

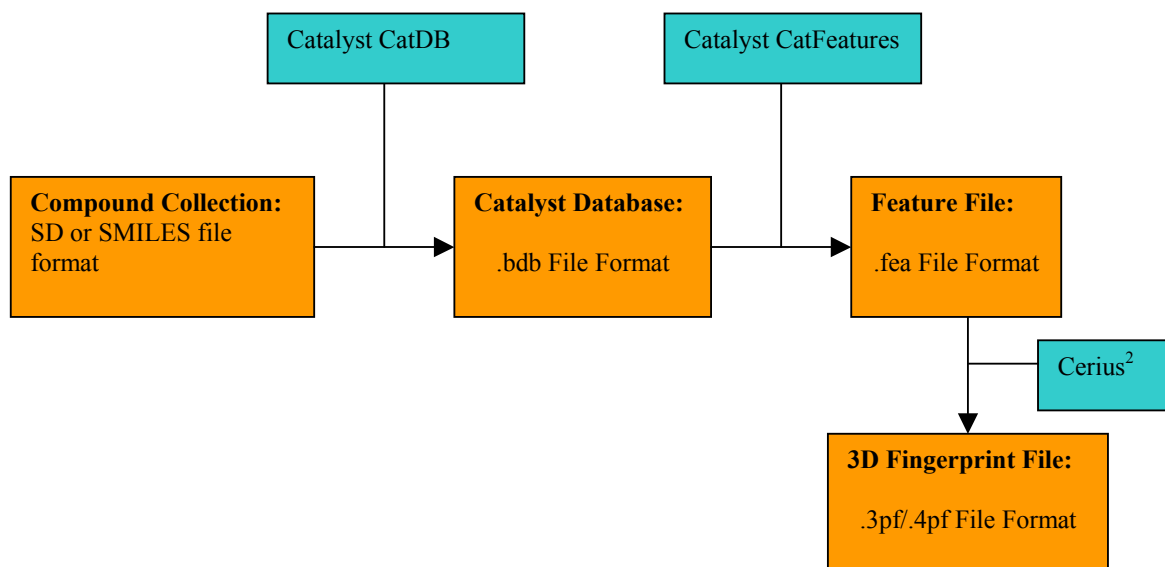
Key products: [C2.SBF](#), [C2.3Dkeys](#), [C2.Diversity](#), [C2.LibCompare](#), [Catalyst](#)
Industry sectors: Pharmaceuticals

FLIP Work Flow

Introduction:

Structure based drug design is the method used to identify and optimize pharmaceutical leads when the crystal, NMR structure or homology model of a specific target protein is known. Virtual screening of corporate libraries, external compound collections and virtual compounds using various docking methods is routine in the drug discovery process. We are proposing a new virtual high throughput screening approach that we term “FLIP” (Fast Lead Identification Protocol) that uses the potential protein-ligand interaction sites in the active site of the target protein to data-mine compound collections. This proposed approach has the advantage of being extremely fast and can potentially be used for any target protein structure.

Step I: Generating 3D Fingerprint File for Compound Collection:



The first step is to generate a catalyst database .bdb file for your compound collection. Detail instructions on how to generate catalyst .bdb database file can be found at

http://www.accelrys.com/doc/life/catalyst48/tutorials/4710_databases.html#1108

You need a username and password to get into this site:

