3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019



3DEXPERIENCE®

Accelerate Science-Led Innovation for Competitive Advantage

BIOVIA Discovery Studio

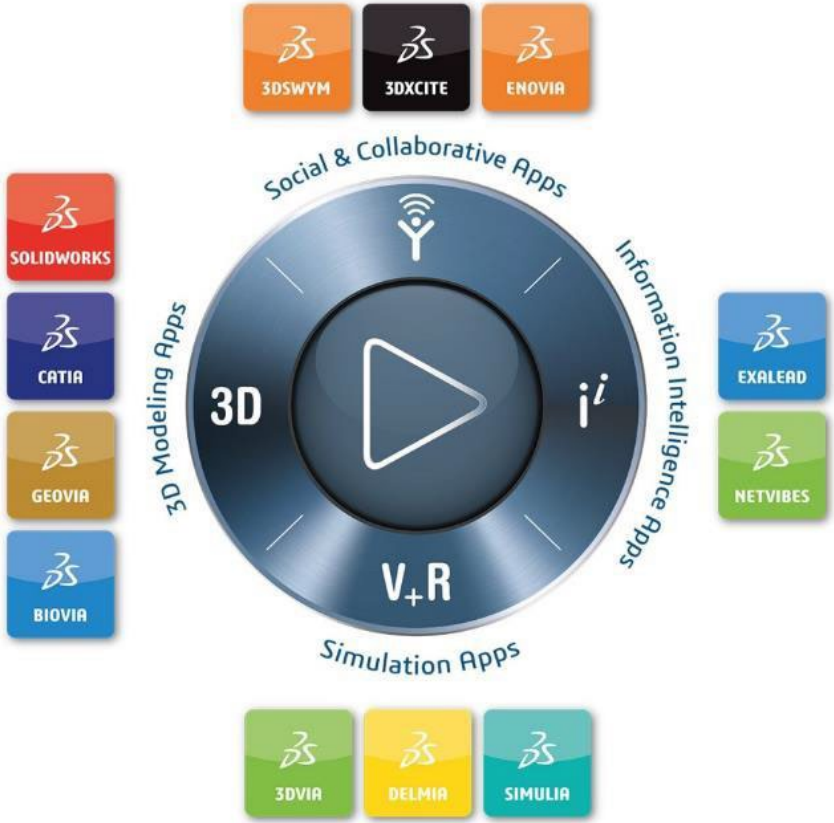
進階分子理性設計課程

創源生技 分子視算中心

經理 陳冠文 (Gene)

創源生技 GGA

DASSAULT SYSTEMES | The 3DEXPERIENCE® Company



Copyright©2019 GGA Corp., All rights reserved.

Copyright and Disclaimer

- Copyright © 2019 GGA corp. All rights reserved.
  - This presentation and/or any related documents contains statements regarding our plans or expectations for future features, enhancements or functionalities of current or future products (collectively "Enhancements"). Our plans or expectations are subject to change at any time at our discretion. Accordingly, GGA Corp. is making no representation, undertaking no commitment or legal obligation to create, develop or license any product or Enhancements.
  - The presentation, documents or any related statements are not intended to, nor shall, create any legal obligation upon GGA Corp., and shall not be relied upon in purchasing any product. Any such obligation shall only result from a written agreement executed by both parties.
  - In addition, information disclosed in this presentation and related documents, whether oral or written, is confidential or proprietary information of GGA Corp.. It shall be used only for the purpose of furthering our business relationship, and shall not be disclosed to third parties.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

GGA is part of the BIONET Group (訊聯生物科技)



CEO: Christopher Tsai, Ph.D. 蔡政憲 博士

Established: Nov. 2008

Main Product & Service Areas:

1. Genetic Testing
2. Molecular Diagnosis
3. **Scientific Informatics & Bio IT**

IPO Date: September 17, 2012

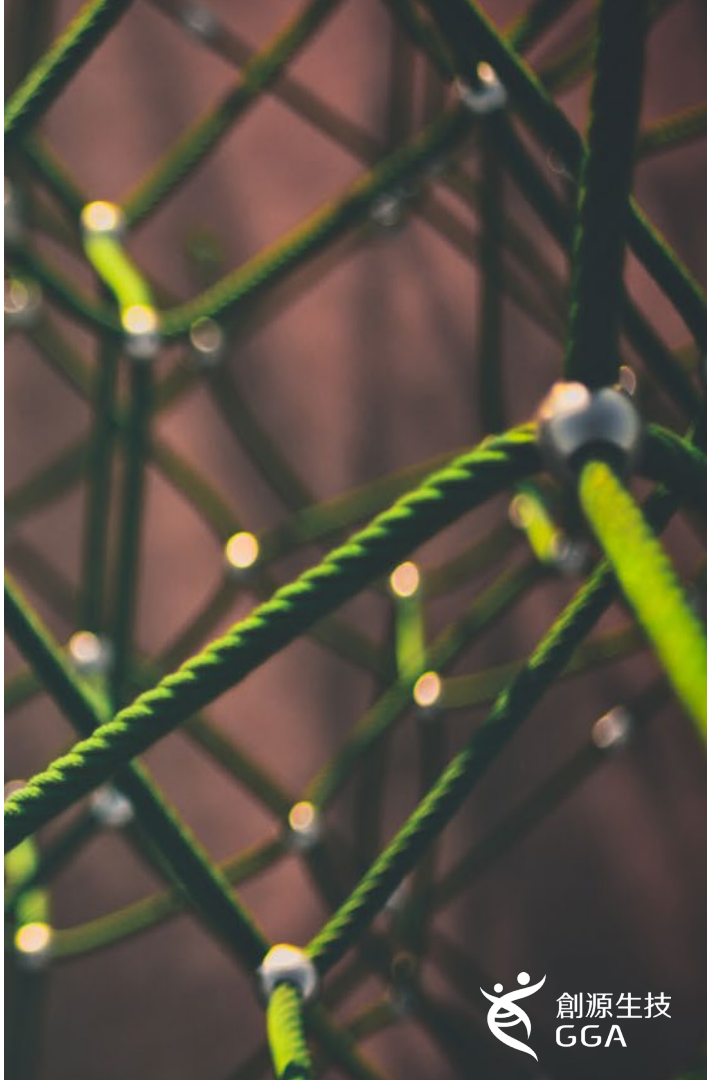
Stock Ticker: 4160 (Taiwan OTC)

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Our Vision

用科學的知識與技術，提昇台灣產業科技創新能量。





Our Mission in 2019

- ✓ High throughput screening and machine learning for electrolyte additives
- ✓ Design optimization for industry 4.0
- ✓ 整合材料模擬與電子實驗記錄系統服務 (台灣前三大石化廠)
- ✓ 執行國家型基因體分析平台建置計劃
- ✓ 連結產學界計算模擬技術

創源生技
GGA



分子視算中心

Be Your Partner

我們是由物理、化工、生物、統計、資訊等超過十位不同領域的專家組成，具備多年產業經驗。

10+

我們服務全台灣超過四十所大專院校，每年舉辦超過100場以上教育訓練課程。

100+

我們擁有包含化學、材料、生物領域，超過百萬筆資料數據，並有實際處理分析案例。

1M+

Agenda

- Briefly Overview - 10 min
- Molecular Docking Modules in DS
  - CDOCKER, LibDock, Flexible Docking
- Pharmacophore
  - Structure-based Pharmacophore
  - Ligand-based Pharmacophore
- Fragment-Based Design
- ADMET and Toxicity Prediction

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Agenda

- Briefly Overview - 10 min
- Molecular Docking Modules in DS
  - CDOCKER, LibDock, Flexible Docking
- Pharmacophore
  - Structure-based Pharmacophore
  - Ligand-based Pharmacophore
- Fragment-Based Design
- ADMET and Toxicity Prediction

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Discovery Studio Product Architecture

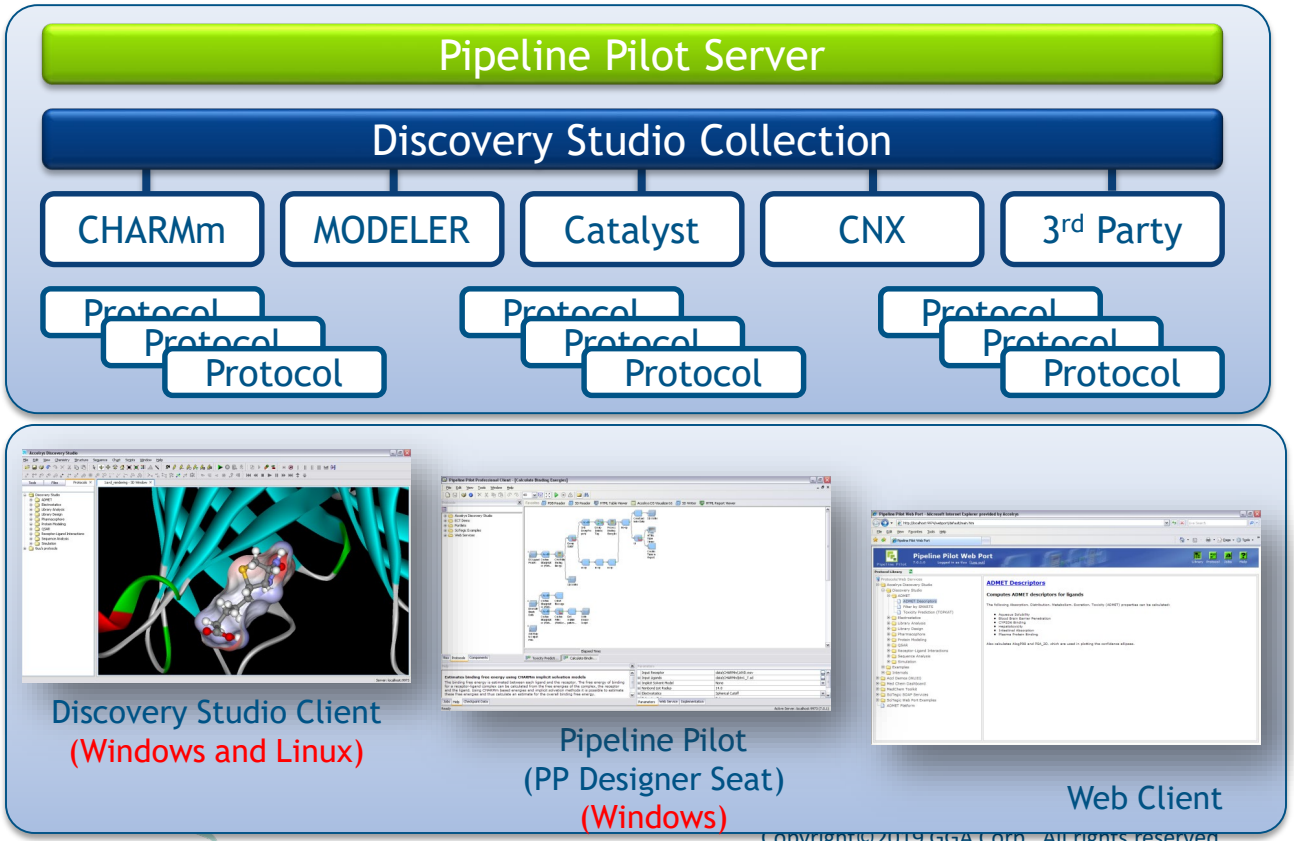
- Discovery Studio science runs on Pipeline Pilot:

- Server
  - AEP
  - PP Client
  - AEP Collections
  - DS collection
  - DS engines





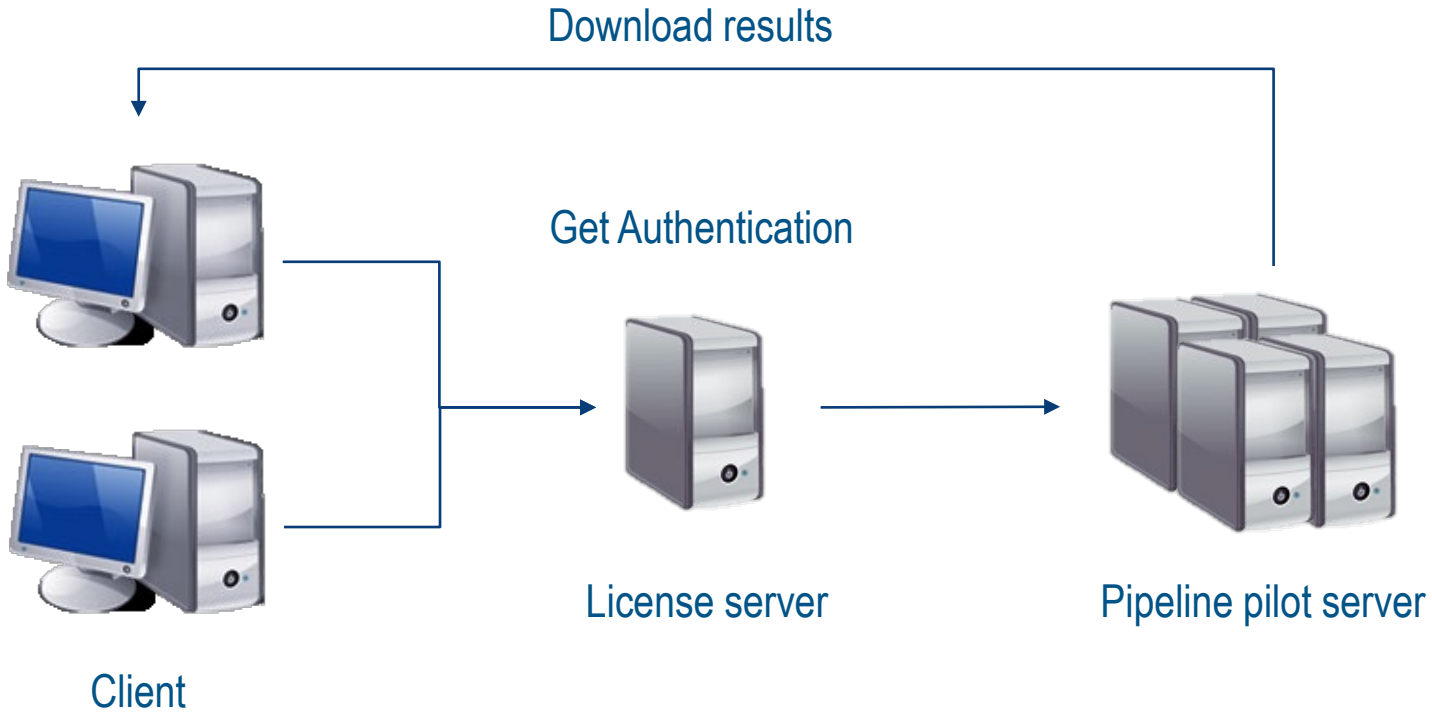
- Client(s)
  - DS client
  - PP Designer Seat
  - Web client



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright© 2019 GGA Corp., All rights reserved.

Discovery Studio Product Architecture

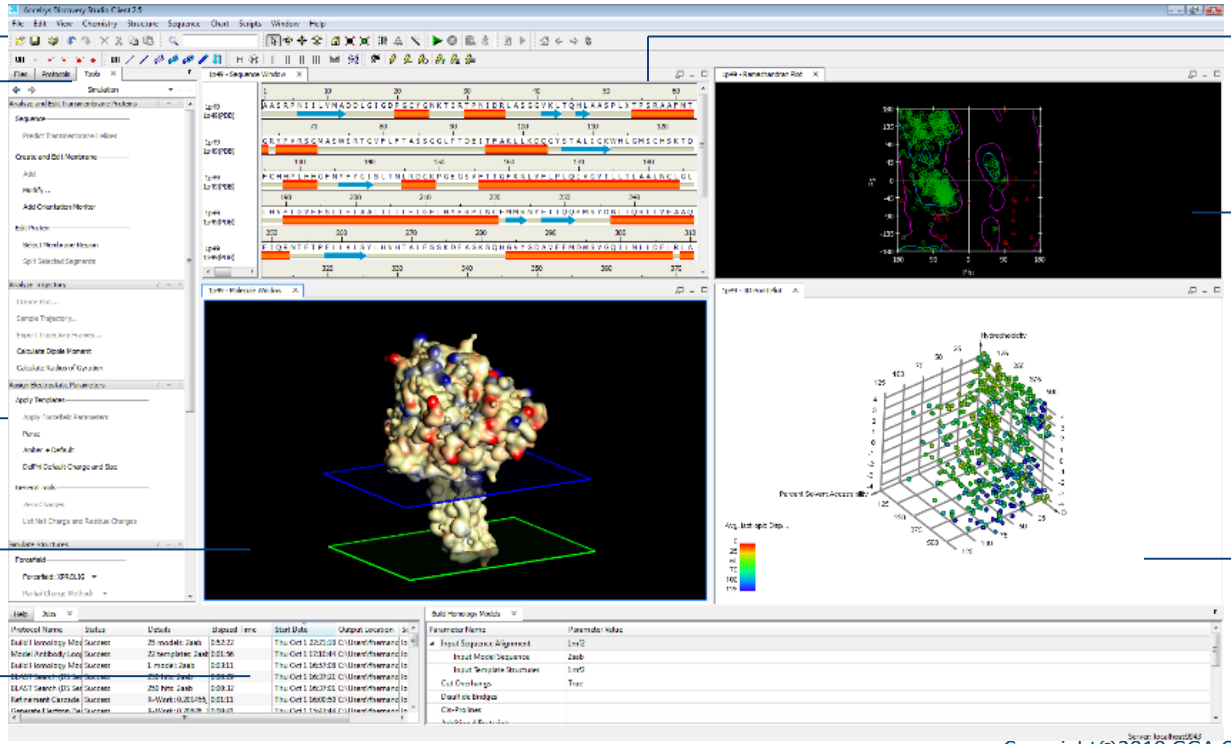


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技
GGA

Copyright©2019 GGA Corp., All rights reserved.

Supporting technology: Discovery Studio Client

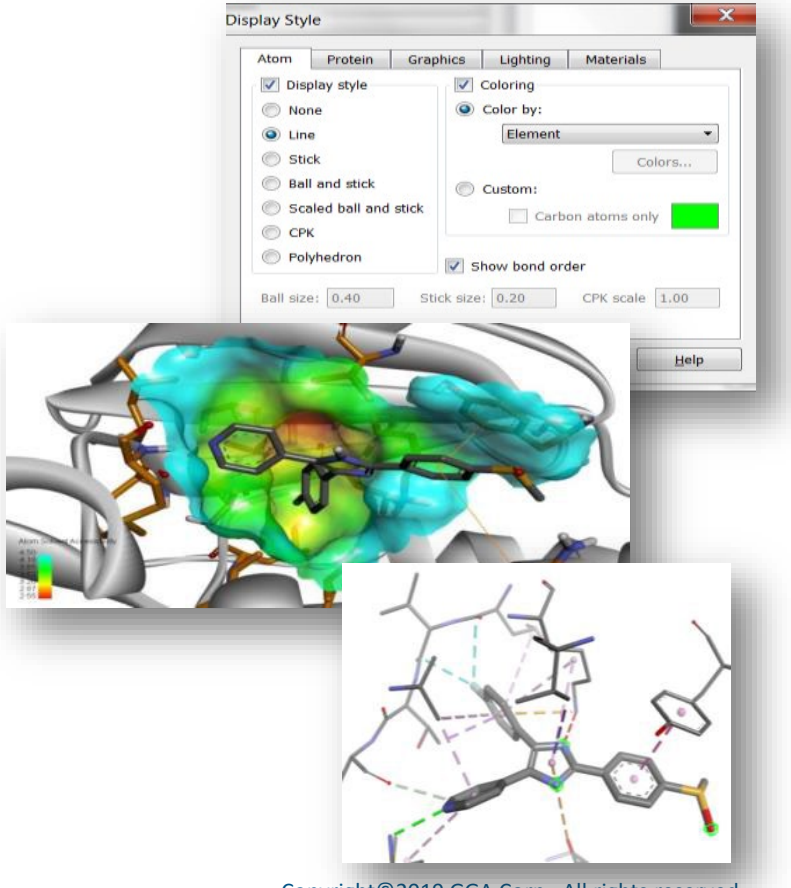


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Discovery Studio Client

- General
  - Display Style
    - Ball and Stick, CPK, Solid Ribbon
    - Surface/Protein Surface
    - Shadow
    - Clipping Plane
  - Monitors
    - Distance, Angle, and Bump
    - Interactions
    - RMSD

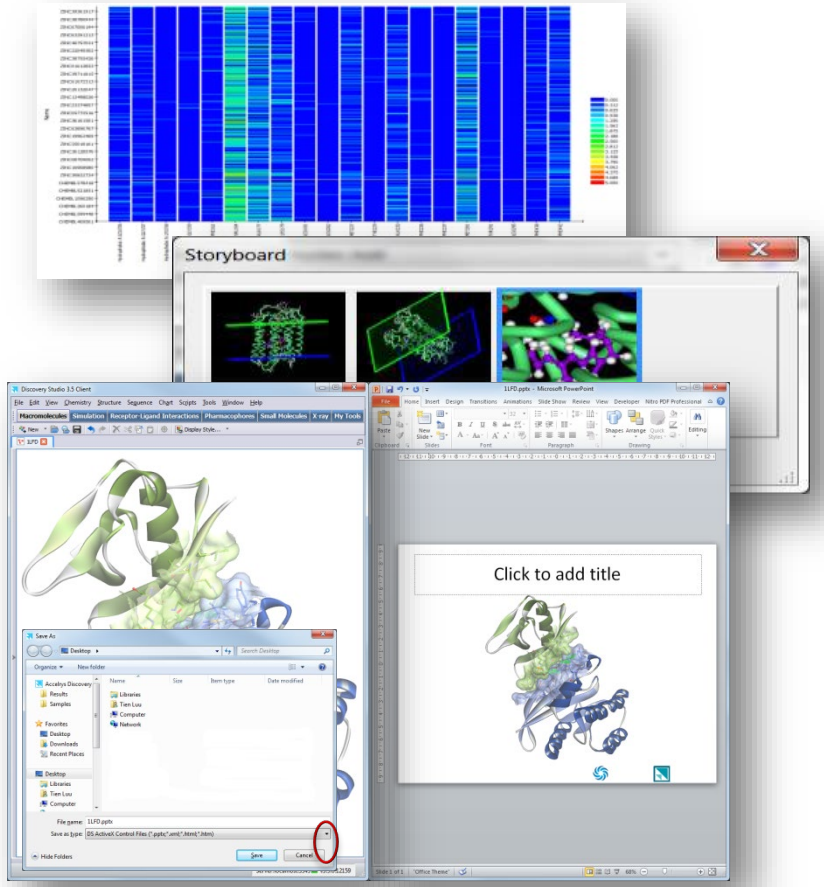


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Discovery Studio Client

- General
  - Sequence view
  - Secondary structure prediction
  - Chart functions and data plots
    - Line plots, point plot, heat maps. etc
  - Collaboration, presentation functions
    - Story board, Active X
- Protocols
  - Automation and customization
  - Perl scripting

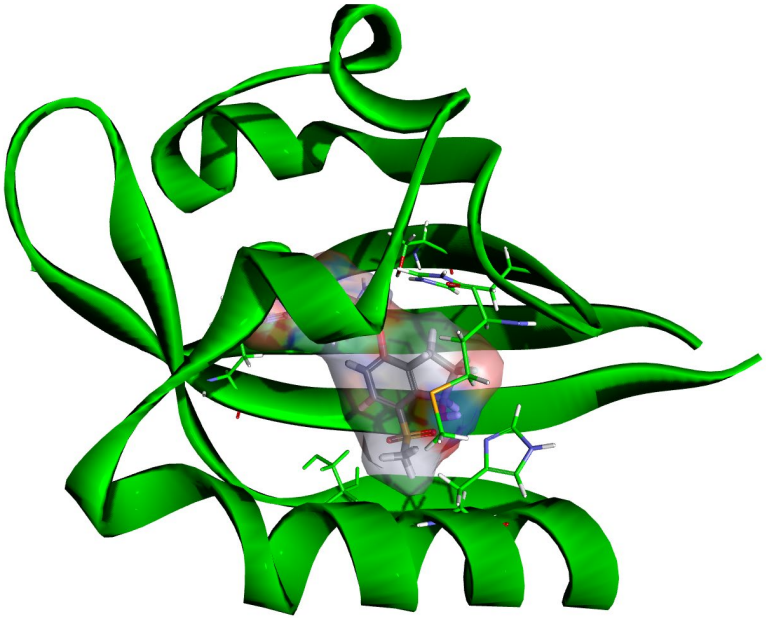


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Hands-on

- PDB code: 5TBM (HIF2 alpha)
- Atom display:
  - His248, Met252, His293
  - 79A401 (PT2385)
- Protein display
  - Solid ribbon in Green color
- Surface
  - 79A401 (PT2385)



