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Mining Three-dimensional Chemical Structure Data

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Advantages of ILP for Pharmacophore Discovery

- Works with 3-dimensional databases without loss of information.
- Multi-relational.
- More comprehensive search of the space than typical greedy or hill-climbing in RP or ANNs.
- Pruning of search space can be achieved using appropriate scoring functions.

Methodology

- Pick active/inactive molecules for system under study.
- Generate 3-dimensional structures via a conformational search (*Charmm*).
- Convert 3-dimensional results into Datalog format.
- Extract point groups from Datalog data.
- Perform ILP search of point groups for a pharmacophore clause.

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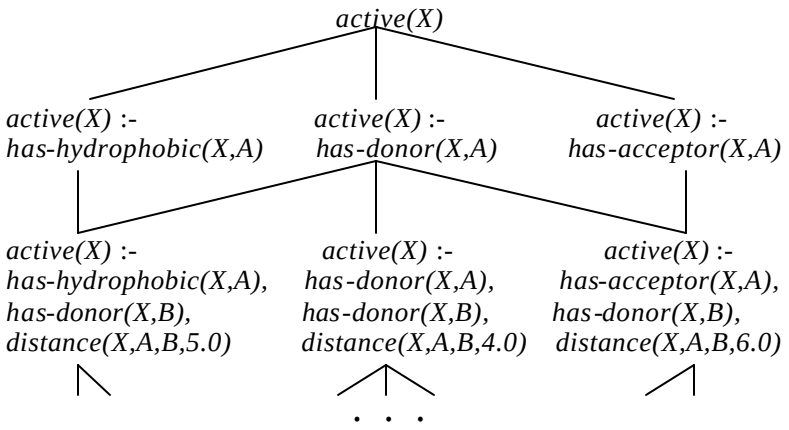
Overview of Aleph ILP Search (Top-down)

- Saturates on 1st uncovered positive example.
- Performs top-down admissible search of the subsumption lattice above this example.
- Use of compression function to limit size of clauses and number of allowed negative example coverage.

Lattice of Clauses for the Given Hypothesis Language



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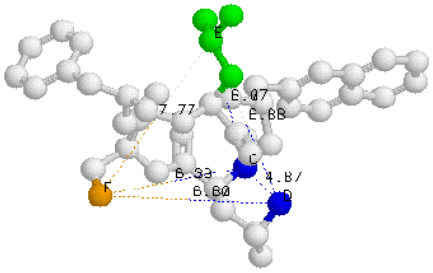
Pharmacophores Found in Pseudomonas Growth Inhibition

Active(A) ← molecule(A), positive(A,B), positive(A,C), hydrophobic(A,D), hydrogen-donor(A,E), distance(A,B,C,4.05), distance(A,B,D,7.45), distance(A,B,E,6.53), distance(A,C,D,6.93), distance(A,C,E,5.90), distance(A,D,E,7.88).

Cross-validation accuracy is 100%.

Example 4-point Pharmacophore Overlayed With an Active Molecule

- Green - hydrophobic
- Blue – positive charge
- Orange – hydrogen donor



Distances are in Angstroms (Å)

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Example Pharmacophore

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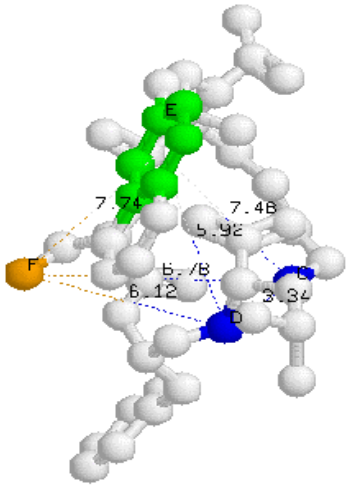

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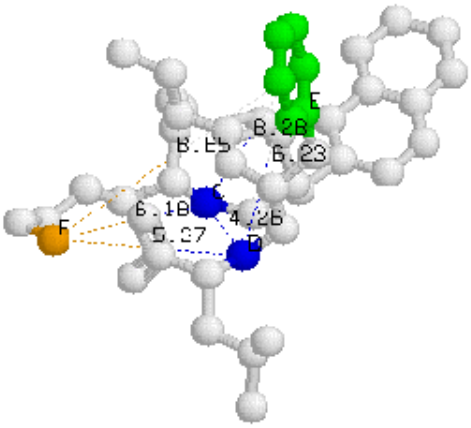

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Conclusion

- Cross-validate results and pharmacophore found shows that ILP is well suited to mining 3-dimensional chemical structure data.
- Directly mines relational data with the use of feature vectors.
- Interacts well with scientists.
- Approach also repeated successfully by Marchand-Geneste, N. (2002).

Future Work

- Testing the proposed pharmacophore with new molecules.
- Application of ILP to related data (drug-discovery, proteomics, SNPs, etc.).

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Aleph

- Maintained by Ashwin Srinivasan publicily available at http://web.comlab.ox.ac.uk/oucl/research/areas/machlearn/Aleph/aleph.html.
- Runs using yap prolog compiler maintained by Vítor Santos Costa obtainable at http://www.ncc.up.pt/~vsc/Yap/ .