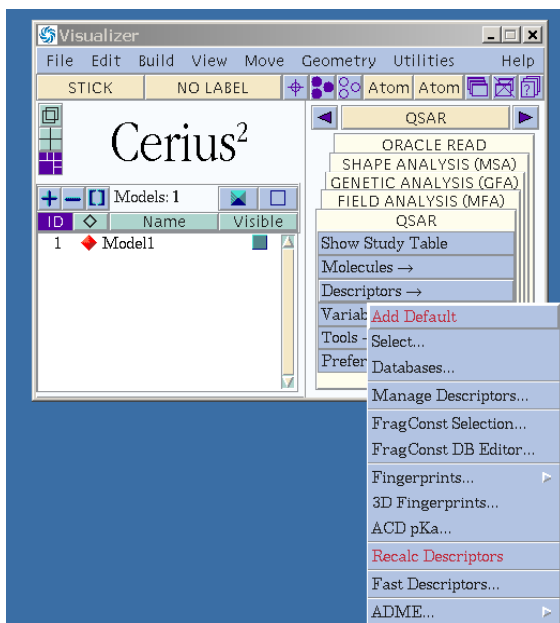
Username: science

Password: faster

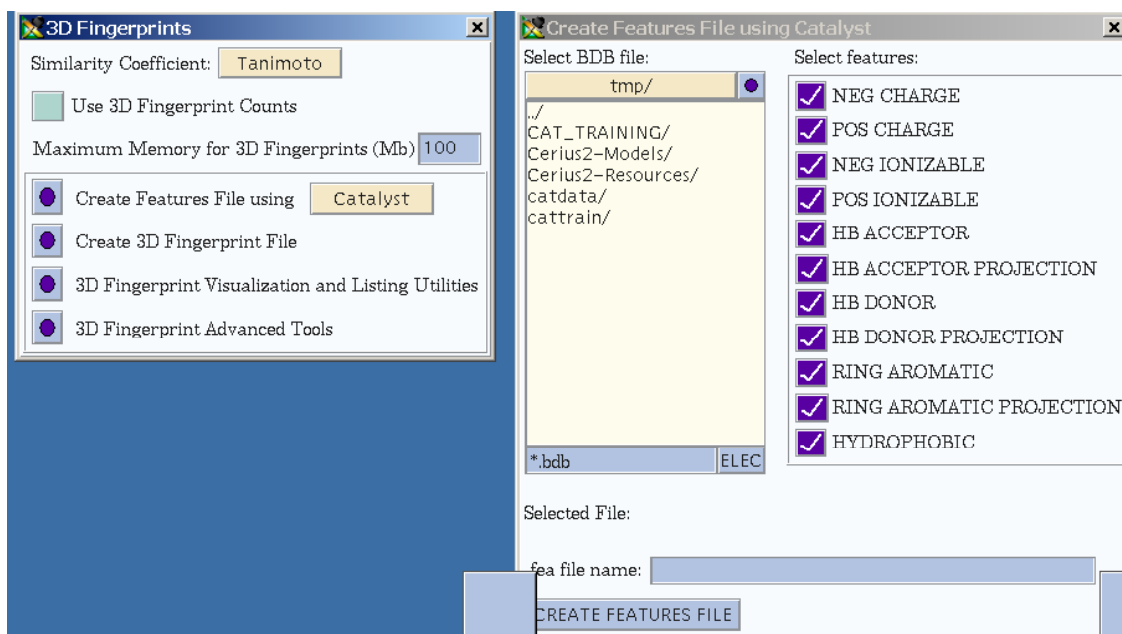
To convert the .bdb file into .fea and .3pf file you need to go to Cerius2.

In Cerius2:

Select QSAR/Descriptor/3D Fingerprints



Select Create Feature File using Catalyst



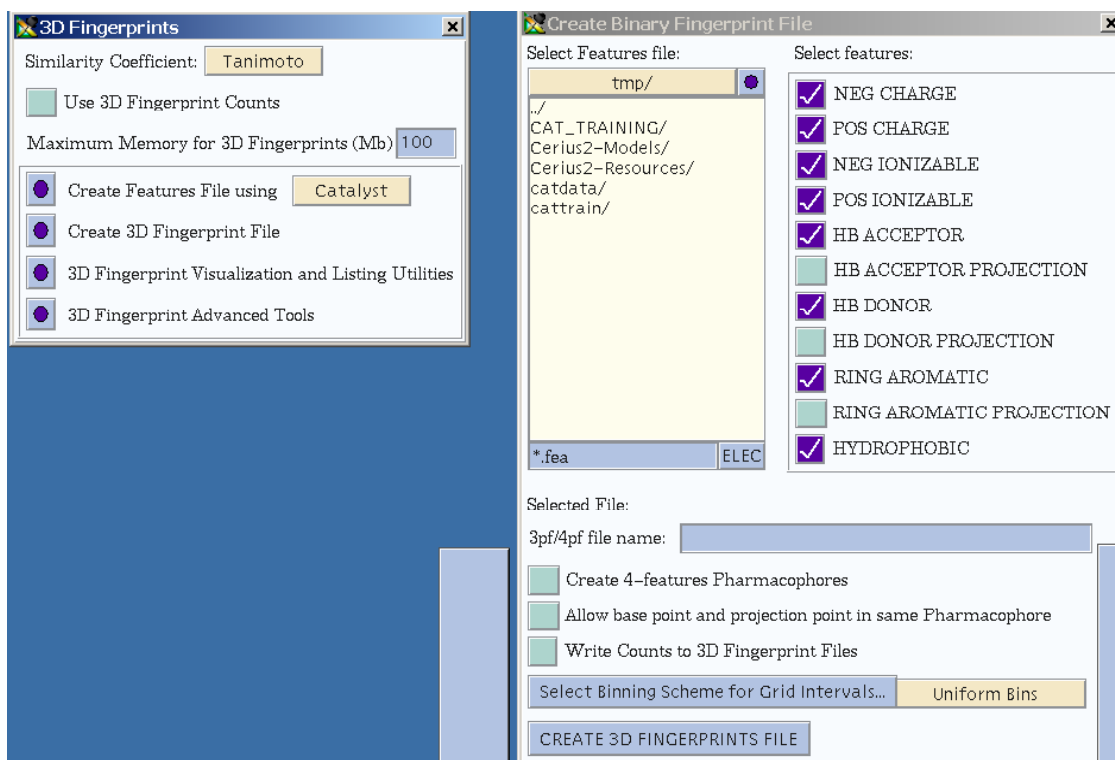
Note: By default LUDI will only generate Donor/Acceptor and Hydrophobic features. So when you generate a fea file for your virtual library only select Donor/Acceptor and Hydrophobic and deselect everything else.

In Cerius2 4.9 release we have implemented other catalyst features like Positive ionizable and Negative ionizable to be defined for receptor fingerprint in addition to default catalyst features.

Select your .bdb file and select **Donor/Acceptor and Hydrophobic** in feature selection and then click on *create feature file*.

This will generate a .fea file that will go as an input to next algorithm that converts it into .3pf file.

Go back to 3D fingerprints menu and not click on *Create 3D fingerprint File*



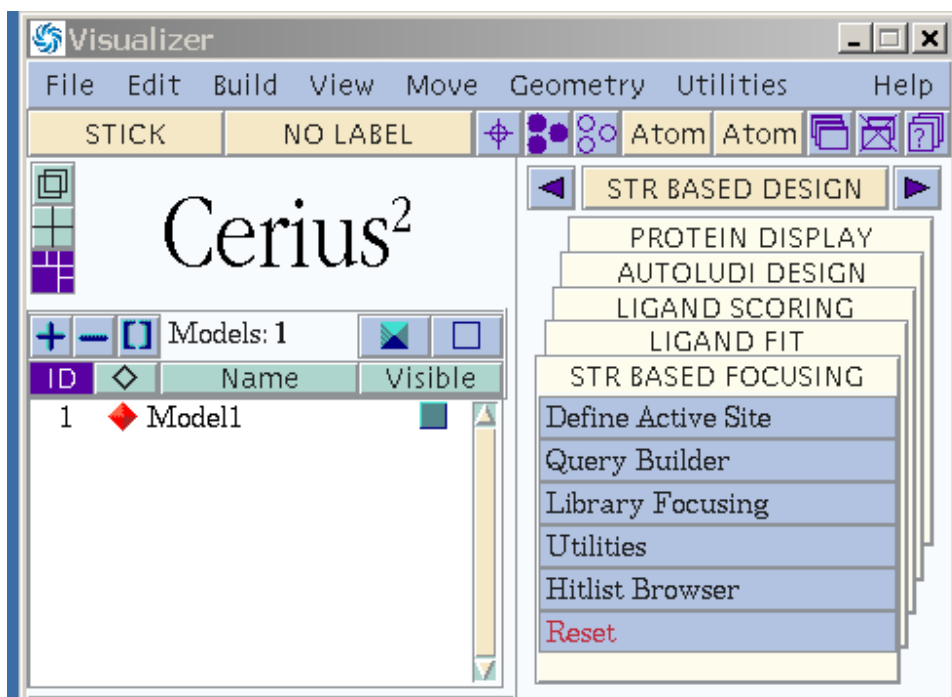
Select your .fea file that you have created previously. Then select only **Donor/Acceptor and Hydrophobic** and de-select everything else.