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Agenda

- Briefly Overview - 10 min
- Molecular Docking Modules in DS
  - CDOCKER, LibDock, Flexible Docking
- Pharmacophore
  - Structure-based Pharmacophore
  - Ligand-based Pharmacophore
- Fragment-Based Design
- ADMET and Toxicity Prediction

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Rationale Small Drug Design

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 For NCKU and NTHU

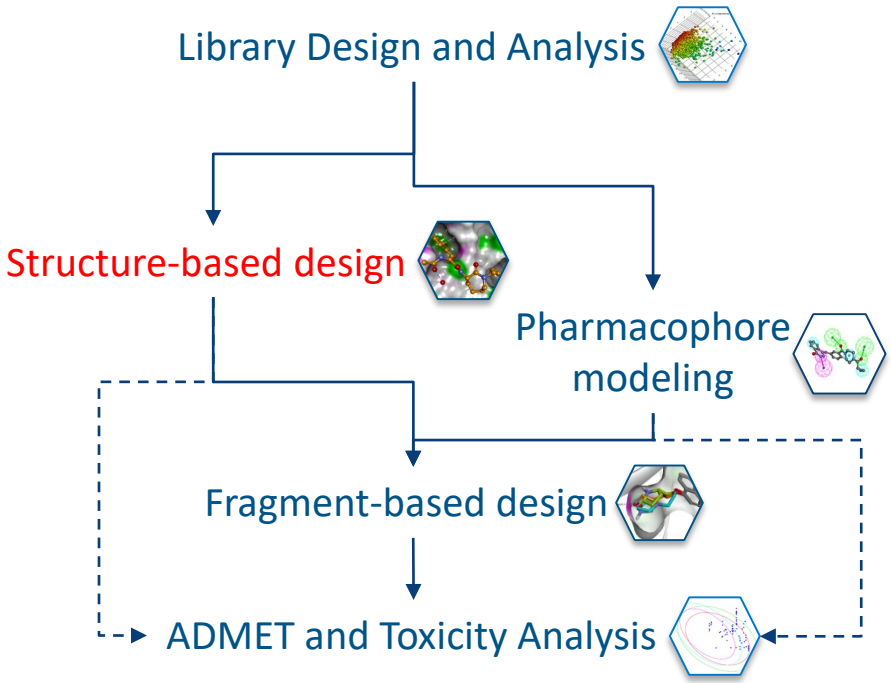
Scales

10^3~10^7 Molecules from Library

10^0~10^2 Molecules As Leads

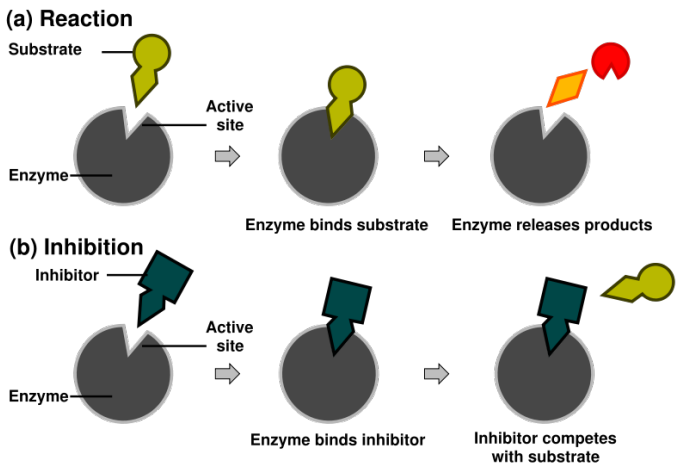
10^2~10^3 Molecules as Novel Derivatives

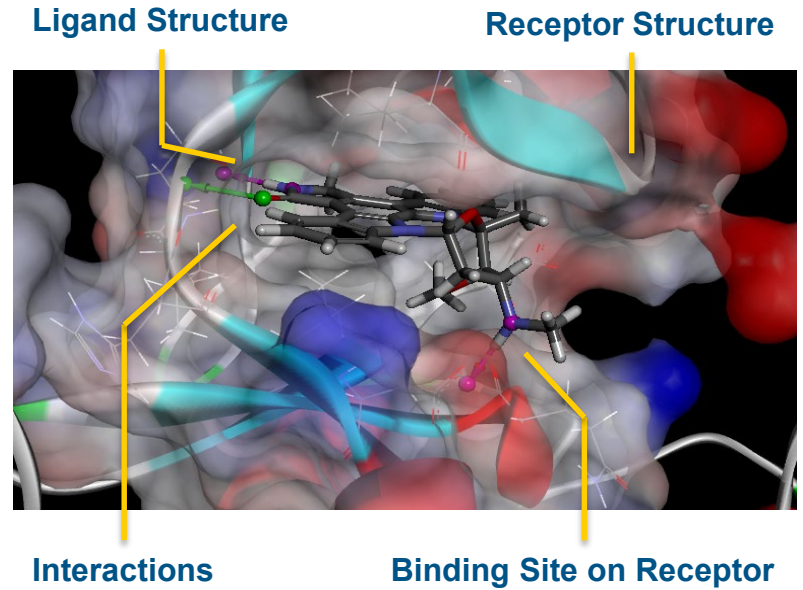
10^0~10^2 Molecules Pass ADMET and Toxicity Screening



Copyright©2019 GGA Corp., All rights reserved.

Docking & Scoring – Structure-Based Design

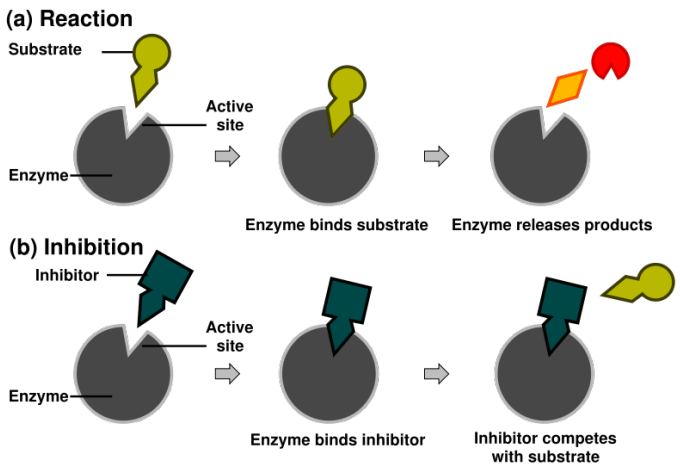


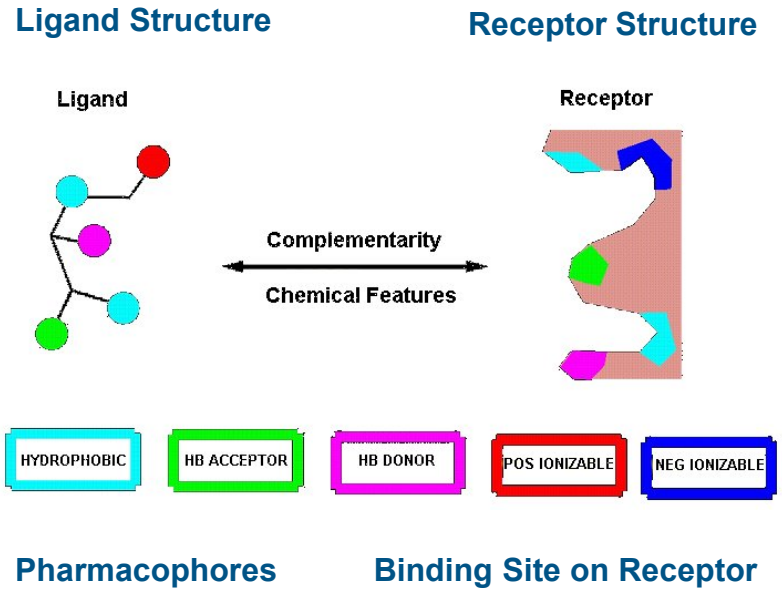


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Docking & Scoring – Pharmacophore-Based Design

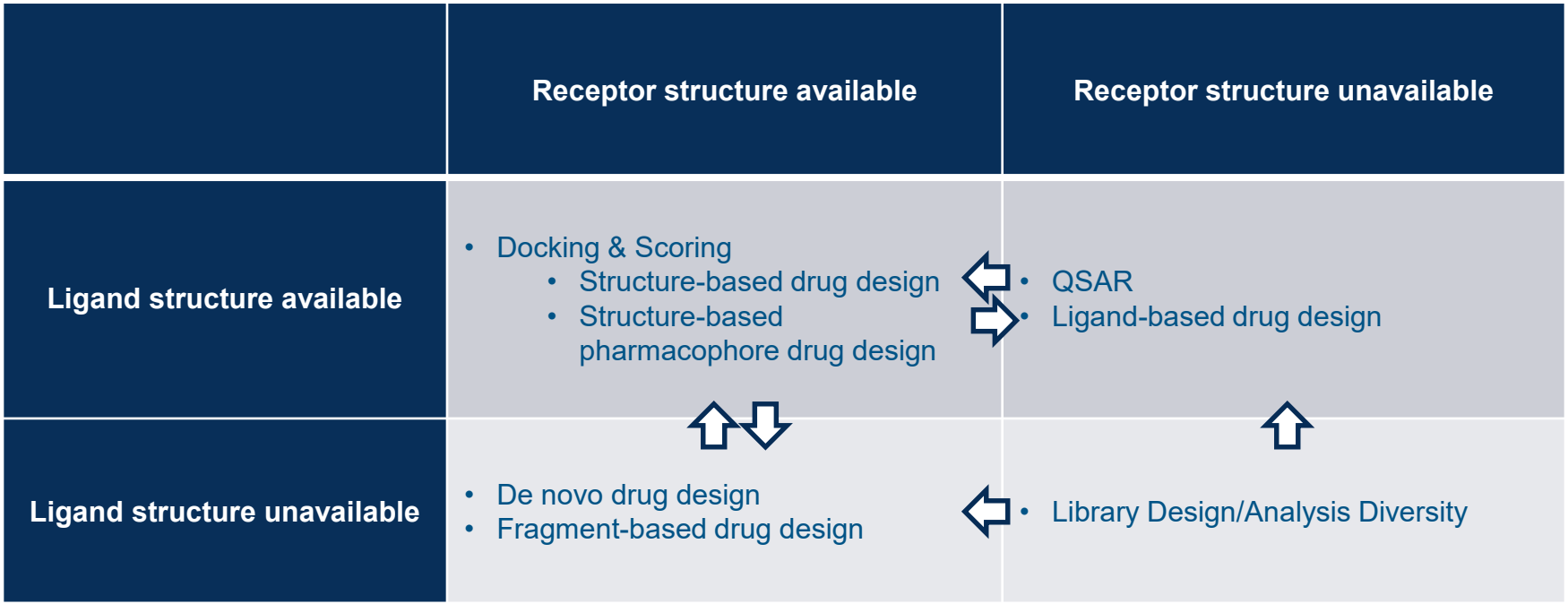




3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

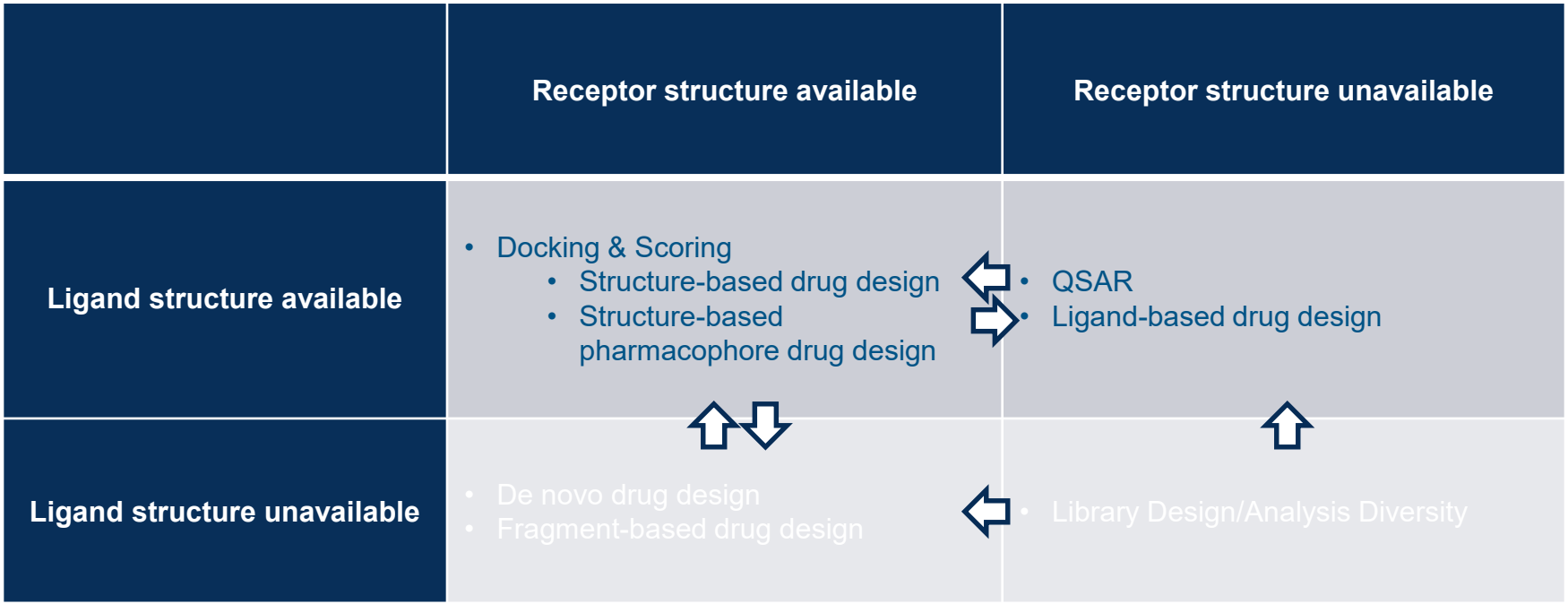
Strategy for Small Molecule Drug Design



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

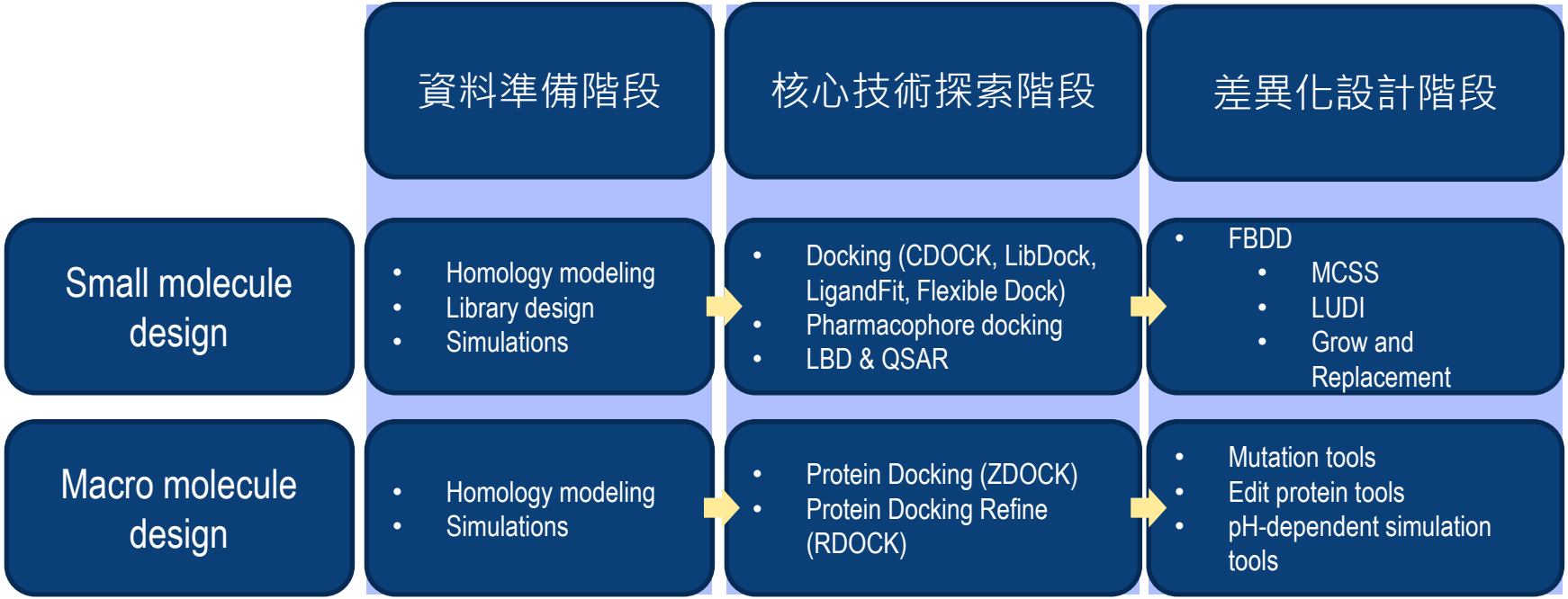
Strategy for Small Molecule Drug Design



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Product design stages

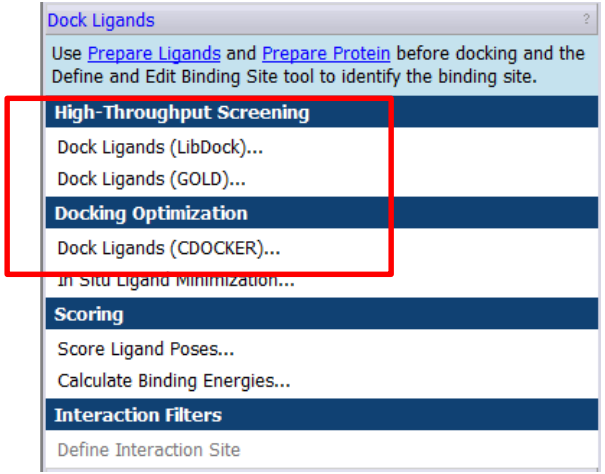


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

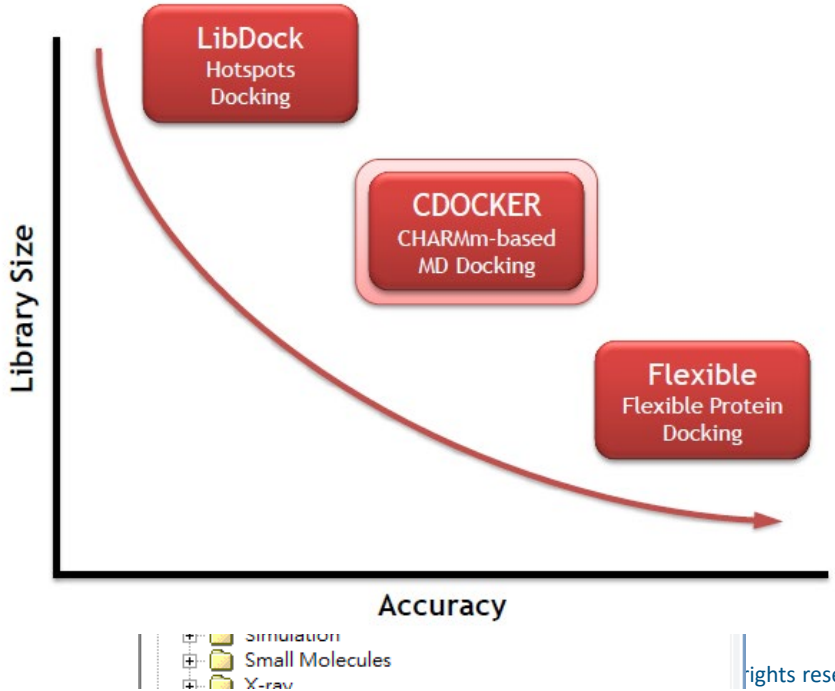
Copyright©2019 GGA Corp., All rights reserved.

Docking from Tool Panel

- Docking tools in DS
  - Dock Ligands (CDOCKER)
  - Dock Ligands (LibDock)
  - Dock Ligands (GOLD)



- Docking tools in DS (Protocol)



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

rights reserved.

