

# PharmaMiner: Geometric Mining of Pharmacophores

# PharmaMiner

- We define a Joint Pharmacophore Space by extracting 3D descriptors from diverse libraries/targets
- Analysis of pharmacophores in the Joint Space
  - Classification and clustering for understanding biological activity
  - Screening for compounds based on presence and/or absence of activity
- Fragment-based discovery and scaffold hopping
- Flexible definition of pharmacophoric features (donor, acceptor, hydrophobic core, etc.)

# Applications of PharmaMiner

- Determine what makes compounds active against a target.
  - Develop pharmacophore models based on analysis results.
  - Find what features impart specific biological activity (e.g., BBB permeability).
- Screen compounds for activity against single/multiple targets
  - Selectivity queries for combination of properties
- Diversity analysis in 3D space
- Scaffold hopping

# Key Benefits

- Only automatic tool that analyzes the 3D space of pharmacophores
- Identification of activity against a target based on a set of actives and inactives (clustering)
- Unique exploration of the pharmacophore space through biological activity (classification)
- Unique querying using proximity and/or distance from clusters
  - Specification of selectivity, toxicity, absorption, side-effects

# Validation Studies

- Activity prediction of 11 NCI cancer datasets (cell-based assays) based on the analysis of the Joint Pharmacophore Space

Name	Size	Description
MCF-7	28972	Breast
MOLT-4	41810	Leukemia
NCI-H23	42164	Non-Small Cell Lung
OVCAR-8	42386	Ovarian
P388	46440	Leukemia
PC-3	28679	Prostate
SF-295	40350	Central Nervous System
SN12C	41855	Renal
SW-620	42405	Colon
UACC-257	41864	Melanoma
Yeast	83933	Yeast anticancer

# Chosen Pharmacophoric Features

- Cations
- Anions
- Hydrogen Bond Donors
- Hydrogen Bond Acceptors
- Hydrophobic Centers
- Aromatic Rings

# Cluster Analysis

- Many clusters of pharmacophores in the Joint Space are enriched with respect to specific activities
  - Examples of some *positive* clusters (i.e., clusters with a much higher percentage of actives than a random set)

Dataset	Pharmacophore Type	Expected Ratio	Observed Ratio
Leukemia	Acceptor-Acceptor-Donor	3.5%	22.6%
Ovarian	Cation-Cation-Acceptor	3.7%	24.6%
Colon	Cation-Acceptor-Anion	4.3%	34%
CNS	Cation-Acceptor-Anion	3.6%	30%
Prostate	Cation-Cation-Acceptor	4.1%	31.6%

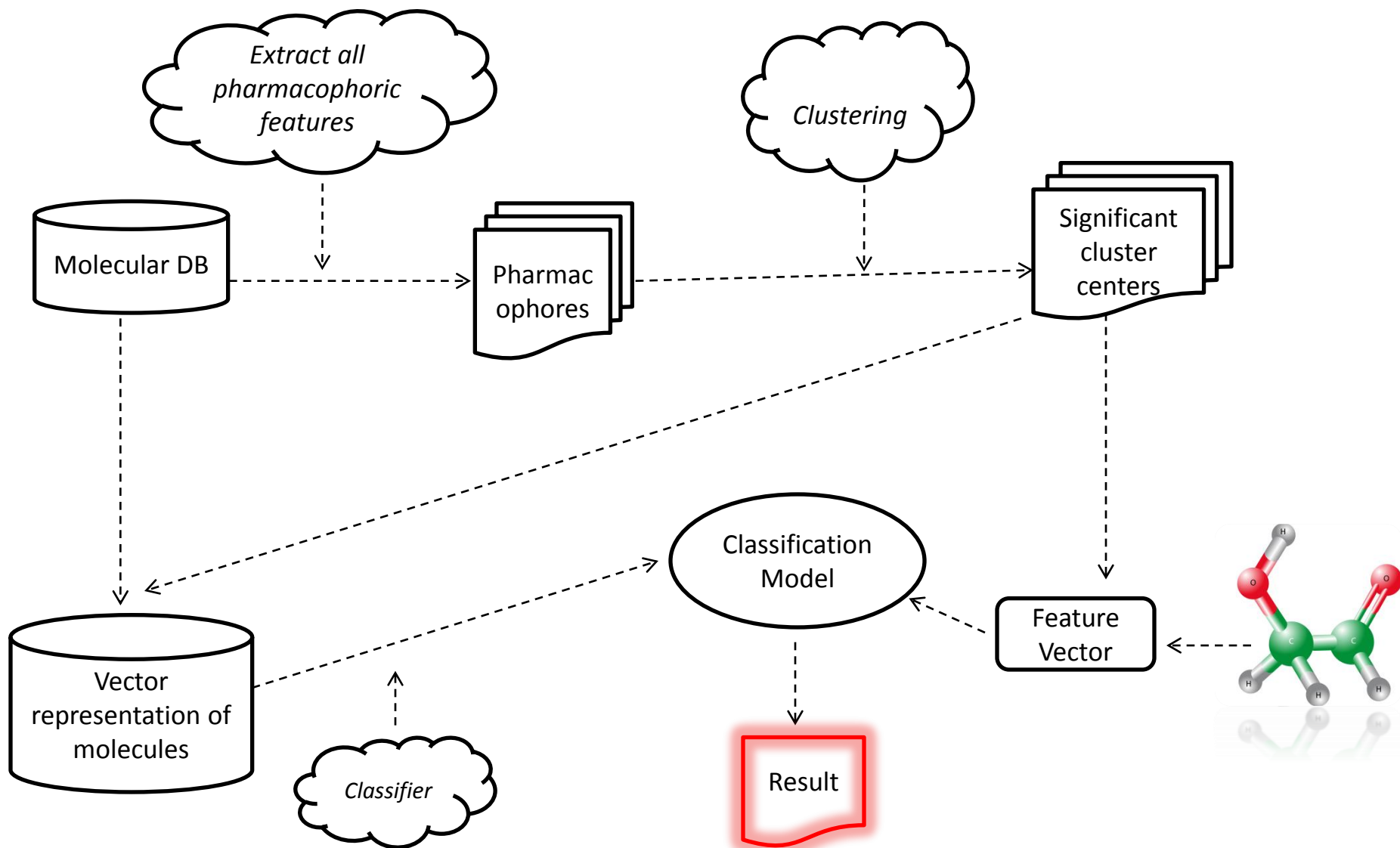
# Not All Clusters Are Enriched!

- Clusters involving anions show strong negative significance:

<b>Dataset</b>	<b>Triangle Type</b>	<b>Expected Ratio</b>	<b>Observed Ratio</b>
Leukemia	Acceptor-Acceptor-Anion	3.5%	0.8%
Ovarian	Acceptor-Acceptor-Anion	3.7%	0.6%
Colon	Acceptor-Acceptor-Anion	4.3%	0.6%
CNS	Acceptor-Acceptor-Anion	3.6%	0.4%

- Each cluster can be annotated with the presence or absence of an activity or property. This enables screening of compounds for selectivity against multiple targets or properties.

# Prediction Pipeline



# PharmaMiner is Complementary to SigFinder

- Graph based approach allows more flexibility and computational efficiency; However, 3D analysis has better accuracy
- Pharmacophoric features allow greater abstraction
  - Scaffold hopping
- Possible to combine the two techniques