You can generate a 3 point or a 4 point 3D fingerprint file. Also you can generate binary or non-binary (with Counts) file.

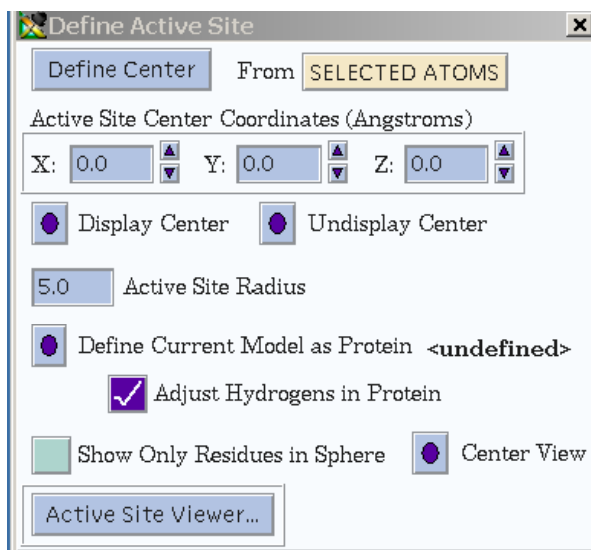
Select the options that you want and then click on *Create 3D FingerPrints File*
This will generate a 3D 3 or 4 point fingerprint file for your entire virtual compound collection.

Step II: Generating 3D Fingerprint file for your Receptor Structure:

To generate the receptor Fingerprint File you need to go to *Structure Based Focusing Module* in C2. It is located under Str Based Design Section of C2.



Click on *Define Active Site*.



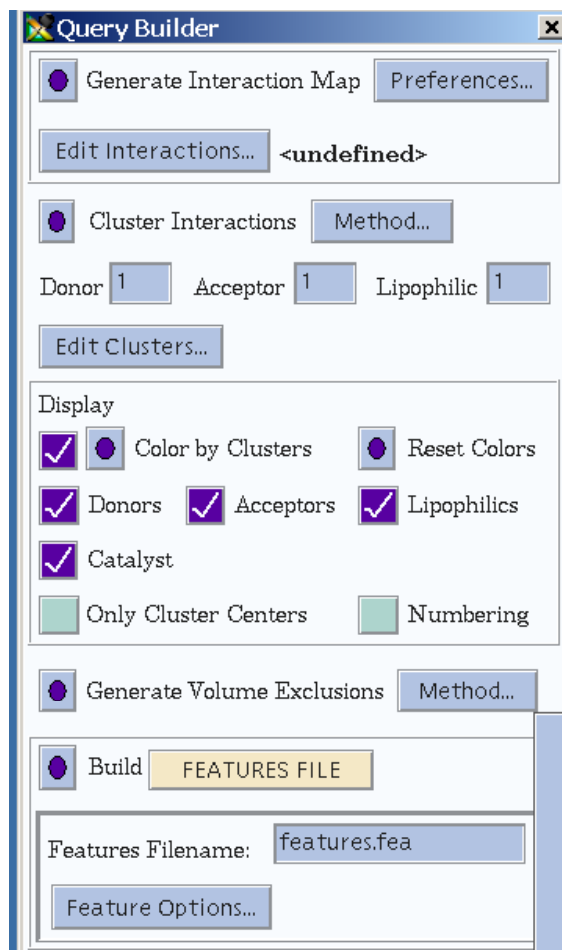
You need to define the center of the active site. So if you have a bound ligand select the ligand and then *click define center from Selected Atoms*:

You make your receptor model current and *Define it as Current Protein*. Also define the radius you want Ludi to search for interactions with the residues.

You can get Details of SBF at

http://www.accelrys.com/doc/life/cerius481/sbf/Output/sbftoc_nf.html

Once you have defined the active site then click on Query Builder:

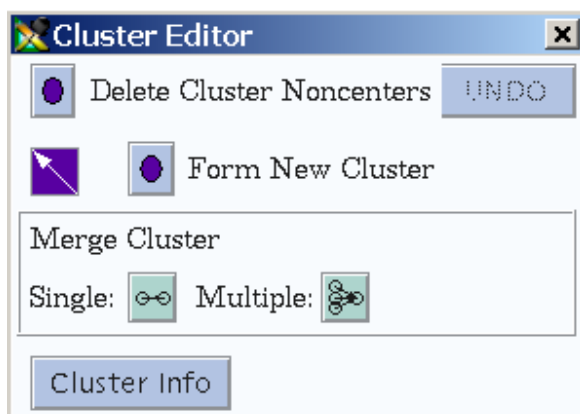


Click *generate Interaction map*. This will use LUDI in background to generate the interaction vectors.