Comparative performance of LibDock and CDOCKER on AstexDiverse dataset

Method	% Docked Accurately (Best)	% Docked Accurately(Top)	RMSD Average (Best)	RMSD Average (Top)	Tim(min)
LibDock	91	50	1.2	3.8	0.5
CDOCER	94	79	0.8	1.5	5.0

LibDock is optimized for speed:
get accurate docked poses in seconds

**CDOCKER is optimized for accuracy:
get significant improvement in rank-ordering of correct pose and RMSD to X-ray structure**

1. Hartshorn, et al. J. Med. Chem., 50 (4), 726 -741 (2007)
3 GHz

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

CDOCKER



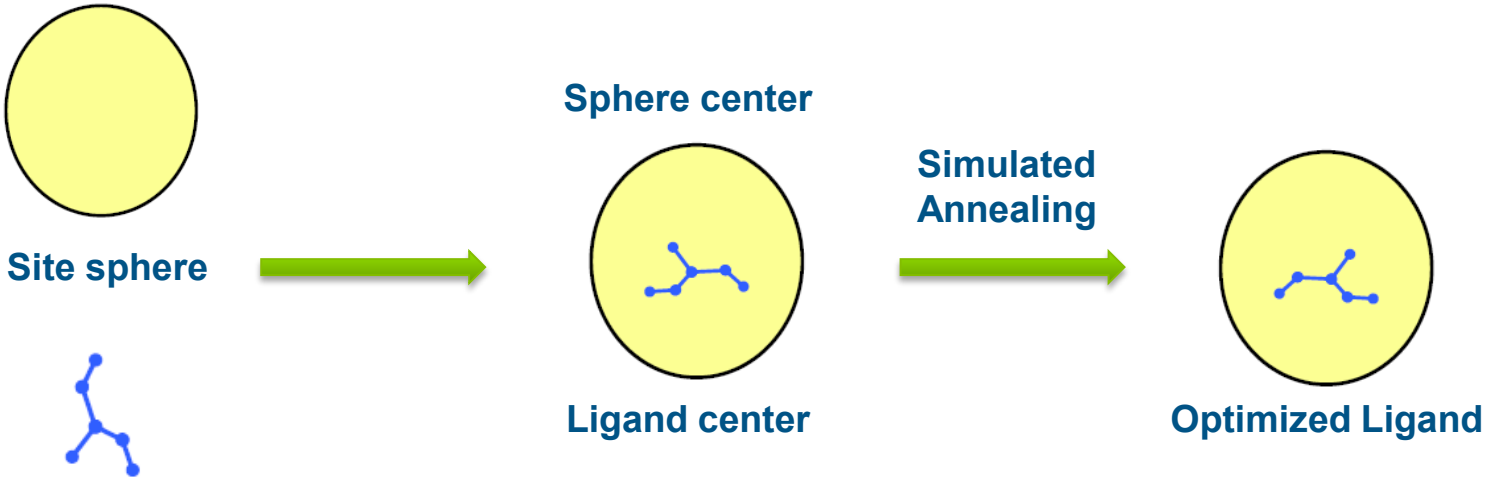
- CDOCK is a grid-based molecules docking method.
- Ligand conformations are obtained by Molecular Dynamic (MD) methods

Wu G, Robertson DH, Brooks CL III, Vieth M. Detailed analysis of grid-based molecular docking: A case study of CDOCKER - A CHARMm-based MD docking algorithm. *J. Comp. Chem.* **2003**, 13, 1549

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

CDOCKER : Ligand Fitting



Ligand

The conformation generated by high temperature MD

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Small Molecule Docking using CDOCKER

- 41 protein-ligand complexes from the PDB
  - Structurally diverse set of ligands
  - All-atom representation used in published work[a]
- Grid-based approach used in Discovery Studio
  - Faster method
  - No significant compromise on accu

Success rates and CPU times for each algorithm

Docking Algorithm	success rate	av/median CPU times
GOLD[b]	46.3	824/708[c]
Dock[b]	51.2	200/114[c]
FlexX[b]	53.7	65/35[c]
CDOCKER (No Grid)[b]	82.9	2012/1740[c]
Discovery Studio CDOCKER (Grid)	78.1	630/580[d]

Single best docking run for each algorithm
(Success is defined as RMSD < 2Å from X-ray structure)

# of rot. bonds	total # of ligands	# of ligands docked correctly				
		Dock[b]	GOLD[b]	FlexX[b]	CDOCKER (No Grid)[b]	Discovery Studio CDOCKER (Grid)
< 8	20	18	14	16	19	18
≥ 8	21	3	4	6	15	14

a. Erickson et al. J Med Chem (2004) 47:45-55

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Flexible Docking

Generate Receptor Side Chain Conformations (ChiFlex algorithm)

↓

Generate Receptor Hotspots for Receptor Conformations

↓

Generate Ligand Conformations (On-the-fly methods, or pre-generated)

↓

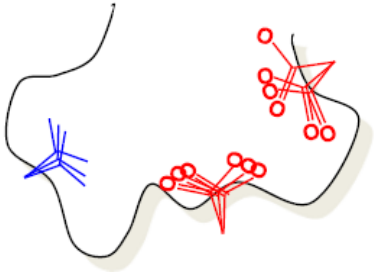
Match Conformations to Hotspots

↓

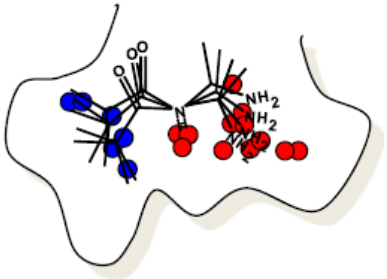
Refine Protein Side Chain Conformations (ChiRotor algorithm)

↓

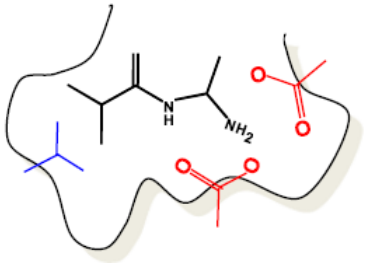
Simulated Annealing and Energy Minimisation of Poses



LibDock



CDOCKER



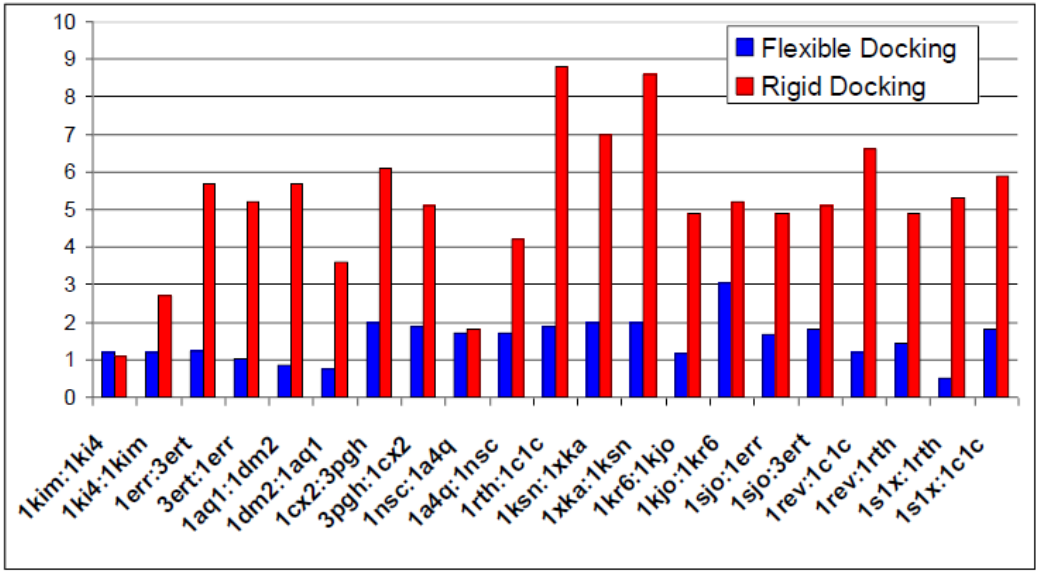
oska J, Spassov VZ, Maynard AJ, Yan L, Austin N, look PK, Venkatachalam CM. Fully automated olecular mechanics based induced fit protein-ligand ocking method, *J. Chem. Inf. Model.* **2008**, 48, 1965-973.

Copyright©2019 GGA Corp., All rights reserved.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Validation of Rational Flexible Docking

Cross-docking: Dock ligands into an alternate conformation of the same receptor



RMSD Values compared to X-ray conformation for cross-docking experiments (1kim:1ki4 denotes 1kim ligand docked into 1ki4 receptor)

CHARMm-based sampling successfully captures receptor movements induced by a non-native ligand

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Agenda

- Briefly Overview - 10 min
- Molecular Docking Modules in DS
  - CDOCKER, LibDock, Flexible Docking
- Pharmacophore
  - Structure-based Pharmacophore
  - Ligand-based Pharmacophore
- Fragment-Based Design
- ADMET and Toxicity Prediction

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Rationale Small Drug Design

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 For NCKU and NTHU

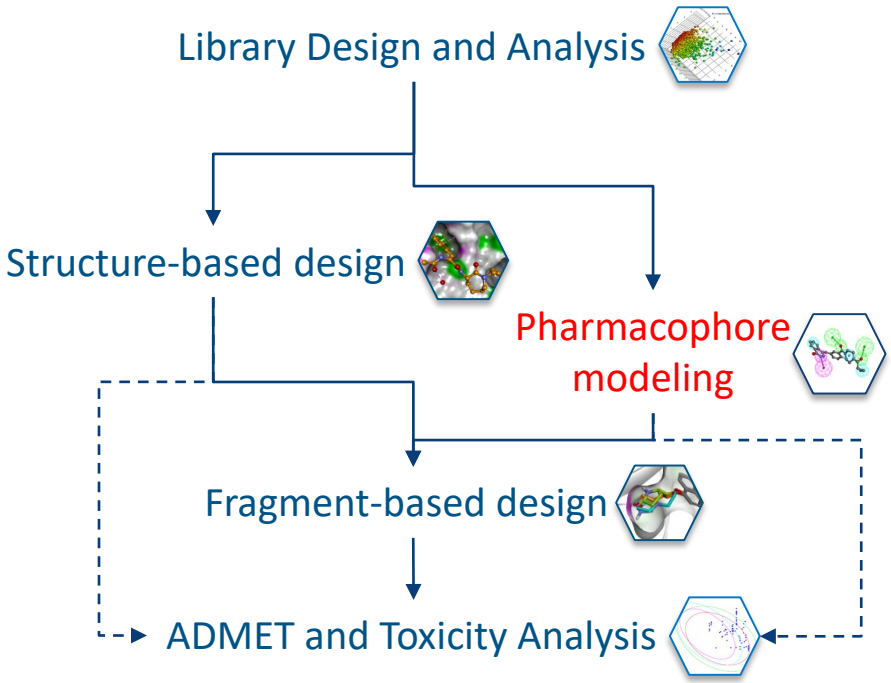
Scales

10^3~10^7 Molecules from Library

10^0~10^2 Molecules As Leads

10^2~10^3 Molecules as Novel Derivatives

10^0~10^2 Molecules Pass ADMET and Toxicity Screening



Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore

- Pharmacophore Modeling in Discovery Studio
- Structure-Based Pharmacophores
- Common Feature Pharmacophore Generation
- 3D QSAR Pharmacophore Generation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore

- Pharmacophore Modeling in Discovery Studio
- Structure-Based Pharmacophores
- Common Feature Pharmacophore Generation
- 3D QSAR Pharmacophore Generation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

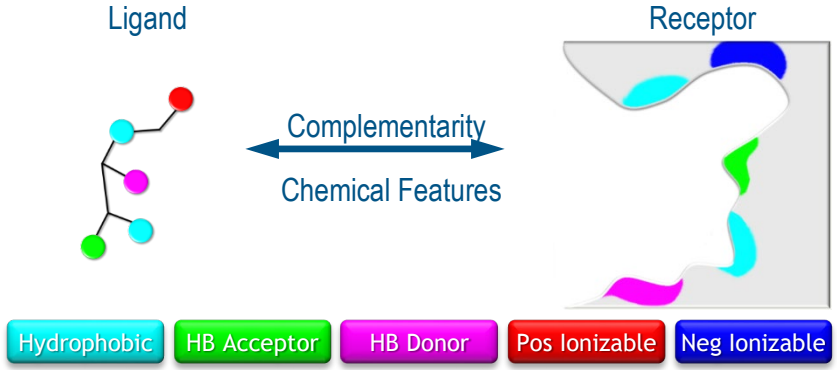
What is a Pharmacophore?

- "The molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon)biological activity."

P. Ehrlich, Dtsch. Chem. Ges. 1909, 42, 17

- "A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response."

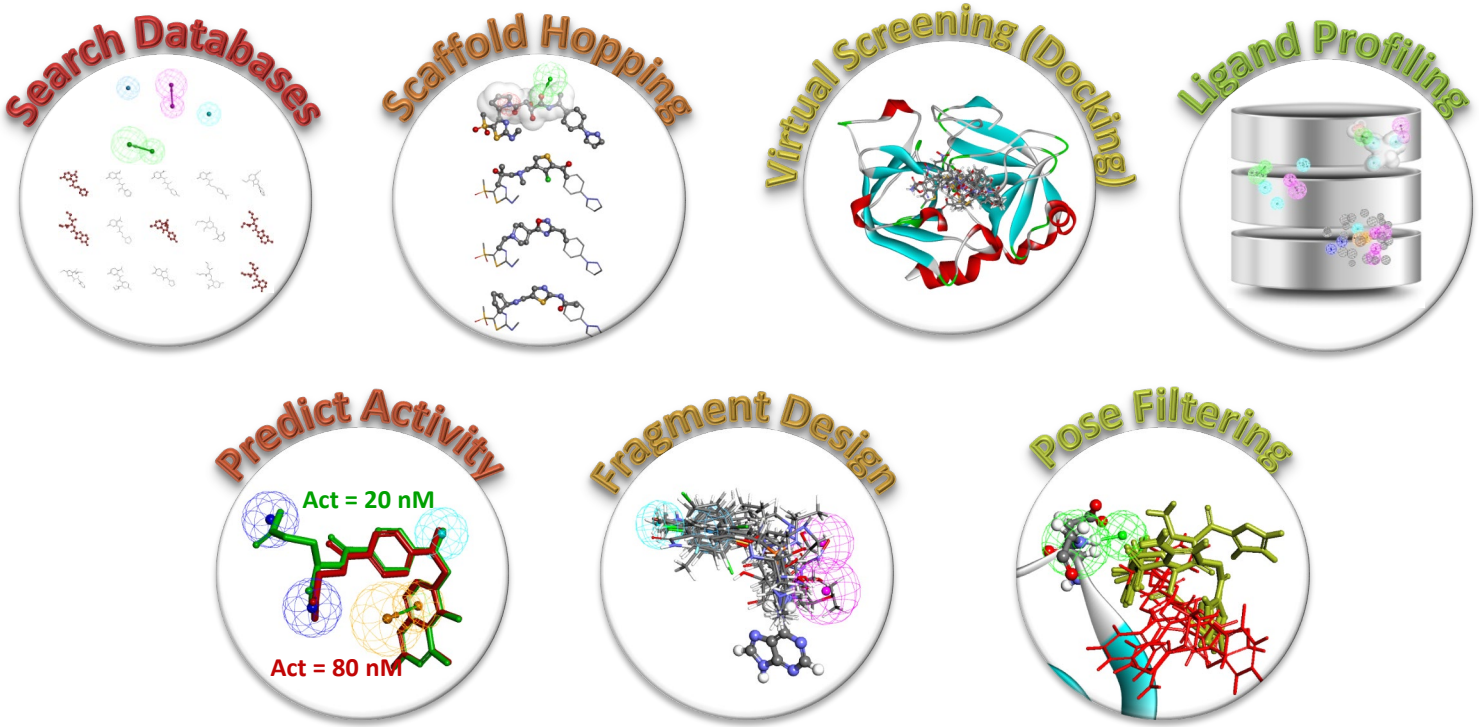
Wermuth et al. Pure Appl. Chem. 1998 70, 1129-43



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophores Applications



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Caveats

- Do not represent real molecules or a real association of functional groups
- Do represent an abstract concept for interactions of a group of compounds towards the receptor
- Can be considered the largest common denominator by a set of active molecules
- Only valid for a specific receptor

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

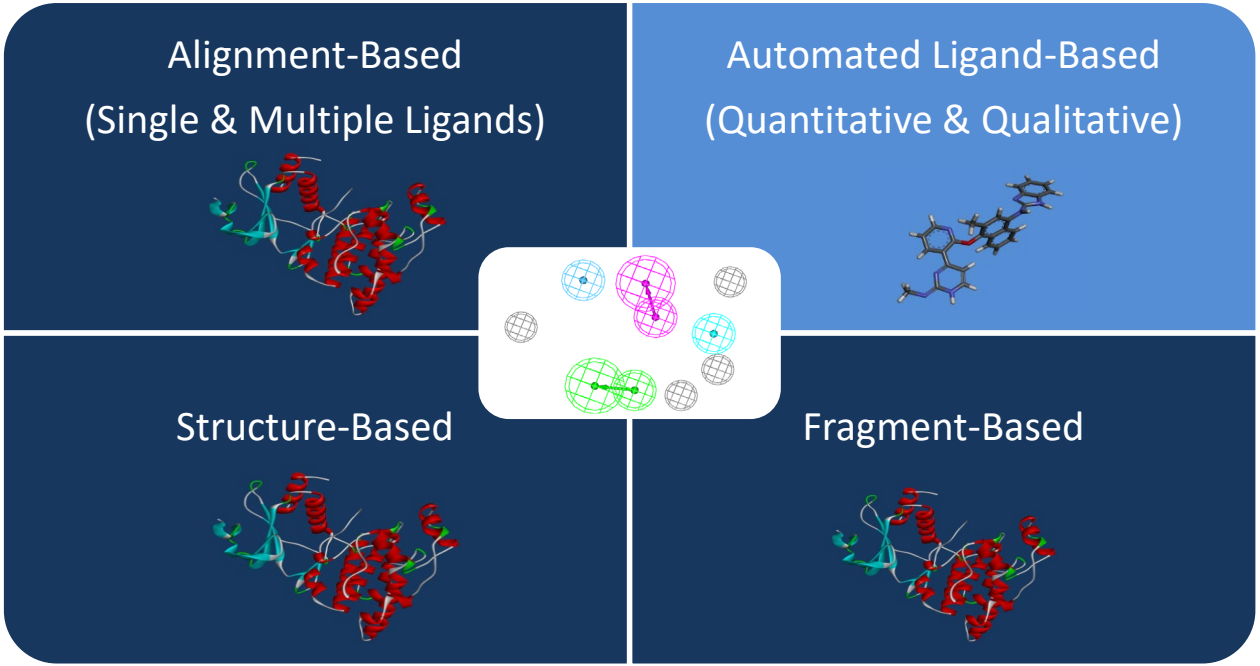
Pharmacophore Generation

- Manual construction
  - Ligand-based
    - Aligned analogs
  - Structure-based
    - Receptor active site (SBP)
- Automatic construction
  - Ligand-based
    - Qualitative
      - Common features hypothesis (HipHop / HipHopRefine)
      - Finds features shared by a set of similarly active ligands
  - Quantitative
    - SAR predicative hypothesis (HypoGen / HypoGenRefine)
      - Finds features that relate to activity
      - Bioactive ligand conformation
  - Structure-based
    - Receptor-ligand complex

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

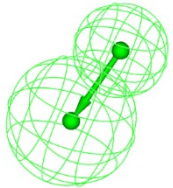
Scope of Pharmacophore Modelling

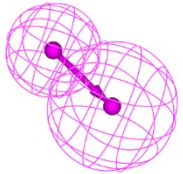


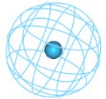
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

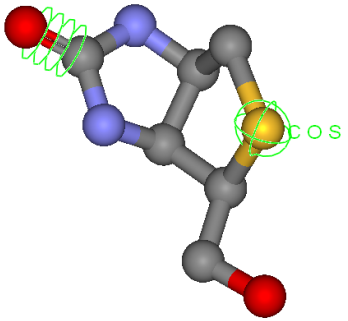
Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Queries

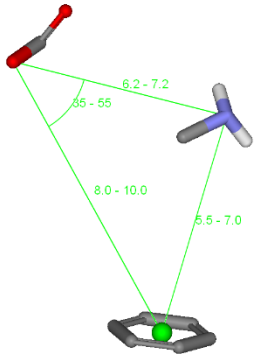


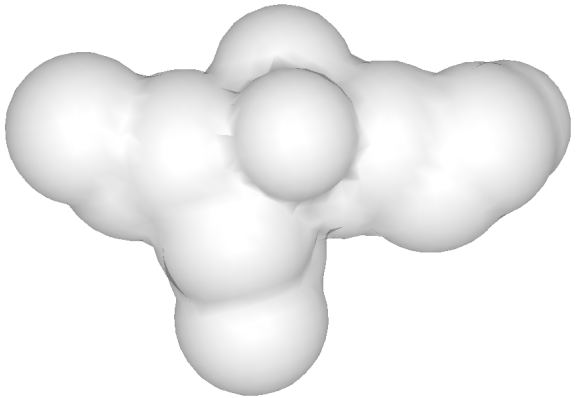






- 2D substructure
  - SMARTS
- 3D Pharmacophore
  - Fragment-based (distance, angle, dihedral constraints)
  - Feature-based
  - Shape
  - Combination
- File format is CHM (or DSV)





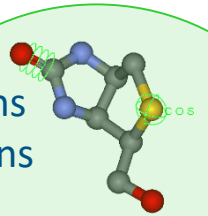
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Combining Pharmacophores Queries

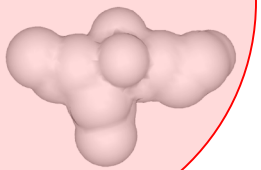
2D Substructure

- Including Boolean operations
- Atom and bond specifications

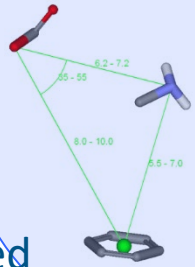


Shape

- Similarity

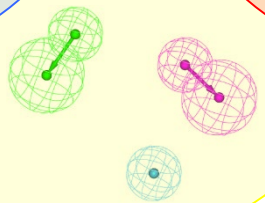


Or any combinati on thereof …



3D Fragment-based

- Geometrical constraints
- Topology



3D Feature-based

- Chemical feature-based
- Location constraints
- Feature customisation

創源生技
GGA

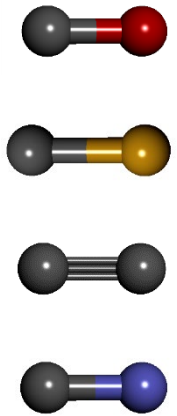
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Features

- Pharmacophore features represent groups of chemical functions which can form the same types of molecular interactions with a receptor
  - Set of rules summarising distinct chemical topologies
  - Examples
    - A hydrogen bond donor feature may be defined as a non-acidic hydroxyl, a thiol, an acetylenic hydrogen or an NH amine
    - A positive ionizable feature may be defined as a basic amine, basic primary or secondary amidine, basic guanidine

Hydrogen bond donor

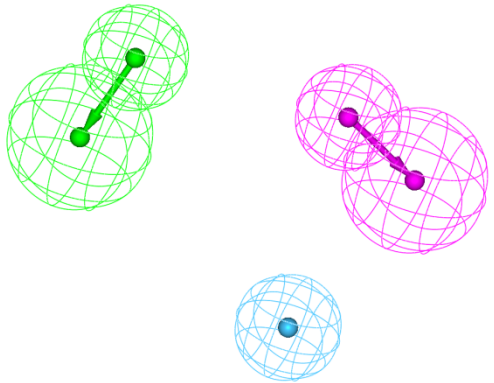


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Features

- Catalyst pharmacophore features can be composed of
  - One or two points in three-dimensional space
    - Single point
    - A vector (directional component)
- A tolerance (location constraint)



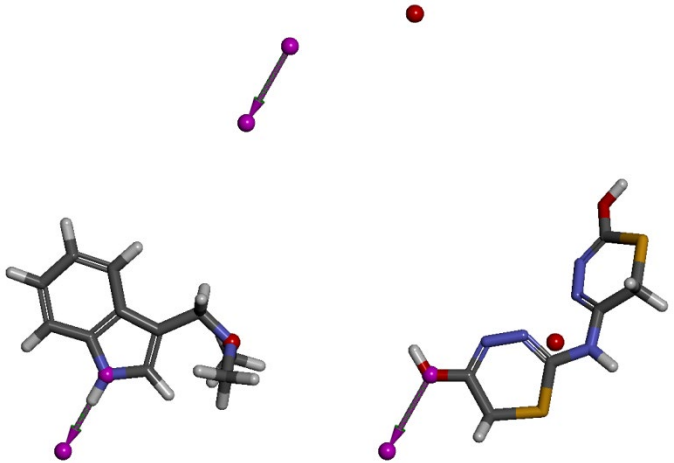
- Points can be the
  - Position of an individual atom
  - Centroid of a group of atoms
  - Position of corresponding atoms projected from a hydrogen bond donor or acceptor atom (projected point)
- Location constraints define the space in which the ligand atom(s) can reside
  - Center of the sphere defines the ideal location for the ligand atom(s)
  - The tolerance represents an allowable deviation of the ligand atom(s) from the ideal position

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

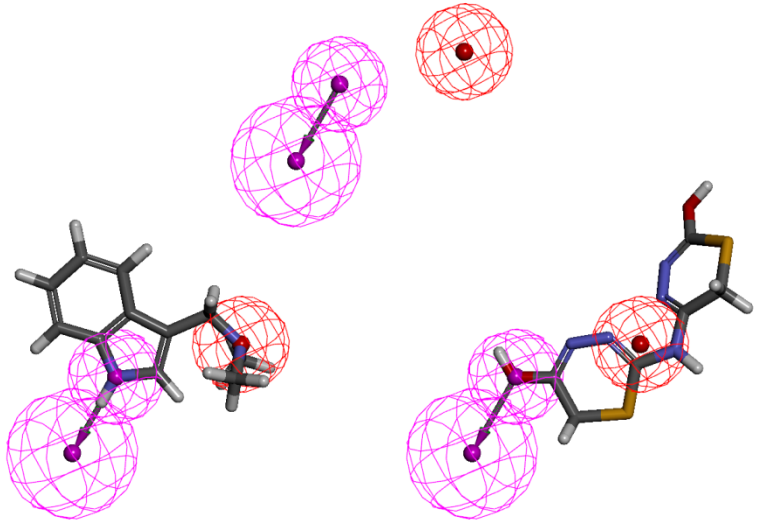
Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Features

A pharmacophore feature without a location constraint only indicates the absence or presence of a chemical function



