary information of the Center for Bioinformatics (ZBH) Hamburg and BioSolveIT GmbH and is protected by copyright. It is provided together with Software of BioSolveIT under a license agreement and may be used only in accordance with the terms and conditions of this agreement. The document serves solely for the purpose of using the Software. No part of the document may be transferred to any third party or reproduced as a whole or in parts without written permission from BioSolveIT.

Contents

Contents	3
----------	---

I Getting Started

1	<i>LeadIT</i> — Thinking of You.	7
1.1	The Basic Idea: An SBDD to Start with Right Away	7
1.2	The Team Building Idea	8
2	Installation	9
2.1	Linux	9
2.2	Windows	9
2.3	Initial <i>ReCore</i> Index File Generation	9
2.3.1	Windows	9
2.3.2	Linux	10
2.3.3	Multiple <i>ReCore</i> Index Files	10
2.4	Directory Structures & Files	10
2.4.1	Preferences, User Settings	11
2.5	Stereo View, Shutter Glasses and 3D Displays	12
2.6	License Scheme	13
2.6.1	Running a FlexLM License Server	15
2.7	Known Issues	15
2.7.1	Referring to all <i>LeadIT</i>	15
2.7.2	Referring to <i>ReCore</i> only	17
2.7.3	Referring to <i>FlexX</i> only	17
2.7.4	Future handling of problems/wishes	17
3	Getting Help	19
3.1	Tutorial movies	19
3.2	PDF documentation	19
3.3	Tool-specific commandline help	19
3.4	The “Assistant”	20

II General Handling

4	Startup, Windows, Dialogs, Widgets	23
4.1	Project Tree	24
4.2	Project Notes	24

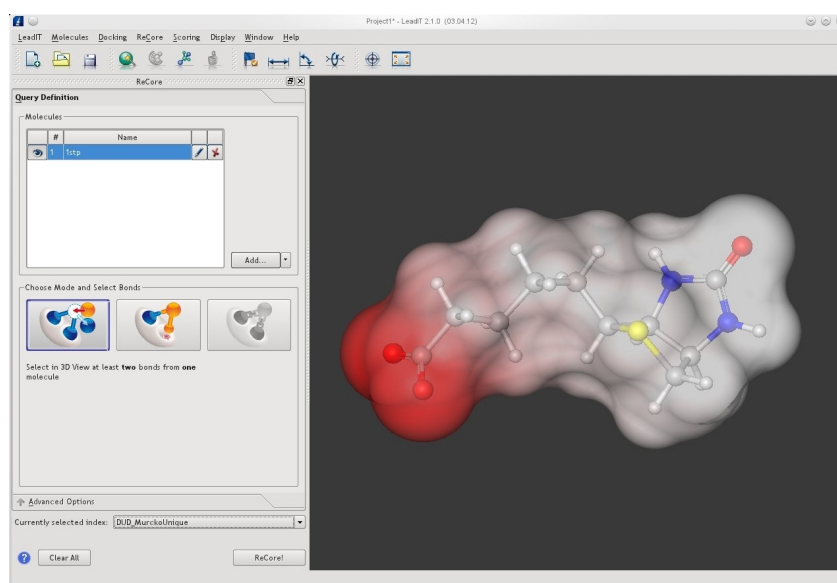
4.3	<i>ReCore</i> Solutions Table	24
4.4	<i>FlexX</i> Solutions Table	25
4.5	Information Stream	25
4.6	Assistant	25
4.7	Not Docked	25
4.8	PoseView	25
4.9	<i>LeadIT</i>	25
4.10	Tools	25
4.11	Measure & Label	25
4.12	Ligand Browser	26
5	Mouse and Key Bindings	27
5.1	Mouse Bindings	27
5.2	Key Bindings	27
5.3	Mouse Pointer Changes, Escaping the Measure&Label Mode	27
6	PoseView	29
6.1	Show PoseView	29
6.2	Assure fast display	30
6.3	Settings	30
6.4	Export to File	31
7	Updates	33
 III Structure and Fragment-Based Design Tools 		
8	In 1 Minute: Docking with <i>FlexX</i>	37
8.1	Receptor preparation	37
8.2	Ligands, the Library	37
8.3	Evoking the actual Docking	37
9	In 1 Minute: FBLD with <i>ReCore</i>	39
9.1	Core Replacement	39
9.2	Fragment Growing and Evolution	40
9.3	Fragment Merging and Linking	40
	Index	41

|

GETTING STARTED

LeadIT — Thinking of You.

1.1 The Basic Idea: An SBDD to Start with Right Away



A screenshot of LeadIT, integrated FBDD and SBDD enhancing MC/CC teamwork

The concept of *LeadIT* is very simple: We wanted to keep tradition and push the boundaries. We wanted the best of two worlds for you fellow users: both Medicinal and Computational Chemists, for both Experts and Novices. Therefore, seen from the solutions or applications side, *LeadIT* combines major application areas in modern early drug discovery:

LeadIT = Docking + Fragment Based Ligand Design.

With *LeadIT*, users now have an interactive graphical user interface which embeds both long-standing and award-winning docking plus one of the most advanced fragment-based design tools: *FlexX* and *ReCore*.

Seen from the usage side:

LeadIT = extremely simple GUI + experts' commandline.