At this point you must delete vectors that are isolated or that do not make any sense. Please spend some time here in manual editing as this is the most IMP step of FLIP. Please see the presentation on FLIP for more details.

If you are planning on using only cluster centers then enter the desired number of Donor/Acceptor and Lipophilic clusters and click *Cluster Interactions*

Please do not forget to delete the cluster Non_Centers. To do this click Edit Clusters



And then click on *Delete Cluster Non_Centers*

To generate a .Fea file for the receptor now just select *Build Features File* from drop menu at the bottom. This will generate a feature file for your target receptor.

Now you need to convert this into a 3D fingerprint file. To do this you go back to *QSAR/Descriptor/3D Fingerprints* and select *Create 3D fingerprint File*

Select your receptor .fea file that you have created previously. Then select only **Donor/Acceptor and Hydrophobic and De-Select everything else.**

Select the options that you want and then click on *Create 3D FingerPrints File*

Step III: Analysis:

Analysis was performed using two methods:

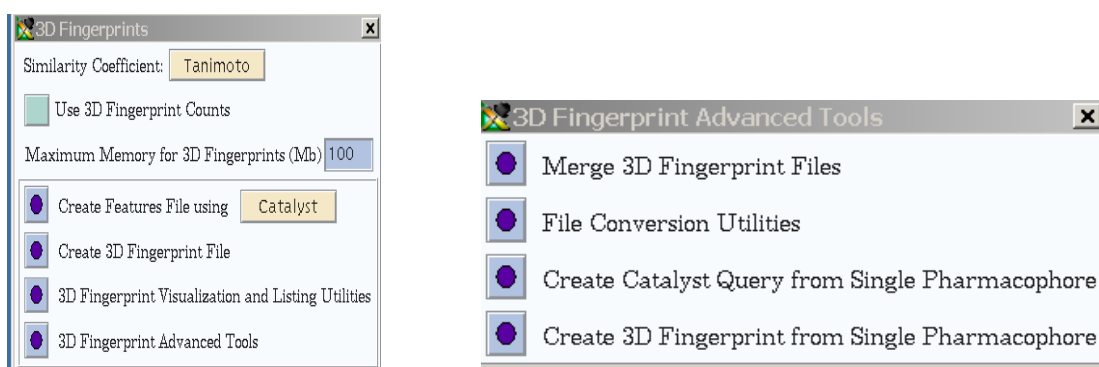
1. Compute similarity coefficients (Tanimoto, Dice, Ochiai, Hamming) between active site fingerprint and fingerprint for each molecule in CATALYST database. Top N% of compounds can be selected by ranking the compounds collection in descending order based on the similarity coefficient
2. Another technique that uses the fingerprints OnBits metric within Cerius2 CombiChem tools can be used with both 2D and 3D fingerprints. It is based on generating a "modal fingerprint" for a set of *N* molecules, in which a bit is **on** if it is present in at least one molecule in the set. The modal 3D fingerprint of the candidate library is compared with the modal fingerprint of the reference library, reporting the number of **on** bits in each library, the number of common bits, the number of **on** bits in the candidate library not present in the reference library, and the number of **on** bits in the reference library not present in the candidate library. Options in the Compare Libraries 3D Fingerprints Onbits control panel allow you to list the molecules in the candidate library with **on** bits present in the reference library and to select the top *N* molecules from the candidate library (the ones with the highest number of common bits). In our study the 3D fingerprint for our

reference library will be defined by receptor and the 3D fingerprint for our candidate library will be defined by a virtual compound collection

Method 1:

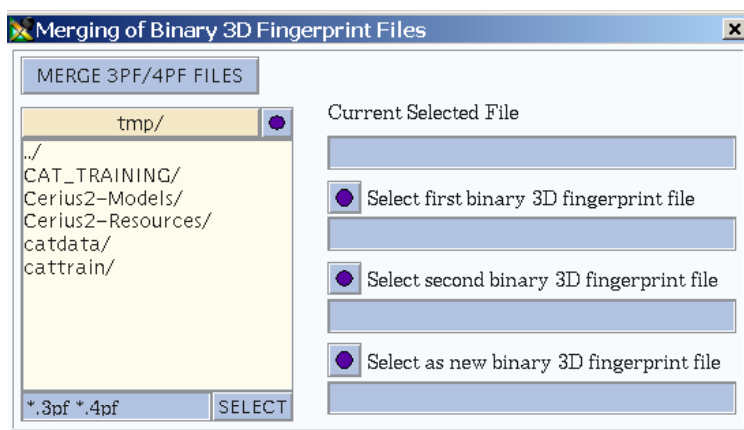
For using method 1 you need to dump in all the fingerprint data into C2. Study and then select molecules having highest similarity to target fingerprint.

To do this first you need to merge the two 3D fingerprint files for receptor and the virtual library.



Select *QSAR/Descriptor/3D Fingerprints* and then select *3D Fingerprint Advance Tools*

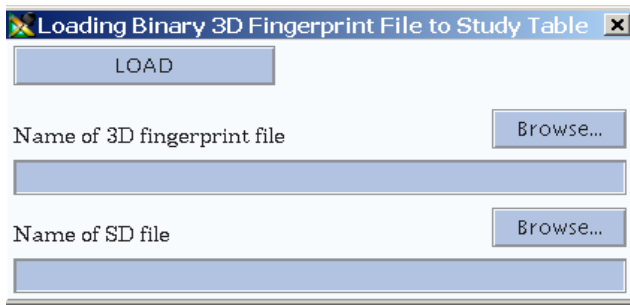
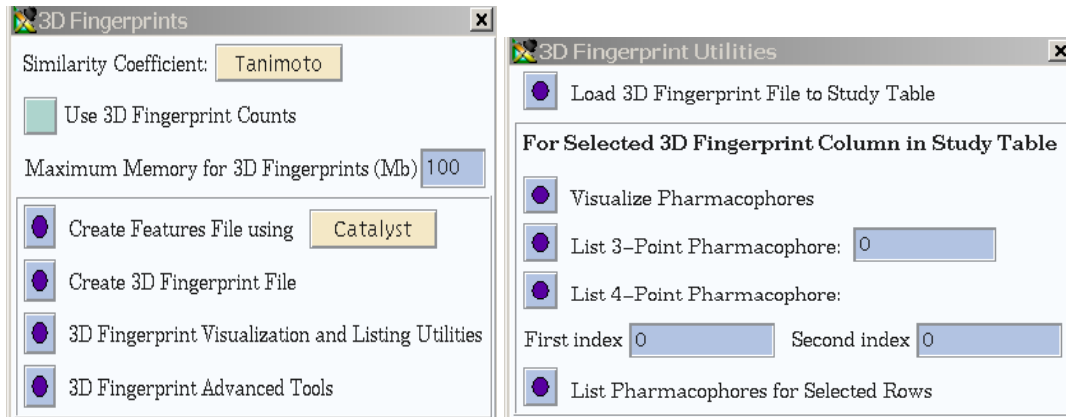
In advance tools options select Merge 3D Fingerprint Files:



Select your receptor 3D Fingerprint as First Binary 3D fingerprint and then select your virtual Library 3D Fingerprint as second binary file.

Give a name to the merged file and then click *Merge 3PF/4PF*.

Now you need to load this merged Fingerprint file into C2. To do this go back to 3D Fingerprint panel and click on *3D Fingerprint Visualization and Listing Utilities*. Under this menu click on *Load 3D Fingerprint to Study Table* and then put in the name of your merged 3D Fingerprint File.