The location constraint specifies the 3D coordinates of the features and defines the spatial relationship of the features to each other



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Standard Pharmacophore Features

- Eleven standard features available in default Dictionary

Feature	Description
HBA ACCEPTOR	Hydrogen-bond acceptor (vector)
HBA ACCEPTOR lipid	Hydrogen-bond acceptor for lipid environment (vector)
HB DONOR	Hydrogen-bond donor (vector)
HYDROPHOBIC	Hydrophobic group (point)
HYDROPHOBIC aliphatic	Hydrophobic aliphatic group (point)
HYDROPHOBIC aromatic	Hydrophobic aromatic group (point)
NEG CHARGE	Negatively charged group (atom)
NEG IONIZABLE	Group that is, or can be, negatively charged at physiological pH, ie. carboxyl (point)
POS CHARGE	Positively charged group (atom)
POS IONIZABLE	Group that is, or can be, positively charged at physiological pH, ie. nonaromatic amines (point)
RING AROMATIC	Five- or six-membered aromatic ring (vector)

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Additional Pharmacophore Features

- Seven additional features in default Dictionary

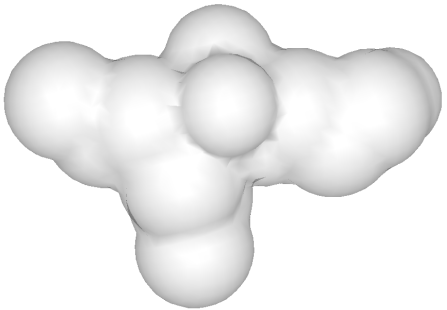
Feature	Description
HBA_Heavy	Matches the heavy atom of a hydrogen bond acceptor
HBA_Projection	Matches the projection point of a hydrogen bond acceptor
HBD_1	The same as the hydrogen bond donor definition, but will also match an aromatic carbon with a hydrogen
HBD_Heavy	Matches the heavy atom of a hydrogen bond donor
HBD_Projection	Matches the projection point of a hydrogen bond donor
POS_IONIZABLE_1	The same as the positive ionizable definition, but will also match a pyridyl group
Zn_Binder	Matches substructures that are likely to bind to Zinc atoms

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Constraint Features: Shape

- Shape similarity searching
  - Not shape containment searching
  - Algorithm tries to fill up the shape, not just fit inside it



- Aligns the shape of the ligand to the query shape
- Computes a similarity value (ratio of intersecting shape volume to combined volume)
- Compares this similarity value to the similarity tolerance
  - Example: a similarity tolerance = 0.5 returns all ligands that, when aligned to the query, have volume of the intersection of the two shapes divided by volume of the union of the shapes ≥ 0.5



$$\frac{V_{shape1} \cap V_{shape2}}{V_{shape1} \cup V_{shape2}} \geq 0.5$$

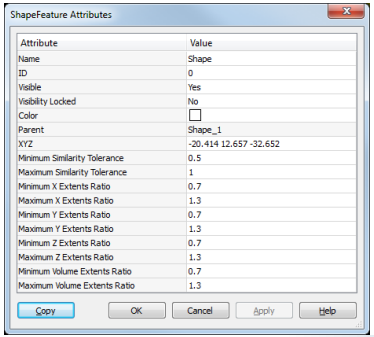
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

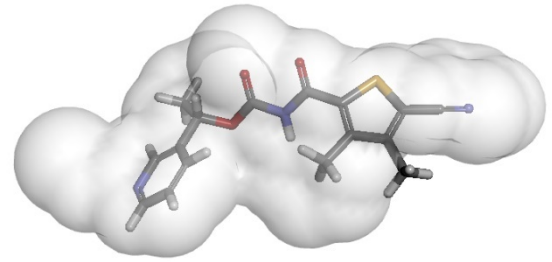
Constraint Features: Shape

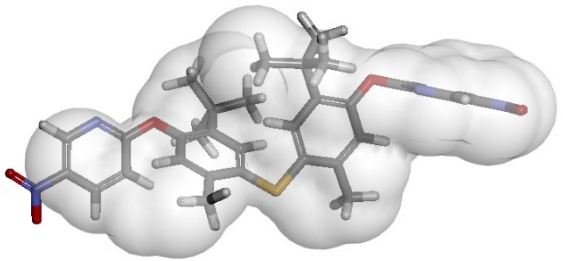


Shape constraints, such as similarity tolerance, can be modified from the ShapeFeature Attributes dialog



A hit may have more or less volume that protrudes from the shape

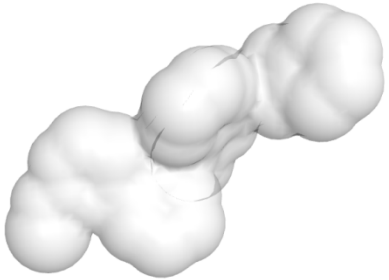


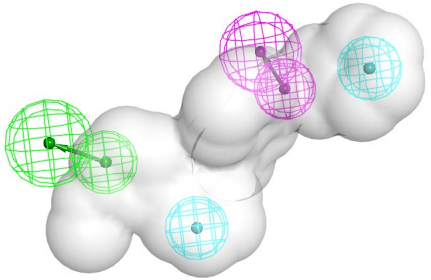


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Constraint Features: Shape





Shape-only queries

1. The shape is aligned to the ligand
2. The similarity is computed, and, if the tolerance is satisfied, the ligand is considered a hit

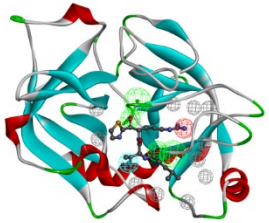
Mixed queries

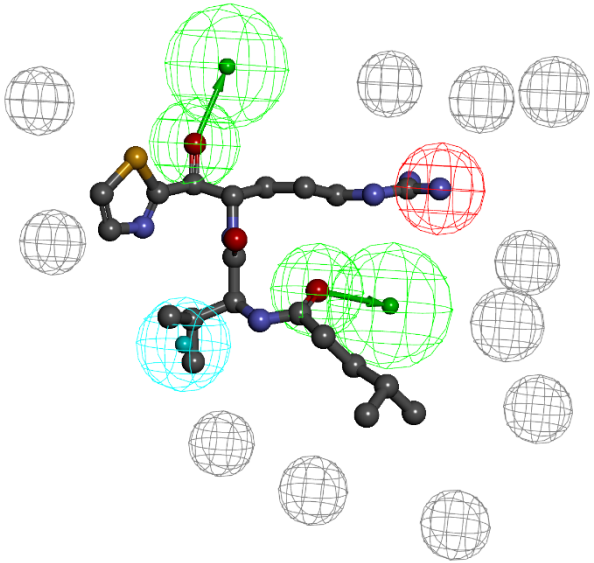
1. The shape in a mixed query is aligned to the ligand, and the tolerance is tested
2. The transformation used to align the location constraints to the molecule is applied to the shape
3. The similarity of the shape to the ligand is computed without any further alignment – if this similarity satisfies the tolerance, then the ligand is considered a hit

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Constraint Features: Excluded Volumes

- Excluded volumes specify one or more spherical spaces in a pharmacophore that must not contain any atoms or bonds
- EVs can be used to constrain a pharmacophore, and may represent the steric restriction of the receptor
- A pharmacophore with an EV only matches if no atoms penetrate the excluded area, but this penetration is not ‘all or nothing’
- Penetration is defined differently in Rigid and Flexible fitting modes



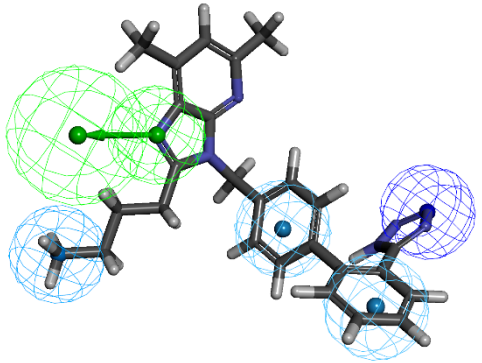


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

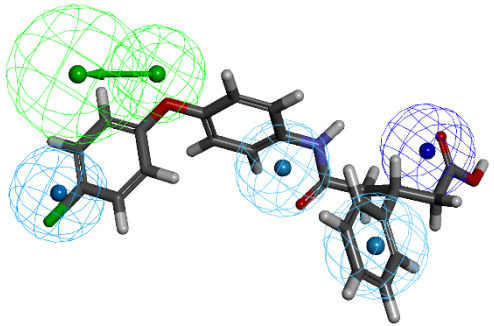
Copyright©2019 GGA Corp., All rights reserved.

Ligand-Pharmacophore Scoring

- When comparing a ligand and a pharmacophore, how is the quality of the matching (mapping) determined and quantified?
- Both of these ligands have atom(s) which map to each of the 5 features of the pharmacophore
- But the atom(s) of the top ligand map the pharmacophore features better (they are closer to the center of the feature; the ideal position for that feature)
- Can this be quantified?



FitValue = 4.44



FitValue = 0.15

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Calculating FitValue

A FitValue gives a measure of how well the ligand fits the pharmacophore
The higher the FitValue, the better the match

The FitValue depends on two parameters
- The weights assigned to the pharmacophore feature(s)
- How close the features in the ligand are to the centers of the corresponding location constraints

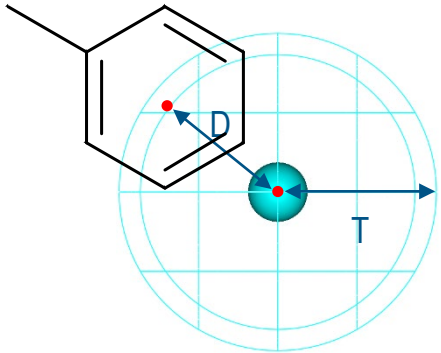
$$\text{FitValue} = \sum W\left[1 - \sum\left(\frac{D}{T}\right)^2\right]$$

W = weight of hypothesis features

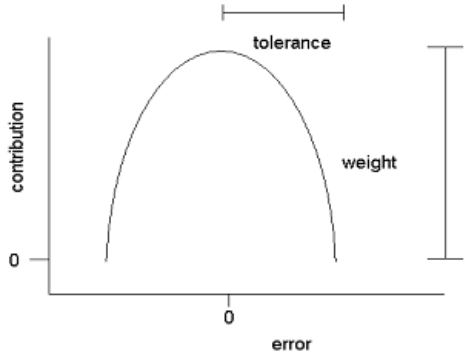
D = displacement of the feature from the center of the location constraint

T = radius of the location constraint sphere for the feature (tolerance

Ligand feature



Pharmacophore feature



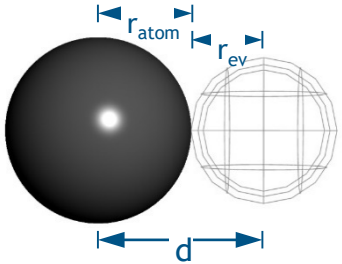
Weights on features indicate the importance of the feature relative to other features
Features have a default weight of 1.0

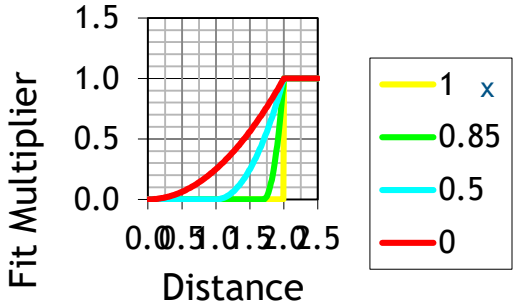
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

FitValue: Excluded Volumes

In Rigid mode, the distance between an atom and an EV (*d*) must be greater than the tolerance of the excluded volume plus the approximate VDW radius of the atom (hydrogen atoms are excluded) (*t*) times the ExcludedVolumeXFactor parameter (*x*)





$t = r_{atom} + r_{ev}$

x = ExcludedVolumeXFactor (default 0.85)

If $d < xt$ then FitValue = 0

If $d > xt$ then FitValue is unchanged

If $xt < d < t$ then FitValue multiplied by $f(d) = \left[\frac{d - xt}{t - xt}\right]^2$

In Flexible mode,

1. Each EV is treated as a pseudo atom with VDW radius equal to its tolerance
2. The VDW interaction energy between the ligand atoms and the resulting EV pseudo atoms is calculated
3. If the excess energy is below a small threshold (40,000 $J.mol^{-1}$) then the EVs are considered satisfied

During the optimization, the position of the atoms of the ligand are optimized such that the best geometry, according to the FitValue, where the EV VDW energy is below this threshold is returned as the hit

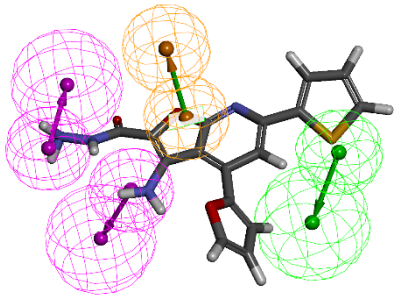
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

All rights reserved.

Ligand-Pharmacophore Mapping

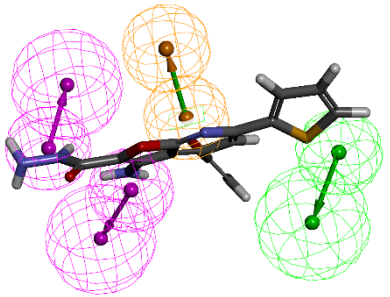
- Same conformation, multiple mappings

Mapping 1: The primary amine of the hydrazide maps to the left-most HBD



Conformation 1
Mapping 1

Mapping 2: The secondary amine of the hydrazide maps to the left-most HBD; the same conformation is 'rotated' in the x-plane



Conformation 1
Mapping 2

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

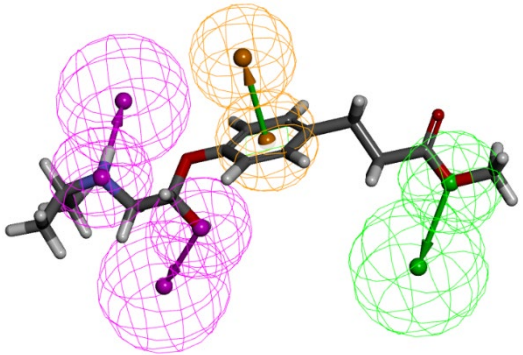
Copyright©2019 GGA Corp., All rights reserved.

Ligand-Pharmacophore Mapping

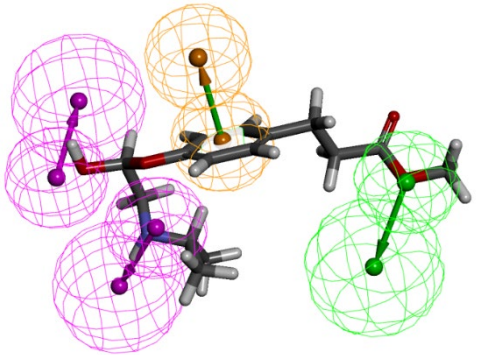
- Different conformations, multiple mappings

Mapping 1: The amine nitrogen is mapped to the left-most HBD, rather than the second HBD (in Mapping 2)

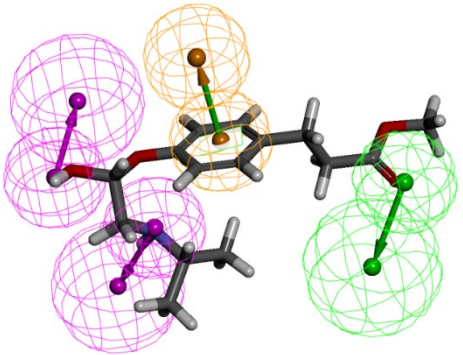
Mapping 3: The carbonyl oxygen is mapped to the HBA, rather than the ester oxygen



Conformation 13
Mapping 1



Conformation 114
Mapping 2



Conformation 122
Mapping 3

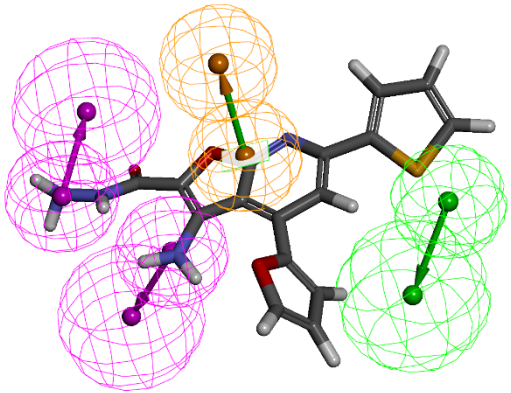
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Ligand-Pharmacophore Mapping

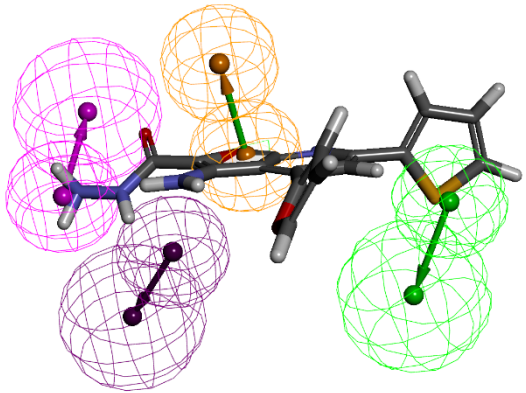
- Partial mappings

Mapping 1: All features of the pharmacophore are mapped



Mapping 1
FitValue = 1.36

Mapping 2: The HBD feature is missed (dimmed color) but the remaining features are more ideally aligned



Mapping 2
FitValue = 2.74

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Ligand Perception

- In pharmacophore modeling ligands need to be properly prepared and represented

Considerations for ligands in pharmacophore modeling:

- Stereochemistry
  - If known, use the absolute stereochemistry of chiral centers
  - Stereoisomers can be generated for unknown chirality
- Ionization
  - Ideally represented in neutral state
- Tautomers
- Salt stripping

Unless the global or bioactive conformation of a ligand is known, conformation generation is necessary to:

- To profile/sample the space of a ligand
- To generate reasonable stable energy configurations of a ligand, amongst which are hopefully the:
  - Bioactive conformation
  - Global energy conformer

Remember: Standard pharmacophore features represent chemistry at pH = 7.0

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

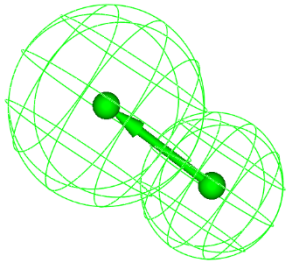
Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Conformation Methods

	FAST	BEST	CAESAR
Quality	• Good	• Better	• Good
Speed	• Fast	• Slow	• Very Fast
Appropriate application	• Database building	• Hypothesis generation	• Large database building
Algorithm to achieve conformer diversity	• Poling algorithm • Optimization of torsions is also constrained within certain torsion angle windows so that the diversity is maintained	• Poling algorithm • Flexibility in bond angle sampling allows better conformer diversity	• Divide-and-conquer and recursive conformation build up algorithm • Simple local rotational symmetry check efficiently eliminates identical conformers due to local rotational symmetry
Treatment of rings	• Generates a few mutually dissimilar, low-energy conformers for each ring system	• Uses a distance geometry approach to find ring conformations • Most comprehensive treatment of flexible ring systems	• Uses a distance geometry approach to find ring conformations

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Hydrogen Bond Acceptor

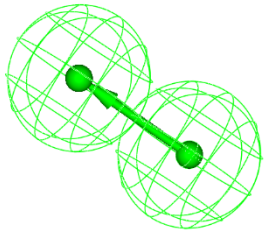
- Matches the following types of atoms or groups of atoms with surface accessibility:
  - sp or sp^2 nitrogens that have a lone pair and charge less than or equal to zero
  - sp^3 oxygens or sulfurs that have a lone pair and charge less than or equal to zero, sp^2 oxygen atoms
  - Non-basic amines that have a lone pair
- Does not match:
  - Basic primary, secondary, and tertiary amines, which are protonated at physiological pH
- No exclusion of electron-deficient pyridines and imidazoles

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技
GGA

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Hydrogen Bond Acceptor Lipid

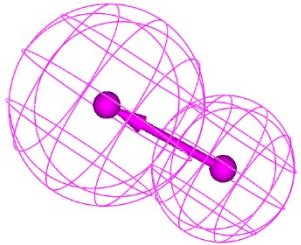
- Matches the following types of atoms or groups of atoms:
  - Nitrogens, oxygens, or sulfurs (except hypervalent) that have a lone pair and charge less than or equal to zero
- Function is the same as HB Acceptor except that it includes basic nitrogen
- No exclusion of electron-deficient pyridines and imidazoles

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Hydrogen Bond Donor

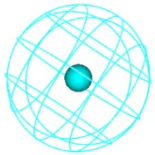
- Matches the following types of atoms or groups of atoms:
  - Non-acidic hydroxyls
  - Thiols
  - Acetylenic hydrogens
  - NH's (except tetrazoles and trifluoromethyl sulfonamide hydrogens)
- Does not match:
  - Electron-rich pyridines and imidazoles that would be protonated at physiological pH
  - Nitrogens that would be protonated due to their high basicity

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Hydrophobic

- A contiguous set of atoms that are NOT adjacent to ANY concentration of charge (charged atoms or electronegative atoms) in a conformer such that the atoms have surface accessibility
- Phenyl, cyclohexyl, isopropyl and methyl



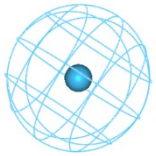
Hydrophobic Aliphatic

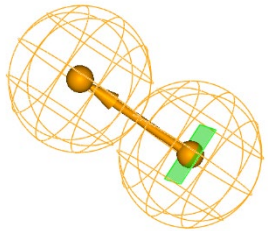
- Proper subset of the hydrophobic function definition that includes only aliphatic atoms
- Cycloalkyl, isopropyl and methyl

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features





3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Hydrophobic Aromatic

- Proper subset of the hydrophobic function definition that includes only aromatic atoms
- Phenyl, indole and other aromatics

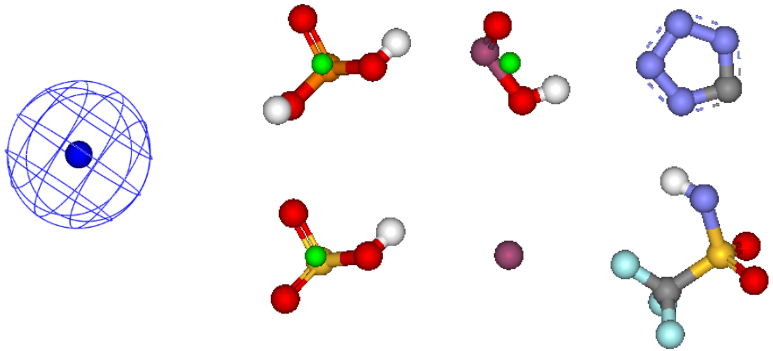
Ring Aromatic

- Matches aromatic rings with five or six member atoms
- Defines 2 points, the ring centroid and a projected point normal to the ring plane
- Projected point can map both above and below the plane

創源生技
GGA

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Negative Ionizable

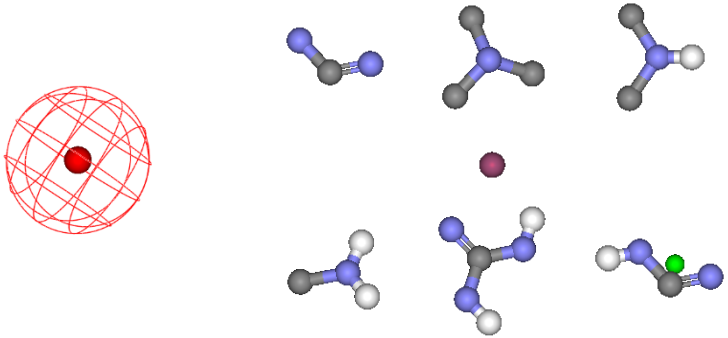
- Matches atoms or groups of atoms that are likely to be deprotonated at physiological pH, such as:
  - Trifluoromethyl sulfonamide hydrogens
  - Sulfonic acids (centroid of the three oxygens)
  - Phosphonic acids (centroid of the three oxygens)
  - Sulfinic, carboxylic, or phosphinic acids (centroid of the two oxygens)
  - Tetrazoles
  - Negative charges not adjacent to a positive charge

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Default Pharmacophore Features



Positive Ionizable

- Matches atoms or groups of atoms that are likely to be protonated at physiological pH, such as:
  - Basic amines
  - Basic secondary amidines (iminyl nitrogen)
  - Basic primary amidines, except guanidines (centroid of the two nitrogens)
  - Basic guanidines (centroid of the three nitrogens)
  - Positive charges not adjacent to a negative charge
- Does not match:
  - Weakly basic aromatic nitrogens such as pyridine and imidazole

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

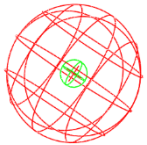
Default Pharmacophore Features

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |



Negative Charge

- Negative charges not adjacent to a positive charge



Positive Charge

- Positive charges not adjacent to a negative charge

創源生技
GGA

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore

- Pharmacophore Modeling in Discovery Studio
- Structure-Based Pharmacophores
- Common Feature Pharmacophore Generation
- 3D QSAR Pharmacophore Generation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Typical Pharmacophore Workflow

Ligand/Protein Perception
Training Set Selection & Configuration
Conformation Generation
Pharmacophore Feature Perception
Protein Preparation

Pharmacophore Generation
Ligand-Based (Qualitative)
Ligand-Based (Quantitative)
Structure-Based
Refinement with Inactive Ligands

Analysis and Validation
Compare Ligands to Pharmacophores
Compare Pharmacophores
LOG File Analysis

Prediction and Prioritization
Estimate Activity/Fit
Identify Potential New Candidates

Use the Prepare Protein tool panel (Macromolecules tool set) to ensure that the correct protein environment is represented

Generate Conformations
Feature Mapping
Prepare Protein

ration
Receptor-Ligand Pharmacophore Generation
Common Feature Pharmacophore Generation
3D QSAR Pharmacophore Generation
Interaction Generation
Steric Refinement with Excluded Volumes

Ligand Pharmacophore Mapping
Pharmacophore Comparison
Screen Library
Ligand Profiler

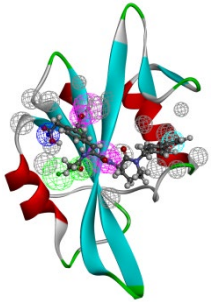
Ligand Pharmacophore Mapping
Screen Library
Ligand Profiler
Search 3D Database

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

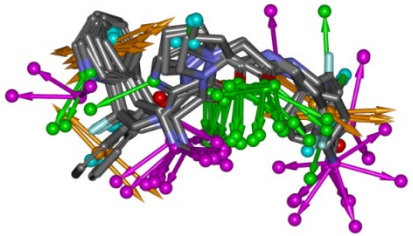
源生技
GA
Copyright© 2019 GGA Corp.; All rights reserved.

