SIOS
(Shop Interface to Other Software)

User Manual

PhD. Guillem Plasencia Gallofré
Lead Molecular Design, S.L.

I. Introduction

SIOS (Shop Interface to Other Software), as its name says, is an interface for Shop to access, configure and execute other programs (Moka, Volsurf Plus and Metasite3) from within Shop. Using it, users can submit, within Shop itself, the rebuilt search hits to either Moka, Volsurf Plus or Metasite3.

SIOS makes use of Shop's "Scripting" feature, that allows Shop users to "bind" the execution of an external program (SIOS in the present case) to completion of a task in Shop (Template Rebuild All in the present case).

In the particular case of SIOS, the execution of this interface must be bound to "Template Rebuild All" (read II. Requisites and Installation for more details), which means that SIOS will be executed after all Shop's search hits have been rebuilt.

II. Requisites and Installation

SIOS is an application written in Perl, which is an interpreted programming language. Unlike other programming languages, interpreted languages rely upon an interpreter to be executed.

We at Lead Molecular Design offer our registered users SIOS as a Perl application, but we do not provide the Perl interpreter to users. This means that users, in order to run a program written in Perl, have to install both the Perl interpreter and the program. Here we will explain how to download and install Perl interpreter and SIOS.

First of all, which operative system Shop client is running under (Windows / Linux)? SIOS needs to be installed in the same machine as Shop client.

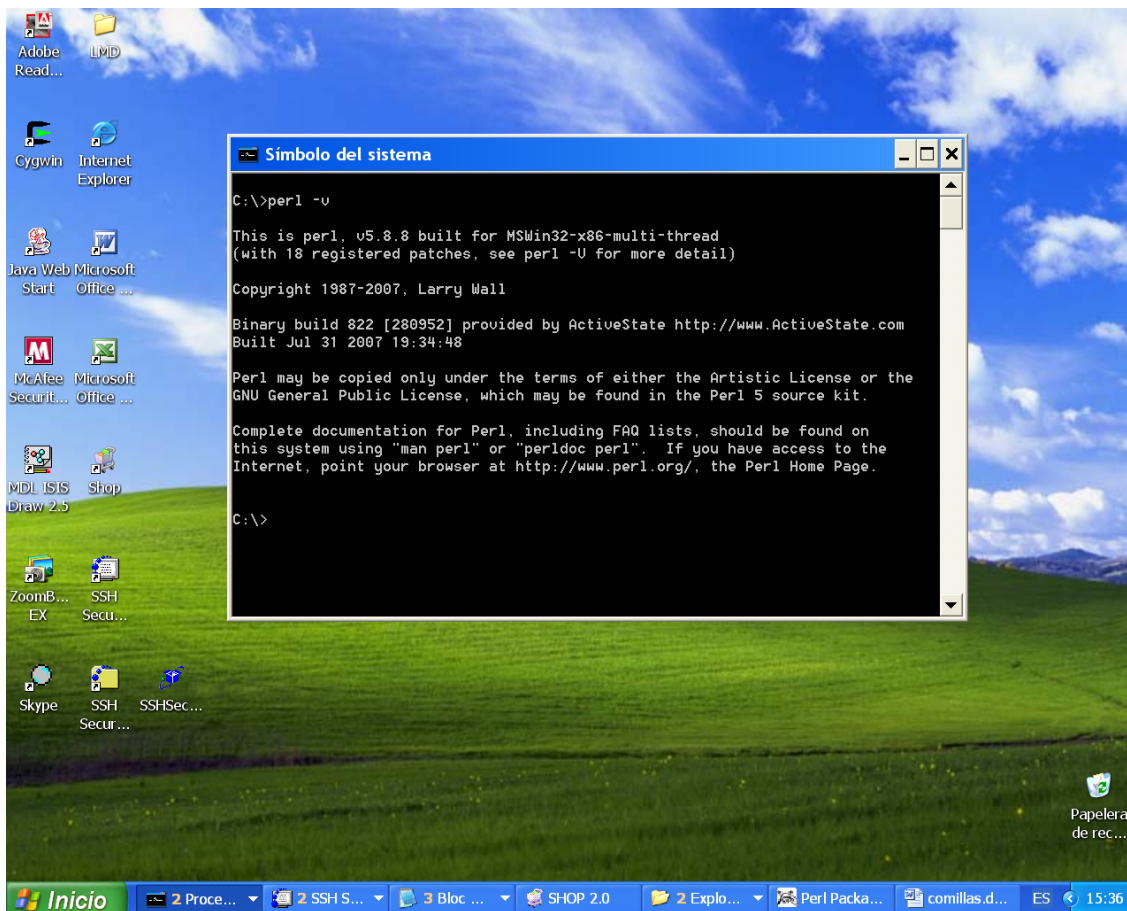## II.1 Installing a Perl interpreter

a) Installing Perl interpreter in Windows systems:

If Shop client is executed from a Windows machine, the easiest way is to download a precompiled executable of Perl interpreter [ActivePerl](recommended version is 5.8.* but not 5.10.* as the newest version lacks some of the required modules needed) from the company ActiveState. This compiled interpreter is completely for free, but ActiveState sells also integrated development tools to help programmers write their own Perl applications.

