



cresset

smarter chemistry | smarter decisions

## Biologically Relevant Molecular Comparisons

Mark Mackey

# Agenda



- > Cresset Technology
- > Cresset Products
  - > FieldStere
  - > FieldScreen
  - > FieldAlign
  - > FieldTemplater
- > Cresset and Knime

# About Cresset

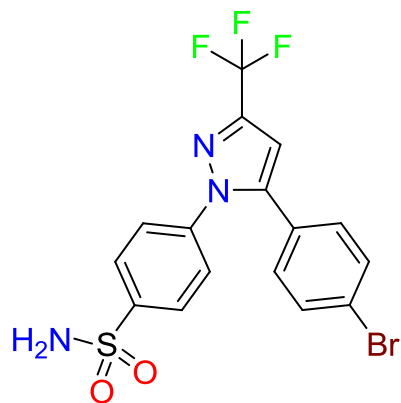


- > Specialist modelling software and services company
- > Started in 2001
- > Virtual screening service run on >80 projects with 80% success rate
- > Software used in big pharma and biotechs
- > Focus on ligand-based drug design, virtual screening, QSAR

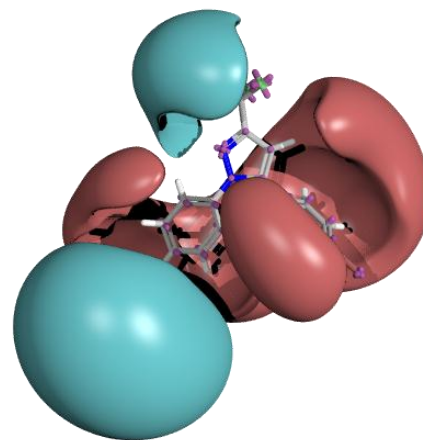
# Field Points

Condensed representation of electrostatic, hydrophobic and shape properties (“protein’s view”)

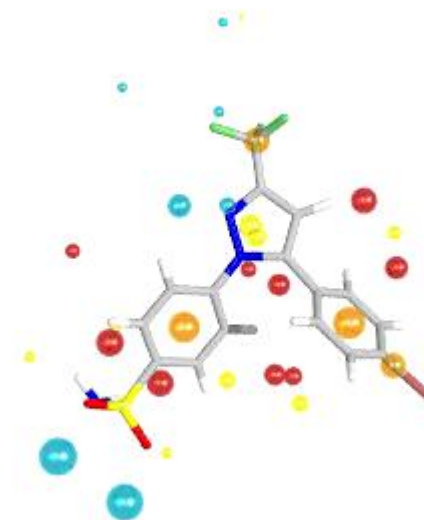
> Molecular Field Extrema (“Field Points”)



2D



3D Molecular  
Electrostatic  
Potential (MEP)

