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smarter chemistry | smarter decisions

Biologically Relevant Molecular Comparisons

Mark Mackey

Agenda

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

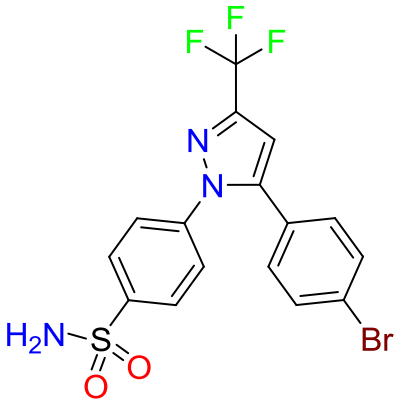
About Cresset

- 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

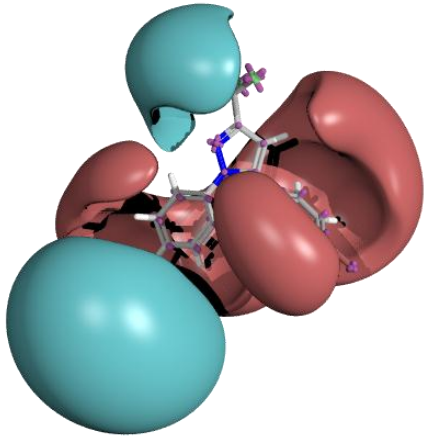
Field Points

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

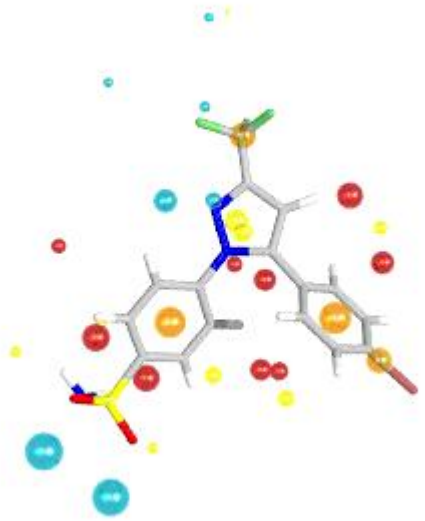
> Molecular Field Extrema (“Field Points”)



2D



3D Molecular Electrostatic Potential (MEP)



Field Points

= Positive
= Negative
= Shape
= Hydrophobic

Explanatory Power of Fields

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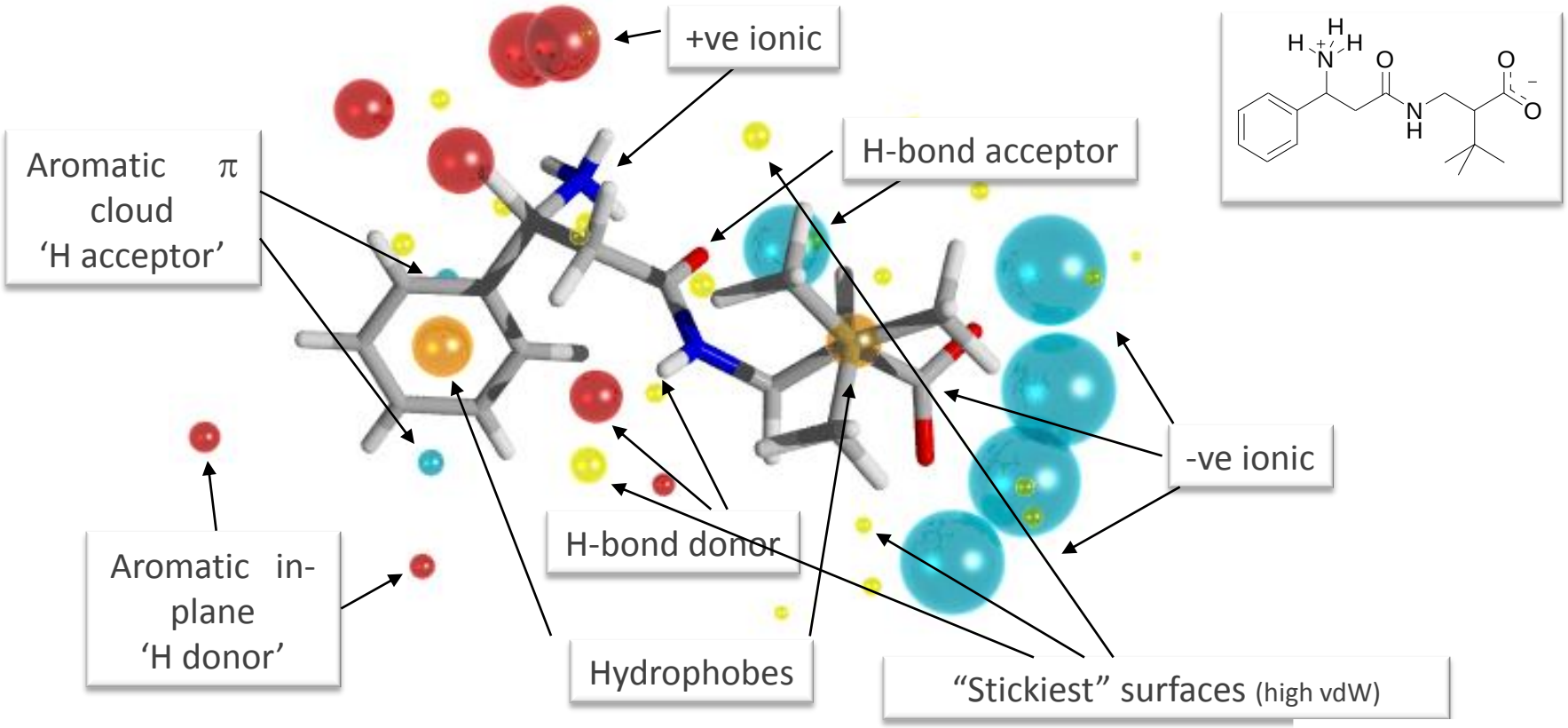
Field points give you new insights into your molecule

