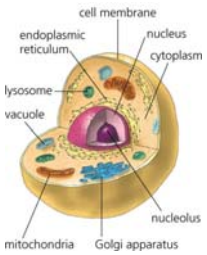
in silico 創薬法の開発
と
その応用例

東海大学・糖鎖科学研究所
平山　令明

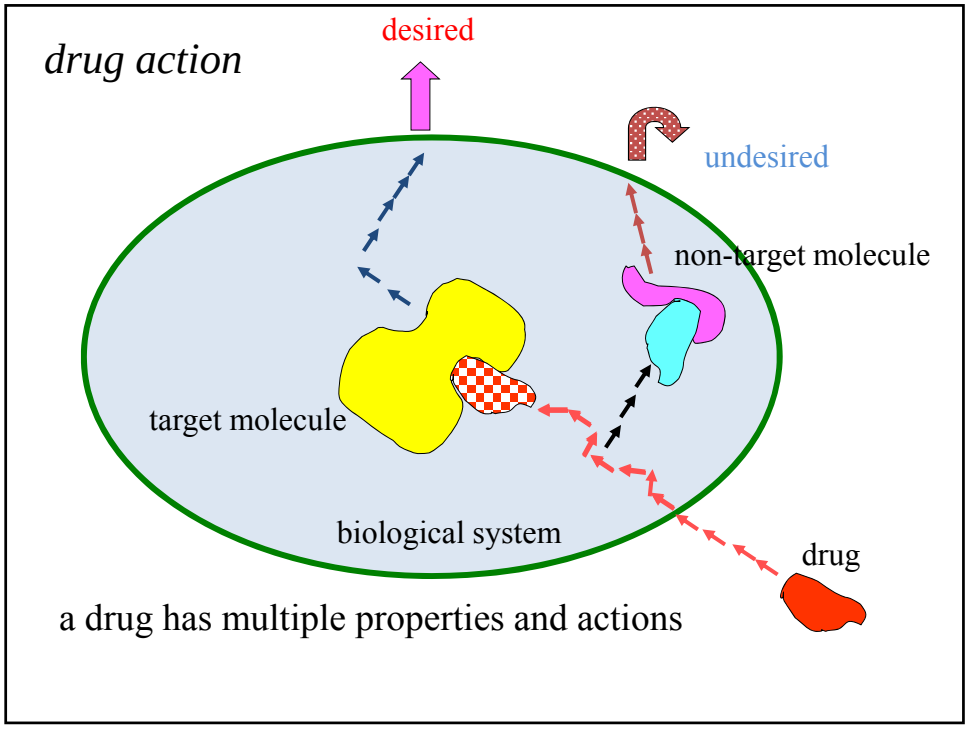
in silico

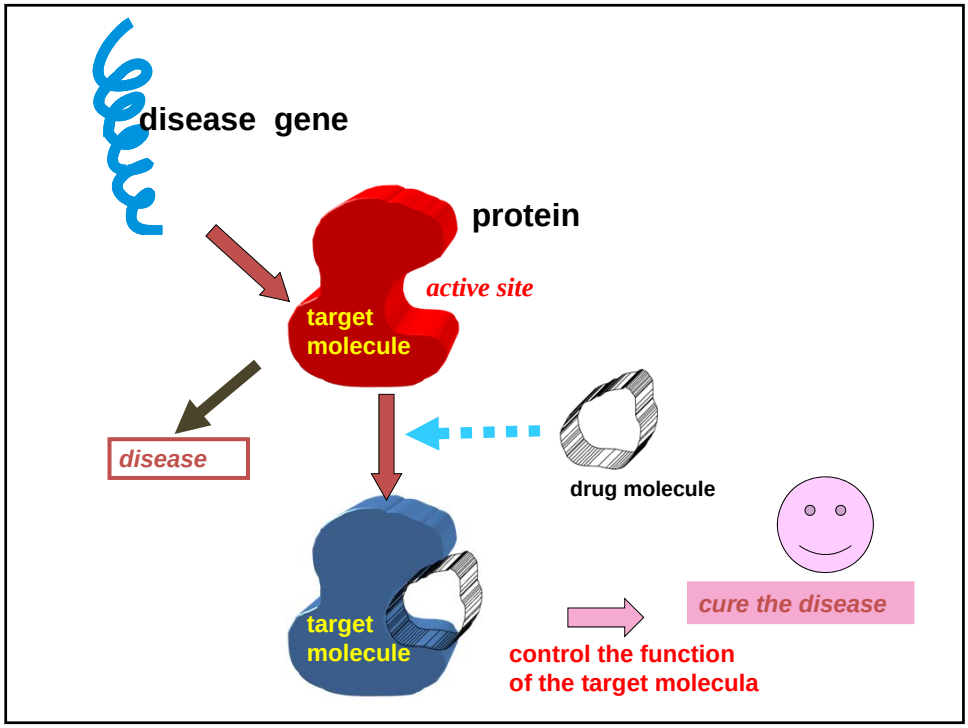
in vitro

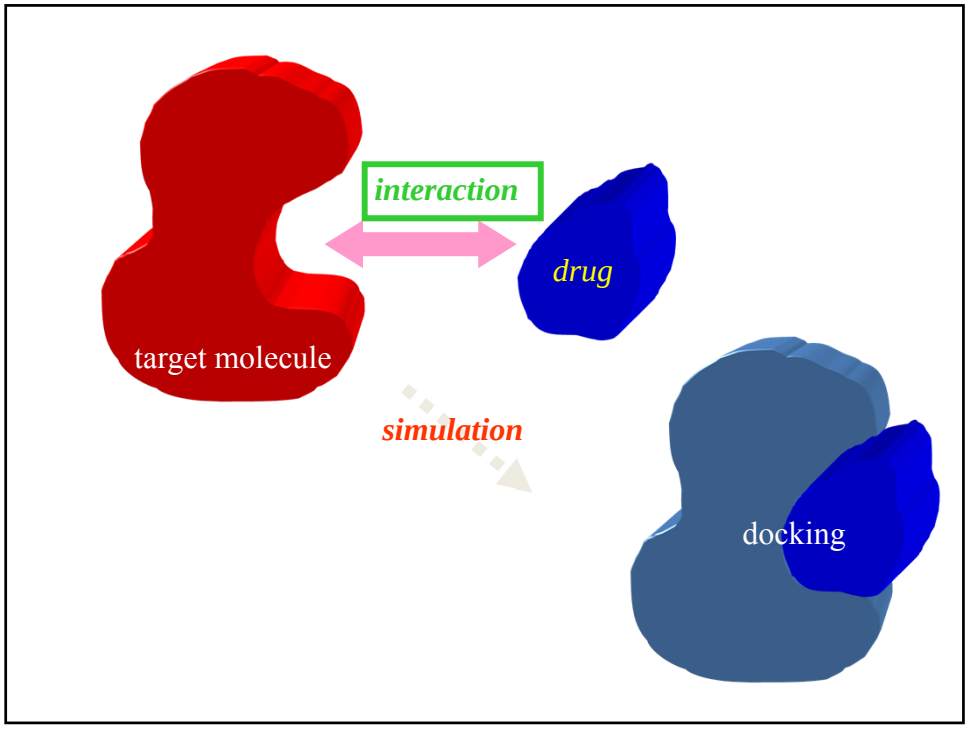


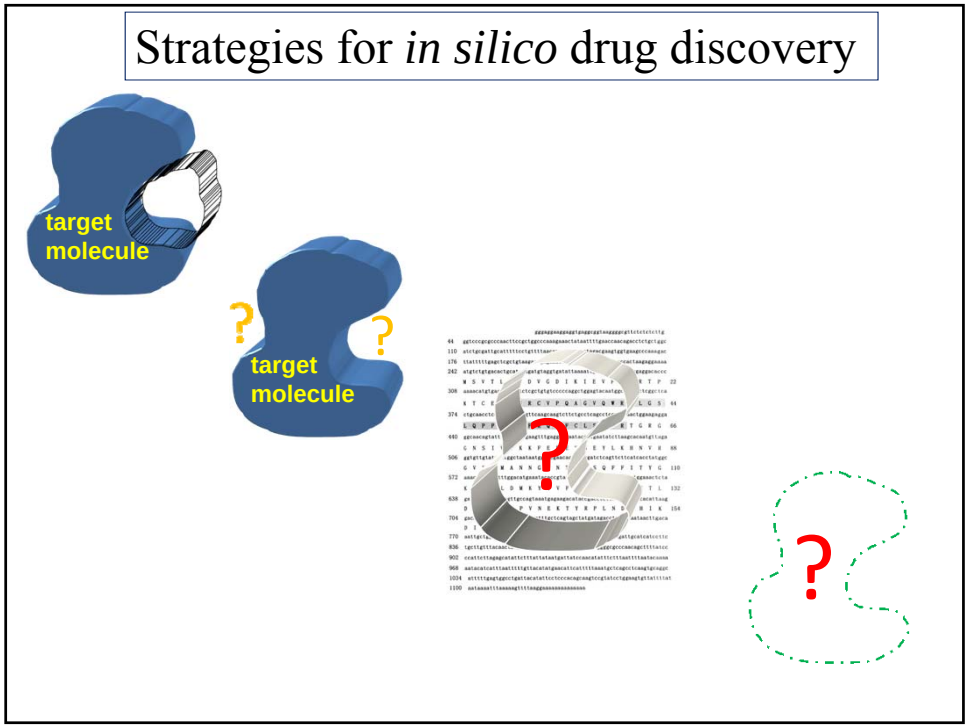
in vivo

2

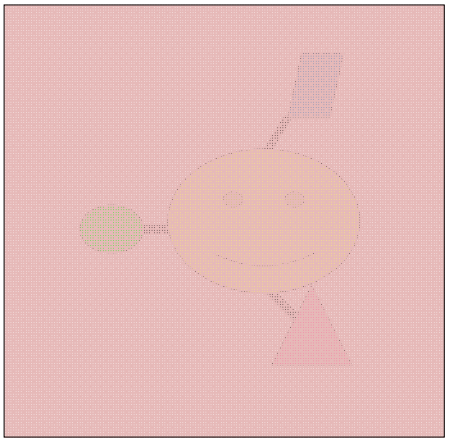

drug action
desired
undesired
non-target molecule
target molecule
biological system
drug
a drug has multiple properties and actions

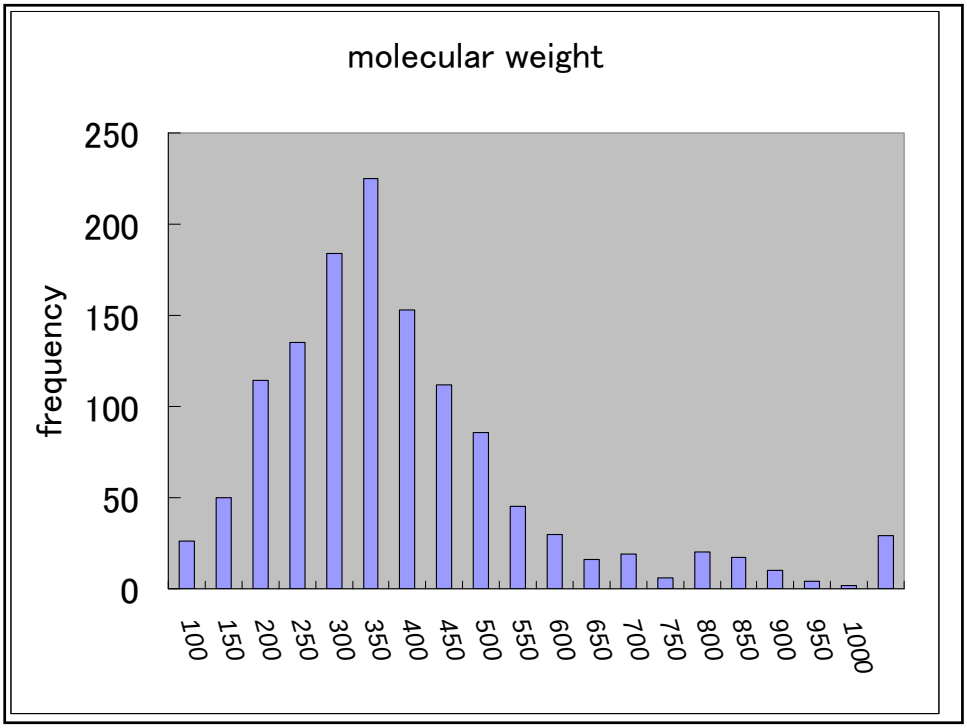