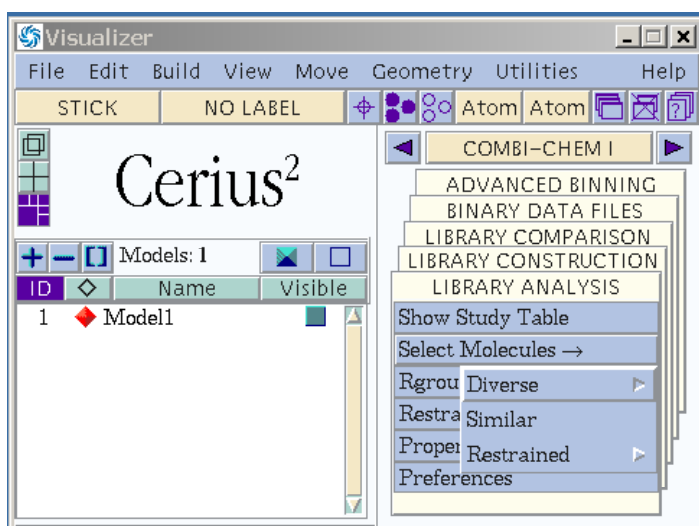
Now when you open the Study Table it will have the merged data for you where the first Row is your receptor fingerprint and below it is the virtual Library.

Select the column with heading 3DFP and mark that as X variable.

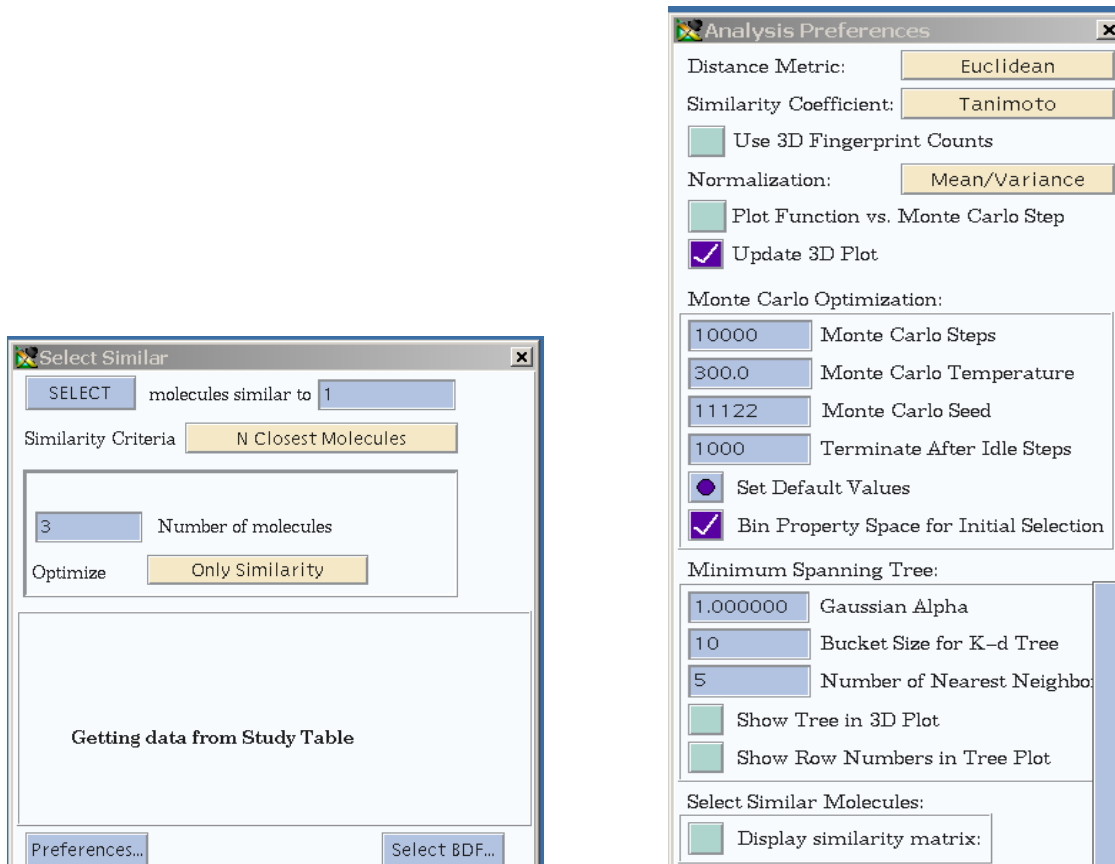
R1 C4:	Structure	Activity	Structure Name	
			Receptor	11
1. ala-S			arg-S	415
2. arg-S			asn-S	151
3. asn-S			asp-S	135
4. asp-S			cys-R	114
5. cys-R			gln-S	247
6. gln-S			glu-S	246
7. glu-S				

Now you need to run Similarity Analysis to select molecules that have highest similarity coefficient to the target fingerprint.