There is basically no learning curve for the most prominent applications in *LeadIT*. However, for the highly configured, advanced applications, e.g., massively parallelized virtual screenings on compute clusters, *LeadIT* represents direct access through its commandline mode, scripting facilities etc.

1.2 The Team Building Idea

This new GUI is targeted at Medicinal Chemists/Bench Chemists and CompChems alike. During the test and design phase, *LeadIT* has been observed to speed up the process of team-building between Medicinal and Computational Chemists. How did this come about? We have always thought speed *is* an issue, and we still do. We found the idea of software supporting the re-investment of won time back into quality improvement very appealing. With *LeadIT*, Medicinal Chemists can give instant feedback to a *ReCore* FBLD Query formulation, and the CompChems can easily incorporate that feedback into the machinery. Unwanted bond formations will occur, but they can be removed for future runs. Unwanted torsions after a *ReCore* run? They can, too, be removed for future runs. Over time (and we suspect this is little time), *LeadIT* will grow into a system which has corporate traces and delivers results which are compliant with what your organization's chemists are happy with. In fact, during extensive testings, several customers have already successfully put *LeadIT* on the desk of bench chemists and thus enhanced productivity, speed of delivery, and work satisfaction of their teams. We are certain that this is only possible if the software

- essentially has no learning curve
- delivers good results in seconds
- allows effective user interaction to improve results rapidly

The combination of these features will render the tool a shoulder-to-shoulder software in front of which teams can iteratively refine results — investing their time focused on delivery.

Installation

With the advent of *LeadIT*, installation is a straightforward and simple thing.

2.1 Linux

You do not need administrator/root rights. Unzip the tarball, start `leadit` from the installation directory. Then read on at Sec. 2.3

2.2 Windows

- Log in as administrator.
- Double-click the installer exe file; the procedure will automatically adapt to your entries if they deviate from the defaults. The rest should be fairly self-explanatory.

Now please read on at Sec. 2.3

2.3 Initial *ReCore* Index File Generation

LeadIT comes with all needed input files to create a larger *ReCore* Index File. Because meaningful *ReCore* Index Files can grow very large, we included the necessary input for you to do create a larger index yourself.

You will not be able to run *ReCore* queries without a *ReCore* Index File.

The creation of the file will take a few minutes on a typical machine. This is a one-time only event, so your *ReCore* Index File can be used on different machines. The creation is child's play. Here comes how this works:

2.3.1 Windows

At the end of your installation the Windows installer will allow you to tick whether you want to expand the input to a *ReCore* Index File.



Index Expansion under Windows

Leave this box ticked if you do not have another index, and the file will automatically be created and found upon starting *LeadIT*.

2.3.2 Linux

Navigate to the `recore_index` directory, and run the script `expand_space.sh` from the console. After a few minutes, your index will have been created, and after a restart of *LeadIT* it will be automatically found and written to your settings.

2.3.3 Multiple ReCore Index Files

If you have multiple *ReCore* Index Files, then you can switch between them using the *ReCore* menu entry

`LeadIT -> Global Preferences -> Parameters & Flags`

Alternatively, you can click the “Link” after “Currently selected Index” in the *ReCore* Query Definition Dialog. This will make the above-mentioned Preferences Dialog pop up. Mind: You cannot change an index while a *ReCore* Query is defined.

2.4 Directory Structures & Files

LeadIT currently comprises *ReCore* and *FlexX*. Most of the tasks you perform will presumably be done using the *LeadIT* graphical user interface (GUI).

For experts, both the *ReCore* as well as the *FlexX* engines can be called in their command-line modes. In commandline the tools may be less easy to use, yet are much more versatile and powerful. To understand what goes on behind the scenes, we will briefly review the directory structure and discuss what files have what contents and purposes.

There are documentation pdf files, examples, and other needed files in the directories after installation. The directory structure is fairly simple and self-explanatory:

```
|-- doc
|-- example
|   |-- FlexX or FlexSIS (Japan)
|       |-- static_data
|   |-- ReCore
|       |-- Query
|       |-- Index
|-- recore_index
|-- tmp
|-- tutorials
```

The `doc/` directory contains this documentation. You can certainly navigate to the directories with the *LeadIT* file dialogs and try out the examples provided in the `example` directories.

The `static_data` directory contains sample files to use different scoring alternatives in docking. Please see the footnote¹ or refer to the *FlexX* User Guide for more details on this.

The `recore_index` subdirectory contains input for a larger *ReCore* Index File; see above, Sec. 2.3.

2.4.1 Preferences, User Settings

LeadIT stores information about Projects, altered chemistry, algorithmic preferences etc. at various hierarchical levels. Higher levels overwrite lower ones:

1. (lowest): Tool settings. These are compiled into the executable.
2. (mid pri): Installation settings. These are the ones which reside in the installation directory. The respective file is `settings.pxx`.
3. (highest pri): User settings. The respective files reside in a directory relative to the user's home directory:

- Linux: `~/.leadit`
- Windows: `$HOME\.leadit`
So, typically this would be something like

– XP: `c:\Documents and Settings\MyName\.leadit`.