disease gene
protein
active site
target molecule
disease
drug molecule
target molecule
cure the disease
control the function
of the target molecula


interaction
drug
target molecule
simulation
docking


Strategies for *in silico* drug discovery
target molecule
target molecule
?
?
?
?

drug-likeness or what drugs look like ?

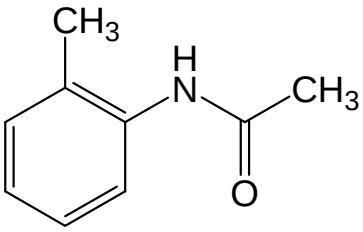




Molecular Descriptors

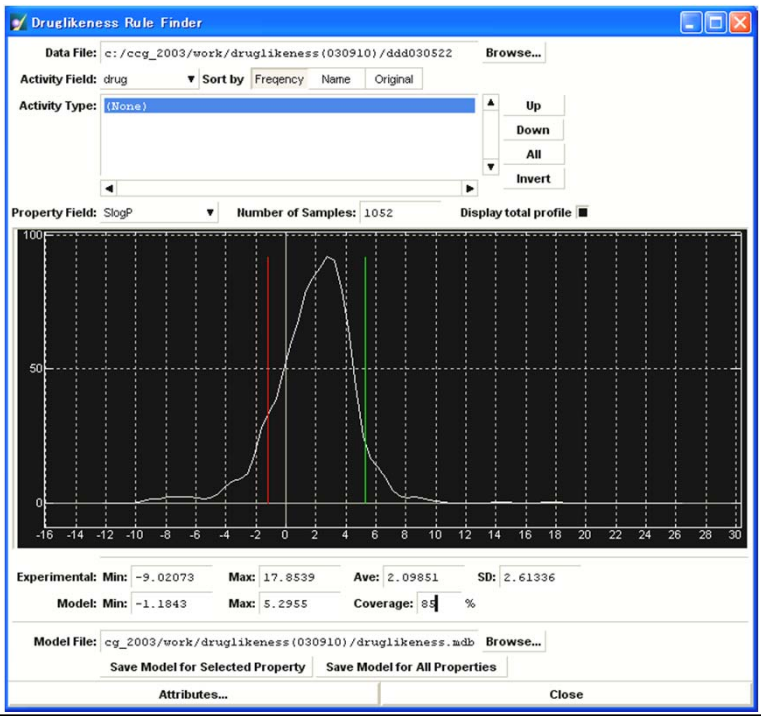
numerical values that characterize properties of molecule