Receptor-Based Pharmacophores Methods

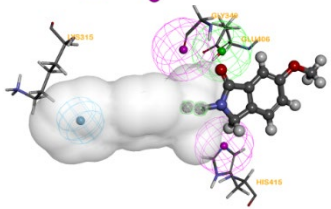
Go to Receptor-Ligand Pharmacophores



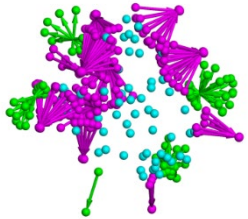
Go to Multiple Ligands Alignment-Based Pharmacophores



Go to Fragment-Based Pharmacophores



Go to Structure-Based Pharmacophores



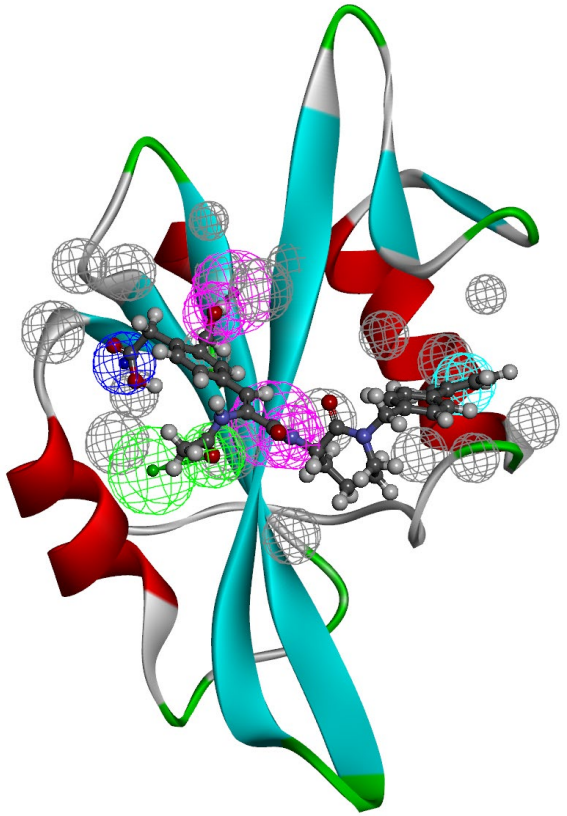
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

GGA

Copyright©20 served.

Receptor-Ligand Pharmacophores

- Input Data and Starting Knowledge
  - Receptor-ligand complex
  - Known active and inactive ligands for receptor (validation)
- Objective
  - Generate (and validate) pharmacophores representing the receptor-ligand interactions of a complex
- Applications
  - Virtual screening
  - Ligand profiling
  - Pose filtering
  - Search databases



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Receptor-Ligand Pharmacophores

Pharmacophore Generation

1. Enumerate Ligand Features
(HBA, HBD, Pos Ion, Neg Ion, Hydrophobic, Ring Aromatic)

2. Prune Features Based on Receptor-Ligand Interactions

3. Add Steric Constraints
(Excluded Volumes or Shape)

4. Enumerate Pharmacophores
(4-6 Features by Default)

5. Rank Pharmacophores
(Return Top 10)

6. (Optionally) Validate Pharmacophores

The distance criteria for receptor-ligand interactions are adjustable

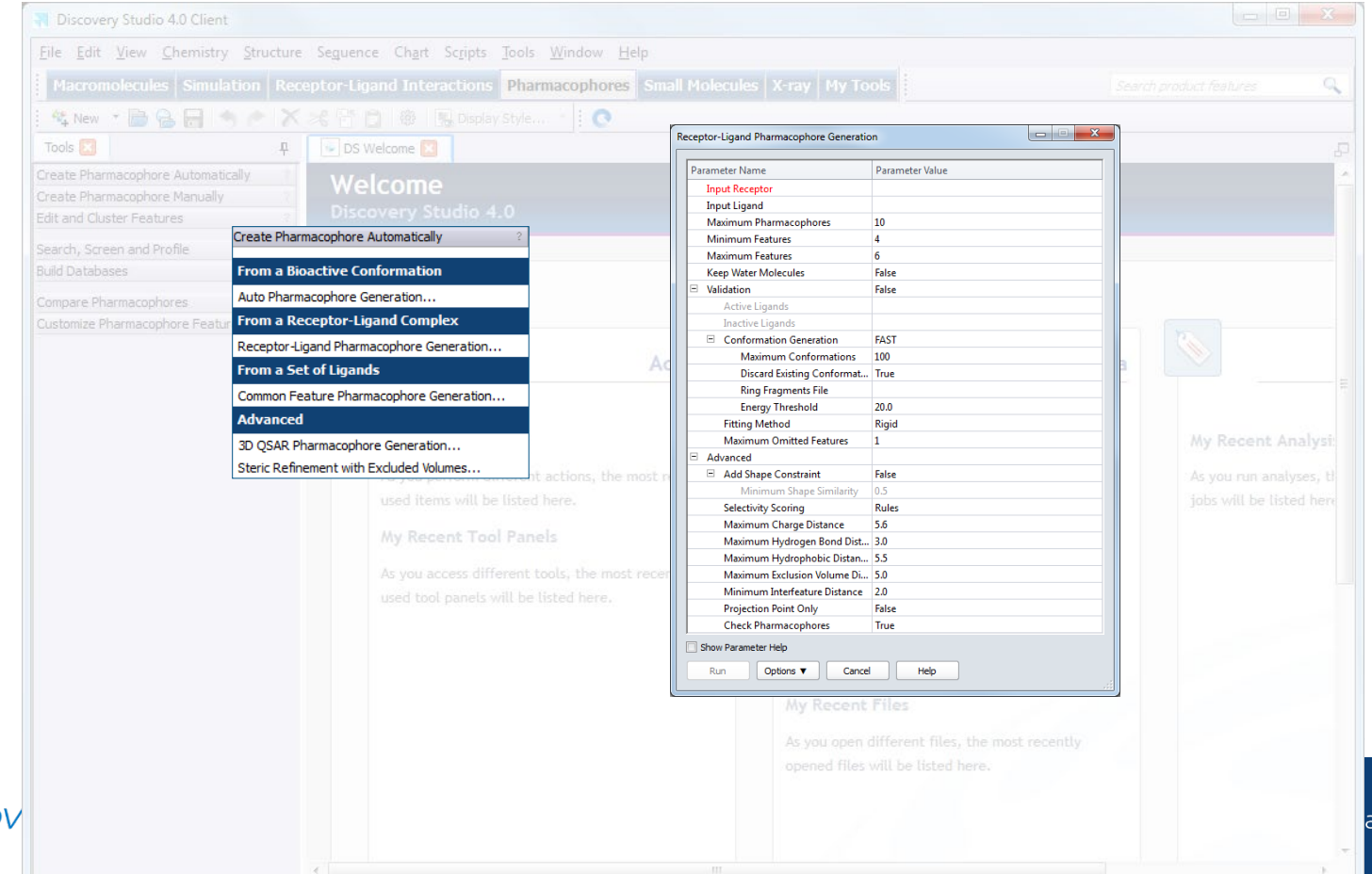
An excluded volume is added for each neighbour residue (within a maximum distance of 5.0 Å) with the size of the EV proportional to the number of neighbouring atoms

Pharmacophores are scored by a rules method based on a specifically developed GFA scoring function, or screening of a diverse ligand database

Ligand-pharmacophore mapping of active/inactive ligands performed to generate confusion matrices and ROC plots

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Protocol in Discovery Studio

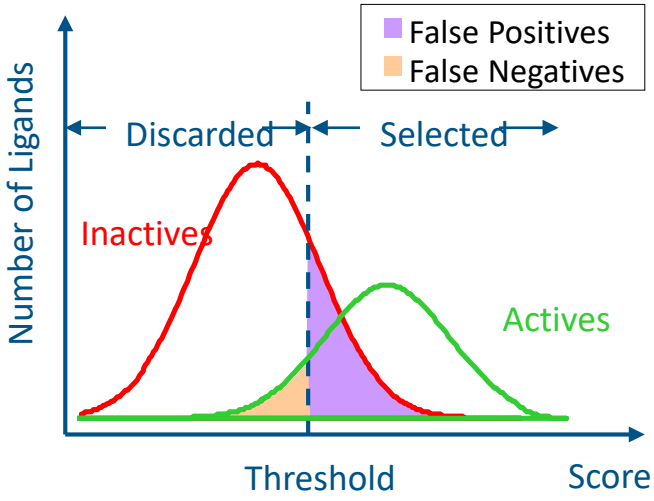


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

reserved.

any

Receiver Operating Characteristic



Sensitivity (S_e) - Ability to retrieve actives (true positive rate)

$$S_e = \frac{TP}{(TP + FN)}$$

Confusion Matrix

in vitro

in silico	Actives	Inactives
Selected	True positives (*TP*)	False positives (*FP*)
Discarded	False negatives (*FN*)	True negatives (*TN*)
	S_e	S_p

Specificity (S_p) - Ability to discard inactives (true negative rate)

$$S_p = \frac{TN}{(FP + TN)}$$

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Report.html

Receptor-Ligand Pharmacophore Generation

Description

Information

Name	Receptor-Ligand Pharmacophore Generation
Status	Success
User	tluu
DS Version	4.0.0.13259
PP Version	9.1.0.13
DS Client Version	4.0.0.13259
Server Name	el4b08 (Windows64)
Server Ports	4044 (4043)
Start Time	12/12/13 12:17:31
Finish Time	12/12/13 12:29:55
Execution Time	00:12:24

Report.html - Job summary

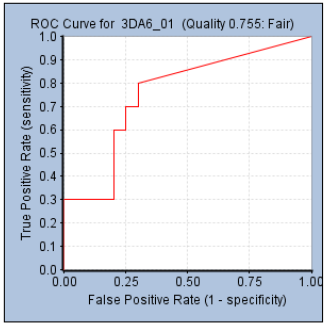
Summary

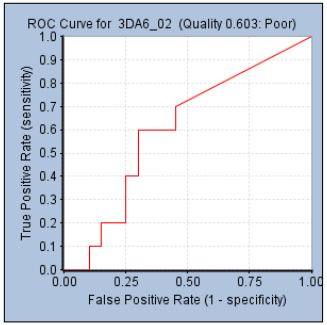
Found 22 features in ligand: 3DA6
7 features match the receptor-ligand interactions: DHHHHHH
10 pharmacophores generated.

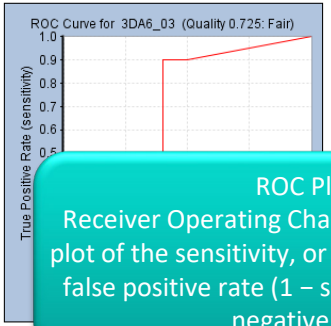
Validation with Known Actives/Inactives

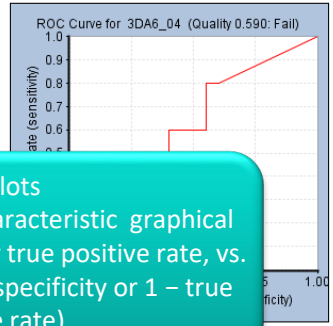
Pharmacophore	Total Actives	Total Inactives	True Positives	True Negatives	False Positives	False Negatives	Sensitivity	Specificity
Pharmacophore_1	10	20	8	14	6	2	0.80000	0.70000
Pharmacophore_2	10	20	7	11	9	3	0.70000	0.55000
Pharmacophore_3	10	20	9	10	10	1	0.90000	0.50000
Pharmacophore_4	10	20	8	8	12	2	0.80000	0.40000
Pharmacophore_5	10	20	8	10	10	2	0.80000	0.50000
Pharmacophore_6	10	20	9	12	8	1	0.90000	0.60000
Pharmacophore_7	10	20	4	17	3	6	0.40000	0.85000
Pharmacophore_8	10	20	10	3	17	0	1	0.15000
Pharmacophore_9	10	20	10	6	14	0	1	0.30000
Pharmacophore_10	10	20	10	4	16	0	1	0.20000

Validation Table
Summary of active and inactive ligands used to validate the pharmacophores; confusion matrix table with Sensitivity and Specificity calculated

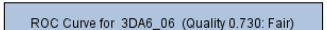


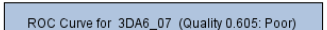






ROC Plots
Receiver Operating Characteristic graphical plot of the sensitivity, or true positive rate, vs. false positive rate (1 − specificity or 1 − true negative rate)

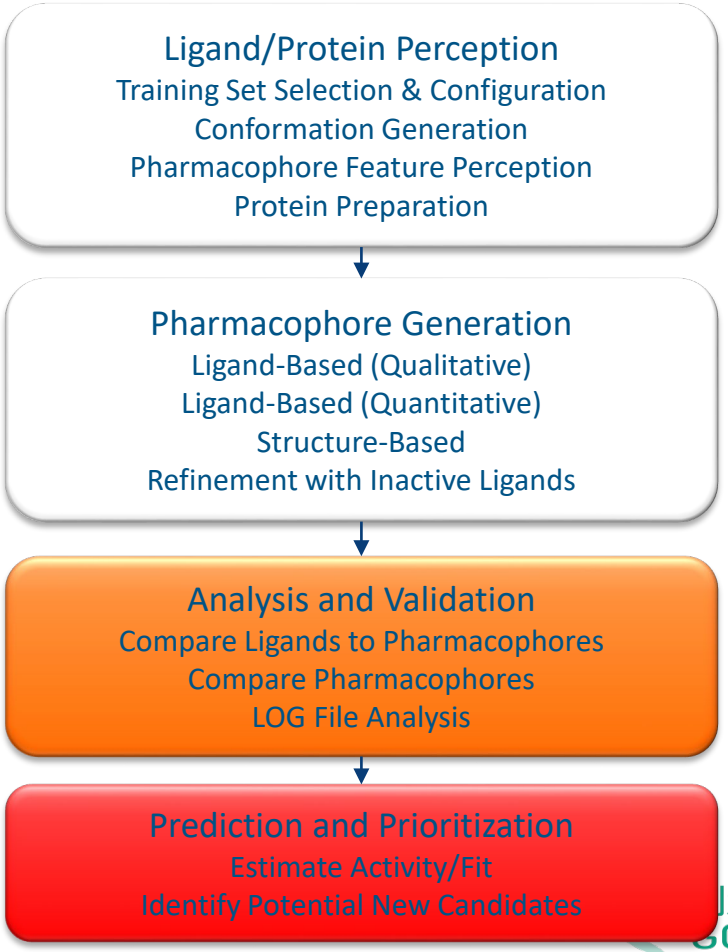




3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

rp., All rights reserved.

Typical Pharmacophore Workflow



- A hypothesis is a falsifiable object
- A receptor-ligand pharmacophore represents the interactions of only one ligand

- Evaluate graphically
  - View all hypotheses
  - Are any redundant → cluster
  - Should some of them be combined?
  - Can they be edited?

- Additional pharmacophore analysis
  - Cluster pharmacophores
  - Compare pharmacophores
  - Merge pharmacophores
  - Average pharmacophore features

Continue to Analysis tools

Continue to Prediction tools

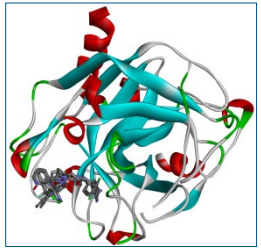
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

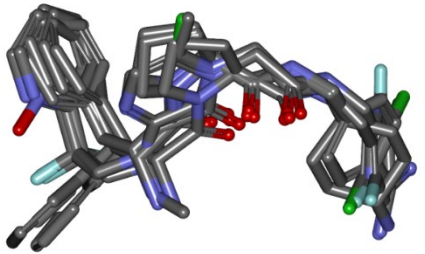
源生技
GGA

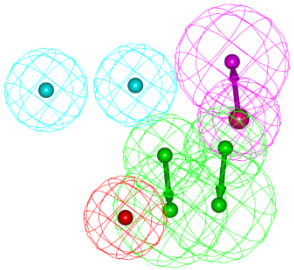
Copyright©2019 GGA Corp., All rights reserved.

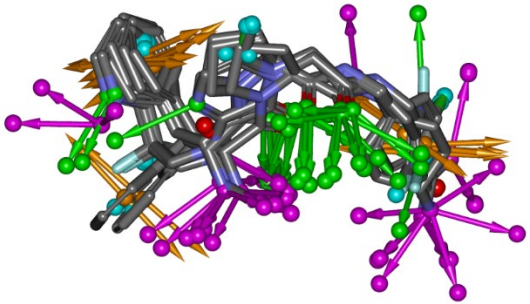
Multiple Ligands Alignment-Based

- Input Data and Starting Knowledge
  - Aligned ligands
    - From aligned proteins
    - From docking results
- Objective
  - Generate (and validate) pharmacophores representing the receptor-ligand interactions of a complex
- Applications
  - Virtual screening
  - Ligand profiling
  - Pose filtering
  - Search databases





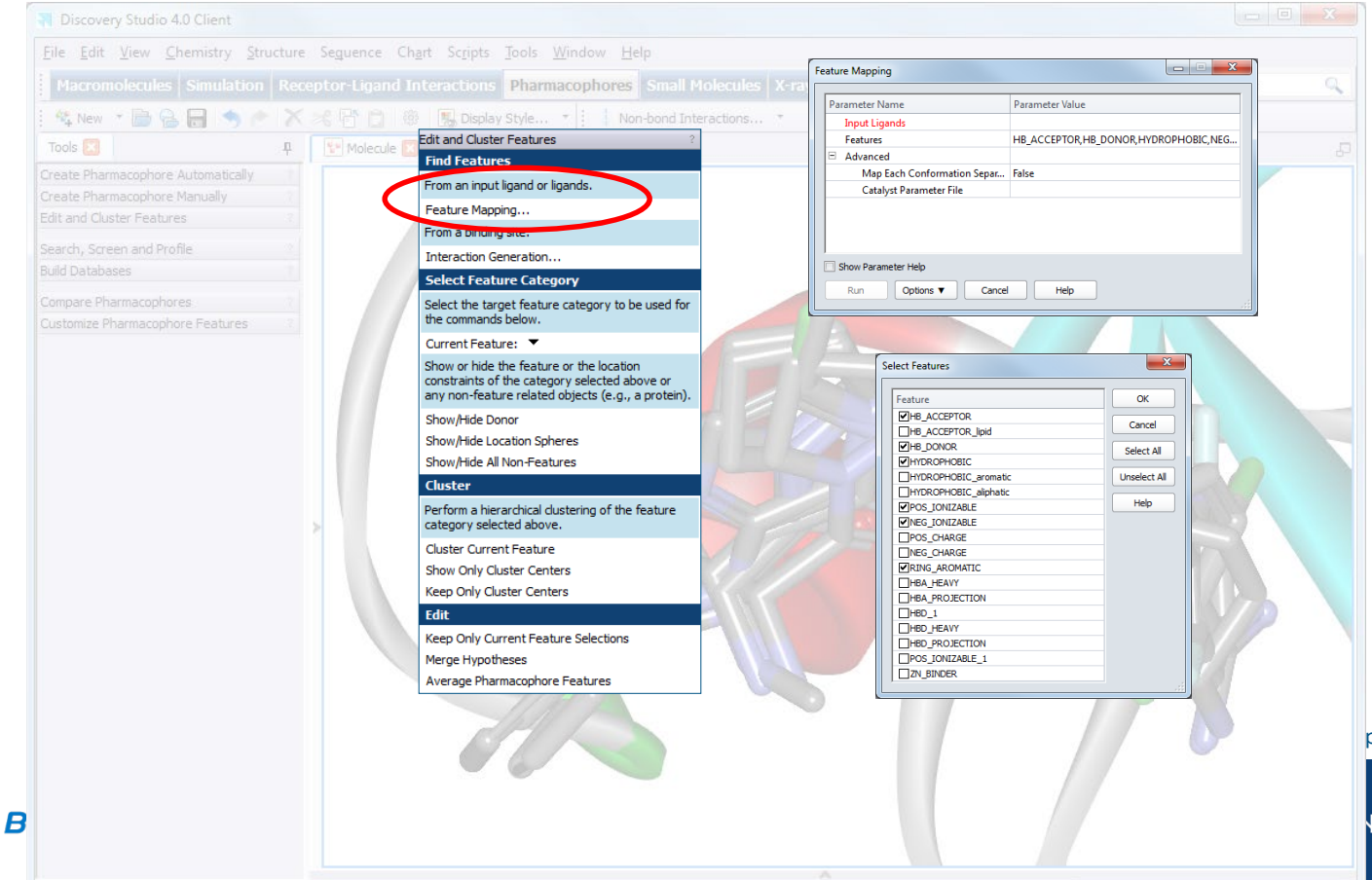




3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Protocol in Discovery Studio



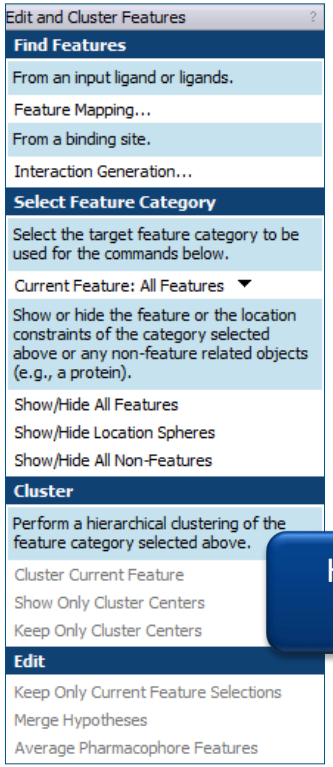
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

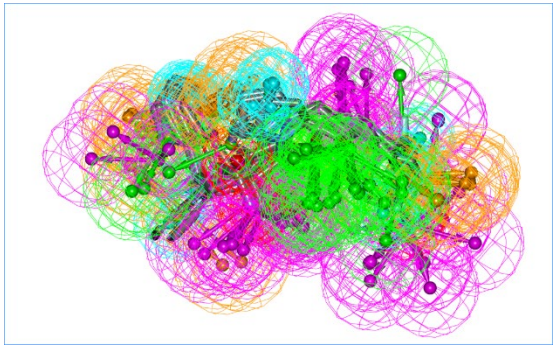
p., All rights reserved.

