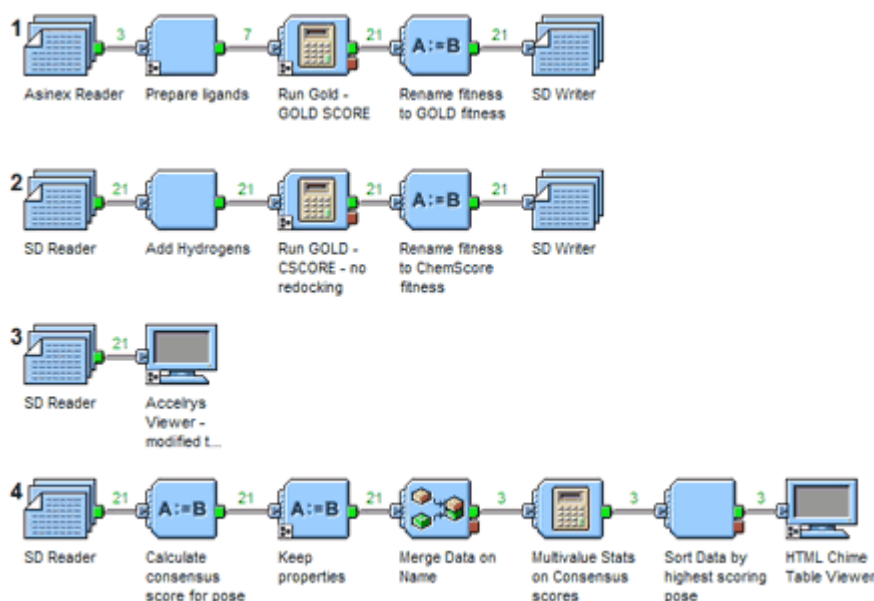




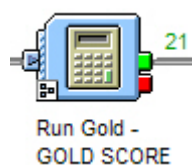
Automation of Docking and Scoring Runs

A rate limiting step in structure-based virtual screening is often the need for the computational expert to process molecules proposed by members of a project team through the docking models. With Pipeline Pilot you can automate this task, and optionally place it in the hands of your project team, leaving you free to spend more time on the building and validation of models.



The virtual screening process can be separated into the model development and validation stage and then the stage in which the model is applied to proposed ligands. The first stage is a highly complex task to be performed by an expert modeler using their favored modeling software. However, once a model is developed and suitably validated, Pipeline Pilot can be used to automate the application of the model and optionally deploy the models to a user community allowing the users to process proposed ligands for themselves.

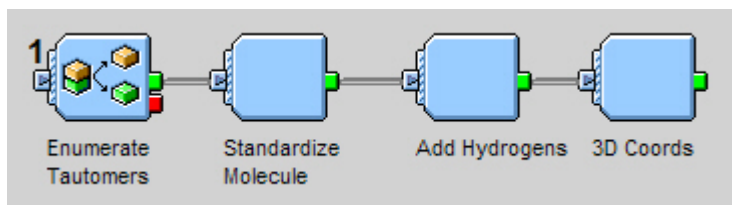
The docking and scoring process starts with the preparation of the protein structure, identification and then validation of the active site. At this point most modeling software allows you to capture that active site in some form or another (e.g. LigandFit and FlexX can store the site in a file, GOLD specifies the site as X,Y,Z and radius parameters). These representations of the active site provide the starting point for Pipeline Pilot to automate the screening process, by loading this site information into a Pipeline Pilot component specific to the docking program in use.



Parameter Name	Parameter Value
SOAP Endpoint	http://192.168.9.128:8081/GoldWebservice/services/Gold
BatchSize	21
ProteinFile	C:\Documents and Settings\ybrown.SCTEGIC\My Documents\Data collections and protoc...
NumberOfPoses	3
Settings	Library screening
UseChemScore	False
cavity_radius	14
cavity_origin_x	40.408
cavity_origin_y	8.195
cavity_origin_z	20.151

When deploying a docking model in an environment in which non-modeling experts will make use of it, it is important that the computational expert define the sequence of steps that must be performed to prepare the ligands for docking, and to post process the results into a form suitable for the end user.