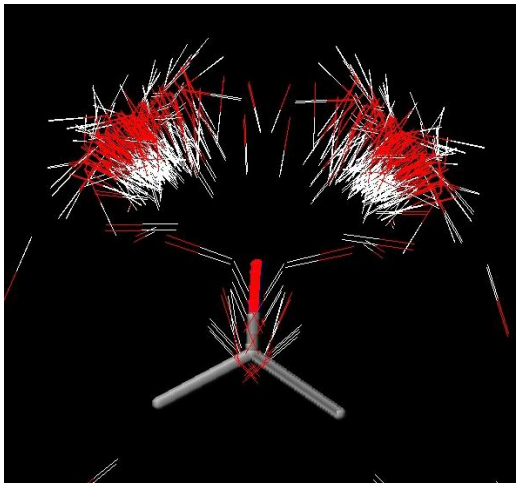


Field point size show importance

XEDs make Fields Work

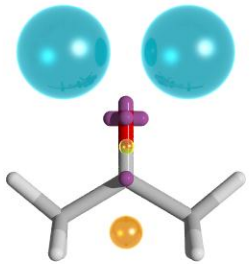
> Field patterns from Cresset's proprietary XED force field reproduce experimental results

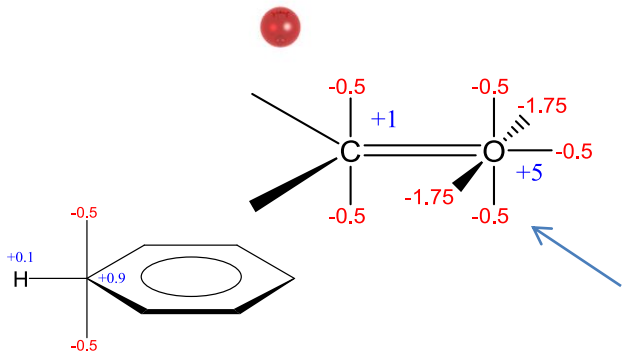
Experimental



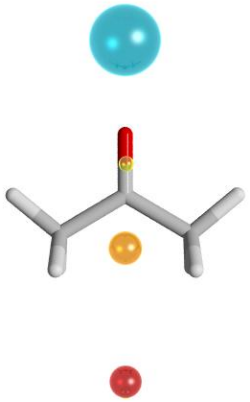
Interaction of Acetone and Any-OH from small molecule crystal structures

