

Catalyst[®] Migration to Discovery Studio[®] An Overview

Pharmacophore Modeling in Discovery Studio

- Discovery Studio provides protocols and tools that allow you to:
 - Generate conformation models for use in pharmacophore modeling
 - Generate pharmacophores from proteins
 - Generate pharmacophores from ligands
 - Fit and Map ligands against a pharmacophore
 - Create databases
 - Search databases using pharmacophores

DS Catalyst in Discovery Studio 1.7

- Protocols:
 - Conformer generation (**catConf**): Diverse Conformation Generation
 - HipHop (**catHypo**): Common Feature Pharmacophore Generation
 - HypoGen (**catHypo**): 3D QSAR Pharmacophore Generation
 - HypoRefine (**catHypo**): Steric Refinement with Excluded Volumes
 - Structure Based Pharmacophore Modeling (via **Ludi**): Interaction Generation and Convert Interactions to features
 - Compare/Fit (**citest**): Ligand Pharmacophore Mapping and Pharmacophore comparison
 - Database building (**catDB**): Build 3D Database
 - Database searching (**catSearch**): Search 3D Database
 - Shape searching (**catShape**): Search by Shape

DS Catalyst Modules

Pharmacophore Analysis
DS Catalyst Conformation
DS Catalyst DB Build
DS Catalyst DB Search
DS Catalyst Hypothesis
DS Catalyst SBP
DS Catalyst Shape
DS Catalyst Score

Catalyst in Discovery Studio 1.7

- Examples of benefits:
 - Windows and Linux
 - UNDO ability
 - Easy Copy/Paste
 - Easy replacement of features and coordinates
 - Easy integration with docking/scoring
 - Opaque visibility option for non-mapped features
 - Combined structure and ligand-based design
 - Ligand-based pharmacophore
 - Receptor-based pharmacophore
 - Improved Visualization, Analysis and Reporting

And Much More !

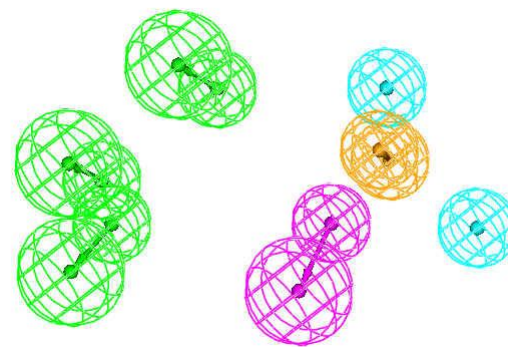
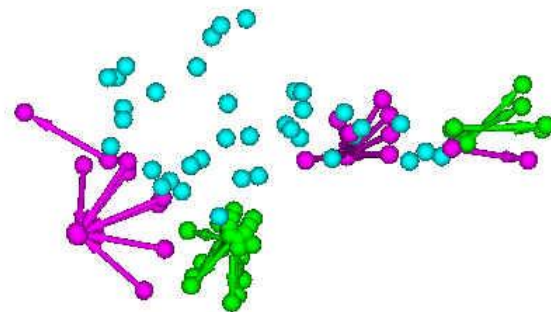
Pharmacophore Generation

- Automated pharmacophore perception from Catalyst[®] technology:
 - Common feature pharmacophore generation
 - HipHop
 - 3D QSAR pharmacophore generation
 - HypoGen
 - Automated model refinement
 - HypoRefine

- Manual construction from feature mapping on one or several aligned compounds

Pharmacophore Generation

- Protein-structure based pharmacophore generation
 - Uses Ludi to detect accessible interaction sites
- Sketch a pharmacophore model using the [Query toolbar](#)



Pharmacophore Protocols in Discovery Studio

- 3D QSAR Pharmacophore Generation
- Build 3D Database
- Common Feature Pharmacophore Generation
- Convert Interactions to Features
- Diverse Conformation Generation
- Feature Mapping
- Interaction Generation
- Ligand Pharmacophore Mapping
- Pharmacophore Comparison
- Screen Library
- Search 3D Database
- Search by Shape
- Steric Refinement with Excluded Volumes

