Exploiting Pharmacophores
Using Oracle
Objectives

- Develop Pharmacophore Technology
- Use the Best Affordable Pharmacophore Calculations
- Provide Tools for Non-experts
Chem-X Definition of Pharmacophore

- Minimum Characteristics for Activity
- 3 or 4 Interaction Centres
  - H Donor
  - H Acceptor
  - Positive Charge
  - Aromatic Ring
  - Base
  - Acid
  - Lipophile
- Distances Between Centres
Calculating Pharmacophores

- Start with 3D Coordinates
- Locate Rotatable Bonds
  - 3 Points for Single
  - 6 Points for Alpha
  - 2 Points for Conjugated
  - 2 Points for Double
- Perform Rule-based Search
  (Random+Rule for > 10 Bonds)
# Chem-X Storage of Pharmacophores

- **Binary as Fingerprint or Bit mask**

<table>
<thead>
<tr>
<th>No of Types</th>
<th>Memory (KB) 3-Centre</th>
<th>Memory (KB) 4-Centre</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>24</td>
<td>6200</td>
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<tr>
<td>5</td>
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<td>15100</td>
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<td>6</td>
<td>79</td>
<td>31300</td>
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<tr>
<td>7</td>
<td>125</td>
<td>58000</td>
</tr>
</tbody>
</table>

- **ASCII as List**
Storage Pros & Cons

- Avoid Repetition of Calculation
- Few Bits Set for Single Molecule Keys
- Reduce Space Used By
  - Compression
  - Reformatting to List
Discovery Architecture

Oracle Host
- Oracle Data
- Property Server
  - Camelot
  - ChemX
  - Properties
  - Toxicity
  - Others...
- Pharmacophores
  - RS3
- Client Host
  - Client Applications

Calculation Host
1. RS3 lists of Structures

2. Property Server creates Chem-X servers

3. Chem-X servers generates conformations and pharmacophores

4. Property Server stores pharmacophores in Oracle

5. Analysis Client

**Process Architecture**

- Oracle
- RS3: Structures
- Property Server
- Pharmacophore Storage: Calculated Pharmacophores
- Chem-X: Conformations and Pharmacophores
Calculation Standard Approach

- Optimise Starting Coordinates
- Rule Search
  - 3 Points for Single
  - 6 Points for Alpha
  - 2 Points for Conjugated
  - 2 Points for Double
- Energy Cutoff
ORACLE Space & Time

- Typically 60Kb per Structure
- Searching ~5s / Pharmacophore for 62,000 Structures in WDI
- Hardware
  - 400 MHz Pentium II
  - 128Mb
  - 3 Disks (4Gb, 6Gb, 18Gb)
Example 1: NDMA Agonists

- 20 Active Molecules
  Tocris Catalogue of Chemicals for Pharmacology and Neurochemistry

- Arbitrary Selection of 10 plus a “False Positive”

- These 11 Structures Exhibit 6669 Different Pharmacophores
Use of Pharmacophores

- Number of Common Pharmacophores
  - 36 for 9 Molecules
  - 6 for 10 Molecules
  - None All 11 (Including False Positive)

- Searching
  - Find 19 of the 20 Known Actives
    Plus 116 Other Molecules from Tocris
  - 1.6% of WDI in 50 Seconds
Example 2: HIV-1 Protease Inhibitors

- Sample of 16 Actives from 157 Structures
  - Q Han, J Med Chem (1998) 41.12 p2019
  - G V De Lucca, J Med Chem (1999) 42.1 p135

- Common Key of 5 Pharmacophores for 10 or more Structures
## Search Results

<table>
<thead>
<tr>
<th>No of Pharm</th>
<th>HIV Hits</th>
<th>% of Known</th>
<th>WDI hits</th>
<th>% WDI</th>
<th>Hit Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>12.74%</td>
<td>1</td>
<td>0.00%</td>
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<tr>
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<td><strong>Total</strong></td>
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<td><strong>62150</strong></td>
<td>4.74%</td>
<td><strong>395:1</strong></td>
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**No of**  
**Pharm**  
**HIV Hits**  
**% of**  
**Known**  
**WDI hits**  
**% WDI**  
**Hit Ratio**
## Interpretation Using DIVA

### Table: HIV-1 Protease Inhibitors

<table>
<thead>
<tr>
<th>C</th>
<th>HIV-1 Protease Structures</th>
<th>D Structure</th>
<th>E ALL 251720</th>
<th>F LLL 202125</th>
<th>G AAR 172117</th>
<th>H ARR 251720</th>
<th>I ARR 251723</th>
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*Note: The table displays the inhibition rate for different HIV-1 protease inhibitors using DIVA software.*
Colour Coded Ki Plot
Conclusions

- Pharmacophores can be Stored in ORACLE
- Architecture Allows
  - Transparent Calculation of Pharmacophores
  - Integration with Various Analysis Tools
- Fast & Flexible Analysis Enables Selection of Molecules to Test by Non-experts
Acknowledgements

- Richard Postance
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