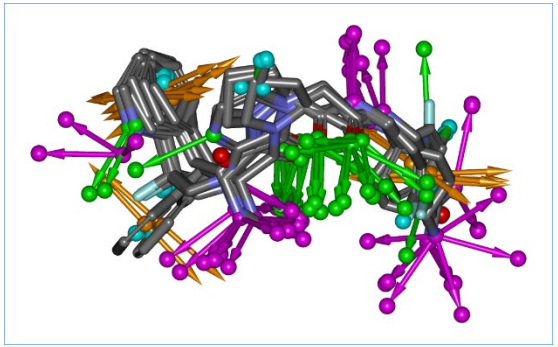
NCE® Company

Editing Alignment-Based Pharmacophores

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |







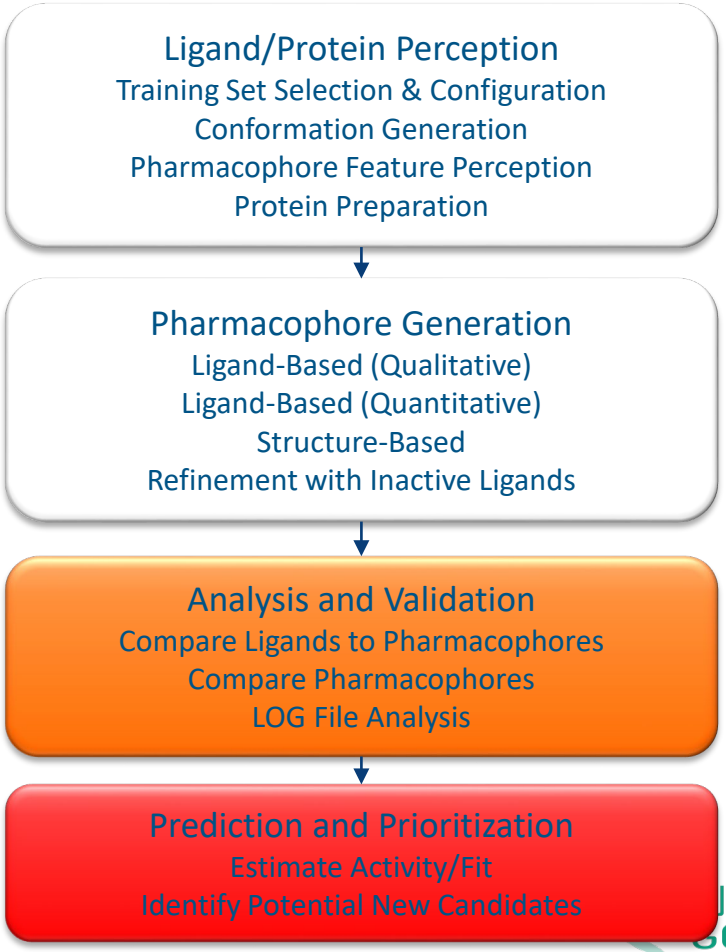
Hide location spheres to simplify display

Tips to bear in mind when editing alignment–based pharmacophores

Alternate showing/hiding aligned ligands and the protein(s) to decide which best features to select/delete/average

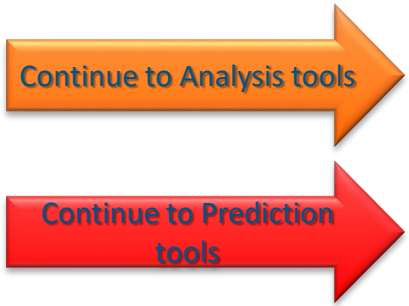
Use the Hierarchy View to select features if mouse or lasso selections are difficult

Typical Pharmacophore Workflow



- A hypothesis is a falsifiable object
- A receptor-ligand pharmacophore represents the interactions of only one ligand

- Additional pharmacophore analysis
  - Cluster pharmacophores
  - Compare pharmacophores
  - Merge pharmacophores
  - Average pharmacophore features



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

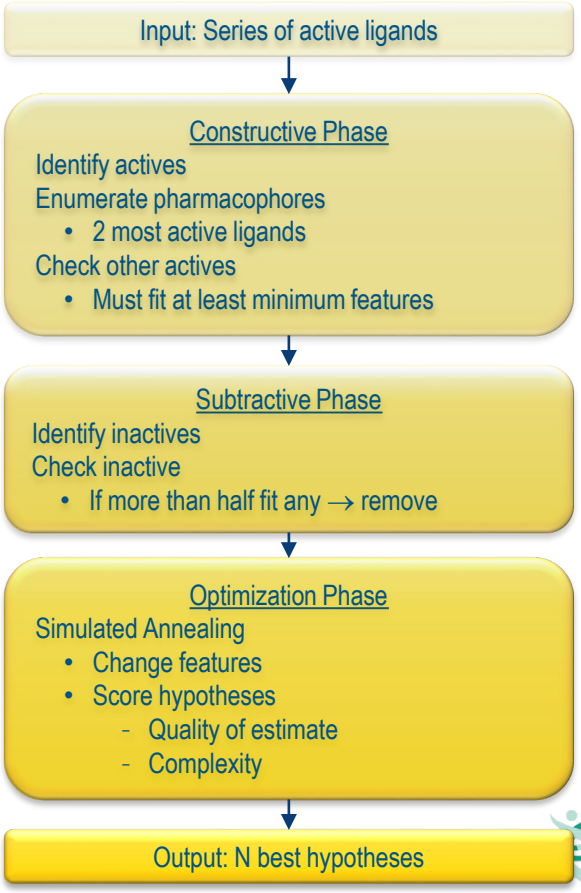
Pharmacophore

- Pharmacophore Modeling in Discovery Studio
- Structure-Based Pharmacophores
- Common Feature Pharmacophore Generation
- 3D QSAR Pharmacophore Generation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Quantitative Ligand-Based (HypoGen)




```
Summary of parameters:
  HyposReported          10
  Spacing               300
  MinPoints               4
  MinSubsetPoints         4
  SuperpositionError      1
  Misses                  1
  FeatureMisses           1
  CompleteMisses      0.0e+000
  ToleranceFactor         1
  CheckSuperposition      1
  WeightVariation       0.3
  MappingCoeff        0.0e+000
  Mem                    60
  IdealHBondGeomOnly  0.0e+000
  VariableWeight      0.0e+000
  VariableTolerance   0.0e+000

Constraints on numbers of features:
Name:       HBA            HBD        HYDROPHOB aliphatiPosIonizable    RING AROMATIC  Total
Min:          0              0              0              0              0              1
Max:          5              5              5              5              5              5


Best records in pass 2.
0
dumping score for hypothesis 1

Definition:    HYDROPHOB aliphHYDROPHOB aliphHYDROPHOB aliphaRING AROMATIC  RING AROMATIC
Weights:          2.07603        2.07603        2.07603          2.07603        2.07603
Tolerances:          1.60           1.60           1.60     1.60     1.60     1.60     1.60
Coords: X            1.36           2.32           5.68    -3.15    -5.27     0.12    -1.03
      : Y           -4.94          -1.82          -7.30     6.59     4.86     1.62     1.95
      : Z           -0.12          -0.60          -0.96    -0.73     0.50     1.07     3.83
                        0              0              0  0--------->  0--------->

HYDROPHOB aliphatic o
HYDROPHOB aliph    3.3
HYDROPHOB aliph    5.0            6.4
RING AROMATIC o   12.4           10.0           16.5
        --->      11.8           10.2           16.4     3.0
RING AROMATIC o    6.8            4.4           10.7     6.2     6.3
        --->       8.3            6.7           12.4     6.8     6.1     3.0

Maximum Fit: 10.3802

Name              Fit  Cnf/Enan       Mapping          Est       Act      Error     Unc
cpd1205kcal      9.72 61     + [33  2   36  47  3  ]      3.3       2.7    +   1.2     3
N8-598kcal      10.04 46     + [33  2   36  48  3  ]      1.6       4.4    -   2.8     3
cpd1195kcal      9.22 145    + [33  2   36  54  3  ]       11       7.1    +   1.5     3
cpd1215kcal      8.75 41     + [33  2   36  47  3  ]       31        26    +   1.2     3
cpd785kcal       7.50 16     + [33  *   36  46  3  ]      540        63    +   8.6     3
cpd-465kcal      7.79 175    + [7   57  4   *   32 ]      280       150    +   1.8     3
cpd-E-135kcal    7.53 4      + [33  *   36  46  3  ]      510       250    +   2       3
cpd-375kcal      7.43 36     + [7   *   4   46  32 ]      650       270    +   2.4     3
cpd-1125kcal     7.22 127    + [33  *   36  47  3  ]     1100       690    +   1.5     3
cpd765kcal       7.69 50     + [33  *   36  46  3  ]      350      1200    -   3.4     3
cpd-345kcal      6.94 219    - [33  *   36  7   3  ]     2000      1700    +   1.2     3
2ADHS            6.21 252    + [50  56  37  *   *  ]    11000      2400    +   4.4     3
cpd-2-195kcal    6.59 56     - [33  *   36  47  3  ]     4400      3100    +   1.4     3
cpd-125kcal      6.58 64     - [7   *   4   46  32 ]     4600      6000    -   1.3     3
cpd-425kcal      7.37 10     + [7   *   4   46  32 ]      740      9600    -  13       3
SDZ-87-469kcal   5.94 71     + [33  *   36  *   3  ]    20000     43000    -   2.2     3
terbinafine5kcal 5.98 7      + [33  *   36  *   1  ]    18000     93000    -   5.2     3
*****************************************************************
Mirror image used.  To turn this option off, put
catHypo.forceAbsoluteStereochemistry=1 in the .Catalyst file.
*****************************************************************
 totalcost=84.3221 RMS=1.02445 correl=0.927129
 Cost components: Error=66.102 Weight=1.15669 Config=17.0634 Tolerance=0


Fixed Cost:
 totalcost=75.3697 RMS=0 correl=0
 Cost components: Error=57.1813 Weight=1.12499 Config=17.0634 Tolerance=0

0
dumping score for hypothesis 2

0
0
0
0
dumping score for the null hypothesis:
 totalcost=120.68 RMS=2.77322 correl=0
 Cost components: Error=120.68 Weight=0 Config=0 Mapping=0 Tolerance=0

Version:      Discovery Studio catHypo  2.0 (365)  Thursday, December 01, 2007 at 12:33 AM
Confs (cpd):  C:\Program Files\SciTegic_ses70\web\jobs\tluu\{c1pF7F41-52E0-45DD-B582-E84550F25E8E}\Intermediate/
Spreadsheet:  C:\Program Files\SciTegic_ses70\web\jobs\tluu\{c1pF7F41-52E0-45DD-B582-E84550F25E8E}\Intermediate/mols.spst
Dictionary:   C:\Program Files\SciTegic_ses70\web\jobs\tluu\{c1pF7F41-52E0-45DD-B582-E84550F25E8E}\Intermediate/Dictionary.chm
Host:         infinity.accelrys.net
Outname:      sqep_training_hypogen
Logname:      sqep_training_hypogen.log
CPU time = 316 s  System time = 0 s
Complexity 81.2042
Concluded pass 2.
Finished generating a hypothesis.
```

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Ligand Perception

Training Set Requirements

3D QSAR Pharmacophore Generation

Common Feature Pharmacophore Generation

- 2 - 32 compounds
- Ideally 6 ligands
- Structurally diverse set of input molecules
- Feature-rich ligands
- Include the most active ligands

- 18 - 25 molecules structurally diverse
  - ≥ 15 ligands necessary
  - Mixture of actives and inactives
- Activities should span
  - 4 log units
  - Smaller activity range allowed by a Catalyst parameter setting
  - Each order of magnitude represented by ≥ 3 compounds
- Include 4-5 pairs that 'teach' algorithm something specific about SAR
  - Ligands with similar structures should differ in activity by at least an order of magnitude
  - Ligands with similar activity must be structurally distinct
- No ligands violating excluded volumes
  - Steric Refinement with Excluded Volumes
- No redundant information

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Training Set Selection

- Methods for training (and test) set selection
  - Manual inspection by eye (recommended method)
  - Based on 2D properties and fingerprints (Small Molecules tool set)
    - Calculate Molecular Properties protocol (Calculate Molecular Properties)
    - Calculate Principal Component protocol (Design and Analyze Libraries)
    - Generate Training and Test Data (Create QSAR Model)
    - Cluster Ligands protocol (Design and Analyze Libraries)
    - Find Diverse Molecules protocol (Select Subset Libraries)
    - Optimise Subset Library with Pareto Method (Select Subset Libraries)
      - Optimize to maximise Unique Value Count of fingerprint properties
      - For 3D QSAR Pharmacophore Generation, optimize to maximize Standard Deviation of activity

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Training Set Configuration

- Ligands require biological activity and degree of confidence of activity data
  - Can also be configured to be considered active or inactive when using ligands to automatically place excluded volumes (HypoGenRefine)
- Activities (IC_{50}, K_i) – Activ property
  - Specifies the ligand's biological activity
  - Smaller values mean more active
  - Always use the same unit
  - No logarithmic values
- Uncertainty – Uncert property
  - Relates to the degree of confidence about the biological data
  - Tolerance factor for activity values
  - Value of 3 (default) means that the actual activity probably falls in a range that is 3 times more or less than the reported value
    - Eg. An activity of 6 and uncertainty of 3 will set up a range of activity values for a given ligand as 2 - 18

Note: If the Uncert property is not provided for the training set, it will be set to 3.0 for all ligands

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation

Pharmacophore Generation

Input: Series of active ligands

Constructive Phase
Identify actives
Enumerate pharmacophores
- 2 most active ligands

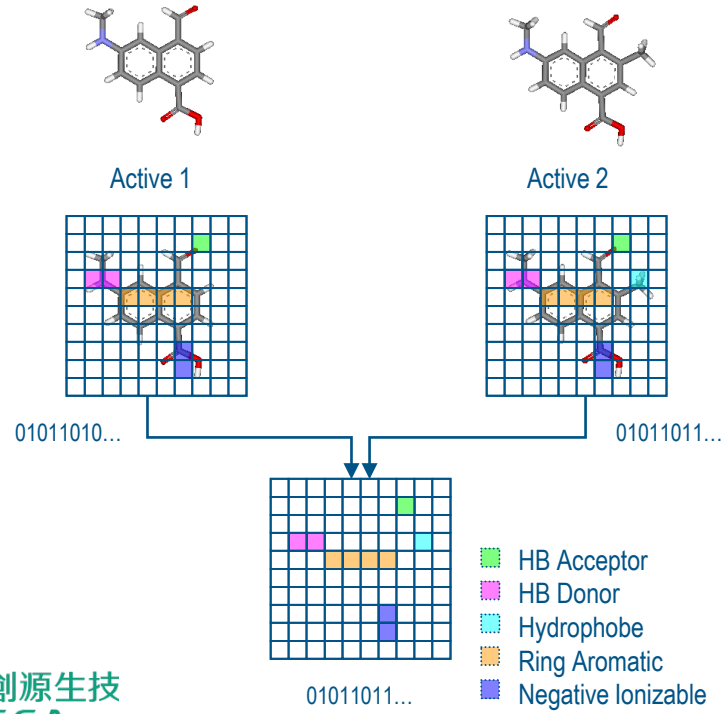
Check other actives
- Must fit at least minimum features

Subtractive Phase
Identify inactives
Check inactive
- If more than half fit any → remove

Optimization Phase
Simulated Annealing
- Change features
- Score hypotheses
  - Quality of estimate
  - Complexity

Output: N best hypotheses

All pharmacophores for the most active compounds are identified and quantized into bins



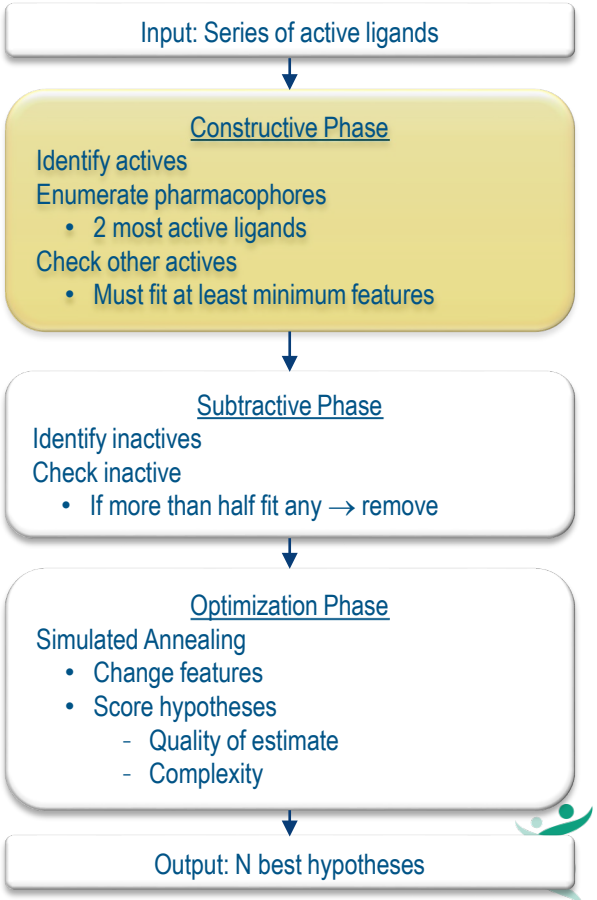
創源生技
GGA

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation

Pharmacophore Generation



- Conceptually very similar to the HipHop algorithm

1. Identify active/lead ligands
   - Most active ligands and ligands where

$$MA \times Unc_{MA} - \frac{A}{Unc_A} > 0.0$$

MA – Activity of most active ligand
Unc – Uncertainty of the ligand
A - Activity of ligand in question

   - If there are more than 8 active ligands, only the top 8 are used
2. Identify and store all allowable hypotheses among the two most active ligands
   - Hypotheses can consist of up to 5 features
3. Keep those hypotheses that fit a minimum subset of features of the remaining active/lead ligands
   - Minimum subset number controlled by Minimum Subset Points parameter (default 4)
   - Minimum Subset Points parameter specifies minimum number of points allowed to define a partial miss (a fit of only n-1 features of a hypothesis)

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Input: Series of active ligands

Constructive Phase
Identify actives
Enumerate pharmacophores
- 2 most active ligands

Check other actives
- Must fit at least minimum features

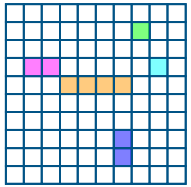
Subtractive Phase
Identify inactives
Check inactive
- If more than half fit any → remove

Optimization Phase
Simulated Annealing
- Change features
- Score hypotheses
  - Quality of estimate
  - Complexity

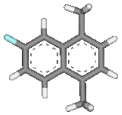
Output: N best hypotheses

Pharmacophore Generation

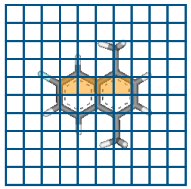
Pharmacophores present in inactive ligands are removed



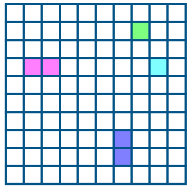
01011011…



Inactive



00010001…

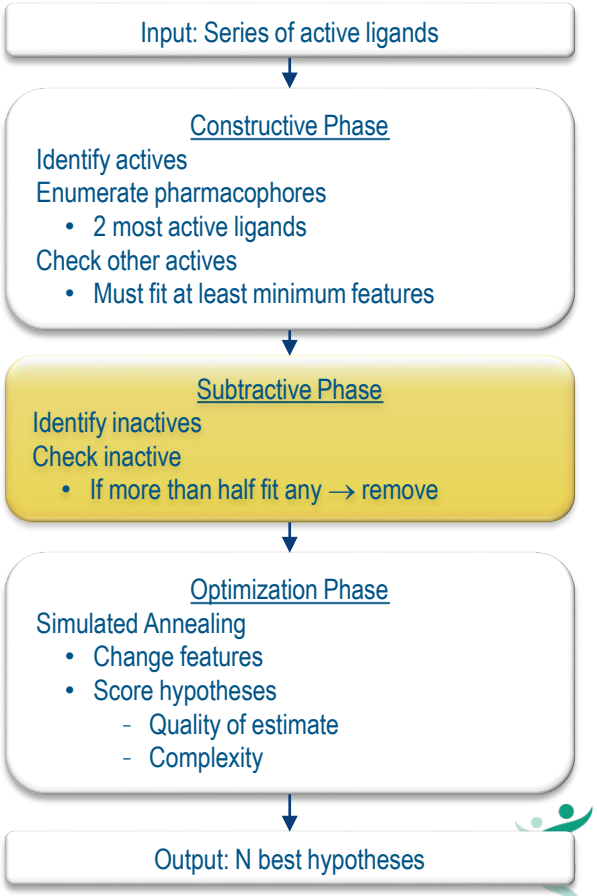


01001010…

創源生技
GGA

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation



- Removes hypotheses that are not likely to be useful

1. Identify inactive ligands
   - A ligand is inactive if the activity is 3.5 orders of magnitude greater than the most active ligand

$$\log(A) - \log(MA) > 3.5$$

MA – Activity of most active ligand
A - Activity of ligand in question

   - User adjustable, Inactive Spread parameter
2. Remove hypotheses that match more than half of the ligands identified as inactive
   - Leaves a set of hypotheses that are potentially able to discriminate actives from inactives
   - If the activity spread is smaller (<3 orders of magnitude)
     - Adjust the uncertainties of the ligands accordingly in order to still differentiate between active and inactive ligands OR
     - Adjust the Inactive Spread parameter
     - Will make it possible to still get useful information from the Subtractive phase if the activity spread is less than the ideal of 4.0

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation

Pharmacophore Generation

Input: Series of active ligands

Constructive Phase
Identify actives
Enumerate pharmacophores
- 2 most active ligands

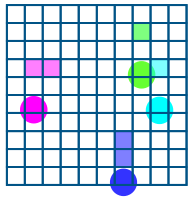
Check other actives
- Must fit at least minimum features

Subtractive Phase
Identify inactives
Check inactive
- If more than half fit any → remove

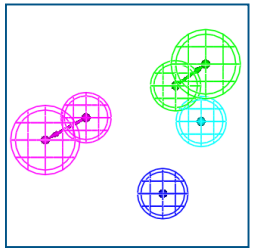
Optimization Phase
Simulated Annealing
- Change features
- Score hypotheses
  - Quality of estimate
  - Complexity

Output: N best hypotheses

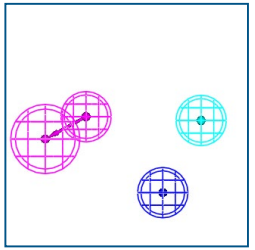
Hypotheses are generated from different combinations of bins and tweaked to improve correlation (cost)



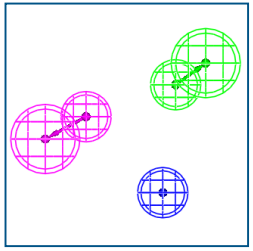
01001010…



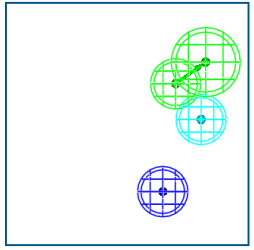
R=0.93



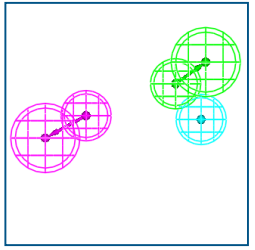
R=0.82



R=0.96



R=0.95



R=0.70

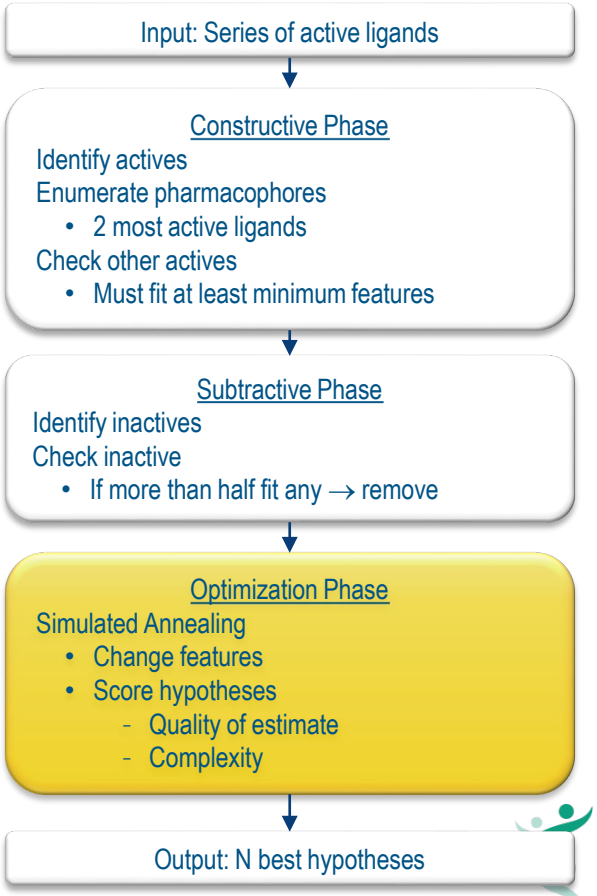
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Pharmacophore Generation

Pharmacophore Generation



- Simulated annealing algorithm where small perturbations are applied to the hypotheses to try and improve score
  - Rotating a vectored feature
  - Translating a randomly selected feature
  - Adding/removing a feature
  - Changing relative weight or tolerance of a feature
- Optimization stops when hypotheses containing the best combinations of RMS and correlation coefficient, and lowest total cost have been identified
  - 10 highest scoring, unique hypotheses are exported
  - Uses Occam's Razor principle (the simplest hypothesis that accurately estimates the activity is considered the best)

1. Calculate geometric fits
   - Fast ligand-pharmacophore comparison algorithm
2. Perform linear regression of -log(Activity) vs. geometric fit
   - Estimate activity of each training set ligand
   - The greater the geometric fit, the greater the activity prediction of the ligand
3. Total Cost is calculated for each new hypothesis

$$\text{Total Cost} = \text{Error cost} + \text{Weight cost} + \text{Configuration cost}$$

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

ghts reserved.