Using XEDs





Not using XEDs



XED adds p-orbitals to get better representation of atoms

Alignment and scoring

- 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

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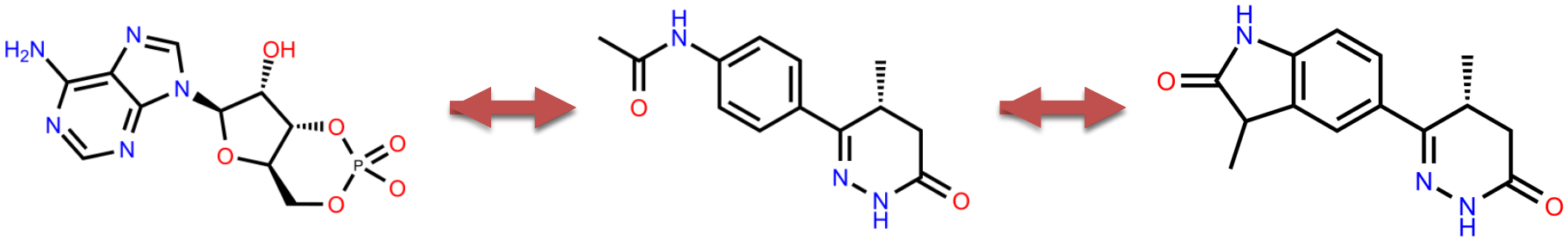
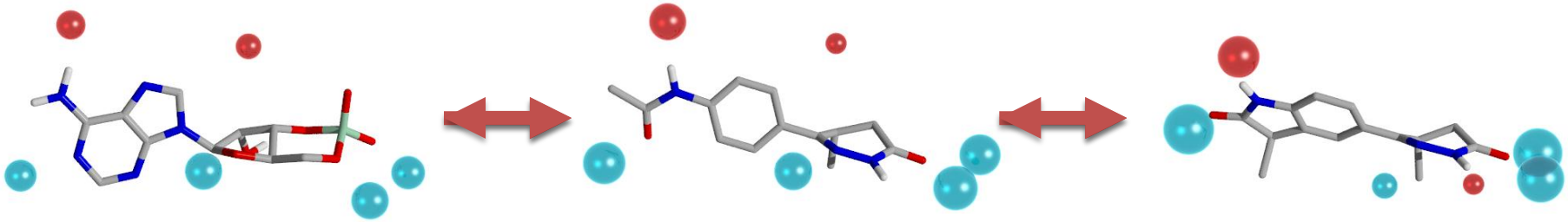
Biologically relevant method for comparing molecules



Bioisosteres

Bioisosteric groups



fieldscreen™ fieldalign™ fieldstere™

fieldtemplater™ fieldview™

Applications of Fields

- 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

Applications of Fields

- 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

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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

KNIME support

- 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(!)

Future

- 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

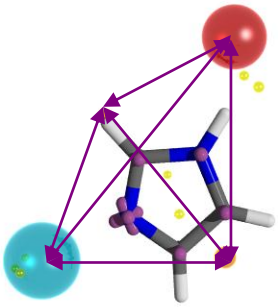
Comparing Molecules

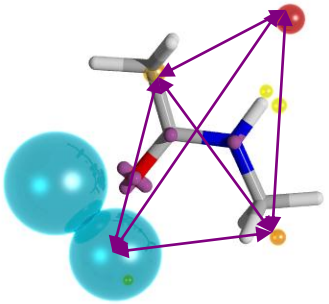
- Clique based initial alignment
  - Uses the distance matrix of Field Points
- Detailed score
  - Single point
  - Uses Field-Point on Field Scoring
- Optional simplex based optimisation of alignment
  - Rigid body - no bonds twisted
  - Uses detailed score as optimisation parameter