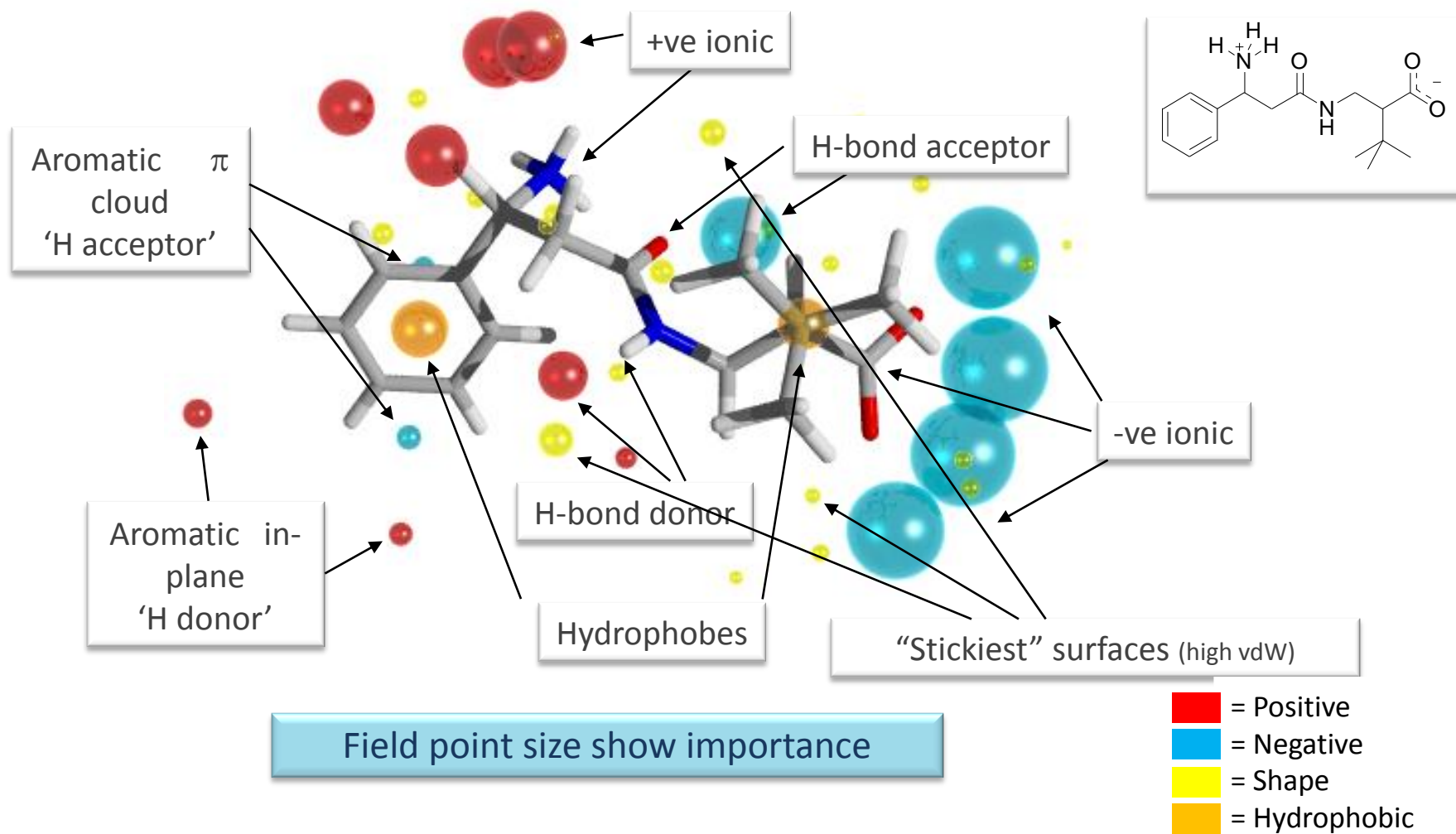


Field Points

- = Positive
- = Negative
- = Shape
- = Hydrophobic

# Explanatory Power of Fields

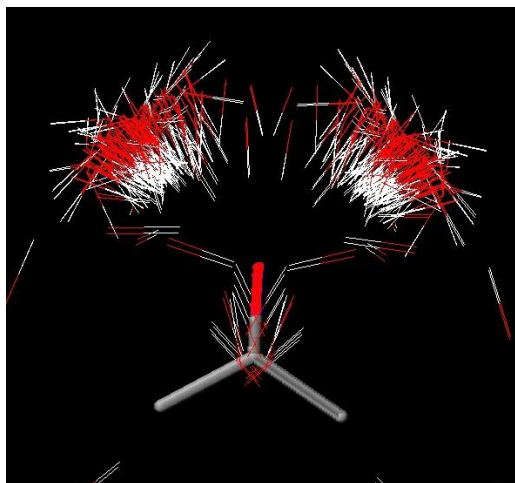
Field points give you new insights into your molecule



# XEDs make Fields Work

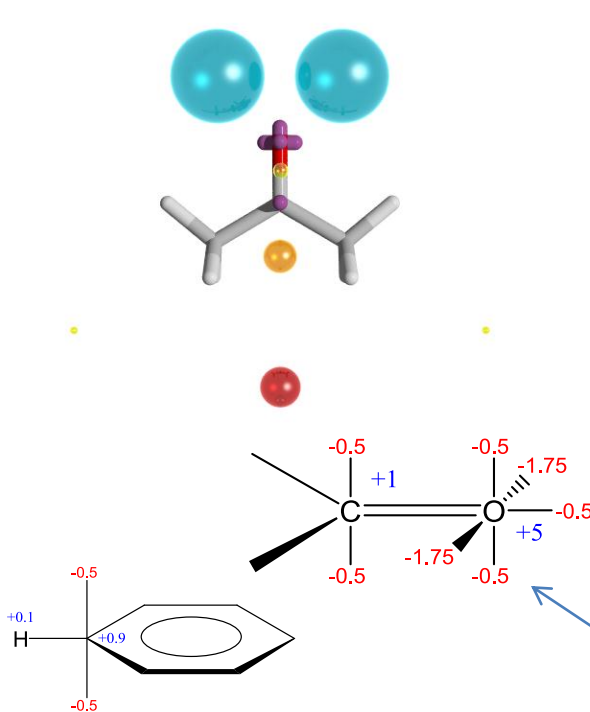
> Field patterns from Cresset's proprietary XED force field reproduce experimental results