Detailed Analysis Report

Analysis and Validation

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

1. Summary of Run Parameters:

HypoGen Parameters	
Spacing	150
Variable Weight	No
Variable Tolerance	No

Features Constraints		
Name	Min	Max
HBA	0	5
HBD	0	5
HYDROPHOBIC	0	5
HYDROPHOBAromatic	0	5
Poslonizable	0	5
Total	1	5

2. Overall Results:

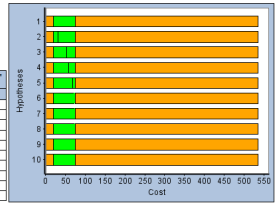
Pharmacophore Space: 1.794562e+006

Best records in pass: 7.

Fixed Cost: 78.7043

Null Cost: 613.375

Cost Analysis (Fixed/Null distance = 534.7 bits)	
Index	Null Cost Distance
1	515.97
2	504.17
3	462.17
4	477.37
5	466.31
6	463.65
7	461.85
8	461.56
9	460.54
10	459.96

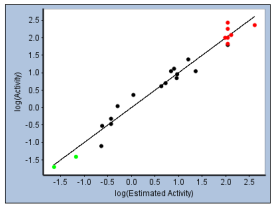


3. Hypotheses Results:

Hypothesis 1

Results	
Maximum Fit	8.36732
Total Cost	97.4045
RMS	1.22667
Correlation	0.983595

Description	
Features	Weights
HBA	1.67346
HBD	1.67346
HYDROPHOBAromatic	1.67346
HYDROPHOBIC	1.67346
Poslonizable	1.67346



Name	Fit	Est	Act	Err	Status	Mapping
sem-40	7.03	0.023	0.02	+1.1	active	[25 50 45 29 9]
sem-34	6.56	0.067	0.039	+1.7	active	[* 5 1 44 53]
sem-31	6.04	0.23	0.079	+2.8	moderately active	[7 18 1 14 *]
sem-39	6.02	0.24	0.3	-1.3	moderately active	[25 * 47 31 9]
sem-29	5.82	0.37	0.34	+1.1	moderately active	[4 27 22 1 *]
sem-14	5.82	0.37	0.48	-1.3	moderately active	[20 * 9 34 2]
sem-30	5.69	0.51	1.1	-2.2	moderately active	[7 18 1 21 *]
sem-44	5.37	1.1	2.3	-2.2	moderately active	[29 11 1 29 *]
sem-08	4.76	4.3	4.1	+1	moderately active	[32 30 29 11 *]
sem-21	4.67	5.3	5	+1.1	moderately active	[* 31 16 12 *]
sem-24	4.43	9.1	7	+1.3	moderately active	[15 * 9 18 *]
sem-22	4.42	9.3	9	+1	moderately active	[31 * 12 28 *]
sem-20	4.02	23	11	+2.2	moderately active	[18 * 44 23 *]
sem-13	4.55	6.9	11	-1.6	moderately active	[* 28 20 10 *]
sem-23	4.49	8	13	-1.6	moderately active	[29 * 12 18 *]
sem-09	4.18	16	24	-1.5	moderately active	[12 3 * 17 *]
sem-58	3.35	110	62	+1.8	moderately active	[* * 17 32 *]
sem-59	3.35	110	67	+1.6	inactive	[* 36 11 * *]
sem-07	3.40	97	100	-1	inactive	[33 69 * 34 *]
sem-48	3.34	110	100	+1.1	inactive	[* 16 7 * *]
sem-12	3.28	130	120	+1.1	inactive	[14 * * 4 *]
sem-46	3.35	110	180	-1.6	inactive	[* * 6 27 *]
sem-49	2.77	410	230	+1.8	inactive	[* * 9 32 *]
sem-47	3.34	110	270	-2.4	inactive	[* * 6 16 *]

Hypothesis 2

Results	
Maximum Fit	7.54347
Total Cost	109.207
RMS	1.55936
Correlation	0.973441

Description	
Features	Weights
HBA	1.50869
HBD	1.50869
HYDROPHOBAromatic	1.50869
HYDROPHOBIC	1.50869
Poslonizable	1.50869

Name	Fit	Est	Act	Err	Status	Mapping
sem-40	6.97	0.013	0.02	-1.5	active	[25 50 45 29 9]
sem-34	5.88	0.16	0.039	+4	active	[* 5 1 41 53]
sem-31	5.66	0.26	0.079	+3.3	moderately active	[7 18 1 14 *]
sem-39	5.71	0.24	0.3	-1.3	moderately active	[25 * 59 31 9]
sem-29	5.52	0.36	0.34	+1.1	moderately active	[4 27 22 1 *]
sem-14	5.23	0.71	0.48	+1.5	moderately active	[20 * 9 31 2]
sem-30	5.30	0.6	1.1	-1.8	moderately active	[7 18 1 21 *]

Pharmacophore generation summary
- Features constraints
- Cost analysis

Individual pharmacophore analysis
- Plot of log(Activity) vs log(Estimated Activity) of training set
- Active and inactive ligands coloured
- Training set ligands prediction and mapping summary

创源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Cost Analysis

Analysis and Validation

- 3D QSAR Pharmacophore Generation distinguishes between hypotheses by applying cost analysis
  - Gives an idea about the statistical significance of the hypothesis(es)
- Simplicity is defined using the minimum description length principle from information theory
  - Cost assigned to hypotheses in terms of the number of bits required to describe them fully
- Overall cost of a hypothesis:

$$\text{Total Cost} = \text{Error cost} + \text{Weight cost} + \text{Configuration cost}$$

2 cost limits – Fixed and Null

- Computed within minutes of the start of hypothesis generation
  - Advanced | Browse parameter will compute statistics for assessing the quality of the training set, but will not run the generation
- Measured in units of bits

Null cost

- Cost of a hypothesis for which we assume there is no structure data
  - Only 1 activity value (average of all activities in the training set)
- Highest cost (upper bound for the experiment)

Fixed cost

- Cost of a perfect hypothesis with no (minimum) deviation between predicted and experimental activities
- Lowest cost (lower bound for the experiment)

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

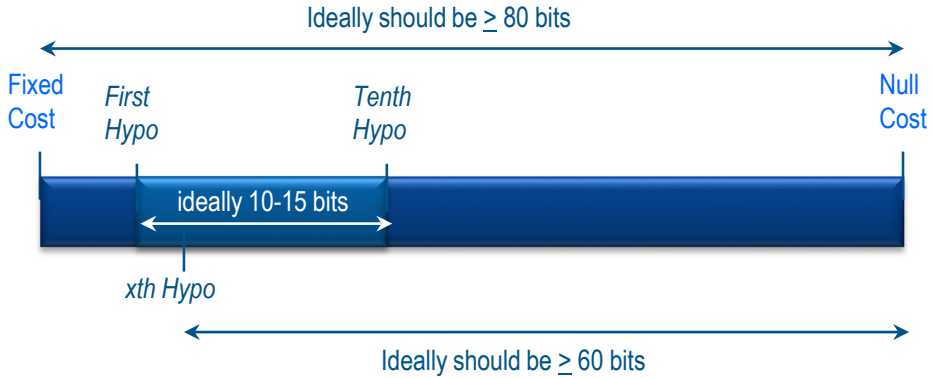
Copyright©2019 GGA Corp., All rights reserved.

Cost Analysis

Analysis and Validation

The greater the difference between the Fixed and Null cost, the higher the probability for finding useful hypotheses

If the difference between the Fixed and Null cost is < 20, then reconsider the training set



if Δ cost > 60 90% 90% statistical significance †
if Δ cost ~ 30-40 70-80% statistical significance
if Δ cost > 20 40-50% statistical significance

† based on randomization tests

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Cost Components

Analysis and Validation

$$\text{Total Cost} = \text{Error cost} + \text{Weight cost} + \text{Configuration cost}$$

Error cost

- A value that increases as the RMS difference between estimated and measured activities for the training set molecules increases
- This cost factor is designed to favor models where the correlation between estimated and measured activities is better
- The standard deviation of this parameter is given by the Uncertainty parameter
- Has a major effect in establishing the Total Cost

Weight cost

- A value that increases in a Gaussian form as the feature weight in a model deviates from an idealized value of 2.0
- This cost factor is designed to favor hypotheses where the feature weights are close to 2
- The standard deviation of this parameter is given by the Weight variation parameter

Configuration cost

- A fixed cost which depends on the complexity of the hypothesis space being optimized
- Equal to the Entropy of the hypothesis space
- This parameter is constant among all the hypotheses

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Other Cost Considerations

Analysis and Validation

Other terms in the Total Cost component part of the log file:

Entropy of Hypothesis space = $2^{\text{Configuration cost}}$

- Describes the complexity of the hypothesis space the algorithms will have to analyze
  - If <18, then thorough analysis of pharmacophore domain (models)
  - If >18, then Catalyst truncates space and some models are not considered
    - Molecules too flexible (?)
    - Consider modifying the training set
  - If = 17, then CPU run time is long and memory required >120Mb
  - Upper limit of 17.0 does not apply to the variable weight or variable tolerance modes

RMS

- Deviation of the log(estimated activities) from the log(experimental activities) normalized by the log(Uncertainties)
- Indicates how well Catalyst was able to correlate actual with estimated activities for a given hypothesis
- Does not actually reveal anything about the predictivity of a hypothesis
- Predictivity of a hypothesis must be determined by estimating the activities of ligands outside of the training set

CorrCoeff

Derived from the fit index (simple linear regression)

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

創源生技 GGA

Copyright©2019 GGA Corp., All rights reserved.

Agenda

- Briefly Overview - 10 min
- Molecular Docking Modules in DS
  - CDOCKER, LibDock, Flexible Docking
- Pharmacophore
  - Structure-based Pharmacophore
  - Ligand-based Pharmacophore
- Fragment-Based Design
- ADMET and Toxicity Prediction

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Rationale Small Drug Design

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 For NCKU and NTHU

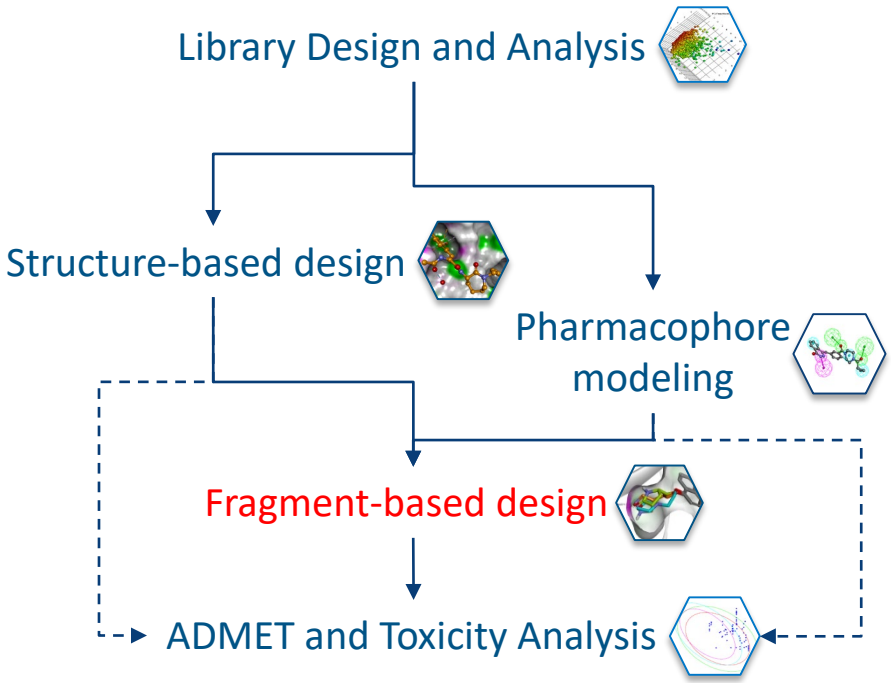
Scales

10^3~10^7 Molecules from Library

10^0~10^2 Molecules As Leads

10^2~10^3 Molecules as Novel Derivatives

10^0~10^2 Molecules Pass ADMET and Toxicity Screening



Copyright©2019 GGA Corp., All rights reserved.

SBD: Fragment-Based Design Methods



Alternative fragment-based methods available
- Fragment Based Pharmacophores

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

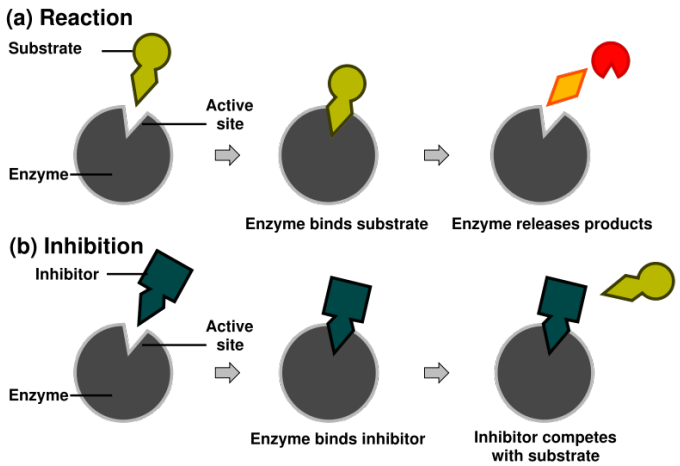
SBD: Fragment-Based Design Methods

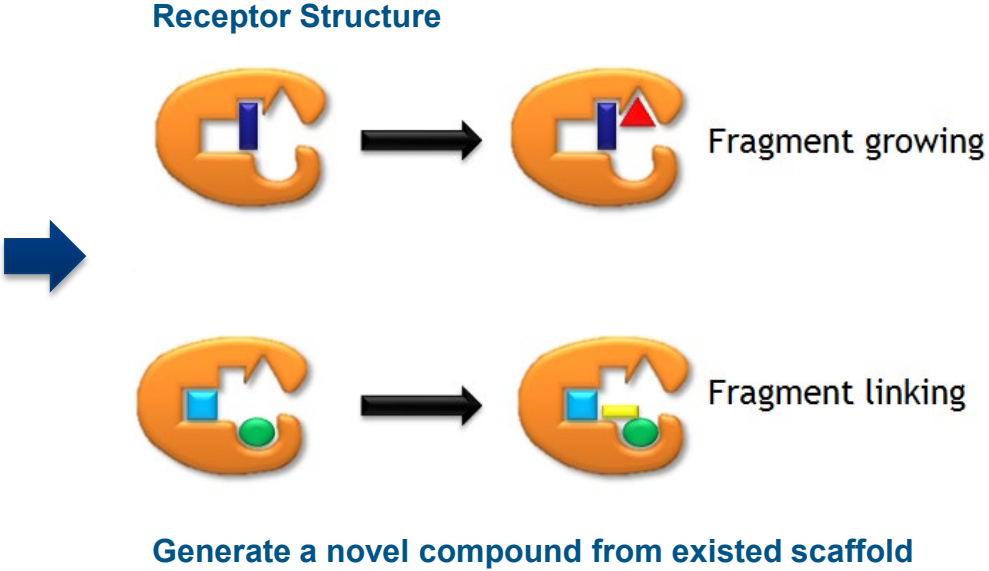
- GROW
  - Reaction-based in situ ligand enumeration
  - E.g., Amide synthesis, Esterification, Hiyama, Kuyama, Negishi, Stille, Suzuki, Williamson Ether
  - Pre-filtered sets of reagents selected from ACD
- REPLACE
  - Fragment based in situ isostere replacement
  - E.g., scaffold-hopping, R-group replacement
  - Pre-filtered set of 1.5M fragments generated from SCD

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Fragment-Based Drug Design



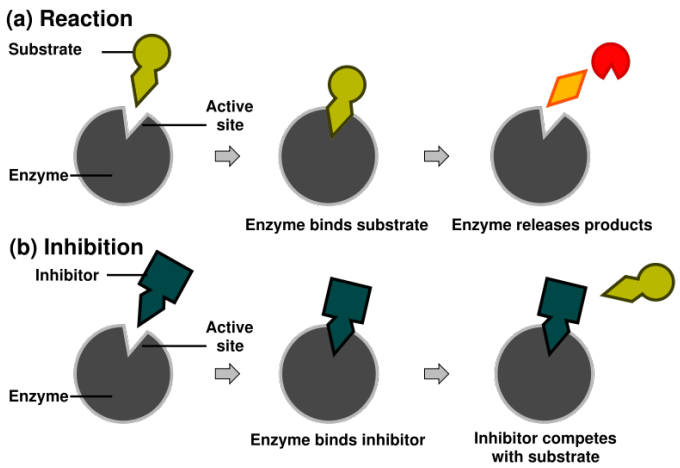


Generate a novel compound from existed scaffold

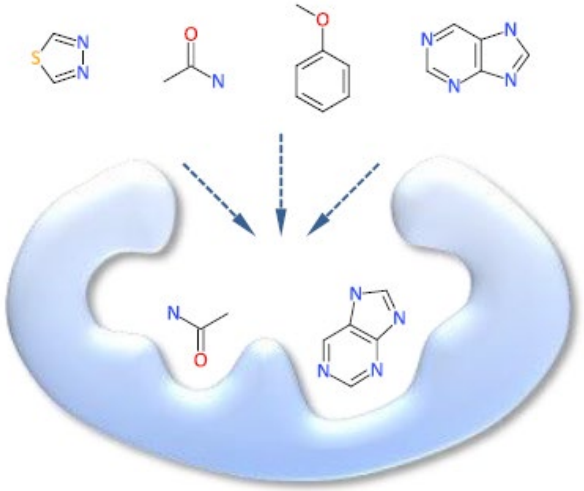
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

De novo Drug Design



Generate a novel compound from fragment DB

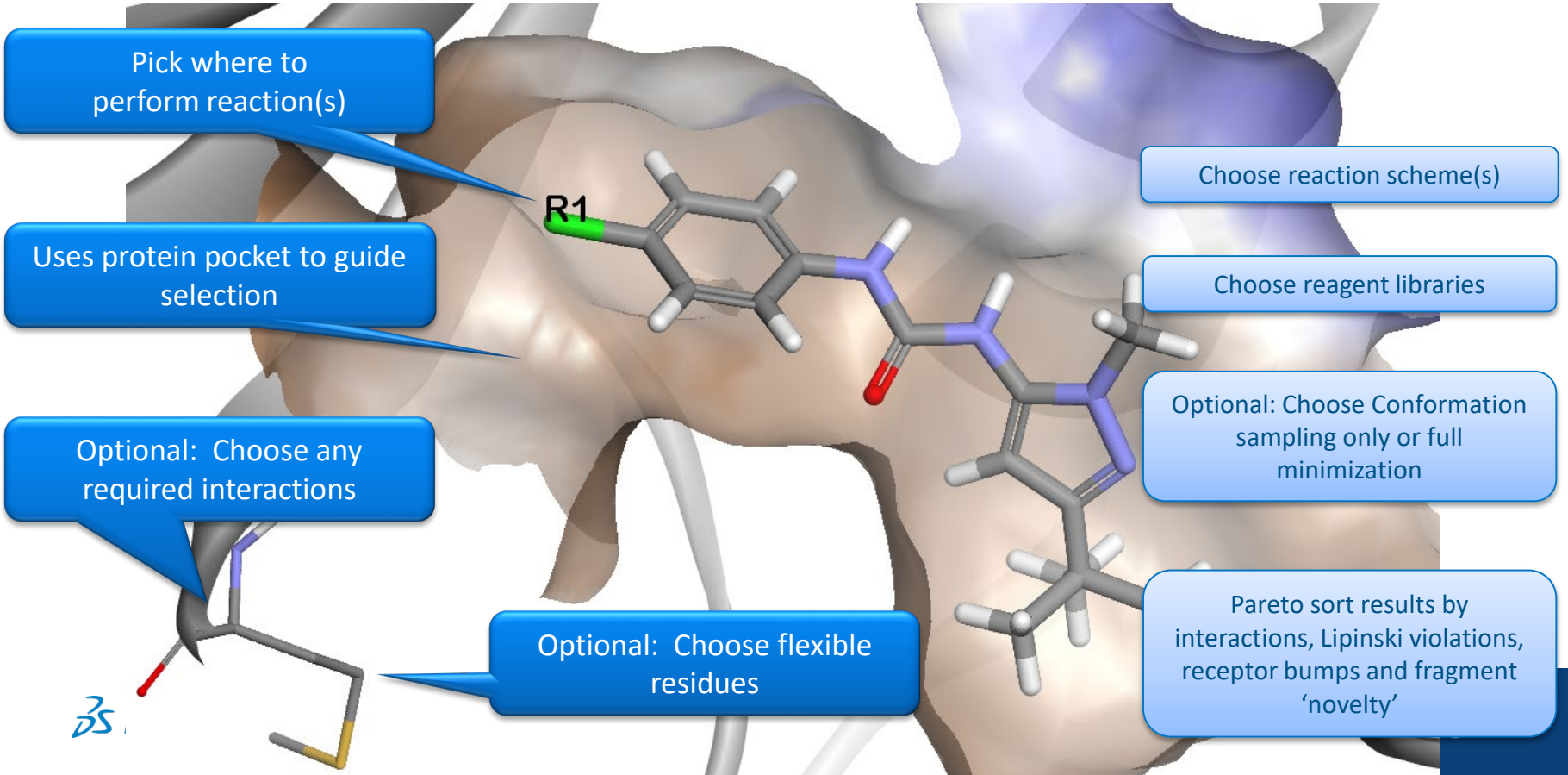


Receptor Structure

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

GROW: Reaction-based *in-situ* Ligand Optimization

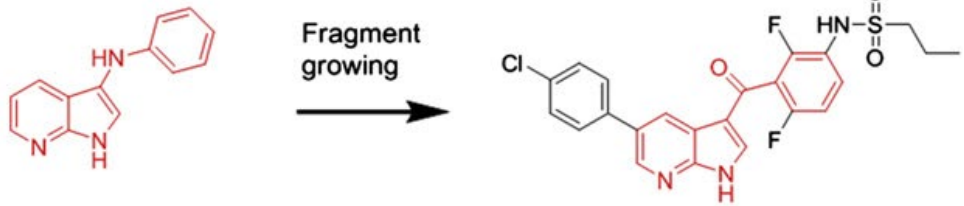


3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Fragment-based design of the BRAF inhibitor vemurafenib.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

First fragment-based drug (Zelboraf) approved in 2011!