- physicochemical properties
  e.g. hydrophobicity, molar refractivity, volume, surface
- numerical values derived by applying algorithmic techniques to the molecular structures
  e.g. topological indices,



hydrophobicity : logP

NH-amide fragment	-1.510
2 aliphatic isolating carbons	0.390
6 aromatic isolating carbons	0.780
10 hydrogens on isolating carbons	2.270
1 chain bond	-0.120
1 benzyl bond	-0.150
ortho substituent	-0.760
total	0.900

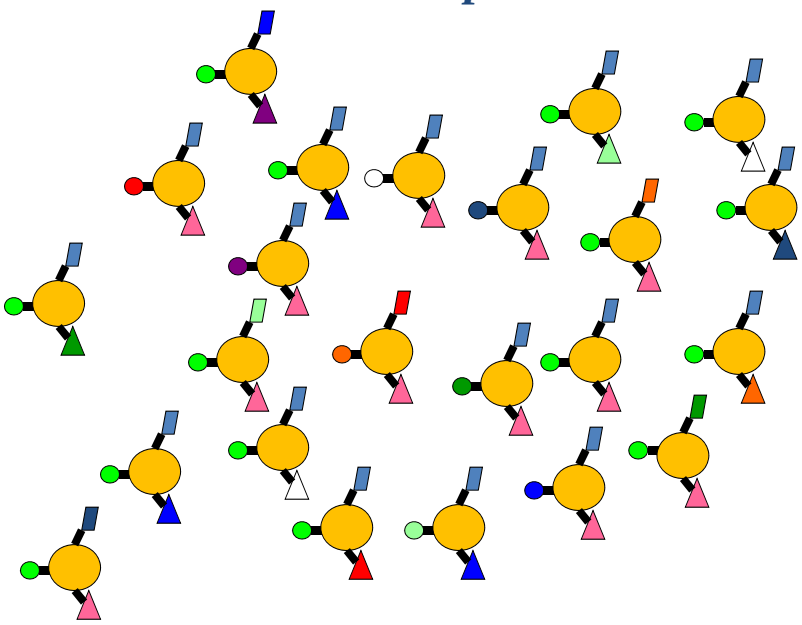


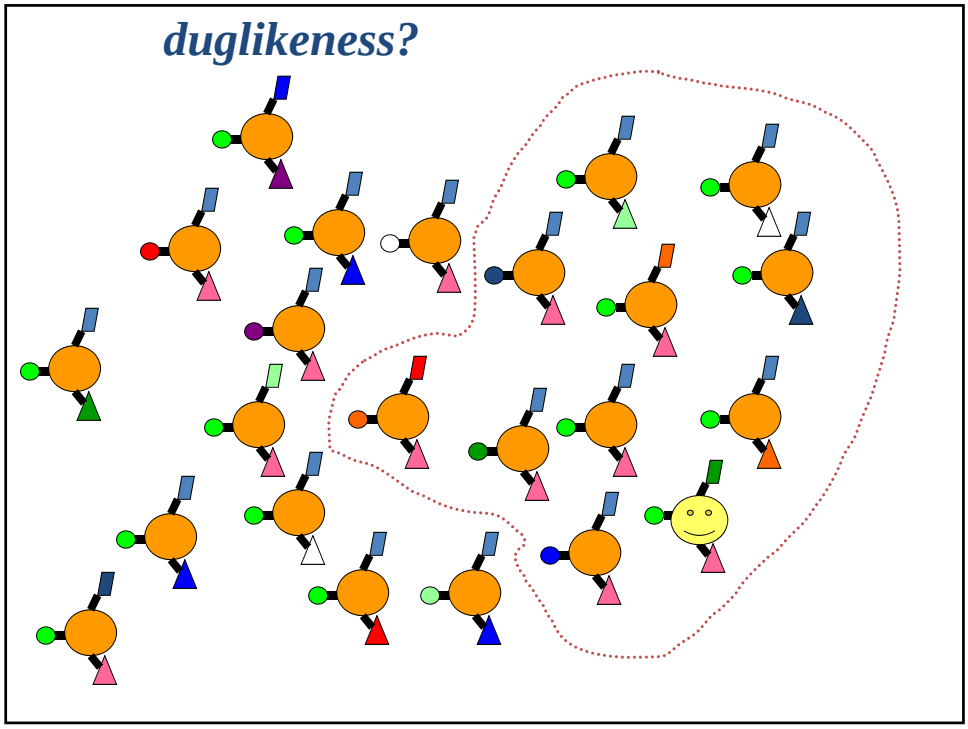
Distributions of some 2D descriptors

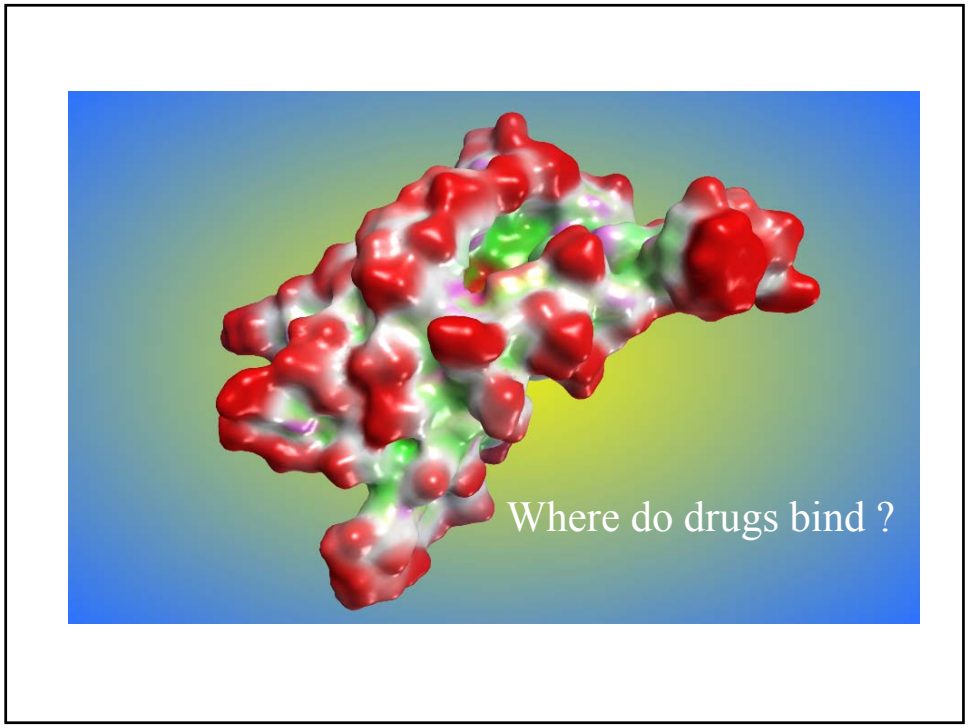
descriptor	range	
weight	165.236	554.73
SlogP	-1.1843	5.2955
SMR	4.336	14.4609
TPSA	12.96	165.15
density	0.726	0.992
vdw_area	164.684	497.032
vdw_vol	180.587	622.558
a_acc	1	7
a_don	0	6
a_hyd	6	26
KierA1	7.82267	26.293
KierA2	3.125	11.8031
KierA3	1.47802	7.32272
KierFlex	1.68402	8.81841