Experimental

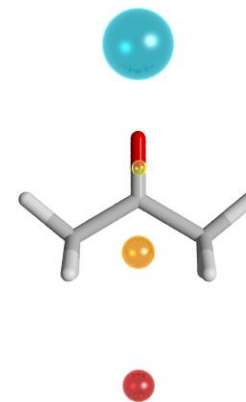


Interaction of Acetone and Any-OH from small molecule crystal structures

Using XEDs



Not using XEDs

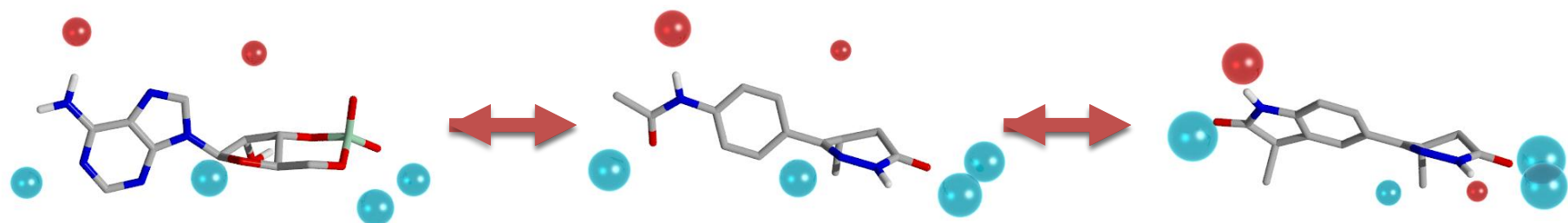
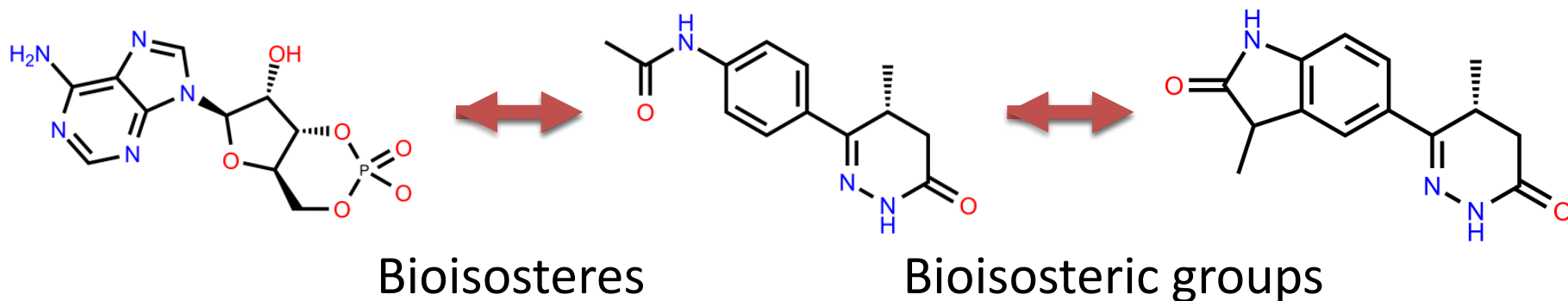


XED adds p-orbitals to get better representation of atoms

- > Fast and accurate 3D field similarity method
  - > *J. Chem. Inf. Model.*, **2006**, 46 (2), pp 665–676
  - > *J. Chem. Inf. Model.*, **2008**, 48 (11), pp 2108–2117
- > Uses field points + full analytical molecular fields
  - > Pharmacophore identification
  - > Virtual screening
  - > Bioisosteres
  - > Alignment
  - > SAR
  - > QSAR