Download ActivePerl as an MSI (Microsoft Installer) package, and install it. Default installation options are OK.

Once finished, open a System terminal (see screenshot below) and write:

perl -v (and press Enter)

If everything went OK you should see a message with the version and license.

b) Installing Perl interpreter in Linux systems:

Even though most Linux operative systems do already have installed some version of a Perl interpreter, we recommend installing ActivePerl for Linux, available for free from ActiveState web site (http://www.activestate.com). Included in ActiveState's ActivePerl precompiled binaries for there is Perl Package Manager (ppm) which really makes it easy to install the required Tk Perl module.

If you still prefer to use the preinstalled Perl in your Linux, check which version (if any) is installed by opening a Linux console and writing

perl -v

If there is a Perl interpreter installed, this will print the version. Any version from 5.8* or higher (including 5.10*) will be OK.

II.2 Installing required Perl modules

Unfortunately we've not yet finished. We need to install (if they're not already installed) one Perl module that give some extra functionality to Perl.

It's named Tk (tested with Tk version 804.028) and is a graphic library that allows Perl applications to have windows. In order to check if it's already installed, please open a terminal and write

perl -e "use Tk"   (press Enter)

if you see a message like: "Can't locate Tk.pm in @INC" it means that most likely you don't have these installed. If you don't see any apparent message, you have it installed and you can skip the rest of this section.

a) Installing Tk in Windows

ActivePerl package comes with its own Perl Package Manager (PPM), a graphical application that allows users to install Perl modules. In order to execute PPM, either write ppm (ENTER) in a terminal, or start Perl Package Manager from the Applications Menu.

Select menu View --> All Packages and scroll down to Tk and right click to select Install (see picture on next page)

Once you're done selecting Tk, go to Action -> Install (or press the small green right arrow in the top right side). PPM will install the required module, as well as any additional required modules that these modules might need as a requisite.
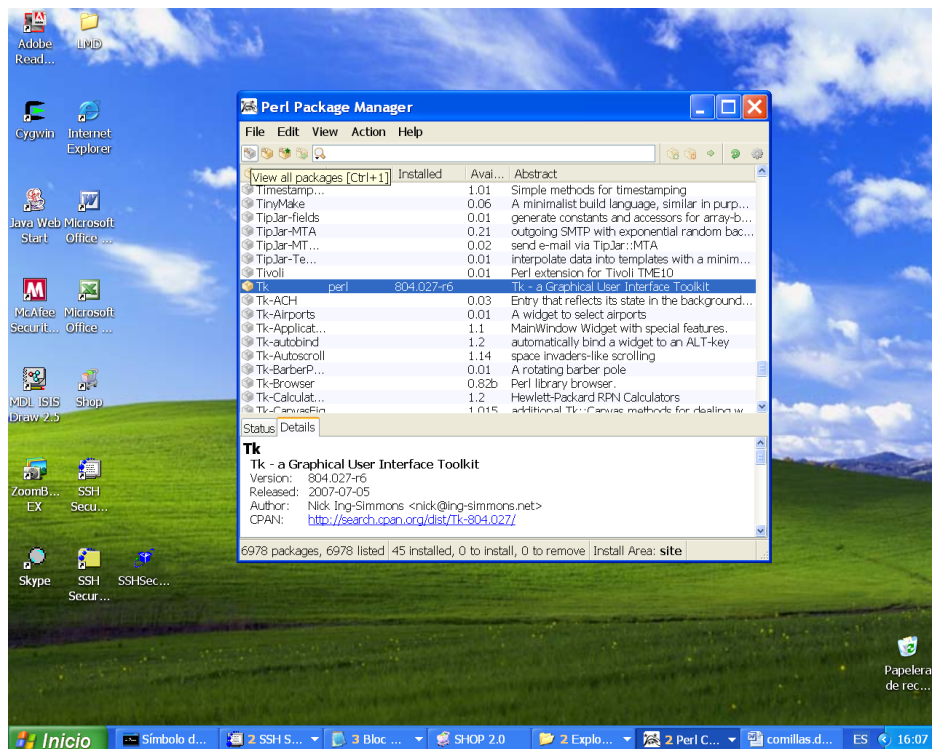
b) Installing Tk in Linux

Linux users that don't have Tk Perl module installed will need to this. If you installed ActivePerl for Linux you have also the Perl Package Manager, try executing ppm in a console. When the graphical program called Perl Package Manager opens, read section II.2a) Installing Tk in windows above.

If you didn't install ActivePerl for Linux, because either Perl was already installed or you compiled it yourself, then the easiest way to install Tk is using CPAN (Comprehensive Perl Archive Network).