4

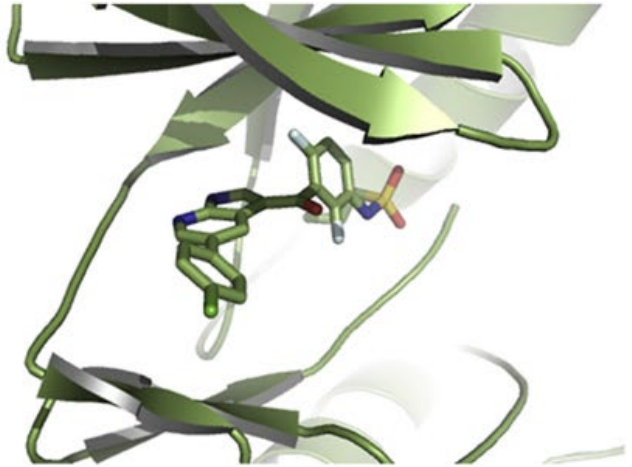
Unselective, weakly potent fragment hit (IC_{50} > 100μM)

PIM-1 IC_{50} ~ 100μM

5 (Vemurafenib)

BRAF (V600E) IC_{50} = 31nM
High degree of selectivity against other kinases

PIM-1 IC_{50} > 100μM



Swen Hoelder, Paul A. Clarke, Paul Workman, 2012

Copyright©2019 GGA Corp., All rights reserved.

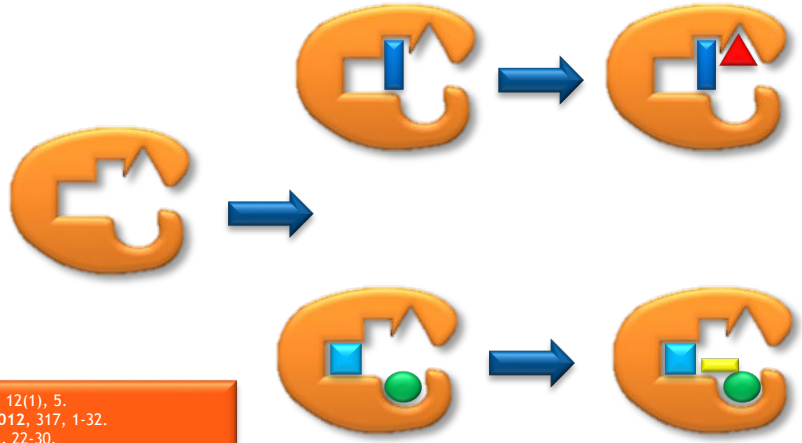
Fragment Based Drug Design (FBDD)

FBDD在過去十年中有很大的發展，目前已被應用於新藥開發領域。。

- 已有大量的論文成功案例
- 至少已促成18種臨床藥物進入臨床試驗階段

DS FBDD工具可應用於以下類型研究，幫助藥物設計開發

- 小分子片段結合模式預測
- 篩選新型候選藥物
- 提供小分子化合物結構置換方案



Baker, M. Fragment-based lead discovery grows up. *Nat. Rev. Drug Discov.* **2012**, 12(1), 5.
Erlanson DA. Introduction to fragment-based drug discovery. *Top. Curr. Chem.* **2012**, 317, 1-32.
Fischer M, Hubbard RE. Fragment-based ligand discovery. *Mol. Interv.* **2009**, 9(1), 22-30.
Congreve M, Chessari G, Tisi D, Woodhead AJ. Recent developments in fragment-based drug discovery. *J. Med. Chem.* **2008**, 51(13), 3661-3680.

Copyright©2019 GGA Corp., All rights reserved.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Fragment-based lead discovery

Definition

低分子量的小分子片段

•分子量: 100-250 Da

•Rule of Three

•最小化可旋轉鍵數

高溶解度

包含適合用於合成的官能基

不包含不必要的官能基

•可降低毒性、毒理反應

化合物結構多樣性

Ro5 (drug-like)	Ro3 (fragment-like)
MW < 500	MW < 300
HBD ≤ 5	HBD ≤ 3
HBA ≤ 10	HBA ≤ 3
cLogP ≤ 5	cLogP ≤ 3

Advantages

- 在目前的醫藥化學領域中

~10^{60} ligand for MW ≤ 500

~10^{7} fragments for MW ≤ 160

用片段篩選將會比配體篩選更加有效率，且組合更加多樣化。

- 利用小分子片段進行藥物設計有以下優勢
  - 消除結構障礙以及氫鍵配位衝突
  - 根據熱力學原理提供有效的化合物片段鍵接、置換、與擴展建議
  - 提高化合物篩選的命中率
  - 降低毒性與代謝不穩定性的風險
- 結構最佳化後化合物特性也較易掌控
- 小分子片段設計能較易得知官能基或該片段是否已具有專利

* Congreve M, Carr R, Murray C, Jhoit H. A 'rule of three' for fragment-based lead discovery? *Drug Discov. Today*. **2003**, 8(19), 876.
† Rees DC, Congreve M, Murray CW, Carr R. Fragment-based lead discovery. *Nat. Rev. Drug Discov*. **2004**, 3(8), 660.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Preparing for FBDD – Fragments

Fragment DB ⟷ Ligand DB

設計片段資料庫時，需考慮以下因素

- 片段和結合位的有效性
- 合成難易度
- 反應活性部位與非活性特性的區分
- 配體酸性、中性、鹼性特性比例的組成
- 溶解度
- 分子結構的多樣性與複雜度
- 片段專利

可透過Pipeline Pilot所提供的Synthetic Accessibility Score# 與Quantitative Estimate of Drug-Likeness (QED)功能計算化合物特性

* Lau WF, Withka JM, Hepworth D, Magee TV, Du YJ, Bakken GA, Miller MD, Hendsch ZS, Thanabal V, Kolodziej SA, Xing L, Hu Q, Narasimhan LS, Love R, Charlton ME, Hughes S, van Hoorn WP, Mills JE. Design of a multi-purpose fragment screening library using molecular complexity and orthogonal diversity metrics. *J. Comput. Aided Mol. Des*. 2011, 25(7), 621.
† Lewell XQ, Judd DB, Watson SP, Hann MM. RECAP--retrosynthetic combinatorial analysis procedure: a powerful new technique for identifying privileged molecular fragments with useful applications in combinatorial chemistry. *J. Chem. Inf. Comput. Sci*. 1998, 38(3),511.
# Ertl P, Schuffenhauer A. Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions. *J. Cheminfo*. 2009, 1, 8.
§ Bickerton GR, Paolini GV, Besnard J, Muresan S, Hopkins AL. Quantifying the chemical beauty of drugs. *Nat. Chem*. 2012, 4(2), 90-98.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Preparing for FBDD - Proteins

用於FBDD的蛋白質結構，可從結構實驗結果中獲得，或是透過同源性蛋白質模擬(Homology Modeling)取得

蛋白質結構要用於FBDD前，應考慮以下因素

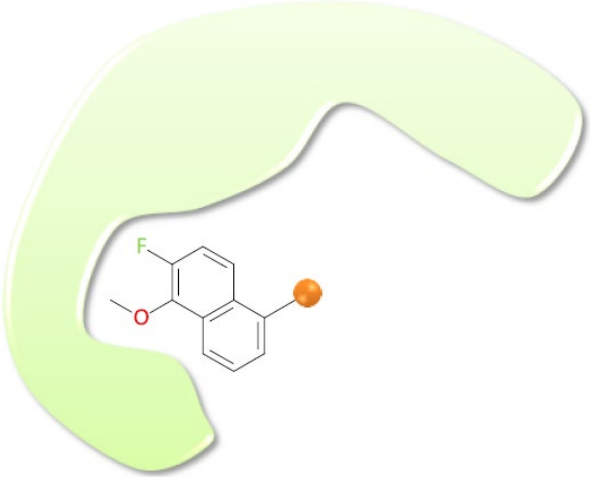
- Resolution
- 溫度(與分子動力學相關)
- 離子化狀態
- 結構是否缺損
- 蛋白質受體 與小分子配體結合模式
- 水分子作用力

Discovery Studio中，相關可應用的模組

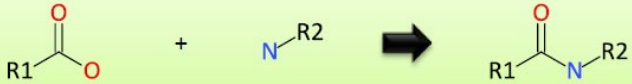
- Protein Report: 可分析蛋白質結構資訊
- Validate Protein Structure: 蛋白質結構的合理性評估工具
- Prepare Protein: 可手動或自動進行蛋白質結構修正
  - 修補缺損原子
  - 修補缺損胺基酸
  - 刪除Alternative conformation
  - 移除配體與水分子
  - 標準化atom與胺基酸名
  - pK預測

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Grow scaffold



Example: Amide Synthesis







Scaffold positioned in the protein active site

Select where to grow (perform reactions)

Choose reaction scheme(s)

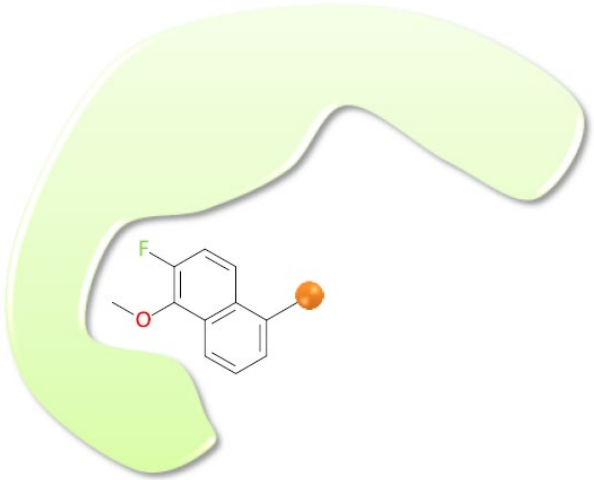
Choose reagent libraries

Grow scaffold

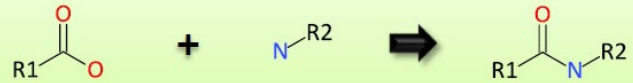
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Grow scaffold

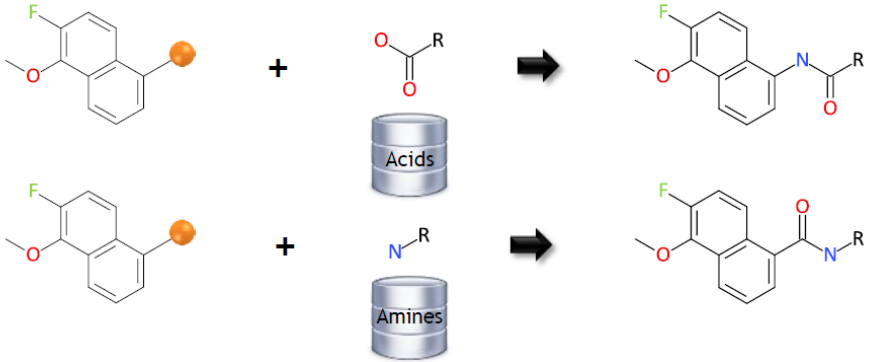


Example: Amide Synthesis



Grow Scaffold

選定骨架上的擴張點後，可以進一步指定反應類型與試劑(Reagent)資料庫，就會自動產生適合的官能基。



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Grow

- Example reactions schemes:
  - Amide synthesis
  - Esterification
  - Hiyama
  - Kuyama
  - Negishi
  - Stille
  - Suzuki
  - Williamson Ether

- Example reagent libraries*:
  - Amines (1000)
  - Alcohols (1002)
  - Carboxylic Acids (1006)
  - Boronic acids (799)
  - Grignard Reagents (240)
  - Halides (998)
  - Organo silanes (107)
  - Organo tins (48)
  - Organo zinc halides (59)

* Diverse sample of reagents, filtered by physico-chemical profile and undesirable functional groups, sourced from at least two vendors in ACD

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.

Rationale Small Drug Design

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 For NCKU and NTHU

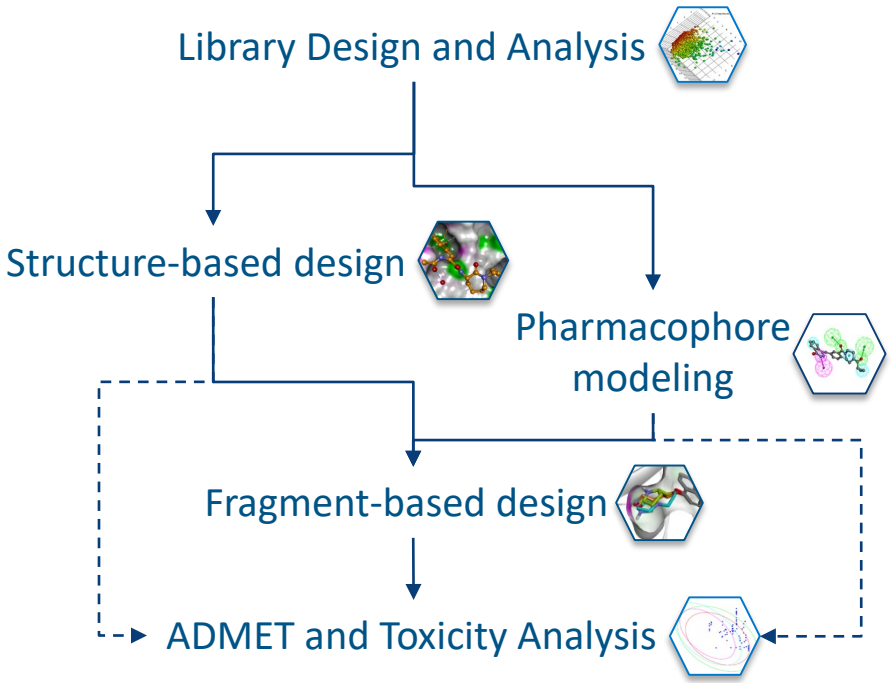
Scales

10^3~10^7 Molecules from Library

10^0~10^2 Molecules As Leads

10^2~10^3 Molecules as Novel Derivatives

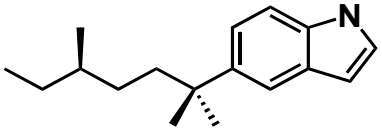
10^0~10^2 Molecules Pass ADMET and Toxicity Screening



Copyright©2019 GGA Corp., All rights reserved.

Predict compound properties by Statistic method: QSAR

- Quantitative Structure-Activity Relationships



Chemical Data



IC_{50} 0.4 μM

Numerical Properties

Molecular Descriptor

MW	AlogP	Surface Area	Dipole	…
243.39	5.601	260.587	0.662	…

Define Correlation

$$IC_{50} = f([MW],[A\log P],\square)$$

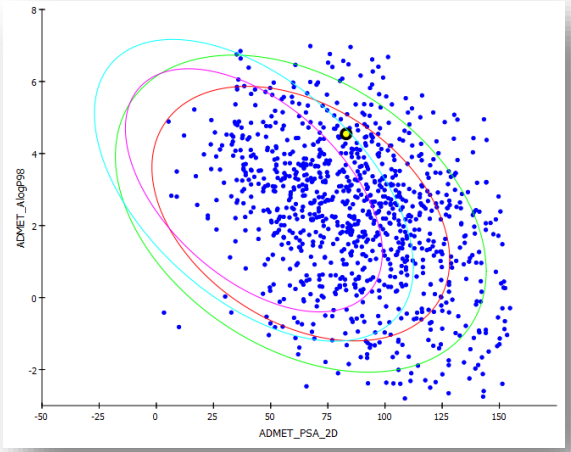
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

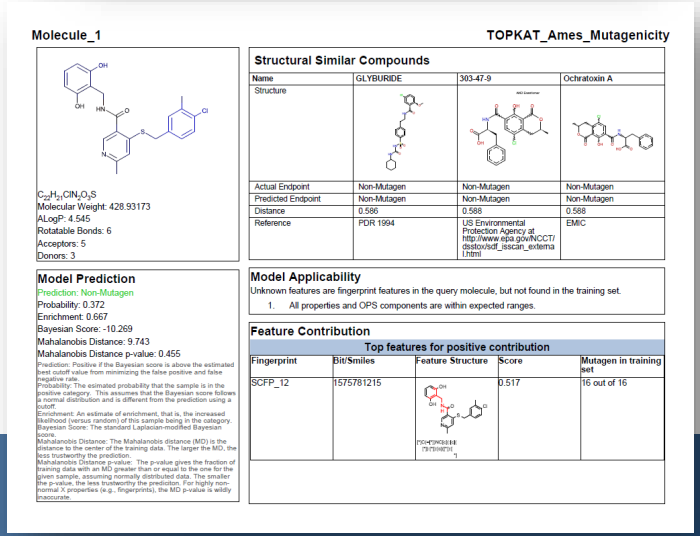
Copyright©2019 GGA Corp., All rights reserved.

ADMET and Toxicology

- ADMET
  - Human intestinal absorption
  - Aqueous solubility
  - Blood brain barrier penetration
  - Plasma protein binding
  - CYP2D6 binding
  - Hepatotoxicity
  - Filter sets of small molecules for undesirable function groups based on published SMARTS rules
- Property calculation
  - 2D and 3D molecular properties
  - Semi-empirical and DFT

- Predictive Toxicology
  - Ames mutagenicity
  - Rodent carcinogenicity (NTP and FDA data)
  - Weight of evidence carcinogenicity
  - Carcinogenic potency TD50
  - Developmental toxicity potential
  - Rat oral LD50
  - Rat maximum tolerated dose
  - Rat inhalation toxicity LC50
  - Rat chronic LOAEL
  - Skin irritancy and sensitization
  - Eye irritancy
  - Aerobic biodegradability
  - Fathead minnow LC50
  - Daphnia magna EC50
  - Log P





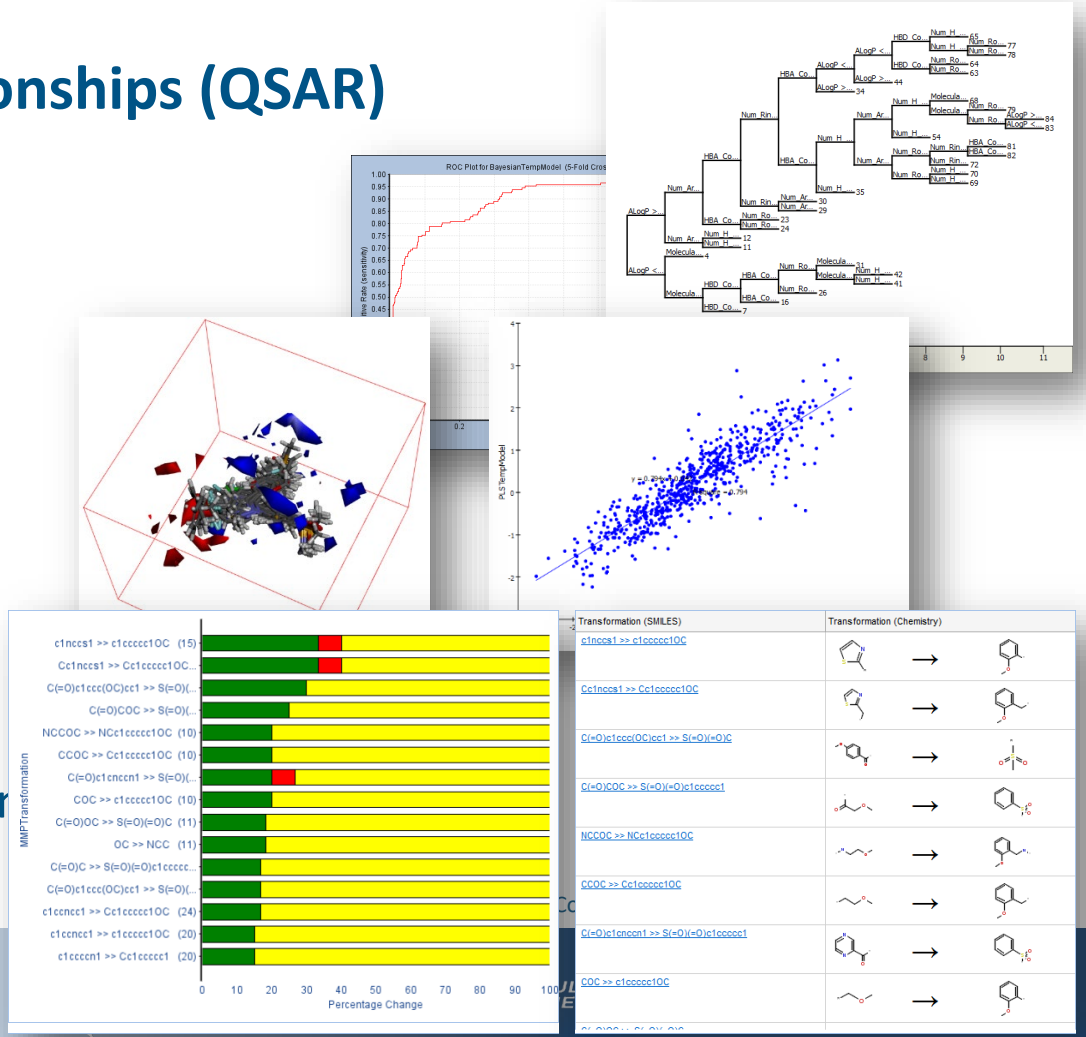
3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

BIOVIA

創源生技 GGA

Structure-Activity Relationships (QSAR)

- Categorical data
  - Bayesian
  - Recursive Partitioning
- Continuous data
  - Genetic Function Approximation
  - Partial Least Squares
  - Multiple Linear Regression
- 3D molecular field-based
- Matched Molecular Pairs (MMPs) transformations ar activity cliffs



3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

BIOVIA

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Q&A

Copyright©2019 GGA Corp., All rights reserved.

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |



創源生技
GGA

For more information please contact…



創源生技
GGA

台北市114內湖區新湖一路36巷28號

中華民國 台灣

Ph: (02) 2795 1777 x 3014 Fax: (02) 2793 8009

msc-support@gga.asia

www.gga.asia

3DS.COM/BIOVIA © Dassault Systèmes | Confidential Information | 4/29/2019 |

Copyright©2019 GGA Corp., All rights reserved.