# Bioisosteres – PDE III

Biologically relevant method for comparing molecules



fieldscreen™ fieldalign™ fieldstere™

fieldtemplater™ fieldview™

## > Hit Identification

- > Evaluating scope of new targets
- > Discovering hit compounds with better properties
- > Acquiring information about the target's active site without need for X-ray crystal structure
- > Patent busting

- > Hit/ Lead Optimization
  - > Efficiently discovering better active compounds
  - > Designing out unwanted ADME and toxicity properties in hits/leads
  - > Gaining valuable insight into Structure Activity Relationships
- > Back-up Candidates
  - > Identifying new core templates (chemotypes) with good properties
- > Patent Protection
  - > Patent Exclusion

# Cresset Products



## fieldscreen™

Effective ligand-based virtual screening using molecular fields

- > Diverse lead like hits
- > Large library design
- > HTS rescue

## fieldstere™

Generates non-obvious drug candidates

- > New directions
- > Patent protection
- > Patent busting

## fieldalign™

Universal alignment tool for medicinal chemists and modellers

- > Understand SAR
- > Improve design
  - > Singles
  - > Libraries

## fieldtemplater™

Find the bioactive conformation

- > Understand binding
- > Relate chemical series
- > Pharmacophores

# Product Deployment



## fieldscreen™

Effective ligand-based virtual screening using molecular fields

- > Linux cluster
- > Web interface
- > FieldView
  - > Desktop GUI, Win, Linux

## fieldalign™

Universal alignment tool for medicinal chemists and modellers

- > Desktop GUI
  - > Windows, Linux, MacOS
- > Command line Spring 2011
- > Workflow Spring 2011

## fieldstere™

Generates non-obvious drug candidates

- > Desktop GUI
  - > Windows, Linux, MacOS
- > Command line
- > Workflow Spring 2011

## fieldtemplater™

Find the bioactive conformation

- > Desktop GUI
  - > Windows, Linux
- > Command Line Fall 2011
- > Workflow Fall 2011

- > Initial set of KNIME nodes in beta
- > Xedex
  - > Biologically relevant diverse conformations
- > Xedmin
  - > Minimisation using XED force field
- > FieldView
  - > Cresset molecule viewer (free!)
- > Fieldalign
  - > Molecular alignment and 3D similarity
  - > Parallelisable across cluster
- > Fieldstere
  - > Intelligent bioisosteres
- > No SDF reader(!)

- > FieldTemplater
  - > Model bioactive conformations from ligand data
- > FieldScreen
  - > Field-based VS on large databases
- > 3D QSAR
  - > Integrated
  - > Data matrix