¹Some background information: *LeadIT* has stored the chemically relevant information as so-called static data information. This information may be assessed using the GUI's Preferences Dialog. You will find the static data section at the very bottom of the Parameters and Flags list. As an example, interaction specifications in *FlexX* are made on the grounds of the well-known *FlexX* interaction scheme. The so-called interaction types are coded in a corresponding container called `contype.dat` in the static data section. The contents of `contype.dat` has its roots in the *FlexX* docking program. The same applies to other data containers relevant to the chemistry reflection in *FlexX*. More documentation about the *FlexX* interaction scheme is available through *BioSolveIT*.

- Vista/Win7: `C:\Users\MyName\.leadit`.
Mind that you may have two home directories defined depending on whether you work in the Cygwin environment or not! If you are unsure what this is, then you do not use Cygwin.

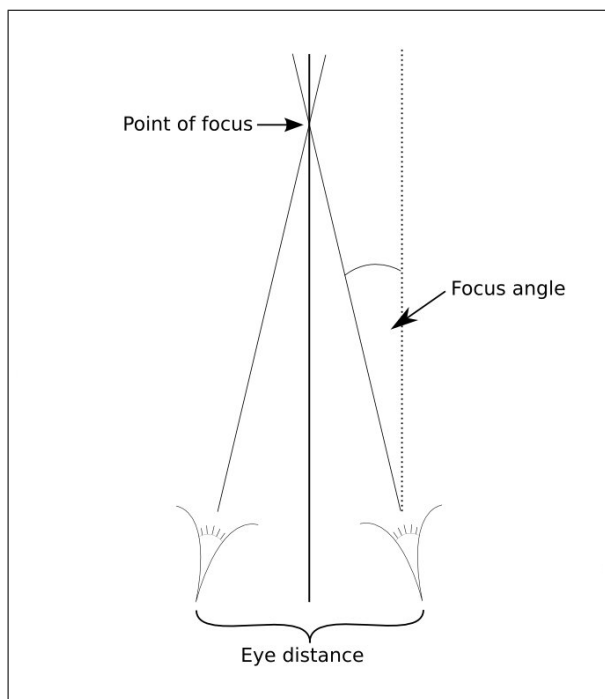
2.5 Stereo View, Shutter Glasses and 3D Displays

If you have special 3D hardware you can view your molecules in real 3D. The requirements for this are a graphics card that supports quad buffer rendering; additionally, you need shutter glasses or a 3D monitor. If the hardware is detected you can turn on the "stereo mode" using the advanced rendering options via:

Display ↔ Settings ↔ Rendering ↔ Projection .

To use the stereo mode, first switch from `Orthogonal` to `Perspective`. Once *LeadIT* successfully detected your stereo hardware you can enable the stereo mode via the respective check box. Then choose between three different stereo algorithms; however, we recommend to use the first one. The other algorithms are still under improvement and may not be included in future versions of *LeadIT*.

You can adjust the 3D effect with the two sliders by changing the `eye distance` between the image for the left and right eye and the `focus angle` that determines the distance between your eyes and the zero parallax plane or focus plane. The focus plane is the plane where there is co-incidence of 2D and 3D display. Every object which is in front or beyond that very plane becomes blurry in 2D due to the distance to the focus plane. Take a look at the sketch to get an impression on how this computation actually works.



The focus angle sets the zero-parallax plane distance

2.6 License Scheme

Our software is license key protected. Please be aware that you cannot run computations under any circumstances without a valid license. *LeadIT* checks out a license as soon as an actual computation is evoked.

Here are the necessary steps to get it all running:

1. Determine your BioSolveIT-HostID and request a license:

To obtain a valid license you must determine and send us the host or system ID of your computer:

In *LeadIT*, go to

LeadIT -> Global Preferences -> License Keys.

Copy the BIOSOLVEIT=... entry from the field

The BioSolveIT host ID of machine...

Please send the copied BioSolveIT-HostID number to license@biosolveit.de, and we will return a license file asap.

Each line of a license file you will obtain includes the name of the licensed tool or module, and — among other information — the version number and the expiration date of the license.

Example

```
INCREMENT FlexX BIOSOLVE 2.0 28-jun-2005 uncounted \  
  HOSTID=BIOSOLVEIT=0BS058665F5FCFFA74EAE1458495A8F65C6 \  
  SIGN="0078 AD79 1445 A900 906E 00A4 AB51 F600 AFC8 \  
  4394 9356 3C87 EBD2 4A7B E88D"
```

2. After you have received your license keys from us, you will need to tell the software where the license is actually located. This depends on whether the license you have requires a license server (we use flexlm) set up or not.

Typically, purchased licenses require a license server, test and evaluation licenses do not. If in doubt please just ask us. Setting up a license server is described in Section 2.6.1 on page 15.

Here are the options how to specify where the license is:

- Own settings, using the graphical user interface (recommended for personal usage):
 - Go to LeadIT -> Global Preferences -> License Keys.

- No license server: Enter the license file location into the field License Directories and Files
- With license server: Enter the server name (a computer's name, or an IP address) into License Server using the Add button
- Using a system-wide setup (recommended for system administrators):

Set an environment variable BIOSOLVE_LICENSE_FILE

No license server: pointing to the directory of the license file(s)

With license server: pointing to @mylicenseserver in which mylicenseserver is the name/IP of the computer which has the license server installed. The at-sign is indeed needed.

If you have to define a port, enter the port number before the "@", like this:

```
BIOSOLVE_LICENSE_FILE=portnumber@mylicenseserver
```

- Windows:

Control Panel -> System -> Advanced -> Environment Variables

- Linux: Use the setenv or export mechanisms of your shell.

