StructureBrowser: Surfing structures, docking and generating ideas

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VERTEX

Chemists ask this

- Questions
  - Show me structures containing similar ligands (2D & 3D)
  - Show my structures aligned in the same frame of reference
  - View selectivity information
- Operations
  - Dock my molecule using known str. info. from target & templates
  - Generate new molecules based on these good binders
  - Analyze & annotate active site
- Collaboration (Bookmarking and sharing views)

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Software Requirements

- Multi-platform (Mac, PC & Linux)
- Automatic installation & updates
  - global sites
- Extensibility
- Ease of use
  - PyMol
    - scripting & complex interface
  - Good GUI
- Pluggable viewer

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The traveled path

- 1997 - Silicon Graphics in chemistry labs
  - Unix a barrier, modeling software too complex

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The traveled path

- 1998 - VB + Weblab viewer
  - Deployment (dll) problems, not cross platform
- 2000 - Java + Weblab viewer
  - not cross platform, Java + ActiveX issues

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The traveled path

- 2001 - Java + Jvida based
  - cross platform, wide acceptance, orphaned codebase

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The traveled path

- PyMol + wxWindows based
  - works great for modelers. Not so for chemists
  - wxWindows
    - Inconsistencies.
    - Some threading issues with PyMol.
    - Doesn’t always work on Mac
  - Deployment problems
- 2004 - Java + Astex Viewer
  - cross platform, works well, some performance issues
- 2005 - Java + JyMol component?

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Where we are now

- Deployment
  - Java webstart based
  - Changes deployed globally within 30 minutes
- Platforms
  - Java (Mac + Linux + PC)
- 3D viewer
  - Designed to be pluggable
    - Currently uses the Astex renderer
    - Will use JyMol when available
- Feature usages are captured & logged on server
  - Helps refine interface and usability

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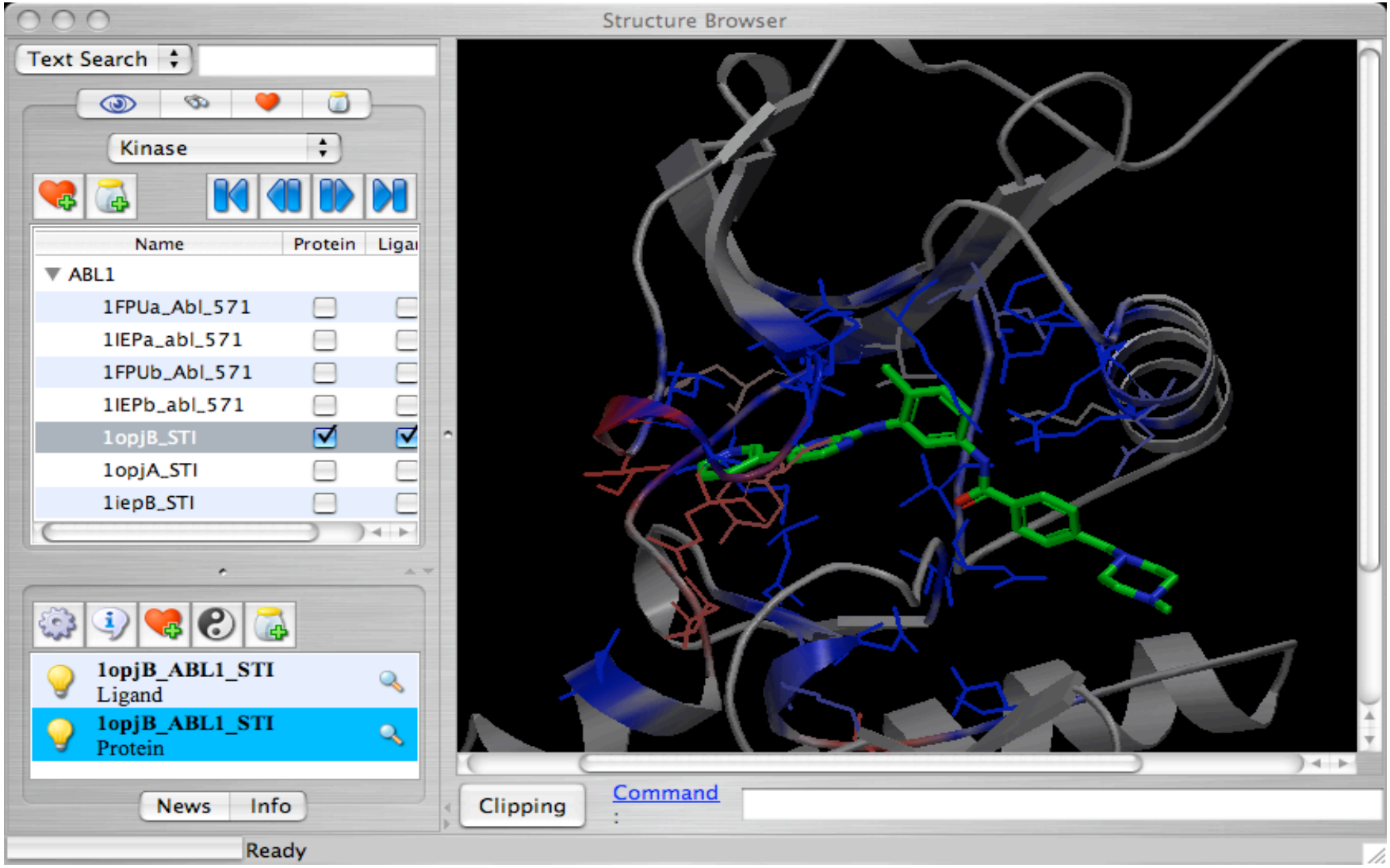
Structure browsing