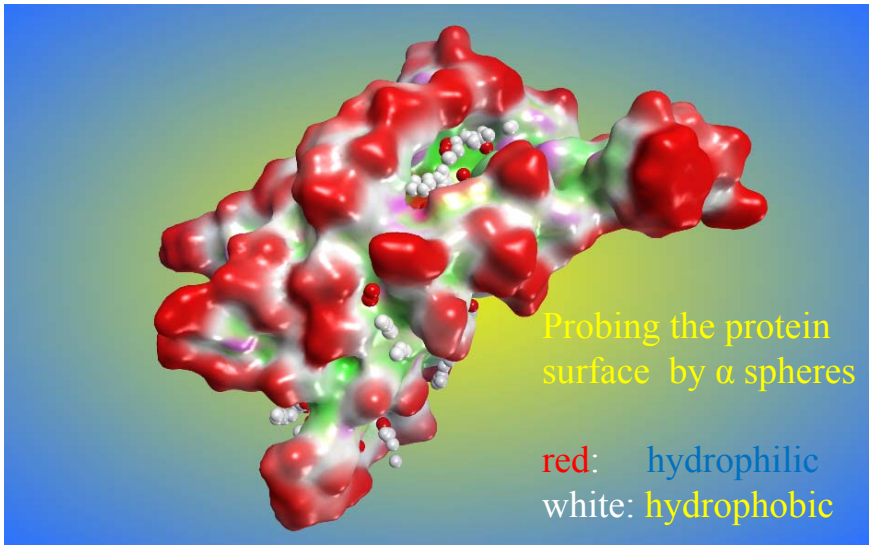
K.Horio,H.Muta,J.Goto, and N.Hirayama,"A Simple Method to Improve the Odds in Finding 'Lead-like' Compounds from a Chemical Library," *Chem. Pharm.Bull.*,**55**, 980(2007)

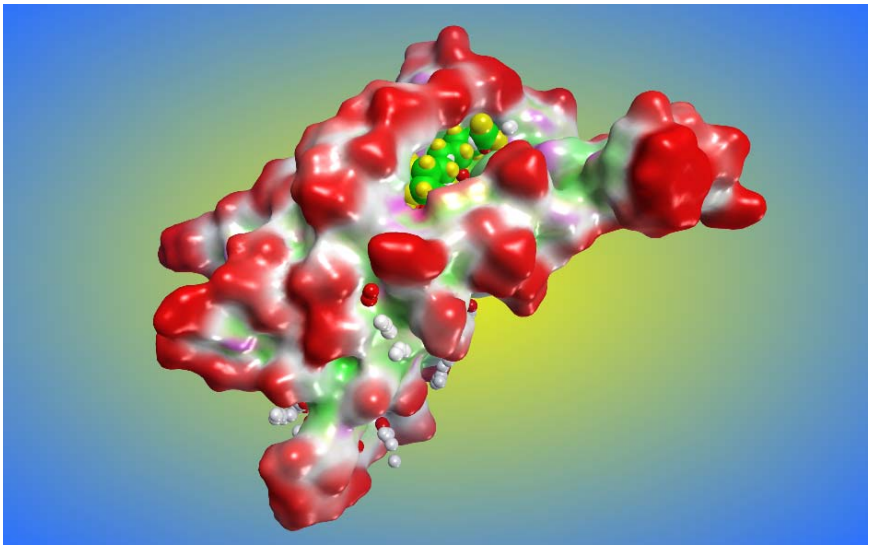
chemical space



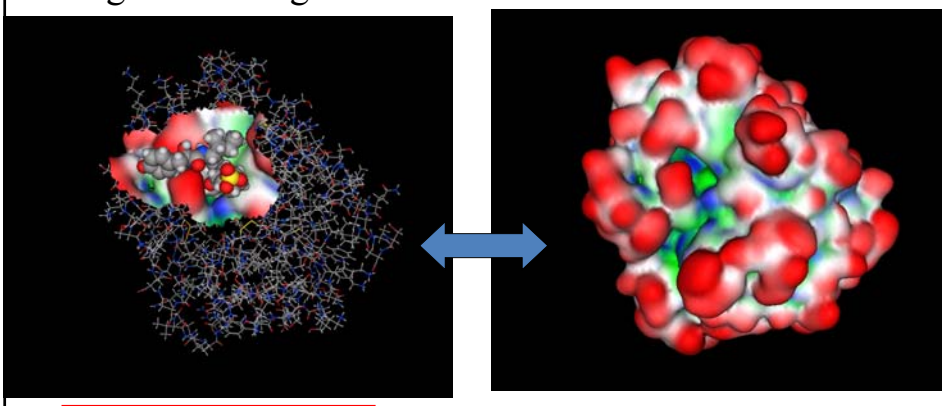

duglikeness?


Where do drugs bind ?


Probing the protein
surface by α spheres
red: hydrophilic
white: hydrophobic



Is there any specific amino acid composition at the ligand binding site ?



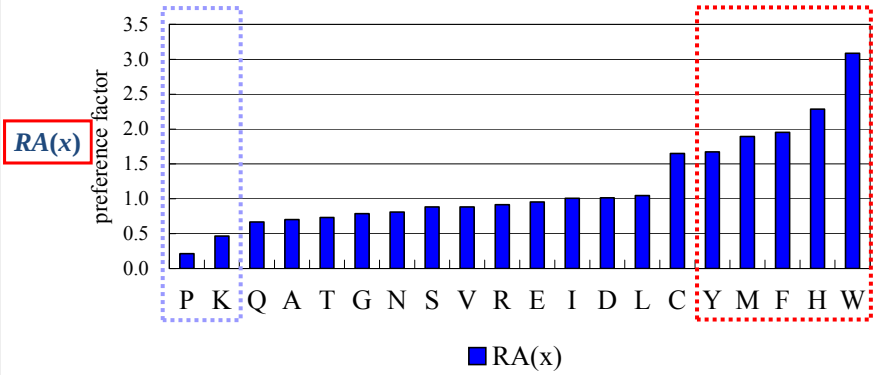
amino acids observed at ligand binding sites

residues whose non-H atom exists within 4.5Å of non-H atoms of a ligand are considered

amino acids observed on the surface of protein in general

residues whose non-H atom contacts with a probe sphere with a radius of 1.4Å are considered

Preference factors for the 20 standard amino acids

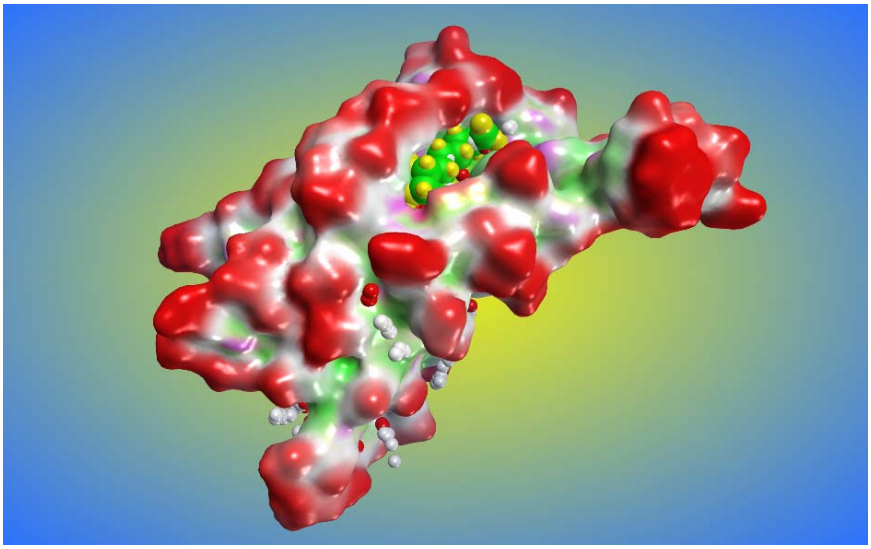


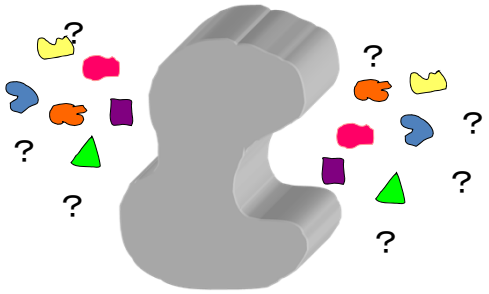
$$RA(x) = CA(x) / SA(x)$$

Performance of PLB in predicting the binding sites of drug-like molecules

	top PLB	top two PLB's	total
true concavity (%)	110 (87%)	120 (95%)	126 (100%)