Pharmacophore Feature Definitions

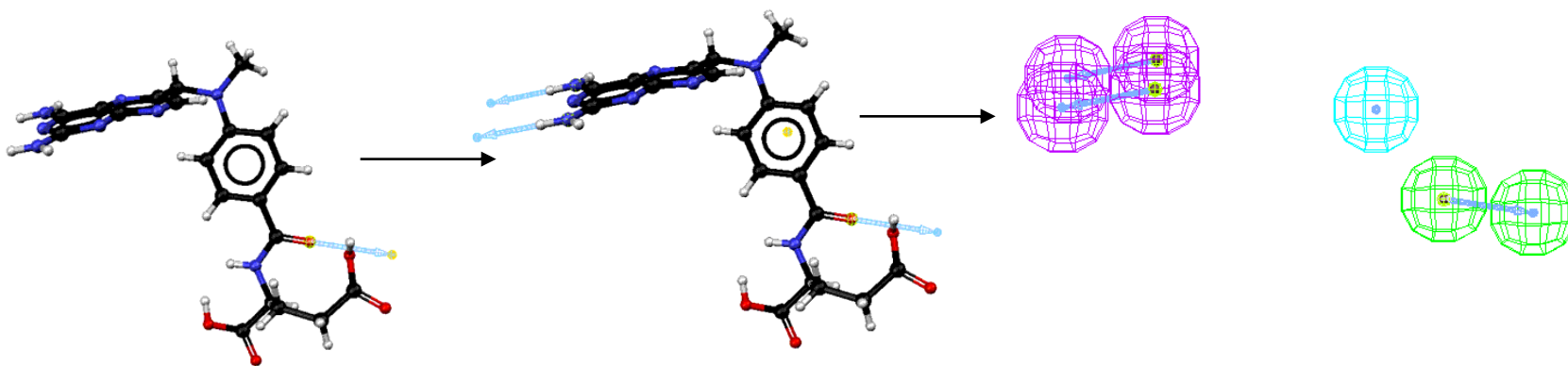
- Eleven standard pharmacophore features available in Discovery Studio
 - HB Acceptor
 - HB Acceptor (lipid)
 - HB Donor
 - Hydrophobe
 - Hydrophobe Aliphatic
 - Hydrophobe Aromatic
 - Ionizable Positive
 - Ionizable Negative
 - Charged Positive
 - Charged Negative
 - Ring Aromatic

Pharmacophore Features

- Situation at pH=7.0
- Each feature is represented by
 - one or two points in three-dimensional space
 - a single point
 - a vector with a directional component
 - projected point of Donors and Acceptors can NOT be directed towards the interior of the molecule
 - a tolerance
- Features must be solvent accessible
 - mapping is conformer dependant

Show function mapping: Catalyst way

- Currently in Catalyst
 - Limited to one feature at a time
 - Limited to one conformer at a time



Feature Mapping Protocol in Discovery Studio

- Computes all possible pharmacophore feature mappings for the selected ligands and features
 - A maximum of 1000 pharmacophore features will be enumerated.
- The generated `Query.chm` file contains all possible solvent-accessible pharmacophore features for the input ligands
 - Open this file in a Graphics View
 - Optionally, open the input ligands in the same Graphics View to view the pharmacophore features aligned to the input ligands
- You may use the [Pharmacophore tool panel](#) to:
 - Create a template pharmacophore from the features, or
 - Cluster the features to create a pharmacophore