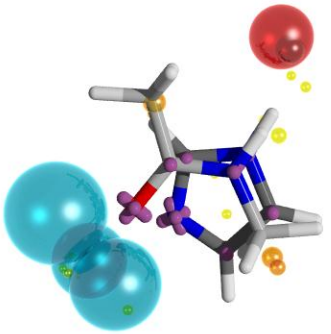
Field Alignment

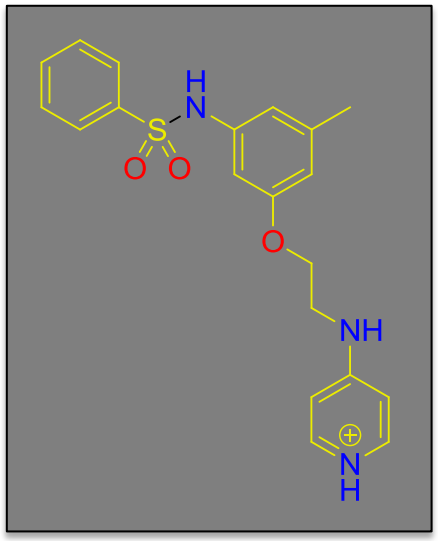
Imidazole

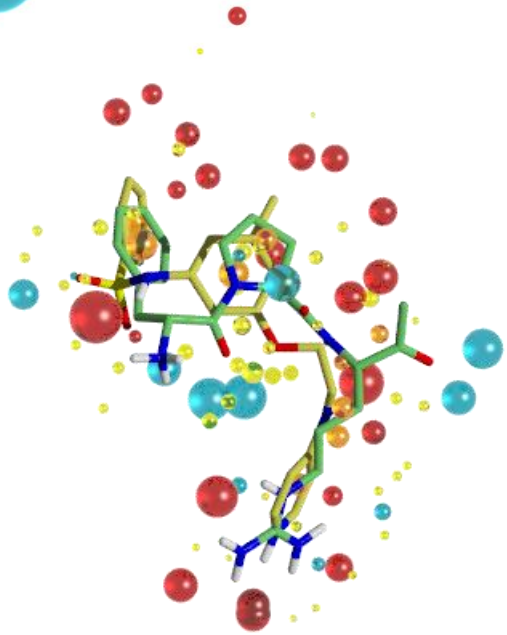
N-methyl acetamide

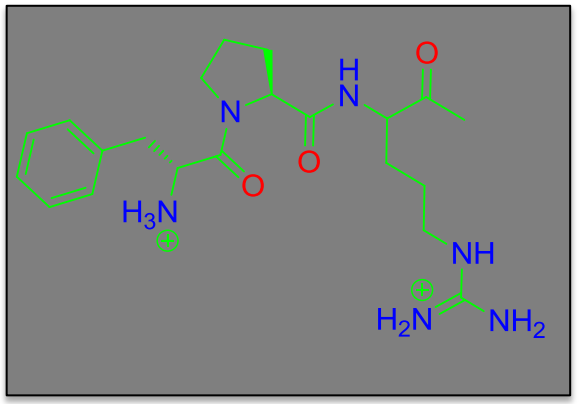