To do this select *COMBI-CHEM I/SELECT MOLECULES/SIMILAR*



In the Select Similar panel enter number of molecules you want to select. If you click on preferences you can change the similarity coefficient that is used for selection. Also if you want to display the entire similarity matrix click the option *Display Similarity Matrix* in the Preferences Menu



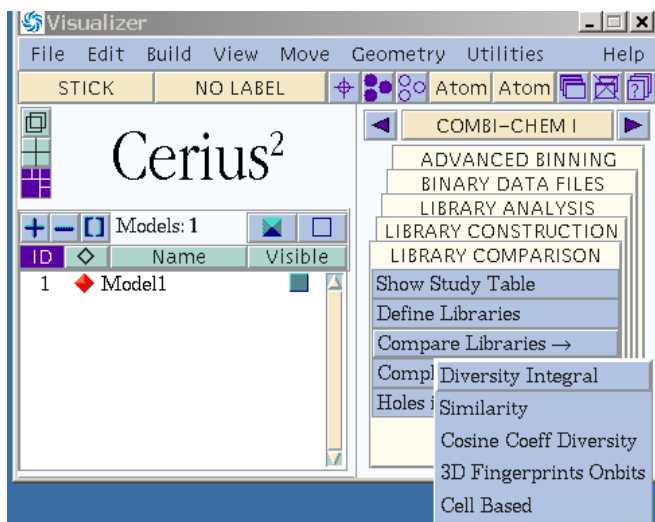
When you hit Select button the molecules rows are selected in the study table also the same information is dumped in the text port.

This Method is not ideal for huge datasets as it will choke the study table. An enhancement request has been submitted that will work directly on the binary 3D fingerprint files.

Method 2:

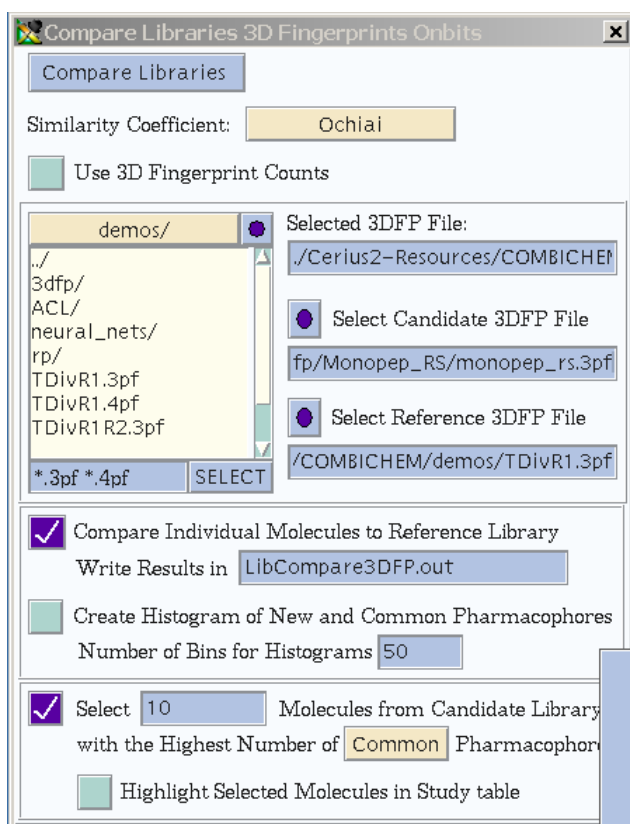
This method can be used for huge datasets as it directly works on binary fingerprint data. No need to dump the data into study table.

Select *COMBI-CHEM-1/Library Comparison/3D Fingerprint OnBits*



Select your receptor Fingerprint and Mark it as Reference. Then select your virtual Library fingerprint and mark it as Candidate.

Click option Compare Individual Molecules to Reference Library



Click option select molecules from candidate library that have highest number of **COMMON** pharmacophores.

When you click compare, most similar molecules are displayed in the text port. Also a file is created that has the profile for entire Virtual Library compared to target fingerprint.