First, you need to have superuser rights to install new Perl Modules (ask the system administrator to install them for you if you don't have them). Once you're superuser, write in a Linux console:

cpan

and a cpan shell loads, that will look like:

cpan shell -- CPAN exploration and modules installation (v1.9205)
ReadLine support enabled

cpan[1]>

Sometimes it might ask you a few questions like the ones below before giving you access to CPAN shell, here are some recommended_answer (empty means simply press Return and accept CPAN default):

-Always commit changes to config variables to disk? [no] yes
-Parameters for the 'perl Build.PL' command? []
-Parameters for the './Build' command?
-Do you want to use a different command for './Build install'?
-Parameters for the './Build install' command?

It might also ask you about your country, this is to select the closest mirror server.

Write the following line to install Tk:
cpan[1]> install Tk (and press Enter)

-Is it OK to try to connect to the Internet? [yes]

It will take some time to download, compile and install everything, and at some point you will see several windows appearing, don't worry cpan is testing Tk windows.

Once finished read the last messages to check if installation went fine and if it succeeded write

cpan[3]> quit

to leave CPAN shell and return to console shell.

II.3 Testing installation of required Perl modules

To test if Tk and Tk::FileDialog modules installation was successful, write in a Linux console:

perl -e "use Tk"

You should not see any answer or error message in reply.

II.4 Installing SIOS

### a) Installing SIOS using the install_sios.exe application

Once you've finished installing Perl interpreter and the needed module Tk, you're ready to install SIOS.

Probably you've already done it, but if not download SIOS-1.zip from http://www.leadmolecular.com web site (you need to be a registered user) and unzip it into a temporary folder (for instance /home/username/tmp) using Winzip (in Windows) or unzip (in Linux).

Open a Linux (or Windows) console and enter into the temporary directory. Write the following line to execute the installation program:

perl -e install_sios.pl

You will see a window like the one in the screenshot below:
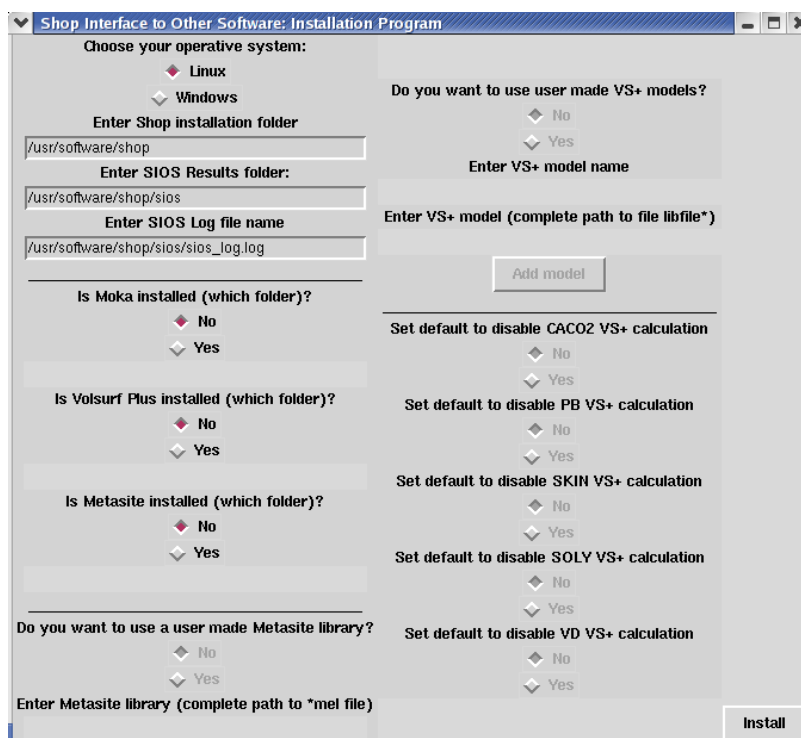
This installation program has two main tasks: create and copy SIOS files to the right place in your machine. In order to be able to install SIOS, users have to choose and fill these fields in a predetermined order:

-First, users must choose their operative system (Linux or Windows) and write down where is Shop installed, and where do they want SIOS results to be stored, as well as the location and name of SIOS log file. Every time you "click" on Linux or Windows, Shop installation folder, Sios results folder and Sios log file change to their default values for the selected operative system, but once the operative system is selected the user can modify them at will. Also, users can select which programs are installed on their machine (Moka, Volsurf Plus and/or Metasite3).

All configuration options specific of one program are blocked until the user clicks on "Yes" to the question "Is <PROGRAM NAME> Installed?".