3. A successfully found license can be checked

- In the GUI: With green checkmarks after pressing the Check Licenses now button in the Global Preferences dialog, or,
- At the commandline: at startup where licenses found will be uttered similar to the very end of this start-up stream:

```

                                     L e a d I T
Copyright      An Interactive Structure Based Molecular Discovery Platform

BioSolveIT GmbH      Version:   1.0.0 (pre)   (09.09.09)
An der Ziegelei 79    Modules:   [CDOCK] [FLEXE] [PHARM] [PPI]
53757 St. Augustin
Germany            Original Author:  Matthias Rarey
www.biosolveit.de  Contact:      flexx@biosolveit.de

```

For information about additional contributors and copyright notes please consult the user guide or type 'help about'.

```
>> Running on ELLA (Windows 5.1) with 2 processors.
>> Loaded settings (v 1.5.0) from 'C:\settings.pxx'.
>> Recore license check (BioSolveIT keys): succeeded.
```

Further details are described below or may be obtained from the BioSolveIT knowledge base page at <http://www.biosolveit.de/faq>.

2.6.1 Running a FlexLM License Server

Instead of specifying a license file directly, it is also possible to serve your licenses from a license server using the FlexLM license management system. Your FlexLM administrator must add the respective license file to the directory from which FlexLM takes its licenses and add the BIOSOLVE vendor daemon to the directory where the `lmgrd` (license manager daemon) resides. A current version of the license manager daemon and the BIOSOLVE vendor daemon can be downloaded from <http://www.biosolveit.de/download>. At the console, use the command

```
lmgrd -c <path_to_licensefiles> -l <logfile>
```

to start the license server.

Using FlexLM, it is also possible to use *floating licenses*, i.e., licenses that are hosted by a server and distributed to *FlexX* clients on demand. Floating licenses have a special layout. A floating license is always locked to the name or the IP address of the server and its BioSolveIT-HostID. Server-bound license files will look similar to the example below.

Example

```
SERVER myserver BIOSOLVEIT=0BS058665F5FCFFA74EAE1458495A8F65C6
USE_SERVER
VENDOR BIOSOLVE
INCREMENT FlexX_base BIOSOLVE 2.0 28-jun-2005 100 SIGN="00C6 1440 7772 \
      E4A8 116C FFFB EDC8 F400 B648 5413 6ECA 8852 4A2E 29B8 E5D6"
```

In this example a site has 100 *FlexX* licenses. Every time a new instance of *FlexX* or *ReCore* is launched the server transfers the license to the application. When the computation of *FlexX* finishes or *LeadIT* is closed, the license is returned to the server.

2.7 Known Issues

2.7.1 Referring to all *LeadIT*

Linux issues

Problematic Distributions There are some Linux distributions we know of which may cause trouble with some of our tools. This list is most probably NOT comprehensive, so we encourage you to use the test and evaluation periods to find out whether the tool runs on the specific platform that you wish to employ.

- Unsupported:
 - RedHat Enterprise Linux 3 is unsupported.
- The 32bit Linux versions may not work correctly on the following platforms because of a missing font interface on the code level:
 - Asianux 2,3
 - BOSS 1.0

- CentOS 4.7, 5.2
- Debian 3.1r2
- Mandriva 2006, Corporate Server 4
- openSUSE 10.2
- Oracle Enterprise Linux 5
- Red Hat Enterprise Linux 3 Update 4
- Red Hat Enterprise Linux 4 Update 5
- Red Hat Enterprise Linux 5
- SLES 10 (SP2)
- Ubuntu 6.06
- Xandros Desktop 4.1, Server 1.0

Libraries *LeadIT* requires the glibc version 2.3 or later. Please consult systems administration if this error (or alike) occurs:

```
leadit: /lib/ld-linux.so.2: version 'GLIBC_2.3' not found (required by leadit)
leadit: /lib/i686/libpthread.so.0: version 'GLIBC_2.3.2' not found (required by leadit)
leadit: /lib/i686/libc.so.6: version 'GLIBC_2.3' not found (required by leadit)
```

Other issues may affect missing libraries. Please consult the FAQ pages on the web (<http://www.biosolveit.de/faq>), or send an email to support@biosolveit.de.

Fonts Customers have reported fonts which were too small or too large. Typically this stems from a so-called Qt configuration file in your home directory. The file is `~/.qt/qtrc`. You may have to adapt the font line, e.g., like this:

```
font=Nimbus Sans 1,10,-1,5,50,0,0,0,0,0
```

Windows issues

Cygwin We have tested *LeadIT* on Windows XP, Vista, and Windows 7. In the Cygwin environment (<http://www.cygwin.com>), *LeadIT* can be started and used; however, Unix-like path specifications in arguments after calls such as `leadit.exe` may not be fully supported.

Graphics Problems Also please make sure you have the latest version of your graphics card drivers installed. We encountered black 3D Views with some customers — a problem which could easily be resolved by updating graphics drivers.

File System Problems Vista and Windows7 only:

Uninstalling *LeadIT* may leave a *ReCore* Index File generated during the installation procedure on your hard disk. Activate the “Compatibility Mode” in your Explorer to make the respective file (*rsx) visible. Then delete the file manually if it is no longer needed.