Feature mapping: a new approach

Pharmacophore tools

NAIDS_COX2_01 - 3D Window

Pharmacophore

Select Feature

Current Feature: Acceptor

Show/Hide

Acceptor Location Spheres

All Non-Features

Cluster

Cluster Current Feature

Show Only Cluster Centers

Keep Only Cluster Centers

Edit

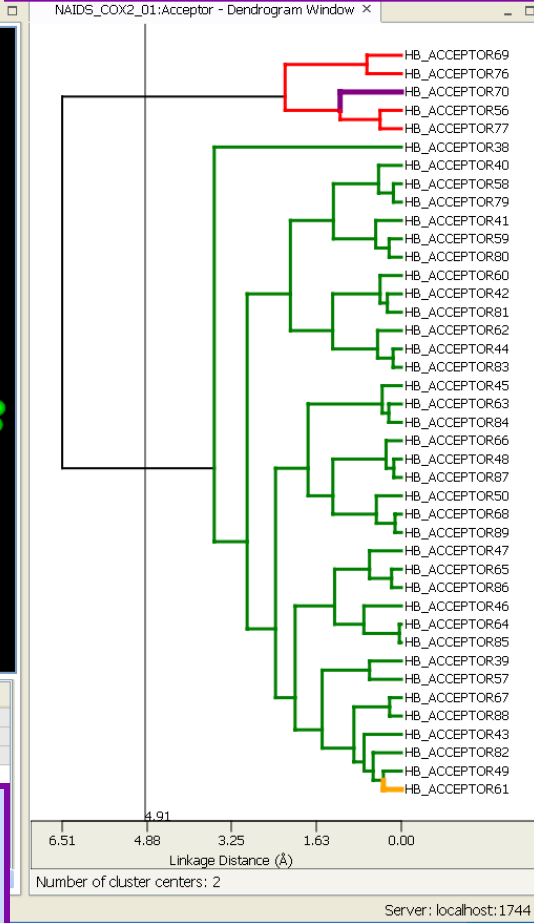
Keep Current Feature Selections

Merge Hypotheses

Name	ID	Color	Parent
1 Celecoxib	0	<input type="checkbox"/>	
2 Rofecoxib	0	<input type="checkbox"/>	
3 Valdecoxib	0	<input type="checkbox"/>	255 255 255

Modify Conformation
Binding Site

Interactive dendrogram for feature clustering



Function mapping on multiple aligned ligands

Query Toolbar

- Used for manual query creation



- Query Atom
- Query Bond
- Acceptor Feature
- Donor Feature
- Centroid Feature
- Point Feature
- Point Offset Feature
- Point Normal Feature
- Aromatic Ring Feature
- Location Constraint
- Exclusion Constraint
- Distance Constraint
- Angle Constraint
- Dihedral Constraint
- Plane Constraint
- Shape Constraint

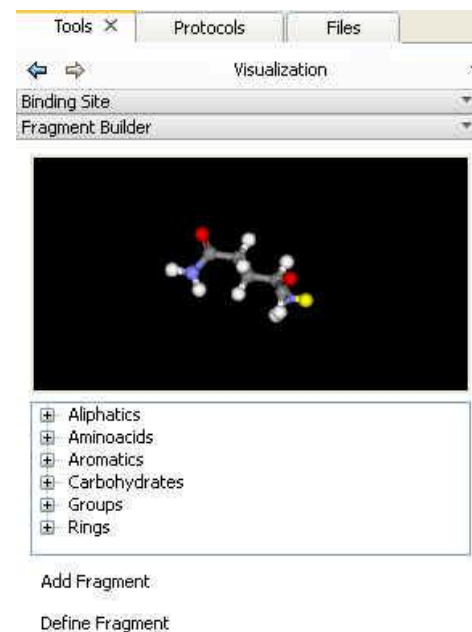
Pharmacophore Modeling

Before hypothesis generation you generally need to:

- Construct or import molecules
- Generate conformational models by performing a conformational search

Fragment Builder Tool Panel

- Allows you to build 3D molecules in the Graphics View from existing fragments, and to define new fragments
- You can choose from the following fragment categories:
 - Aliphatics
 - Aminoacids
 - Aromatics
 - Carbohydrates
 - Groups
 - Rings



Diverse Conformer Generation Protocol

- Uses the two algorithms from catConf
 - BEST (poling)
 - FAST
- A third method based on the divide and conquer approach (CAESAR) is provided with DS 1.7 via Pipeline Pilot Client

The screenshot displays the Accelrys Discovery Studio interface. The central 3D window shows a molecular structure with a highlighted conformer. Below the 3D view, there are two tables of conformer data. The left table is labeled 'Input Ligand table' and the right table is labeled 'conformer table'. The 'Input Ligand table' has columns for Structure, Name, Index, Absolute Energy, and Relative Energy. The 'conformer table' has columns for Structure, Name, Index, Absolute Energy, and Relative Energy. The 'Jobs' panel at the bottom shows the 'Diverse Conformation' protocol settings, including 'Maximum Conformations' set to 255, 'Advanced' checked, 'Save Intermediate Files' unchecked, and 'InName' set to '{Input Ligands}'. The server information 'Server: localhost:1744' is visible in the bottom right corner.