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Questions welcomed

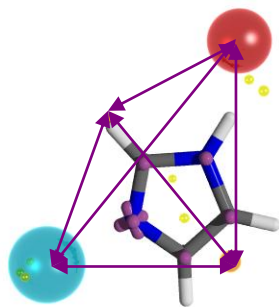
# Comparing Molecules



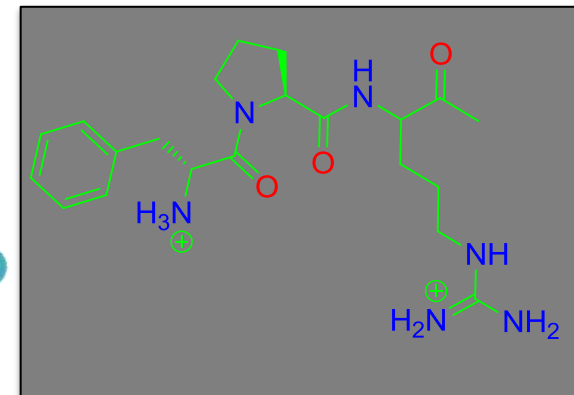
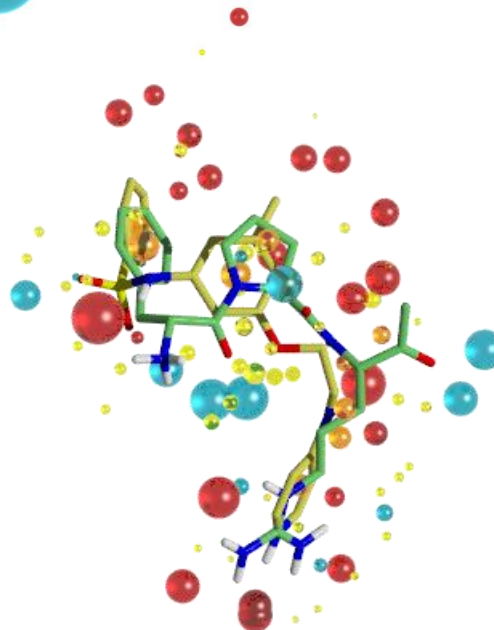
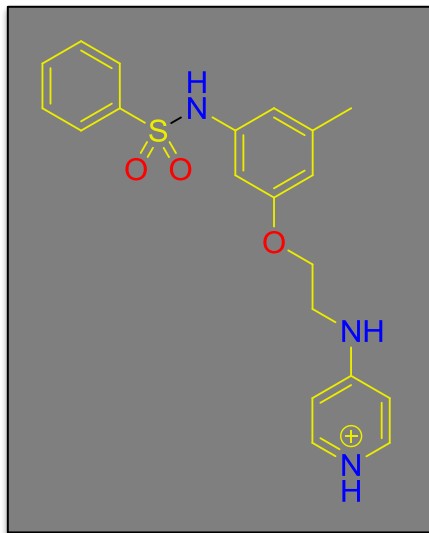
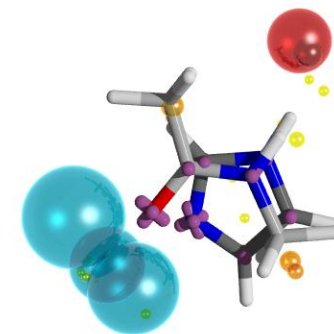
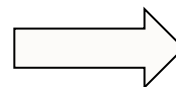
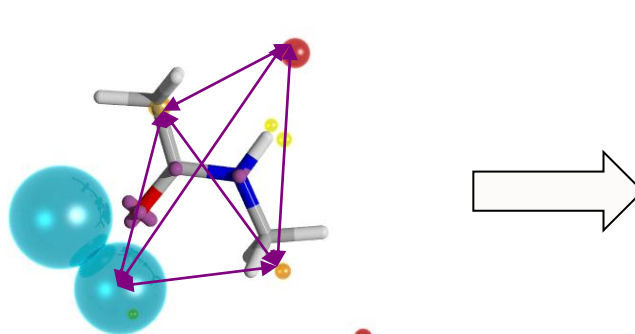
- > Clique based initial alignment
  - > Uses the distance matrix of Field Points
- > Detailed score
  - > Single point
  - > Uses Field-Point on Field Scoring
- > Optional simplex based optimisation of alignment
  - > Rigid body - no bonds twisted
  - > Uses detailed score as optimisation parameter