2.7.2 Referring to *ReCore* only

LeadIT does not support all options available in the commandline version (`leadit --recore`) when using *ReCore* through *LeadIT*. Especially, currently unsupported are:

- Building your own *ReCore* Fragment Index Files.
- Apply ring atom filters in ranksearch queries (however SMARTS spherical constraints are supported).

LeadIT will continue to be developed to incorporate more and more functionality in due course; one option is to cut and paste the *ReCore* call issued from the GUI to the console and to augment this call with more advanced filters etc.

2.7.3 Referring to *FlexX* only

LeadIT does not support all options available in the commandline version of *FlexX*. Especially, currently unsupported are:

- the add-on module E(nsemble) for protein flexibility/induced fit.
- parallel computing (PVM support) under Windows

2.7.4 Future handling of problems/wishes

LeadIT will continue to be developed to incorporate more and more functionality in due course; one option is to cut and paste the *ReCore* call issued from the GUI to the console and to augment this call with more advanced filters etc.

If there are any features you would like to see in *LeadIT*, please write to

leadit@biosolveit.de,

and we will take your input very seriously.

Getting Help

LeadIT help is available in several ways:

- tutorial movies
- PDF documentation (this guide)
- tool-specific commandline help
- using the “Assistant”.

3.1 Tutorial movies

LeadIT comes with several Macromedia Flash-based introduction movies. They can be looked at from the following sources

- on the web using the pointers on <http://www.biosolveit.de/LeadIT>
- in the `tutorials` folder in your installation
- Once *LeadIT* is installed you can simply navigate to `Help -> Tutorial~Movies` and pick the one which interests you.

3.2 PDF documentation

Despite this not being the Section about the graphical user interface (GUI), this guide can be displayed using the `Help` menu in the GUI. You should have an application to read PDF files installed. It resides in the `doc` folder of your installation.

3.3 Tool-specific commandline help

ReCore help is evoked using

```
leadit --recore --help
```

FlexX help is evoked using

```
leadit -h
```

3.4 The “Assistant”

The Assistant gives you context-sensitive help during the usage of *LeadIT*. It is evoked

- either by pressing the F1 key or
- using a right mouse click in the gray area of the icon bar

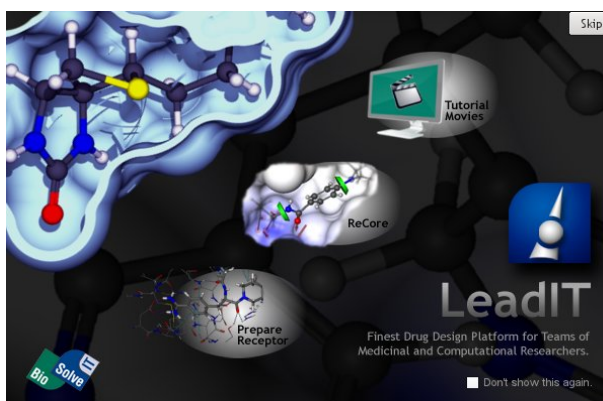
If you do not see the Assistant though it should be there please control whether it's hidden, e.g., underneath a tab, or on a separate monitor.

II

GENERAL HANDLING

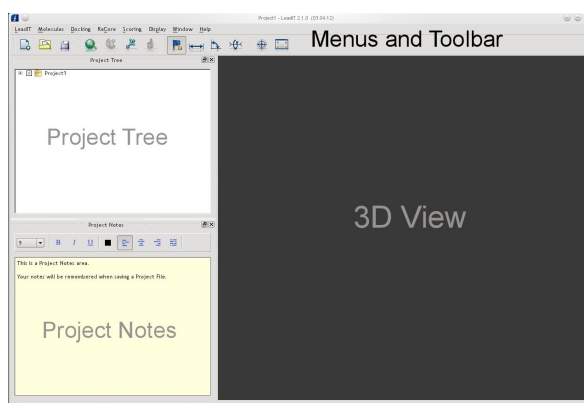
Startup, Windows, Dialogs, Widgets

Upon your first start, you will see the Application Gallery which lets you choose the respective applications within *LeadIT*.



The Application Gallery

The organization and phrasing for some of the parts of the GUI are as follows:

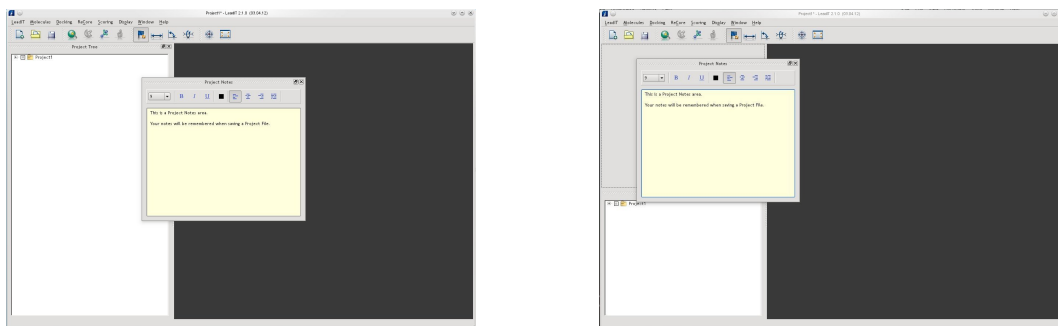


Phrasing of the GUI parts

All of the respective parts can be “torn apart”, so that you can fully customize your window

setup according to your needs. We call such parts of *LeadIT* “dock widgets”. For example, you can use monitor 1 as your 3D View monitor in which you purely look at molecules in 3D while your second monitor has all controls. The dock widgets can be “dropped” into certain regions of the GUI. You will automatically tell when this is the case because a little gap opens up.