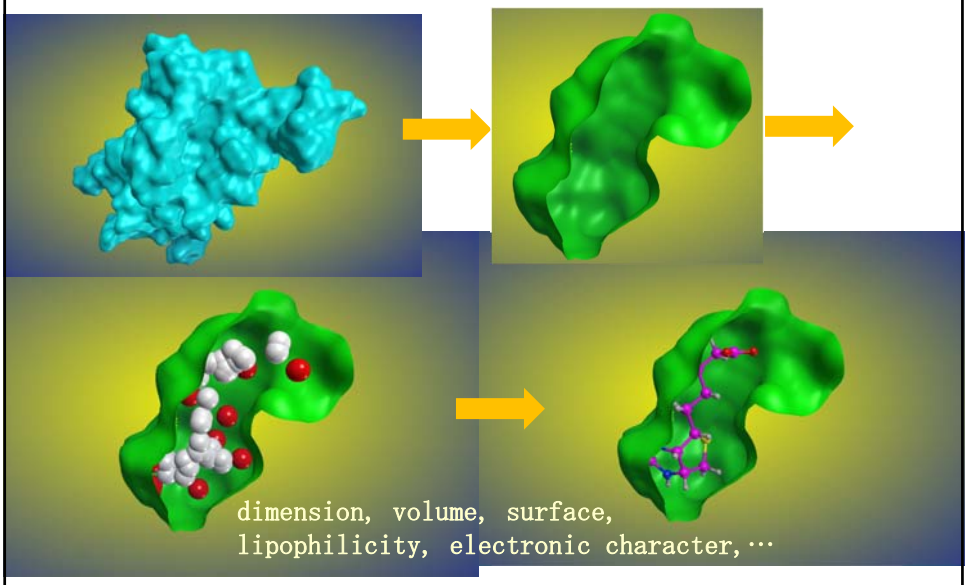
"Use of Amino Acid Composition to Predict Ligand-Binding Sites"
S. Soga, H. Shirai, M. Kobori and N. Hirayama
J.Chem.Inf.Model., 47, 400-406 (2007)

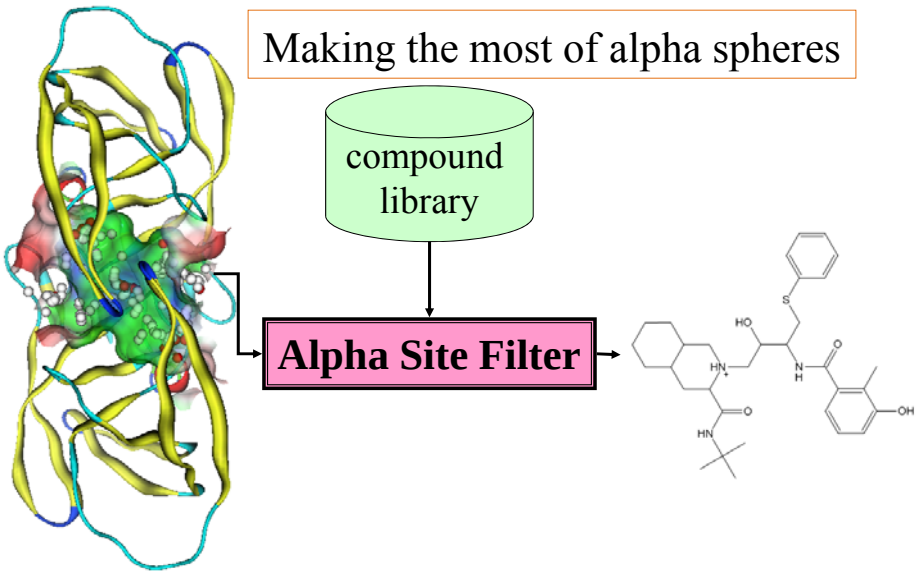




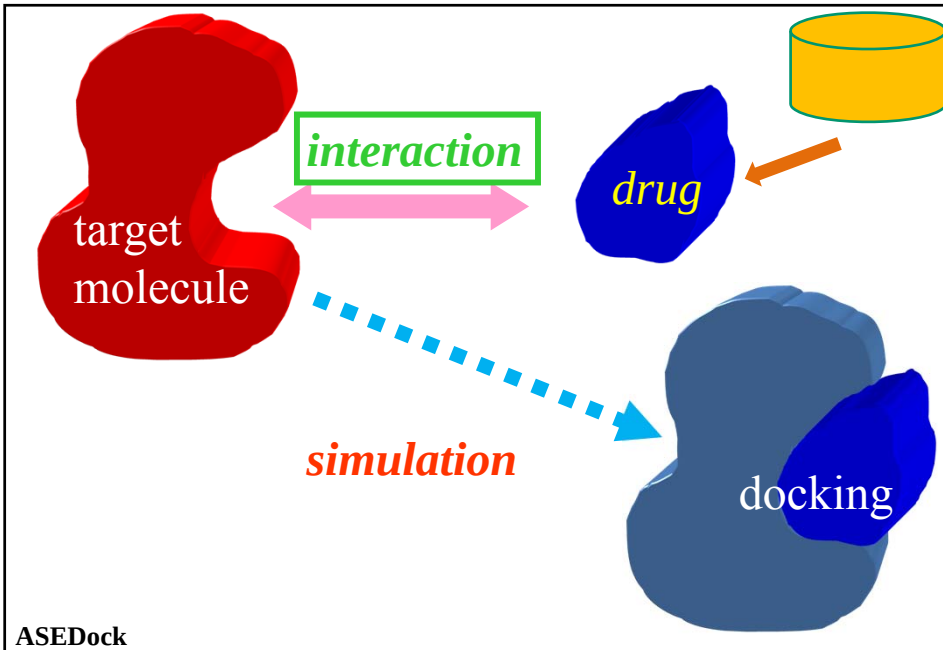
What kind of molecules can bind to the supposed binding site?
How can we select the relevant molecules from the *immense chemical space*?

Quick search for a reasonable number of promising molecules compatible with the binding site !