Structure	Name	Index	Absolute Energy	Relative Energy
7	Celecoxib	236	54.5682	2.57503
8	Rofecoxib	242	59.5767	0.293295

Structure	Name	Index	Absolute Energy	Relative Energy
1	Rofecoxib	237	59.2916	0.00823707
2	Rofecoxib	238	59.2834	0
3	Rofecoxib	239	59.6267	0.343316
4	Rofecoxib	240	59.5662	0.282895
5	Rofecoxib	241	59.5949	0.311547
6	Rofecoxib	242	59.5767	0.293295

Jobs Help x

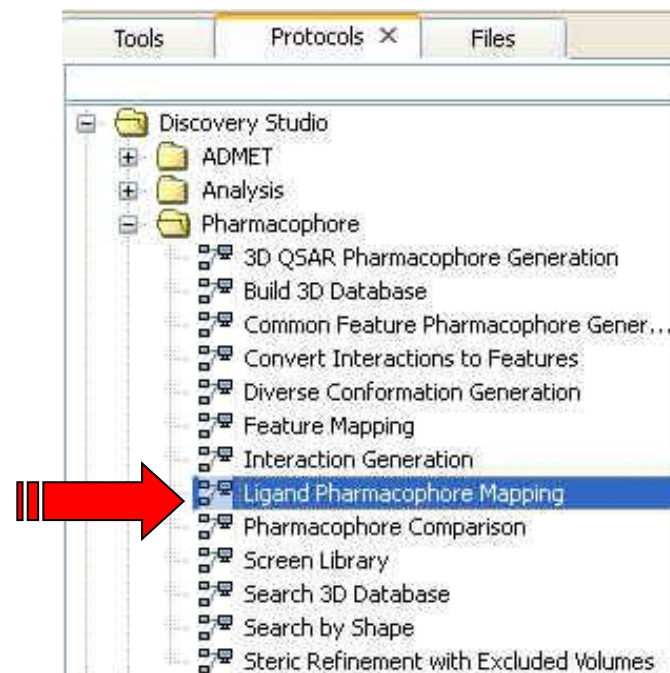
Diverse Conformation
This protocol calculates 3D conformations.

Maximum Conformations: 255
 Advanced
 Save Intermediate Files
 InName: {Input Ligands}

Server: localhost:1744

Ligand Pharmacophore Mapping

- Compare/Fit (citest)
- The **Ligand Pharmacophore Mapping** protocol compares a set of ligands to a pharmacophore
- The relevant ligand-pharmacophore mappings are exported aligned to the pharmacophore



Ligand Pharmacophore Mapping

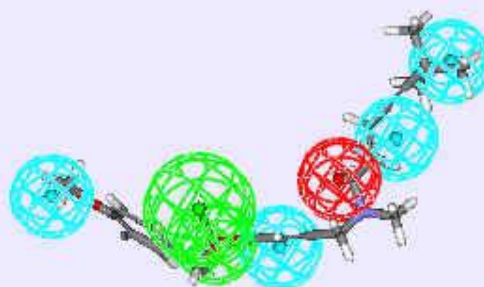
- A set of mappings between the pharmacophore features and matching features in the conformers of the molecule is calculated
- You can require that all features must map to a corresponding feature on the ligand or you can consider mappings of a subset number of features
 - Controlled by the [Maximum Omitted Features](#) parameter
 - E.g. if this parameter is set to 1, Discovery studio considers mappings of the ligands with N features of the pharmacophore and N-1 features of an N feature pharmacophore
 - A value of -1 for this parameter instructs Discovery Studio to use all combinations of feature subsets