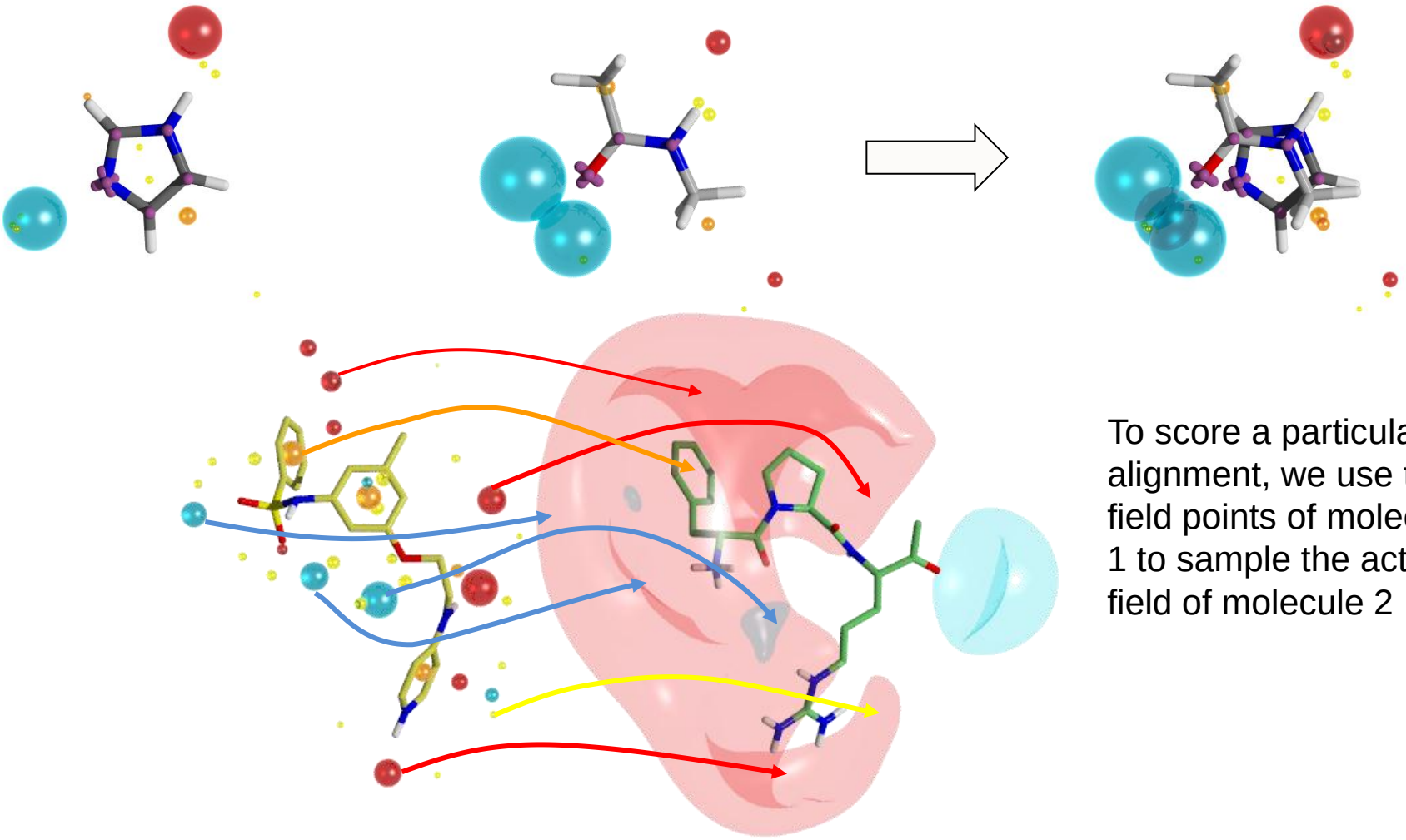




Field Scoring

Imidazole

N-methyl acetamide



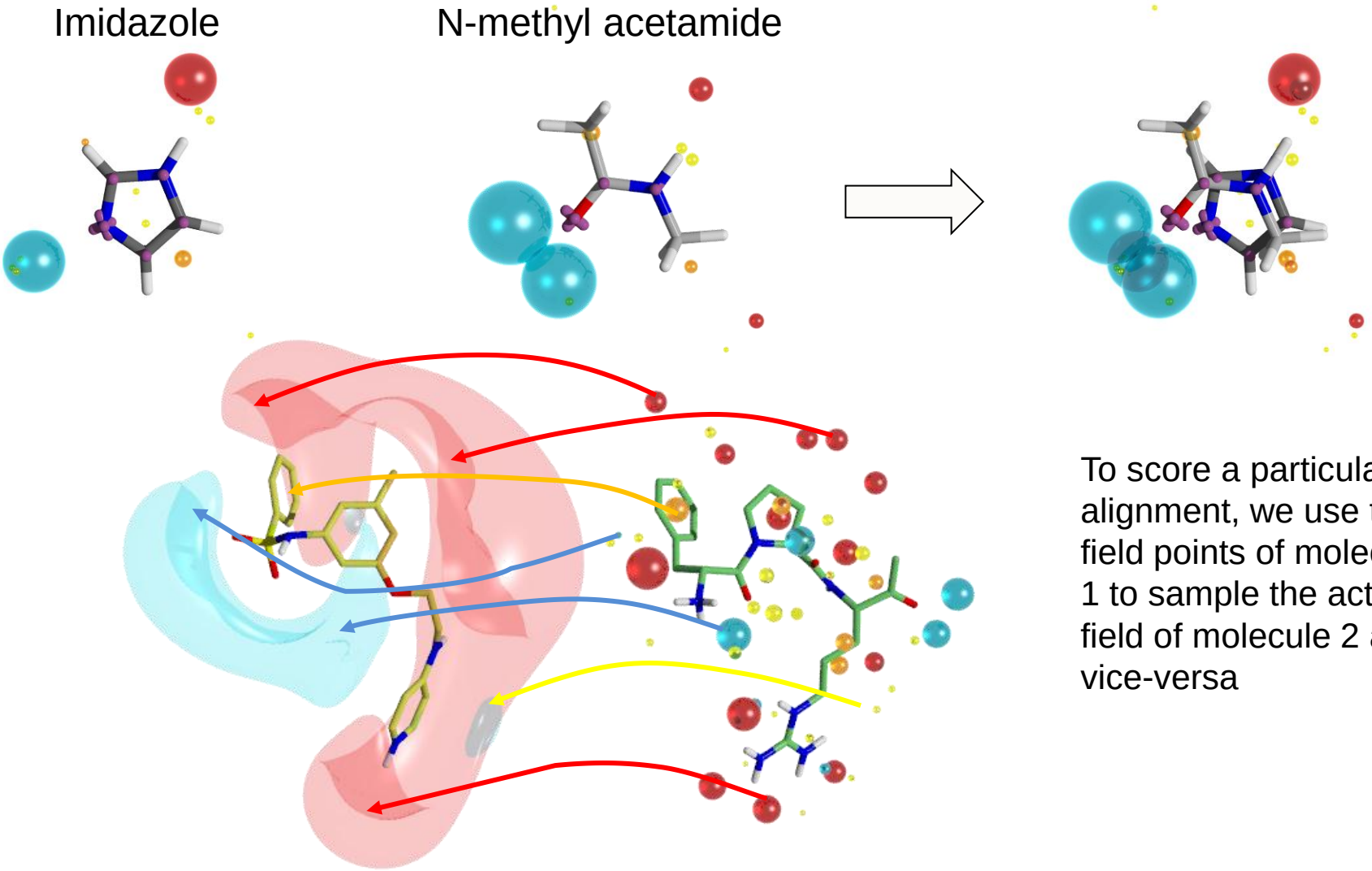
To score a particular alignment, we use the field points of molecule 1 to sample the actual field of molecule 2