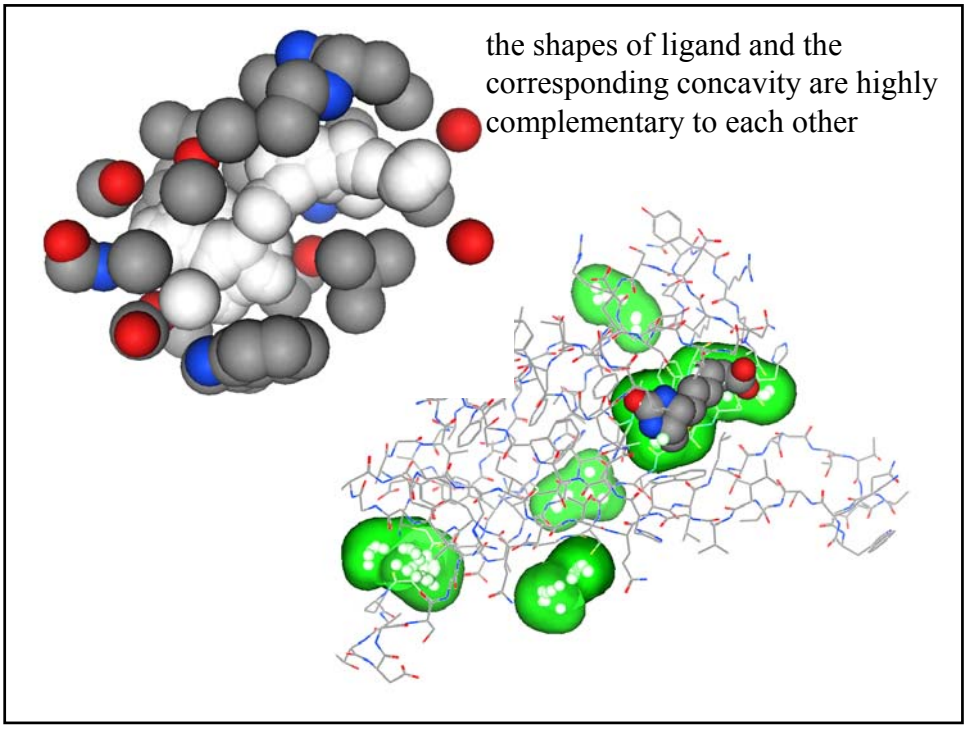


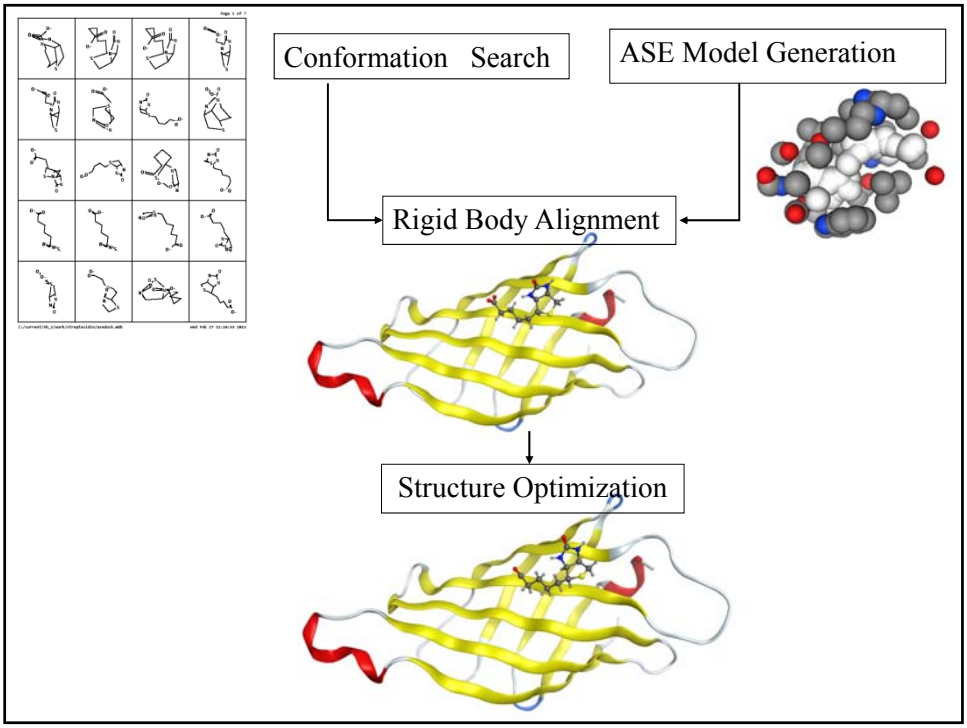


"Alpha sphere filter method: Application of pseudomolecular descriptors in virtual screening of 2D chemical structures"
H.Muta and N.Hirayama, *J.Comput.Chem.*, Published Online Mar.25,2010



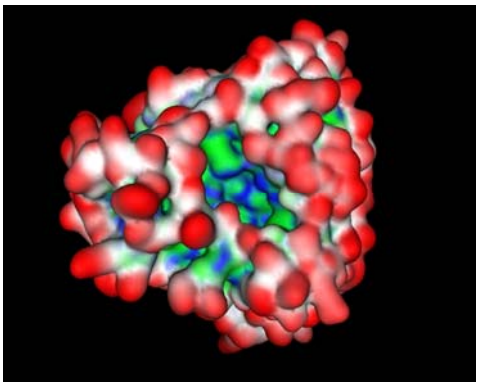
ASEDock
J.Goto, R.Kataoka, H.Muta, and N.Hirayama, "ASEDock-Docking Based on Alpha Spheres and Excluded Volumes," *J.Chem.Inf.Model.*, **48**, 583(2008)

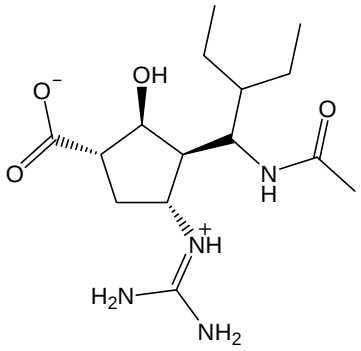

the shapes of ligand and the corresponding concavity are highly complementary to each other

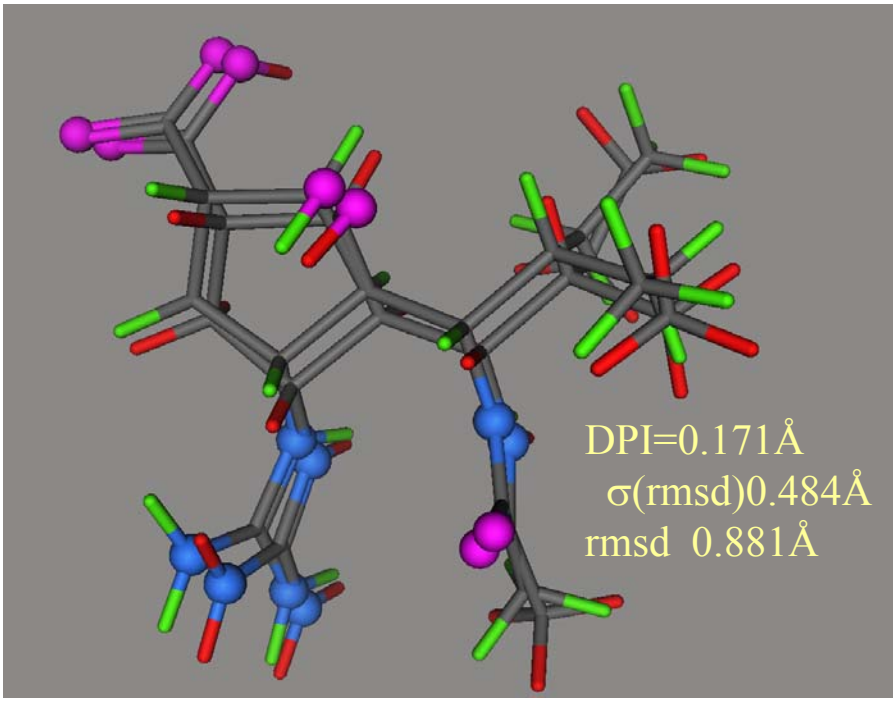

Conformation Search
ASE Model Generation
Rigid Body Alignment
Structure Optimization