Users have to write the absolute path (i.e. /usr/software/metasite3) to the installation folder of each program. Here is a short explanation on each field:

- *Choose your operative system*: click on either Windows or Linux.
- *Enter Shop installation folder*: write the absolute path to Shop installation folder (i.e. /usr/software/shop).
- *Enter SIOS results folder:* the absolute path to a folder where SIOS results and SIOS log file will be saved.
- *Enter SIOS log file name:* the file name of SIOS log file. This file will be saved inside SIOS results folder.
- *Is <PROGRAM> installed (which folder)?*: click on either "Yes" or "No" and don't forget to write the absolute path to the installation folder of the program.
- *Do you want to use a user made Metasite library?*: click on either "Yes" or "No" and provide the absolute path to the *mel customized file.
- *Do you want to use user made VS+ models?*: click on either "Yes" or "No". For each model, you have to provide the exact name of the model (as is shown in column "Name" of table displayed in vsmodeller menu Edit -> Library (Control+L)) as well as the absolute path to the libfile* corresponding to that model. BEWARE ! all user models have to be stored inside the same folder !. Once the model name and file have been written, click on button Add model to include it, and repeat as many times as models you want to include.
- *Set default to disable [CACO2 | PB | SKIN | SOLY | VD] Volsurf Plus calculations*: SIOS by default will select all Volsurf Plus models to be calculated. If there is one or more VS+ system models that you know beforehand that you will not use you can save yourself a few clicks by just disabling the option to calculate them in SIOS. BEWARE! Choosing to disable one or more of VS+ models means that you will never have the option to calculate them using SIOS unless you run install_sios again !

When finished choosing options, click on Install button (bottom right). The program will do a few trivial checks (filenames and paths must not be empty, for instance) and if it finds some problem, it will be displayed colouring the form in a darker grey colour. If the Install button turns green, the configuration for the installation was found to be Ok, and the installation itself probably succeeded. If it turns red, it means there was some problem while creating folders and files associated with the installation, read the following section for more information on how to install SIOS by hand.

b) Installing SIOS yourself

The application install_sios was written just to make a simple process even easier. Here there is an explanation of what install_sios does, just in case you need to do it yourself.

- The most important step is writing the sios.conf file, that contains necessary information to execute SIOS (like the operating system SIOS is running under, or where are the programs installed...). You can see a sample of the contents of a sios.conf file and some instructions on how to write one sios.conf file yourself in the Annex A.

- It creates any needed folder (for instance, the folder where you want all results of predictions sent through SIOS to be stored in, or the folder where sios log file will be stored, if it's a different one...)

- It creates or copies files: sios.exe, install_sios.exe, sios.conf, sios_env.bash, and run_sios.bash (for Linux) or run_sios.bat (if it's a Windows operating system) into <Shop installation folder>/bin.

II.5 Checking SIOS installation

If you want to test whether SIOS was correctly installed, simply open a command terminal (either in Windows or Linux) and enter into <Shop installation folder>/bin.

Write run_sios.bash (or run_sios.bat if you're in Windows) followed by the complete path to a multimol2 file (provided inside sios package there's a test.mol2 file):

./run_sios.bash   /path/to/test.mol2 (for Linux)

run_sios.bat UNIT:\path\to\test.mol2 (for Windows)

If installation was successful, you should see a window like:
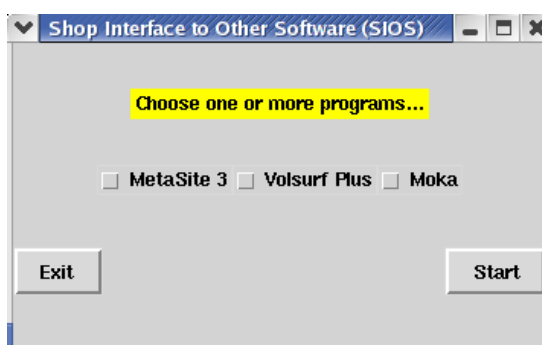
Using this method, SIOS can be executed as a standalone interface completely independent of Shop to launch MetaSite3, Volsurf Plus or MoKa tasks.

<u>II.6 Binding SIOS to Shop</u>

SIOS can be executed by itself, or it can be bound to Shop so that it's run just after Shop performs one task.

In order to bind SIOS to one Shop task, run the graphical client (<Shop Install Folder>/shop-run) and select Menu Edit --> Preferences --> Scripting (Tab). Scroll down to "Template Rebuild All", then click on checkbutton "Call script" and browse through the filesystem to <Shop Install Folder>/bin/run_sios.bash (or <Shop Install Folder>/bin/run_sios.bat if you're running Windows).