- **Ligand Preparation:** Since a chemist may enter structures from a 2D sketcher or may retrieve structures from a 2D database, Pipeline Pilot would first be used to define an automated ligand preparation procedure. This may include components from the Pipeline Pilot Chemistry collection such as enumeration of tautomers, calculation of charges, correction of protonation states, removal of salts and the preparation of 3D coordinates. Alternatively, third-party software that you already own, such as CONCORD or CORINA for the preparation of coordinates may also be included in this procedure. The exact nature of the ligand preparation procedure will be determined by the requirements of the docking algorithm.



- **Automation of docking and scoring.** Using Pipeline Pilot's integration collection, your preferred docking and scoring algorithms can be incorporated as components – some integration components are already available from SciTegic (e.g. GOLD) or our (e.g. FLEXX), other can be developed by you or SciTegic services using methods from the integration collection such as SOAP or Telnet/FTP. This integration can cross machine boundaries to execute docking and scoring on remote machines. Typically a generic docking component will be populated with parameters that define a particular active site and settings and saved so that this component contains the docking models for a particular system. In this way a library of available docking models can be assembled as a collection of components.
- **Post-processing of results.** The output of a docking and scoring program will typically be a set of conformers with one or more scores. Pipeline Pilot provides all the tools necessary for the expert computational chemist to define and capture a post-processing procedure to turn this information in a form suitable for use by a project team. This may consist of automatically populating an end user program such as Accelrys DS Viewer or Tripos Lithium with docked conformations, and/or it may consist of summarizing data and presenting it in an end-user report. One example of such a post-processing might be to calculate a consensus score for each conformer, identify the highest scoring conformer of each molecule and then sort the molecules by the score of their 'best' conformer – thus presenting a prioritized list of molecules for the end user to browse.

The Structure	Name	Fitness_GOLD	Fitness_CScore	Consensus	Consensus_Mean	Consensus_StdDev	Consensus_N	Consensus_Max
	BAS 0000725	33.4077	12.1360	22.77185	13.4930666666667	5.9019530923152	6	22.77185
		24.1340	6.0698	15.1019				
		15.8949	-0.3463	7.7743				
		22.1133	10.4438	16.27855				
		21.4663	7.3854	14.42585				
		9.3930	-0.1811	4.60595				
	BAS 0000525	22.4761	20.5914	21.53375	16.0533	4.02369973055479	3	21.53375
		14.7165	9.2573	11.9869				
		13.4369	15.8416	14.63925				
	BAS 0000636	30.0843	9.7402	19.91225	13.052575	5.25201789702064	12	19.91225
		25.7154	6.2865	16.00095				
		15.3849	-1.5780	6.90345				
		17.0251	5.7475	11.3863				
		12.5738	4.4946	8.5342				
		6.8162	-0.3189	3.24865				
		27.4999	5.2876	16.39375				
		27.3228	8.1300	17.7264				
		22.8204	12.9838	17.9021				
		26.3647	6.3397	16.3522				
		19.3332	12.2509	15.79205				
		15.7900	-2.8328	6.4786				

This entire procedure can be deployed as a web application in Pipeline Pilot Pipeline Pilot Web Port, or any Pipeline Pilot Web Portal that you already maintain; alternatively it can be called from a thick client already familiar to your end users such as DS

Viewer from Accelrys or Benchware 3D Explorer from Tripos.

scitegic Pipeline Pilot Webport
Pipeline Pilot 5.1.0.100 Logged in as rbrown Library Protocol Jobs He

Parameters Help VirtualScree...

virtual screening w

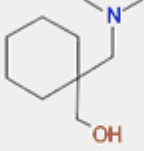
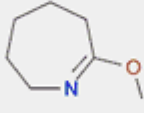
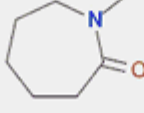
Run Bayesian, RP and Dock

ActivitiesToCalculate:
MAOInhibitorLike
EstrogenAntagonist
RP_NCI_5K
1A1E

SD File to Screen:
data\MAO\mao.sd

Maximum Mols to Screen:
10

Submit

Molecule	Name	EstrogenAntagonist	MAOInhibitorLike
	89	-0.3	-0.9
	92	-9.1	-8.3
	93	-5.2	-10.2

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