R292K Mutant Influenza Virus Neuraminidase in Complex with BCX-1812 :1L7H

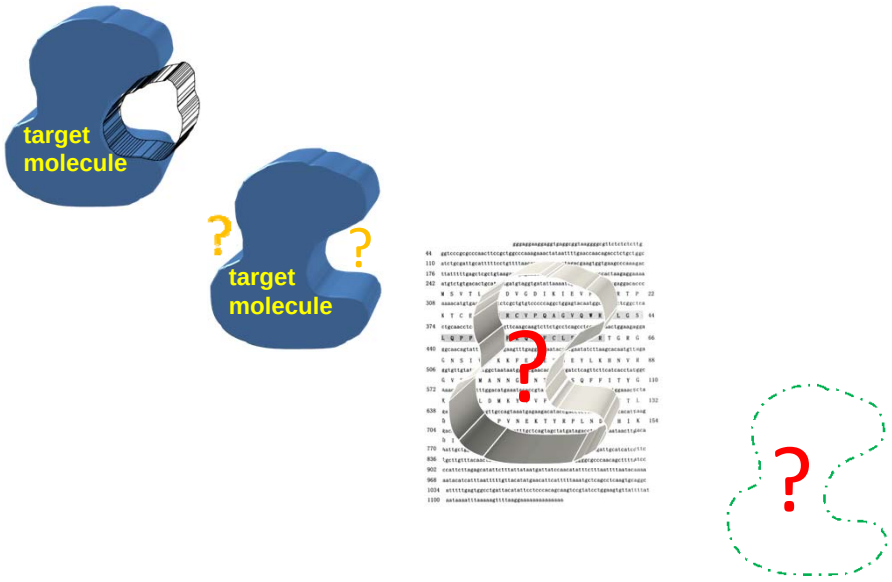
R_{free} = 0.177 DPI=0.171Å BCX-1812







Strategies for *in silico* drug discovery



Biological response (A) is determined by many parameters(p_1,…,p_n)

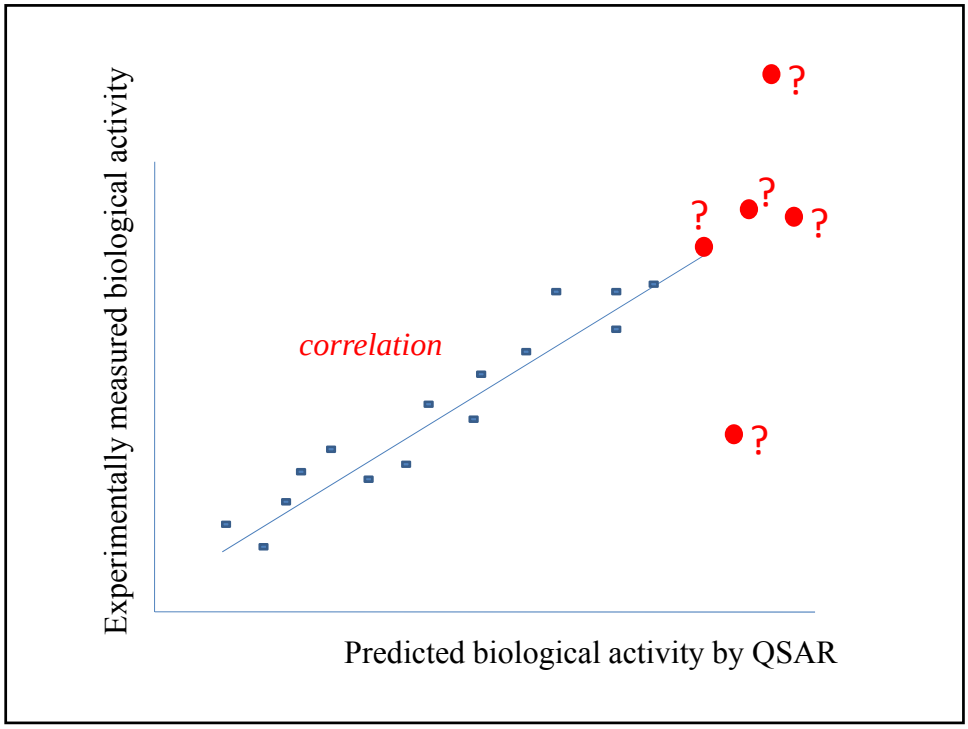
$$A = f(p_1, p_2, \ldots\ldots p_n)$$

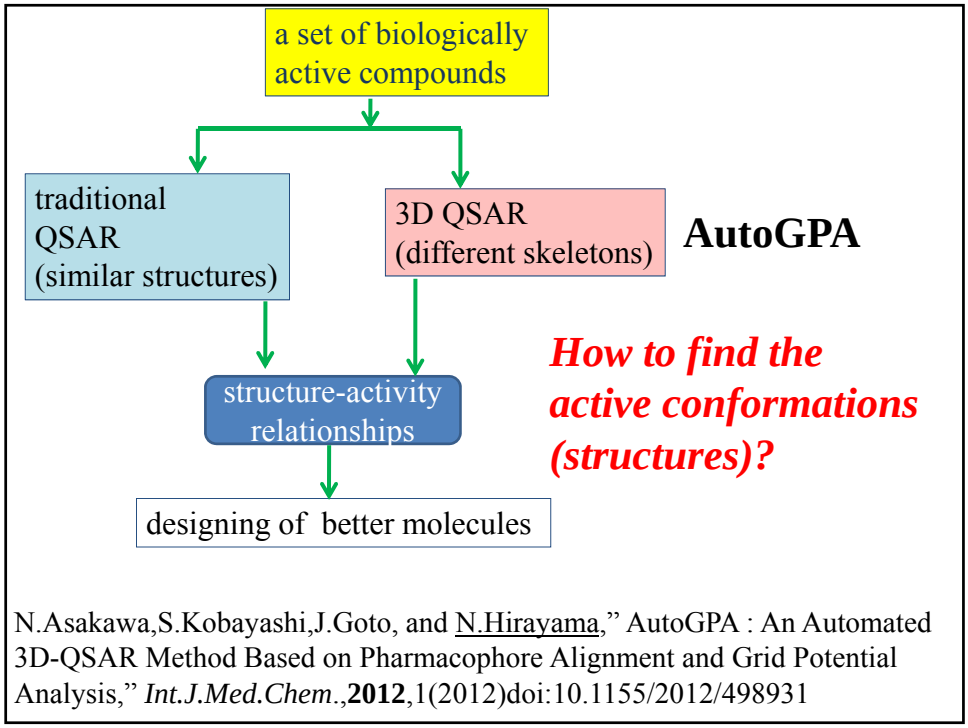
p_n : geometric and chemical characteristics

[$\log(1/C) = k_1 \log P + k_2 \sigma + k_3$]

If we know the function type and parameters, we can predict the biological response of new compounds. The function is usually so complex, and it is almost impossible to count out all the parameters. Only approximate function and a handful parameters can be deduced

And yet, it is very(!) valuable to use such function in drug discovery process, especially in optimization process.





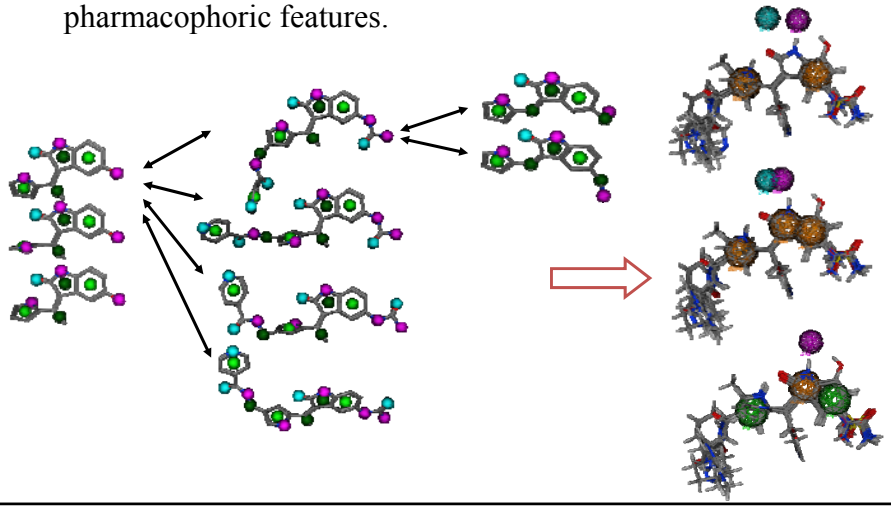
AutoGPA

How to find the active conformations (structures)?