Here are two examples:



Dock widgets: Separate Project Notes; re-organizing the Project Notes

4.1 Project Tree

From the Project Tree you can control a magnitude of functions: Besides control of visibility, hiding objects etc., you can also trigger the pop-up of the *ReCore* Query Definition Dialog, or, set up a Receptor for docking.

The Project Tree has several parts in which context menus are available. We recommend to play around with those and find out for yourself: For example, use a right mouse click on *ReCore*.

4.2 Project Notes

What you type in here will be saved in the Project Files. This is a very convenient way to annotate something for your fellow colleagues and sending it over to somebody.

4.3 *ReCore* Solutions Table

This will pop up a table for detailed information about *ReCore* computation results. We distinguish between fragments and Composites. “Composites” are the newly formed results molecules in which link atoms/dangling bonds have been saturated with hydrogen. With a right mouse click you can export selected fragments or Composites. Multiple results selection is possible using the SHIFT and CTRL keys.

4.4 FlexX Solutions Table

This will pop up a table for detailed information about *FlexX* docking poses. Again, you can export poses using a right mouse click after a selection.

4.5 Information Stream

This dock widget contains diagnostic output during your *LeadIT* usage. It includes errors and warnings during the docking computations, but it also facilitates setting up highly complex *ReCore* Queries at the commandline, because you can cut and paste calls from this window to, e.g., an editor in which you prepare scripts.

4.6 Assistant

The Assistant delivers highly context sensitive short help. If you would like to speed up getting over the learning curve, then simply leave this window open.

4.7 Not Docked

After a *FlexX* screening run, this window contains the collection of molecules which were not docked. Please mind that this does not mean that the program misperformed. This *could* be, however often it means that the tool could not fit in the ligand into a Binding Site — so, *FlexX* deems it a ligand with negligible binding energy.

4.8 PoseView

Show or hide the PoseView widget, see chapter 6 on page 29. This switch is only enabled if there are docking solutions and exactly one solution is currently selected.

4.9 LeadIT

Makes the icons for saving and loading Project Files in the toolbar hide or show up.

4.10 Tools

Makes the *FlexX* and *ReCore* icons in the toolbar show up or be hidden.

4.11 Measure & Label

Toggles the visibility of the label and measuring icons in the toolbar.

4.12 Ligand Browser

This pops up or de-activates the Ligand Browser, needed to browse through multiple docking solutions.

Mouse and Key Bindings

5.1 Mouse Bindings

In the 3D View, rotation and translation can be controlled with your mouse (and sometimes the SHIFT key).

Here is an overview:

Function	Mouse/Key Combination
translation x/y	middle mouse button
translation z (zoom)	mouse wheel or SHIFT+right mouse button
free rotation	right mouse button
z rotation	SHIFT+middle mouse button

5.2 Key Bindings

Some keys have special functions for those who like to navigate using the keyboard. We distinguish between “hotkeys” (which evoke an action as long as they are pressed) and “shortcuts” which evoke an action once the key has been pressed.

Function	Key
<i>Shortcuts:</i>	
open Project	CTRL+o
save Project	CTRL+s
save Project As	CTRL+SHIFT+s ...
help/Assistant (show/hide)	F1
fullscreen Mode (enter/leave)	F5
fit everything visible to the 3D View (“Fit to Window”)	F10
<i>Hotkeys:</i>	
measure distances	d
measure angles	a, or w
measure torsions	t

5.3 Mouse Pointer Changes, Escaping the Measure&Label Mode

Certain modes will give feedback through a changing mouse pointer. For example, during Receptor Preparation, the mouse pointer changes to the magic wand to denote you are

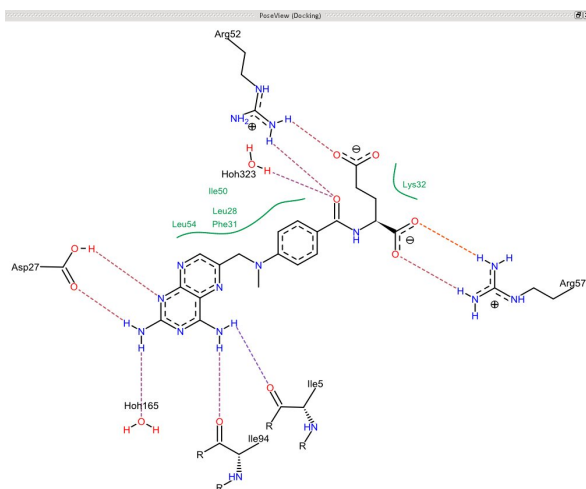
now in the Receptor Wizard. At this time, Measure&Label functions are still accessible, and the mouse pointer will change accordingly to give feedback to you. This would lead to problems in case you were in fullscreen mode, since there, the buttons are no longer visible. To have a simple way out, there will be a little button which lets you escape from the Measure&Label modes and get back to the special functions, e.g., the Receptor Preparation Wizard or the ReCore Query Definition Window. The Measure&Label Escape Button is actually also available when using the (temporarily active) keypad shortcuts from above. The icon of the Measure&Label Escape Button will show to what mode the button will “escape”.