Ligand Pharmacophore Mapping

- The pharmacophore-ligand mappings are then fitted to minimize the distance between the pharmacophore features and the mapped atoms on the ligand
 - The fitting is done using the algorithm published by Kabsch ([1978](#))
- Three types of fitting methods
 - **Rigid fitting** - the conformations are held rigid and the best fit is computed using the Kabsch algorithm
 - **Flexible fitting** - the conformers are manipulated within a specified energy threshold to minimize the distances between pharmacophore features and mapped atoms on the molecule.
 - **None** - no manipulation of the conformation is done and no Kabsch fitting is done either, instead, the fit value between the pharmacophore and ligand is computed in the current pose
- The best fitting mappings with multiple conformations are optionally returned

Ligand Pharmacophore Mapping

Visualization of ligand pharmacophore mappings



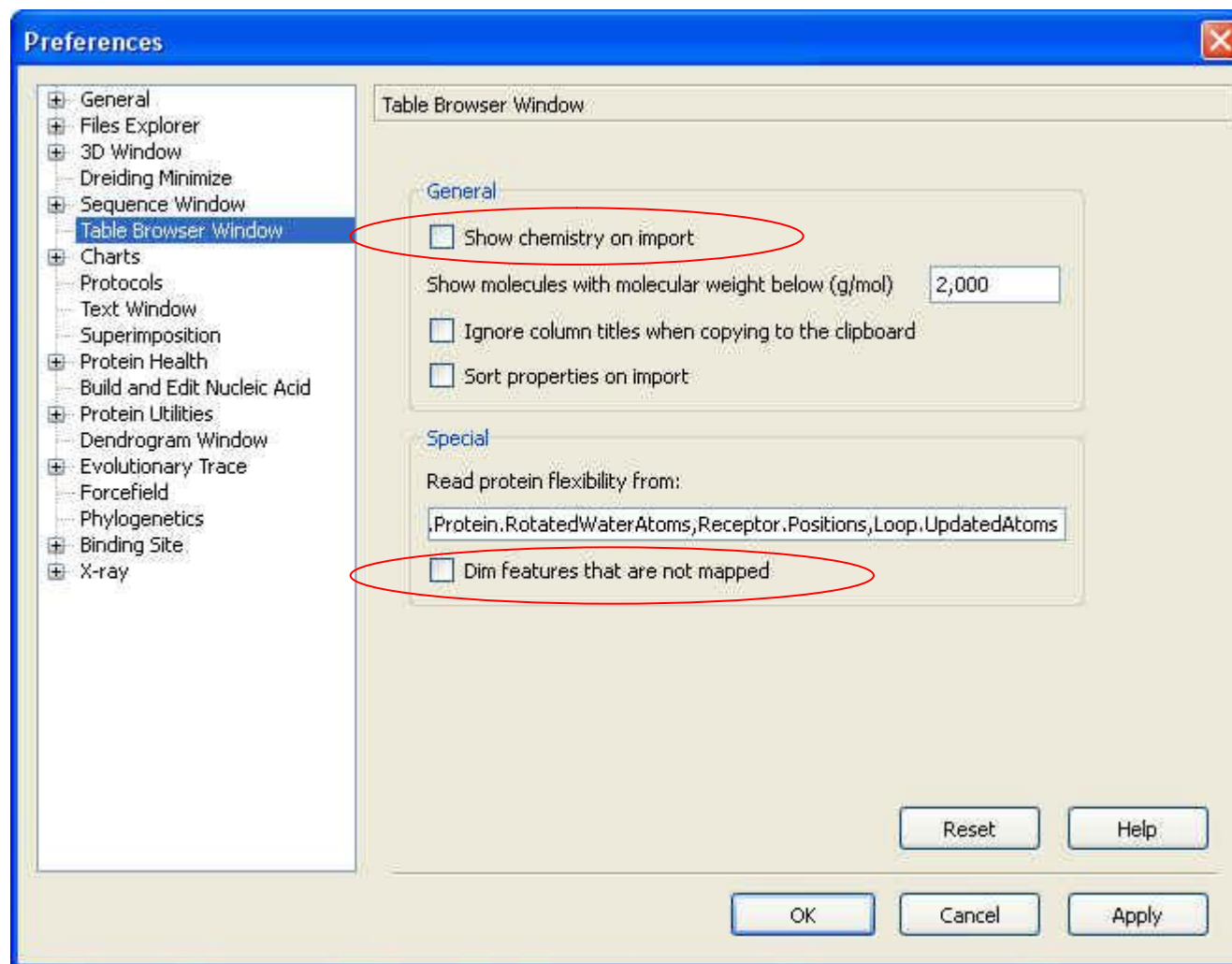
Structure	Name	Fit Value	Pharmprint	PosIonizable_10	HYDROPHOBIC_21	HYDROPHOBIC_32	HYDROPHOBIC_43	HYDROPHOBIC_5
1	cpd-12	3.96953	'111111	1	1	1	1	1
2	cpd-120	2.86856	'111101	1	1	1	1	0
3	nb598	3.60104	'111111	1	1	1	1	1