# Field Alignment

Imidazole

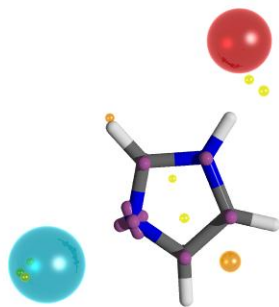


N-methyl acetamide

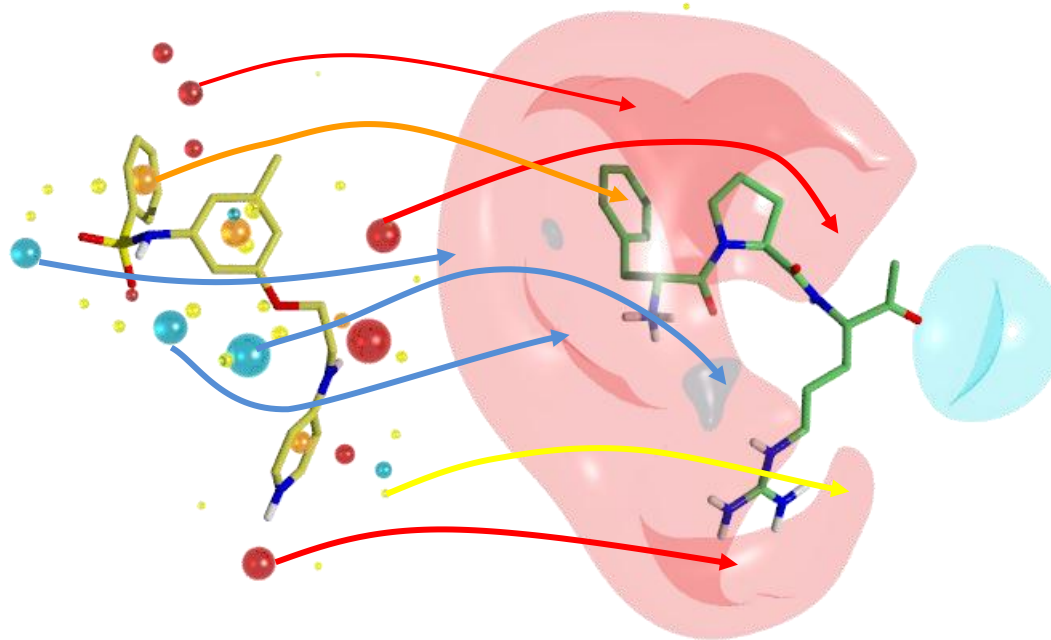
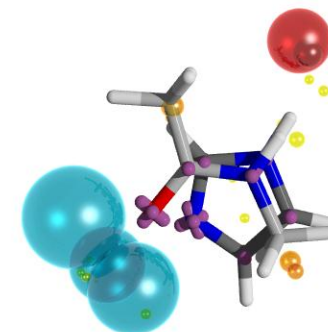
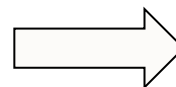
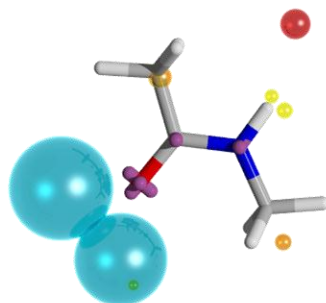


# Field Scoring

Imidazole



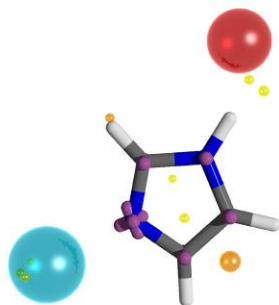
N-methyl acetamide



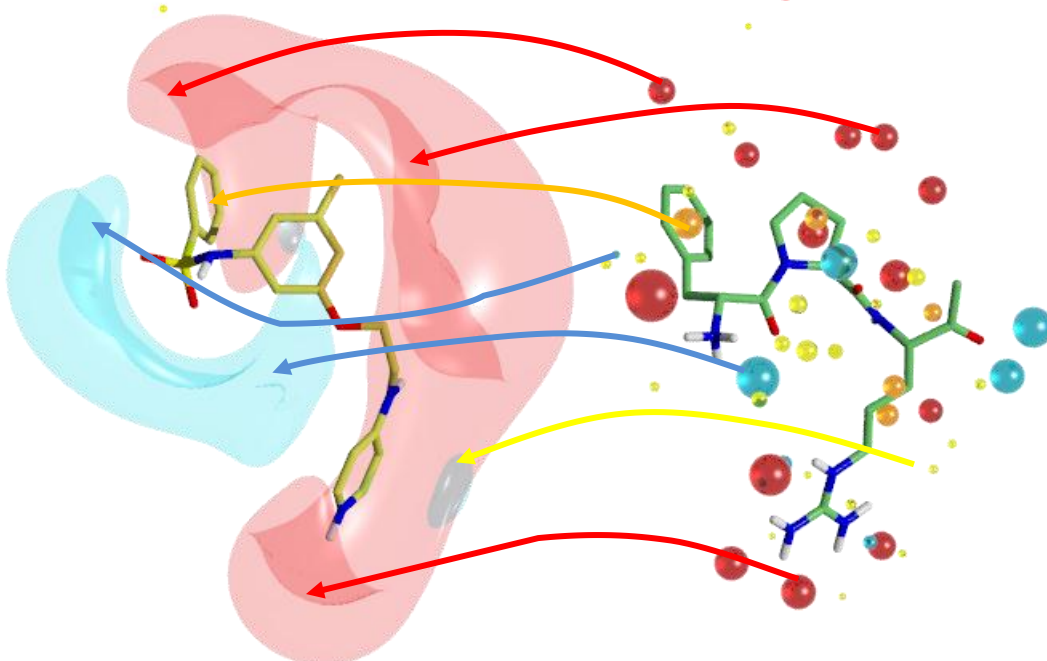
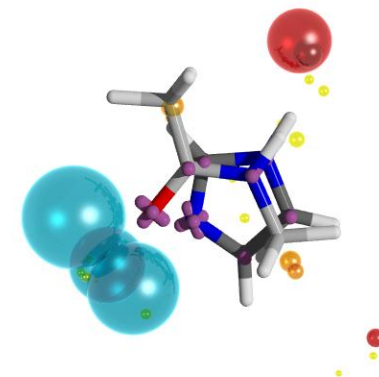
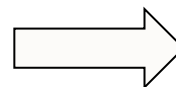
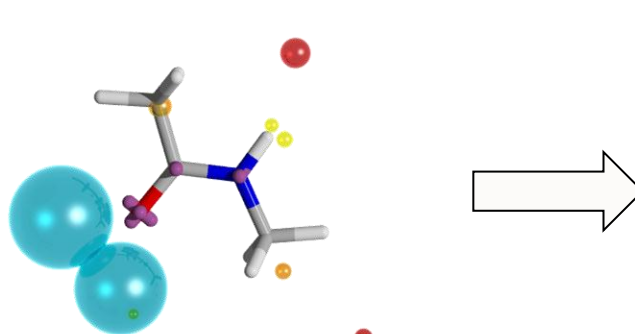
To score a particular alignment, we use the field points of molecule 1 to sample the actual field of molecule 2