<mark>Please be aware that you must enclose the whole path inside double quotes (like "/usr/software/lead molecular design/shop/bin/run_sios.bash" or "C:\Program Files\Shop\bin\run_sios.bat") if in the path there is/are empty spaces. Otherwise SIOS will NOT run !</mark>
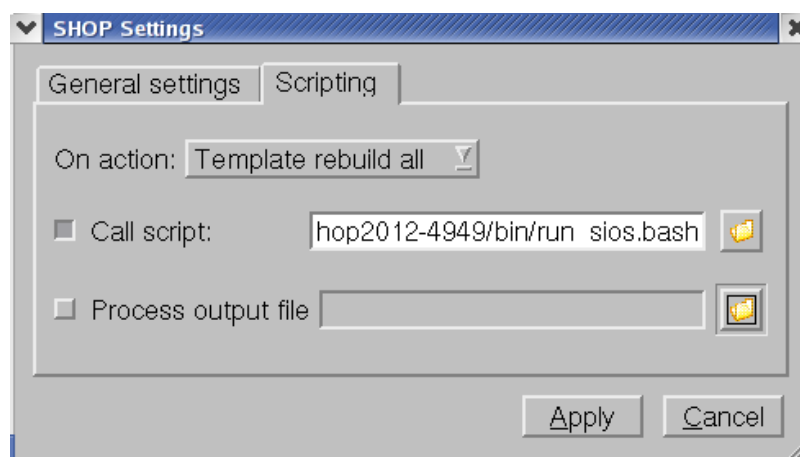

You could also select "Process output file" so that Shop displays any *txt or *html file after SIOS has been executed.

III. Running SIOS

SIOS can be executed both as a standalone application interface (simple write in console run_sios.bash or run_sios.bat followed by the complete path to a multimol2 file) or as an application bound to Shop's task "Template Rebuild All" as explained above.

How can you trigger Shop's Template Rebuild All task? First, you need to connect to a Shop server and select the database you want to search. Then, select menu Query --> Load Query and choose an sdf or mol2 file containing a whole molecule.

Shop automatically detects that the loaded query doesn't have any anchor points, and loads a 3D interface for you to choose where to place them by clicking on the precise atom (see picture below).
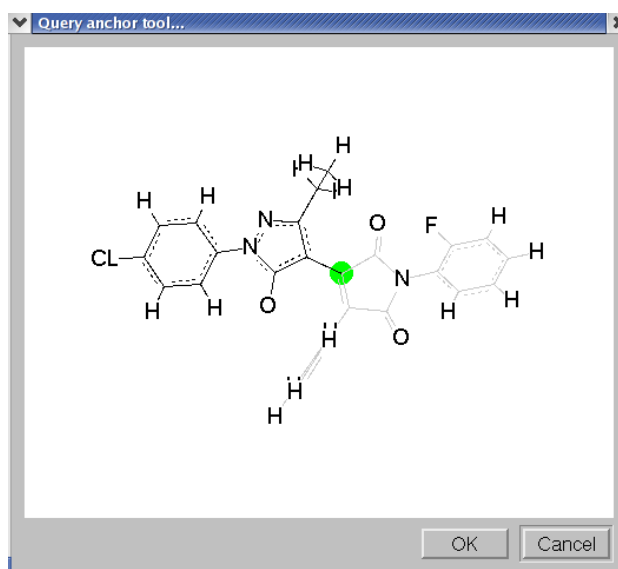
This step is crucial, it is by selecting where do you want the anchor points using this interface that Shop will be able to re-attach the removed fragments (displayed in a lighter grey in the above picture) to the all search results (Template Rebuild All).

Automatic recognition of molecules missing anchor points is not implemented in the "Draw Query" tool (Menu Query --> Draw query), so if you're using it to draw your query you must first draw it, choose the mol file name and submit it (without any Dummy atoms, draw the whole molecule) and then discard the wrong query and load the saved file after drawing it using Menu Query --> Load Query.