Fit Value

PharmPrint

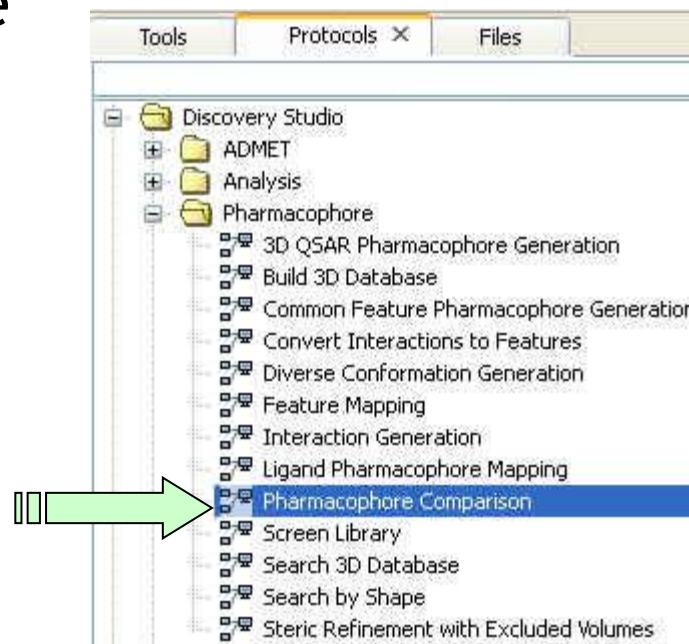
PharmType

Table Browser Window Preferences



Pharmacophore Comparison Protocol

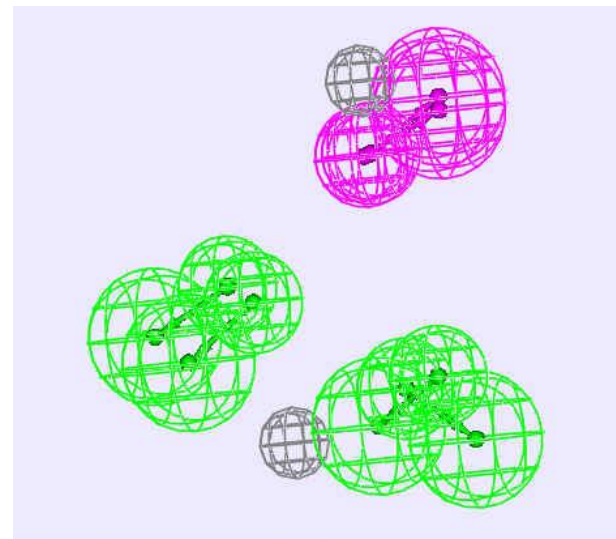
- Aligns an input pharmacophore to a reference pharmacophore and exports it using the aligned coordinates
- Double-click on **Pharmacophore Comparison** protocol to open the Parameters Explorer



Parameter Name	Parameter Value
Input Pharmacophore	
Input Reference Pharmacophore	
Advanced	

Pharmacophore Comparison Output

- **Query.chm:** This file contains all the locations of the pharmacophore features of the input pharmacophore aligned to the reference pharmacophore
- **ViewResults.pl:** Opening this file allows you to view the input pharmacophore and the reference pharmacophore aligned to the each other



Visualization

- *Visualization of Hypotheses and Fitting Molecules to a Pharmacophore*

Hands-On Exercises

- Visualization
 - *Viz 1*
 - *Visualization of Hypotheses and Fitting Molecules to a Pharmacophore*

- Building and Conformation Generation
 - *Build 1*
 - *Building a Peptide and Performing a Conformational Search*