# **Virtual Screening**

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### Introduction

Understanding the relationship between a molecule and its biological activity are the central theme in medicinal chemistry.

But the biological activity of a molecule cannot be calculated from its chemical structure by first principles.

### **Problem:**

Given a structure of the target or a ligand of the target find new ligands



### Introduction

#### When is Virtual Screening Relevant?

	Ligand Structure Known	Ligand Structure Not Available
Target Structure Known	Docking	Docking
Target Structure Not Available	Pharmacophore Modeling, Fingerprint Search, Autocorrelation Methods.	HTS

Appropriate for Computational Chemistry Not Appropriate for Computational Chemistry



#### **Pharmacophore Concept**

## Concepts

Observations that modification of some parts of a ligand results in minor changes of activity, whereas modifications of other parts of the ligand results in large change of activity.

**Pharmacophore element**: Atom or functional group essential for biological activity

**3D Pharmacophore mode**: Collection of pharmacophore elements including their relative position in space



## Concepts

#### Lock & Key Concept

The structure(s) of a molecule determines the biological activity of that molecule.

There must be a structural and electronic complementarity between the receptor and the ligand.









Describe the molecule as a bit-string of features. For each feature: If feature present write 1 If feature absent write 0

## Fingerprints

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Answers to simple questions you can ask about molecules Fingerprints are almost unique. Reduced representation that are easy and fast to calculate. Excellent for searching large databases (>10 million compounds).



Example of Pharmacophore fingerprint

Each bit in the fingerprint represents a triangle with a particular geometry

Purely abstract representation based on the concepts of Hydrophobe, HB-donor and HB-acceptor.

Red arrows: The representation (of the molecule) Blue triangles: The features (of the fingerprint)

# Fingerprints





### Fragments

Describe molecule in terms of its buildingblocks and substituents Connectivity between fragments are not encoded



Closer to the traditional way that chemists think about molecules. A fussy way of doing substructure search.

Link to Fingerprint Search



### Fragments

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### Fragments





#### Does not encode information on the global topology



≡1.00

0.91

## Topology

How the chemist think of a molecule Consider the explicit bonding and atom types. Usually distances are measured in bonds between atoms. Each atom encodes a property e.g. partial charge or polarizability.





### Autocorrelation

Excellent for searching large databases (>1 million compounds).

Construct a graph from each atom pair distance. The Y-axis will be the sum over distance and the product of the property the atom pairs encode.



## Chirality

All proteins are chiral, so protein ligands usually have different affinities depending on their chirality.

Distance-dependent descriptors cannot encode chirality.

Chirality is a 3D property.







3D

More than 30 million compounds are known. Only 250,000 compounds (<1%) are crystalised.

X-ray bond distances, angles and torsion angles provides information for the construction of forcefields in which molecules can be represented as equations.





## Docking

#### Structure-based methods like docking

Excellent for searching databases up to  $\sim 100,000$  compounds).



Computer graphics visualisations of forcefield koordinates

Link to Docking



## Docking

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Note: Off

100% 👻





- •Highest ranked pose not experimental bindingmode.
- •Use available ligand data to evaluate Docking
- •Select compounds by visual inspection, Dont rely on docking score alone



# Flexibility (4D)

Single bonds are rotatable, so most molecules have more than one conformation (shape).

In most 3D methods finding the bioactive conformation is essential and this remains one of the main challenges of medicinal chemistry today

$$\mathbf{E} = \sum_{1}^{\text{Nangles}} \frac{\mathbf{k}_{\theta}}{2} (\theta_{i} - \theta_{0})^{2} + \sum_{1}^{\text{NBpairs}} (\frac{\mathbf{A}}{\mathbf{r}_{ij}^{12}} - \frac{\mathbf{B}}{\mathbf{r}_{ij}^{6}}) + \sum_{1}^{\text{all pairs}} \frac{\mathbf{q}_{i} \mathbf{q}_{j}}{4\pi\varepsilon_{0}\mathbf{r}_{ij}} + \sum_{1}^{\text{Nbonds}} \frac{\mathbf{k}_{r}}{2} (\mathbf{r}_{i} - \mathbf{r}_{0})^{2} + \sum_{1}^{\text{Ntorscors}} \frac{1}{2} \mathbf{V}_{i} (1 + \cos\phi_{i})$$
Find the minima of the forcefield equation
$$\mathbf{V} = \mathbf{V} + \mathbf{V$$



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### Conclusion



Increased complexity Increased computational expense

1D

2D

3D

4D