Once you've selected the anchor points, do a search on the database and click on any of the results. Then, select Menu Search --> Rebuild Ligand (see picture below)
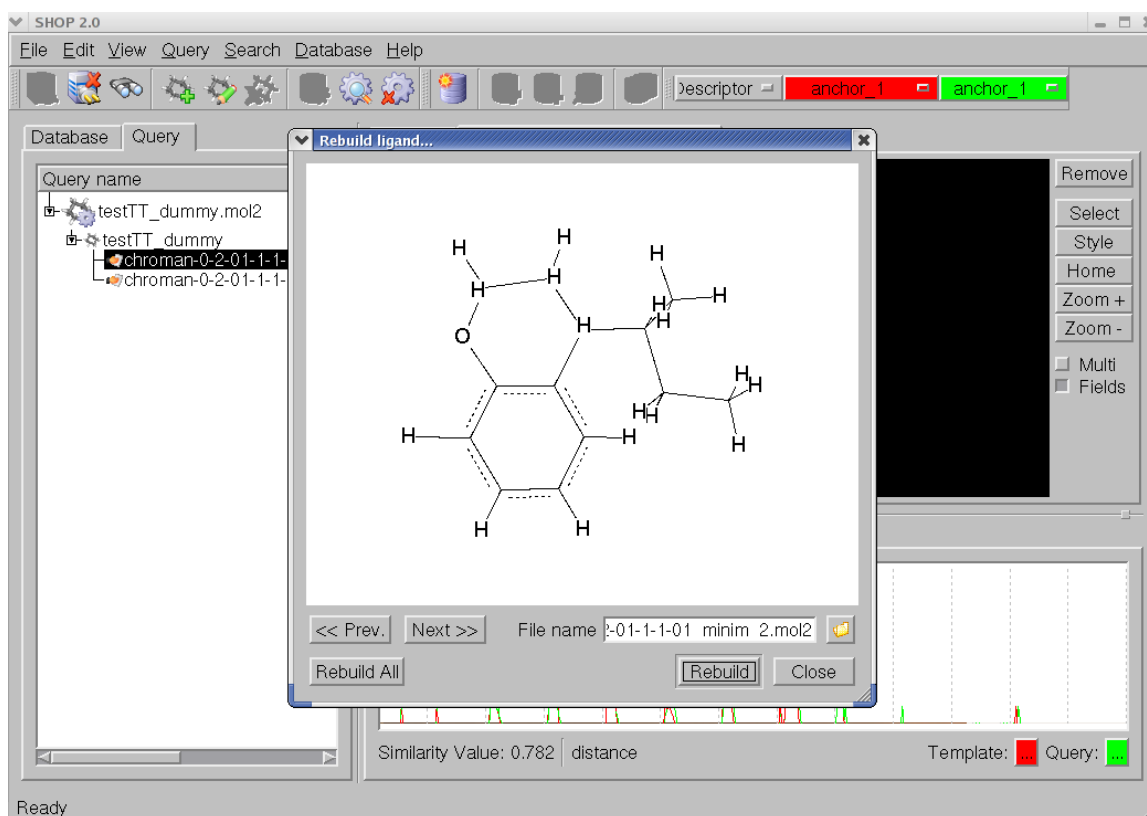
You must then select the button "Rebuild All", and after Shop has rebuilt all search hits by attaching the removed fragments of the original molecule to their anchor points, SIOS will be executed and you will see a window like this:
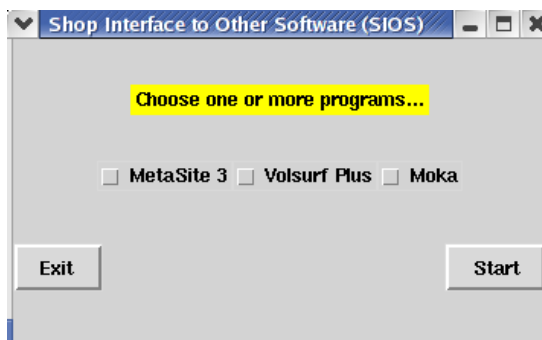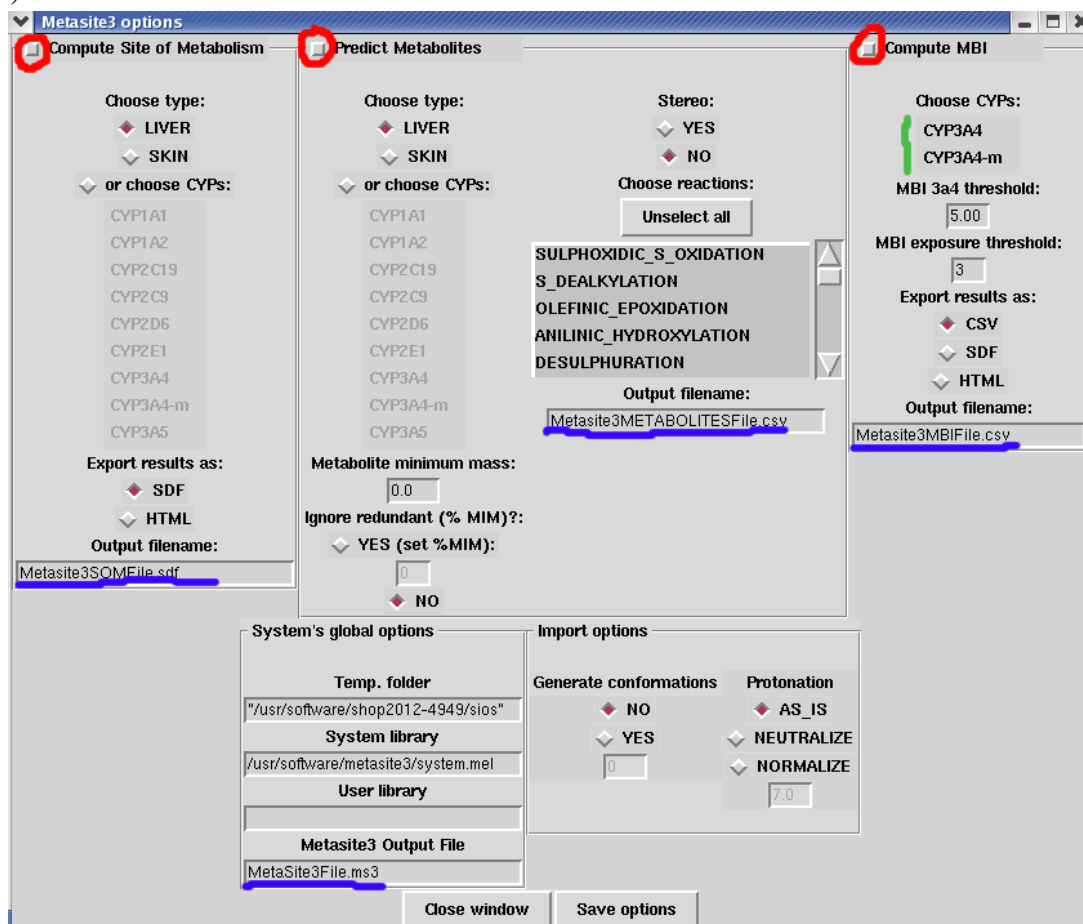