PoseView

The *PoseView* dock widget displays a 2D view of the docked poses. Each pose will be drawn with hydrogen and metal interactions and its corresponding residues.

For most residues only the interacting atoms of the side chain are drawn, except for small residues or where the interaction takes place with the backbone.

Hydrophobic interactions are displayed as green contact curves with only the names of the interacting residues attached to these lines. A residue name with the corresponding line segment will be displayed, if that residue has hydrophobic contacts to at least 3 different ligand atoms; this value may be configured by the `POSEVIEW_IA_CONTACT_CNT` variable of the global preferences, see section 6.3 on the next page.



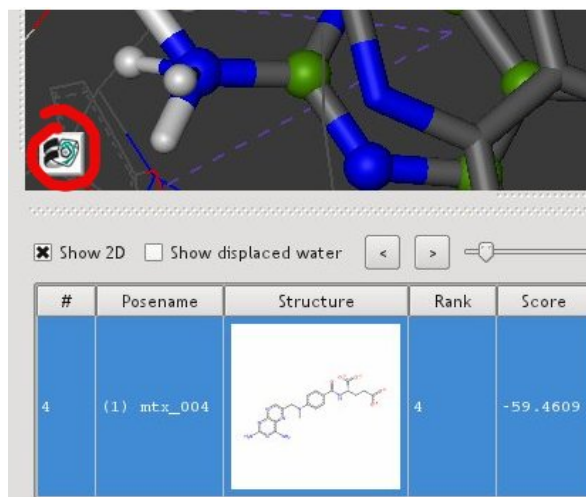
PoseView image for a docking pose of redocked MTX in *1dwd* (rank 4)

6.1 Show PoseView

When the docked poses in the FlexX solution table (see section 4.4 on page 25) are present, the *PoseView* will be generated and displayed as soon as a solution is selected from the solution table. As the *PoseView* widget portrays a single pose, only one solution should be selected.

The use of portable widgets permits the user to unlock and drag the *PoseView* widget into any available separate screen. Therefore you may have one fullscreen 3D view and another fullscreen 2D view!

If you close the PoseView widget it remains closed, even when selecting another pose in the solution table. A button in the lower left corner of the 3D view (see image below) will appear to let you re-open the PoseView widget. Please also refer to the switch `POSEVIEW_SHOW` in section 6.3.



Button to show PoseView in 3D view

6.2 Assure fast display

When using the slider in the solution table to select a pose the PoseView image will always be generated on the fly, which of course leads to some slowdown. To speed up visualization of solutions whilst using the slider you may lower the `POSEVIEW_TIMEOUT` setting. If the PoseView image can not be generated in the given time (the default is 500 ms) a short message will be displayed in the PoseView widget instead of an image. Or you may close the PoseView widget which will completely switch off PoseView image generation.

The timeout message offers to override the timeout setting once and generate the PoseView image for the particular pose in question without a time limit. Generating the PoseView image without time limits is currently performed in the main execution unit which may lead to a program blocking for several seconds up to minutes.

6.3 Settings

Choose Global Preferences > Parameters & Flags to open the Global Preferences dialog, then enter `POSEVIEW` into the quick find field. The following variables and switches allow you to configure the appearance and performance of *PoseView*.

`POSEVIEW_IA_CONTACT_CNT` With this threshold you may reduce the amount of contact splines displayed in PoseView. Hydrophobic contacts are shown only if this minimum number of lipo interactions¹ are given. Default: 3.

¹See *Special commands for analyzing docking results (ANALYZE/CONTACT)* in the *FlexX* reference for computing the lipophilic contact area

POSEVIEW_IA_ENERGY Show PoseView interactions only below or equal this energy value. Default: 0.0.

POSEVIEW_IA_LABELS Show energy values at PoseView interaction lines. Default: 1 = show labels.

POSEVIEW_SHOW If set to 1 the PoseView widget stays open when switching between different solutions in the solution table, otherwise you have to open it manually for each pose. Default: 1 = stay open.

POSEVIEW_TIMEOUT Timeout for generating PoseView images, given in milliseconds. A value of 0 disables the timeout. Default: 500 ms.

6.4 Export to File

The context menu of the FlexX solutions table contains the action “Export PoseView Image...” to write the selected solution into a file; supported formats are *Scalable Vector Graphics (svg)*, *Portable Document Format (pdf)* and *Portable Network Graphics (png)*, *pdf* is the current default. Again, this action also is only enabled when having selected exactly one solution.

Updates

LeadIT will automatically check for updates if you have a connection to the internet. If updates are found you will see a little icon in the system tray, typically at the very bottom of your screen. Clicking on it will take you to the BioSolveIT download pages.

III

STRUCTURE AND
FRAGMENT-BASED DESIGN
TOOLS

In 1 Minute: Docking with *FlexX*

The docking algorithms in *LeadIT* use the well-known, award-winning algorithms of *FlexX*. Here, we only briefly describe the needed steps to set up a docking experiment. Full coverage of the needed steps can be found in the separate documentation which are available from the `Help` menu. You need a respective license to perform docking.¹

8.1 Receptor preparation

FlexX needs a fully prepared Receptor to work with. A Receptor here comprises the full definition of your Binding Site, any contributing co-factors, etc.