# Field Scoring

Imidazole



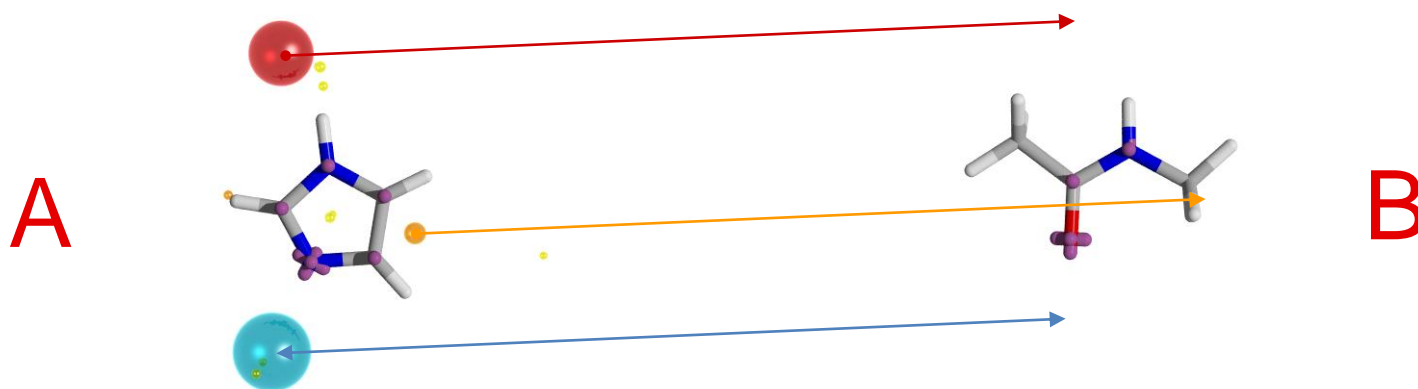
N-methyl acetamide



To score a particular alignment, we use the field points of molecule 1 to sample the actual field of molecule 2 and vice-versa

# Similarity Scoring function - 1

$$E_{A \rightarrow B} = \sum_{fp_A} size(fp_A) \times F_B(position(fp_A))$$



# Similarity Scoring function - 2

$$E_{A \rightarrow B} = \sum_{fp_A} size(fp_A) \times F_B(position(fp_A))$$

$$E_{AB} = \frac{E_{A \rightarrow B} + E_{B \rightarrow A}}{2} \quad S_{AB} = \frac{2E_{AB}}{E_{AA} + E_{BB}}$$

$E_{A \rightarrow B}$  = "Energy",  $S_{AB}$  = Similarity