Click on any checkbutton to select which program do you want to run. If, during SIOS installation, you didn't enter some of the programs' installation folders you will not be able to select them now.

III.1 MetaSite3 options window

Whenever you click to select on Metasite, the Metasite options windows appears (see picture below):

You can select which type of MetaSite3 computation to perform on the rebuilt Shop search hits: click in the checkbuttons (marked as red circles in the above picture) besides Compute Site of Metabolism (SOM), Predict Metabolites and/or Compute MBI to select these tasks. Once one task is selected, you will see the checkbutton checked and the text will have a darker grey background colour.

For each task, you can choose type (Skin, Liver or select one or more cytochromes). Cytochromes' list is a multiple selection list (Control+click, or Shift+Click or drag select allows the user to select more than one cytochrome). Be aware the MBI has NO default cytochrome, so if you select to Compute MBI you must remember to choose either or both CYP3A4 or CYP3A4-m or it will not work (marked as a green line in the above picture) !! For each Metasite3 task the user can select to export the results of that task to one file (marked as a blue line in the above picture) and choose the filename.

The predict metabolites task has a list of possible reactions to apply to the substrate to generate the metabolites, all are selected by default but the user can modify it to apply only some of them.

The lower block of the window contains import and global options, which are set for all tasks. There users can choose whether to calculate conformations, or protonation options (as is, neutralize or normalize to a user given pH), or even the output filename for the MetaSite3 results file (this file can be opened by MetaSite3).

Users are warned to use integer numbers (without any decimal point) when setting the %MIM, the MBI exposure threshold or the number of conformations, and float (with a decimal point) in all other numeric fields like Metabolite minimum mass, MBI 3a4 threshold or Protonation NORMALIZE pH.

Once finished, click on Save options button below and the window will disappear. You can check at any time later the options you selecting by unselecting and selecting again Metasite in the main window.

III.2 Volsurf Plus options window

Whenever you click to select on Volsurf, the Volsurf options windows appears (see picture below):
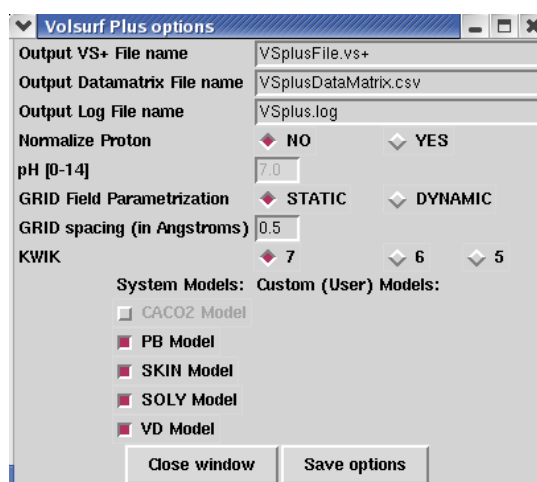
Users can select the name of the Volsurf Plus output file, as well as the filename where the data matrix (in comma separated format, CSV) will be stored, and the name for the Volsurf Plus log file.

Users can also select whether to normalize protonation state by assigning themselves a pH value (it must be a decimal number, don't forget the decimal comma or it might not work !). They can also choose GRID parameters as well as which System models and/or Custom models use.

Default is that all system models are used. If, during installation, you choose to disable one of the system models its checkbutton will not be "selectable". Also, if during installation one or more customized user models were included, they will be listed (and selected by default). Click on any checkbutton to add/remove making predictions on that model (be aware that System model projections will anyway be included in the data matrix CSV file).

Once finished, click on Save options button below and the window will disappear. You can check at any time later the options you selecting by unselecting and selecting again Volsurf in the main window.

III.3 Moka options window

Whenever you click to select on Moka, the Moka options windows appears (see picture below):
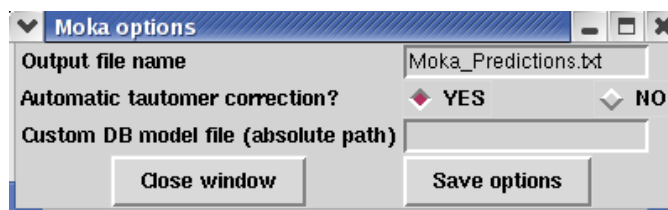
Here you can set Moka output file name, as well as to choose whether to perform automatic tautomer correction (check whether your version of Moka supports this feature), and, if given during SIOS installation, it will display the absolute path to the customized DB file that will be used.