We have built in Receptor Intelligence in the Receptor Wizard which will assist you to set up your Receptor fast and accurately.

Use the menu `Receptor -> Define` to evoke the wizard, or use the Wizard's Magic Wand icon in the toolbar.

8.2 Ligands, the Library

To dock ligands, you will need to load them. This is evoked using `Library -> Load`.

8.3 Evoking the actual Docking

Once a Receptor has been prepared and the ligands have been loaded as the Ligand Library, the dialog for docking control will be enabled.

Use `Docking -> Define FlexX Docking` to pop up a fairly self-explanatory dialog.

Details for all this can be found in the *FlexX* documentation available through the `Help` menu.

¹Experts, please note that the *FlexX* commandline can be called using `leadit --commandline`. See the *FlexX* documentation for more details please.

In 1 Minute: FBLD with *ReCore*

ReCore's initial task was to replace unwanted core parts of molecules. From there it has grown to a comprehensive, world renown fragment-based ligand design (FBLD) tool. It has become famous owing to its unrivaled speed and the versatile usage. In *LeadIT ReCore* is implemented in an aggressively easy dialog. Please note that you need a respective license to perform *ReCore* runs.

Here, we will very briefly cover the respective parts in *LeadIT* which trigger the computation of the major FBLD workflows. They are all controlled from the *ReCore* menu entry.

Please mind that **the *ReCore* menu entry is only available as long as the Receptor Wizard is not active.** These two dialogs mutually exclude each other.

For all scenarios one rule applies:

A valid *ReCore* Query needs 2 vectors of which one must be an Exit Vector!
Further Pharmacophore Features can be added in the Advanced Options.

9.1 Core Replacement

Core Replacement is used with the left icon in the *ReCore* Dialog.



The Core Replacement Button

The Core definition takes place by cutting at least two bonds exiting from the respective part-to-be-replaced. Simply click them, and as soon as a valid *ReCore* Query has been defined, the *ReCore!* button is no longer grayed out.

9.2 Fragment Growing and Evolution

Fragments can be grown, e.g., from one pocket to another. *ReCore* supports this mimicking the cut of one bond (an Exit Vector definition) and subsequent selection of a Pharmacophore Feature.



The Growing Mode Button

Pressing this button will entail the loading of one molecule, and you will have to define the Exit Vector by clicking onto a bond, and the Pharmacophore Feature using a selection in the 3D View. More Pharm. Features can be added using the Advanced Options tab.

9.3 Fragment Merging and Linking

Two or more fragment binders can be merged to form one — hopefully more potent — molecule. This scenario is termed Fragment Linking. If such fragments overlap, we speak of Fragment Merging. Use the right icon to evoke this mode. It will only be made available after having loaded **at least two molecules** using the Add button.



The Linking & Merging Mode Button

After definition of two Exit Vectors, you may add more options and Pharmacophore Features using the Advanced Options tab.

Further information about *ReCore* can be found in the respective documentation.

Index

- Rendering , 12
 - FlexE*, 17
 - FlexX* Solutions Table, 25
 - ReCore* Index File, 9
 - ReCore* Solutions Table, 24
 - 3D display, 12
- annotations, 24
- Assistant, 25
- assistant, 20
- BioSolveIT Host ID, 13
- BioSolveIT-HostID, 13
- COMPOSITE-ID, 13
- console, 25
- Cygwin, 12, 16
- debug console, 25
- dock widgets, 24
- errors, 25
- exporting *ReCore* Solutions, 24
- exporting docking poses, 25
- FAQs, 14
- flexlm, 13, 15
 - port number specification, 14
- fonts, 16
- fullscreen mode, 27
- graphical user interface, 7, 10
- graphics cards, 16
- GUI, 7, 10
- help, 19, 25
 - assistant, 20
 - commandline help, 19
 - movies, 19
 - PDF documents, 19
 - tutorial movies, 19
- HostID, 13
- Information Stream, 25
- installation
 - admin rights, 9
 - Linux, 9
 - Windows, 9
- key bindings, 27
- known issues, 15
- LeadIT, 7
- license
 - flexlm port number, 14
 - Linux/Windows, 15
 - server, 15
- license server, 13
- limitations, 15
- Linux
 - installation, 9
- lmgrd, 13, 15
- magic wand, 27
- Measure&Label Escape, 27
- monitors
 - multiple, 24
- mouse pointer, 27
- multiple monitors, 24
- notes, 24
- parallel computing, 17
- port number for flexlm, 14
- PoseView, 29
 - Button in 3D, 30
 - Dock Widget, 25
 - Example: 4dfr, 29
 - Export to File, 31
 - Second Screen, 29
 - Settings, 30
 - Timeout, 30
- problems, 15
- Project Notes, 24
- Project Tree, 24
- PVM, 17
- screening, 25
- settings, 10
- shutter glasses, 12
- static_data, 11
- stereo view, 12

text window, 25

troubleshooting, 15

undocked ligands, 25

user settings, 10

visibility of objects, 24

warnings, 25

Windows, 16

Admin rights, 9