Cheeseright et al, *J. Chem Inf. Mod.,* 2006, 665

Field Scoring

Imidazole

N-methyl acetamide

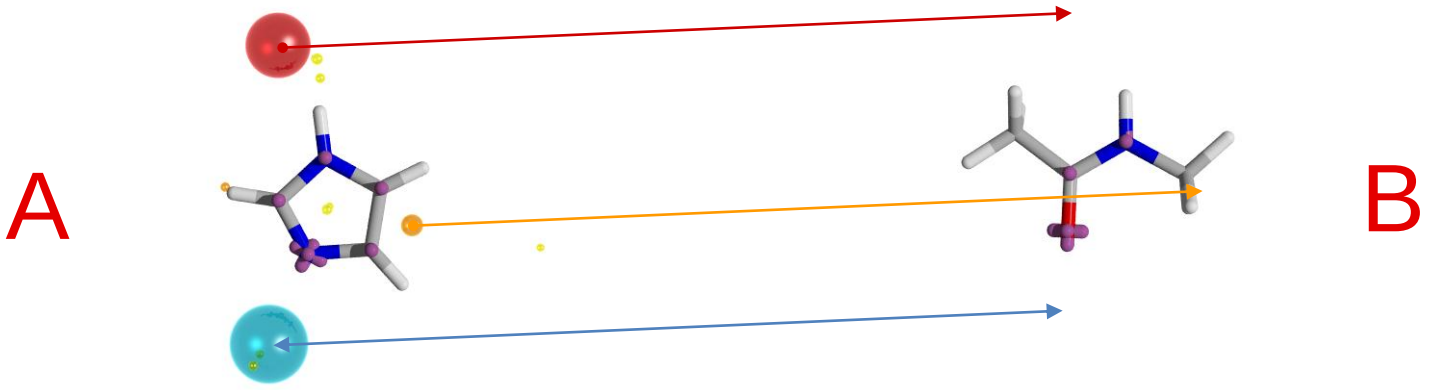


To score a particular alignment, we use the field points of molecule 1 to sample the actual field of molecule 2 and vice-versa

Cheeseright et al, *J. Chem Inf. Mod.,* 2006, 665

Similarity Scoring function - 1

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



Similarity Scoring function - 2

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

$$E_{AB} = \frac{E_{A\to B} + E_{B\to A}}{2} \qquad S_{AB} = \frac{2E_{AB}}{E_{AA} + E_{BB}}$$

$E_{A\to B}$ = “Energy”, S_{AB} = Similiarity