Once finished, click on Save options button below and the window will disappear. You can check at any time later the options you selecting by unselecting and selecting again Moka in the main window.

III.4 Running tasks

Once finished configuration of tasks to be run, simply click button Start in the main SIOS windows, and wait a few seconds / minutes until you see a message indicating that all tasks have been finished.

Then, if you chose the option "Process output file" when you bound SIOS to Shop, Shop will display the chosen *txt or *html file in a window. Otherwise, users can use Volsurf or Metasite to load the vs+ or ms3 output files stored in results folder. Results from Moka can be viewed with any text editor.

Annex A: sios.conf file explained

Users can find a sample sios.conf file included in SIOS package. Its contents are similar to:

Lines with a hash symbol (#) at the beginning are NOT used
OS=Linux
LOG_FILE=/home/guillemp/shop_script/LOG.log
MOKA_DIR=/usr/software/moka
VSPLUS_DIR=/usr/software/vsplus-0.9.26-Linux
VSPLUS_USER_MODELS_DIR=/home/guillemp/shop_script
VSPLUS_USER_MODELS_FILE=/home/guillemp/shop_script/libfile0000:TestUserModel
VSPLUS_USER_MODELS_FILE=/home/guillemp/shop_script/libfile0001:TestUserModel2
METASITE3_DIR=/usr/software/metasite3
#METASITE3_USER_LIBRARY=/usr/software/metasite3/pepe.mel
SHOP_DIR=/usr/software/shop2012-4949
RESULTS_DIR=/usr/software/shop2012-4949
#DISABLE_CACO2
#DISABLE_PB
DISABLE_SKIN
DISABLE_SOLY
DISABLE_VD

Any line beginning with a hash (#) will be ignored by SIOS, and can be used to include comments, or simply to disable some option. Each line contains a KEY (in upper case), followed by an = and a VALUE. The KEY must be in uppercase and exactly as displayed above. The equal sign and VALUE are not mandatory for all KEY, but when they are, they must contain either one of several fixed options (indicated between brackets, separated by the symbol "|"). For instance, OS KEY lines can be

OS=Linux
or
OS=windows

and it will be indicated as:

OS=[Linux|windows]

VALUES can be of type <COMPLETE_PATH_TO_FILE>, <COMPLETE_PATH_TO_FOLDER>, or <COMPLETE_PATH_TO_FILE:MODELNAME>

The first two lines that any sios.conf file must contain are:

OS=[Linux|windows]
LOG_FILE=[<COMPLETE_PATH_TO_FILE>]

These need to be in this order (first the OS, then the LOG_FILE) so that every time SIOS is executed and reads sios.conf file it can print its options in the log file for later inspection.

MOKA_DIR, VSPLUS_DIR and METASITE3_DIR are the options that point to the folder where each program (if available) is installed. The folder must be written WITHOUT any double quotes, but including any empty spaces that the path might have. The folder path must not end in "/" (or "\" for Windows).

VSPLUS_USER_MODELS_DIR, if included, must point to the folder that contains Volsurf Plus user models files. If VSPLUS_USER_MODELS_DIR is included in sios.conf, sios.conf must contain at least one VSPLUS_USER_MODELS_FILE line.

Each VSPLUS_USER_MODELS_FILE line has the following syntax:

VSPLUS_USER_MODELS_FILE=<COMPLETE_PATH_TO_FILE>:<MODELNAME>

Where <COMPLETE_PATH_TO_FILE> is the path to the libfile* containing the model data, and <MODELNAME> is the name of the model exactly as displayed in the column "Name" of vsmodeller menu Edit --> Library table. Please note that <COMPLETE_PATH_TO_FILE> and <MODELNAME> are separated by a colon (":"). Any customized model included with this method will be automatically selected to be used by default, but users can unselect them if they wish so.

In a similar way, METASITE3_USER_LIBRARY is the option that has to be used if a user wants SIOS to use a customized Metasite3 library. It must point to the <COMPLETE_PATH_TO_FILE> of a *mel file.

SHOP_DIR is not strictly needed by SIOS, but it stores the <COMPLETE_PATH_TO_FOLDER> of Shop installation folder. This path was used by install_sios to copy SIOS files (inside its "bin" folder).

RESULTS_DIR contains the <COMPLETE_PATH_TO_FOLDER> where all tasks executed through SIOS will store their result files and log files.

DISABLE_CACO2, DISABLE_PB, DISABLE_VD, DISABLE_SKIN, DISABLE_SOLY are parameters that don't use a VALUE. Simply include them (or delete/comment them out with a # symbol) if you want that SIOS disables by default any of these Volsurf Plus system models (they are all selected by default).