N.Asakawa,S.Kobayashi,J.Goto, and N.Hirayama," AutoGPA : An Automated 3D-QSAR Method Based on Pharmacophore Alignment and Grid Potential Analysis," *Int.J.Med.Chem.*,**2012**,1(2012)doi:10.1155/2012/498931

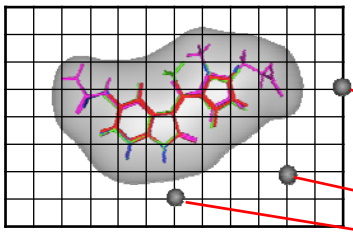
Step 1 : Alignment of conformers

- Pharmacophore Elucidation implemented in MOE.
- Enumerate alignments by superposing the common pharmacophoric features.



Step 2 :Running Grid Potential Analysis (GPA)

3.PLS(Partial Least-Squares) is used to derive 3D-QSAR models based on grid potentials.



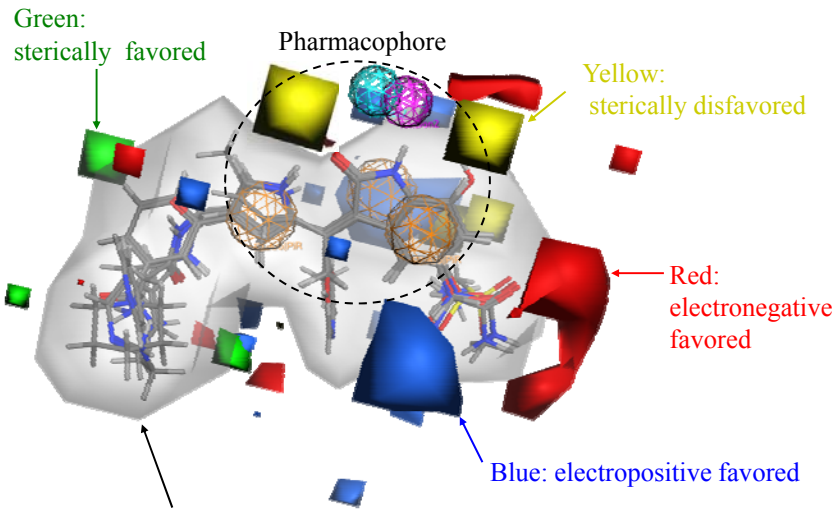
$$activity = \sum_{i}^{L} \sum_{j}^{P} C_{ij} G_{ij}$$

i : grid point

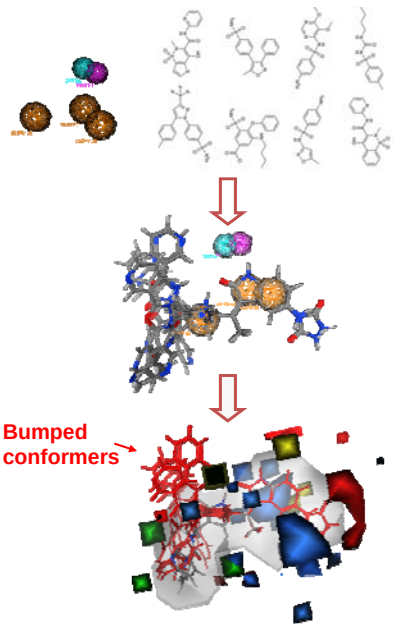
j: probe

cmpd	activity	G001 st	G001 el	G002 st	G002 el	G003 st	G003 el	…
1	0.95							
2	1.2							
3	2.4							
4	0.63							
…								

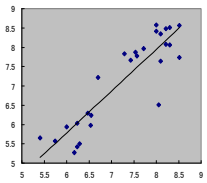
AutoGPA model

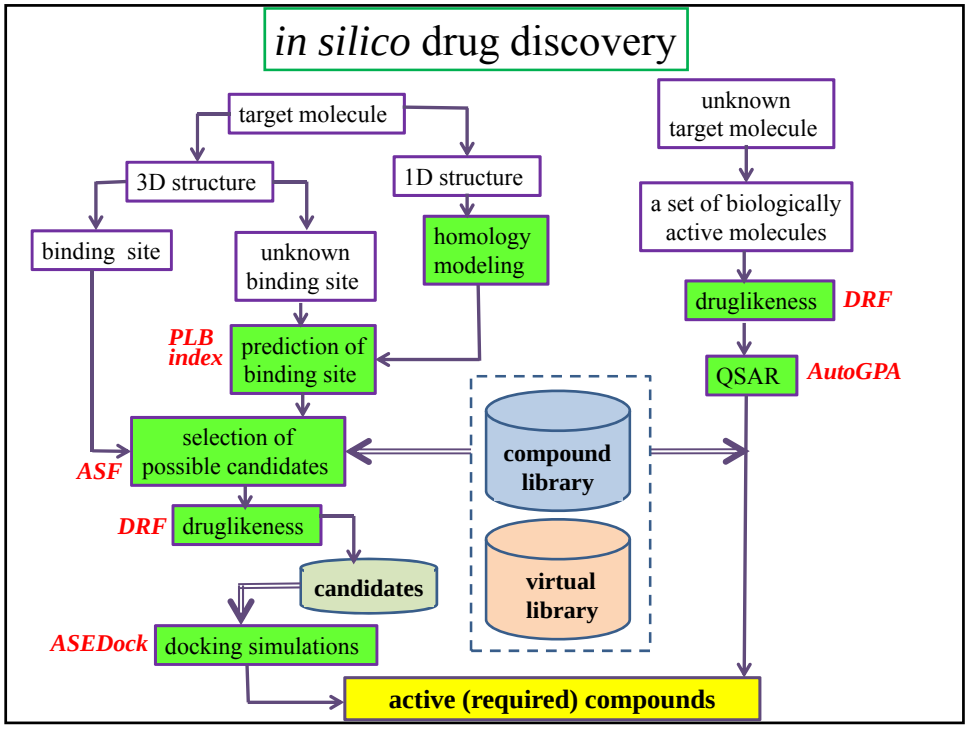


Screening by AutoGPA model



- Align input molecules based on the pharmacophore model
- Reject conformers which bump against the receptor region
- Predict activity by use of the AutoGPA model





EXAMPLE 1
(structure-based *in silico* drug discovery)

inhibitors of
plasminogen activator inhibitor 1(PAI-1)

Y.Izuhara *et al.*, *J.Cereb. Blood Flow Metab*, **30**, 904(2010)

EXAMPLE 2
(ligand-based *in silico* drug discovery)

anti-amyotrophic lateral sclerosis (ALS) drugs

K.Tanaka *et al*., *PLOS ONE* 9: 1-17 (2014)

Acknowledgements

Methodology Developments
Mr.Junichi Goto (Ryoka Systems Inc.)
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Dr.Hajime Muta (Tokai University School of Medicine)

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