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Structure browsing

- Aligned Structures
  - ~700 kinase complexes (internal & public)
  - Other gene families also available
  - Structures sequence aligned in a common frame of reference for all families we are interested in
  - Instant comparisons of heterogeneous structures in the same gene family

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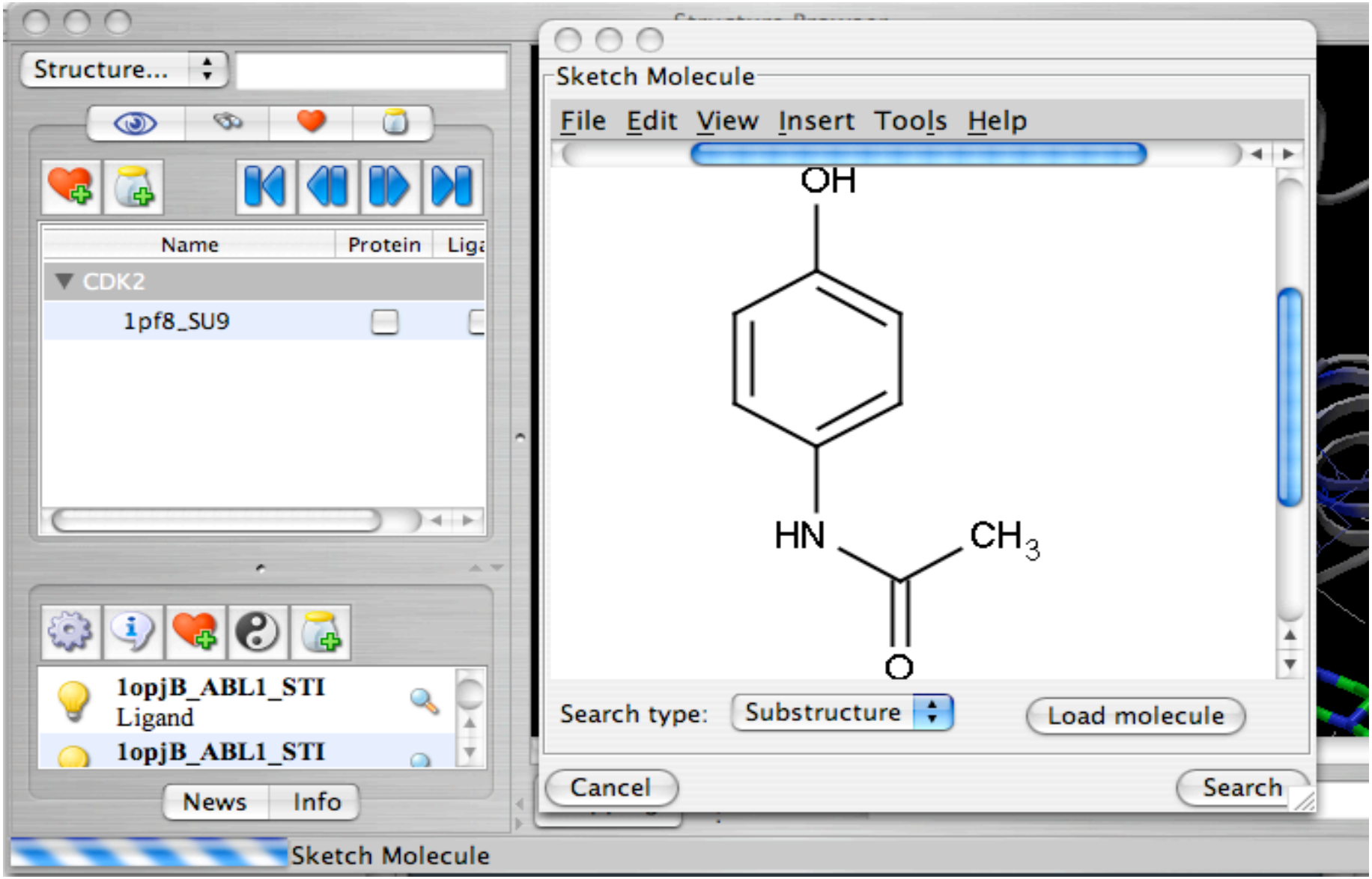
Text and structure searching



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Bookmarking views

- Views saved to database replicated at all sites
  - Allows instant sharing via email of views
  - script files of 3D viewer plugin
  - any externally loaded ligand files
- All data replicated at sites in UK, Cambridge MA & San Diego

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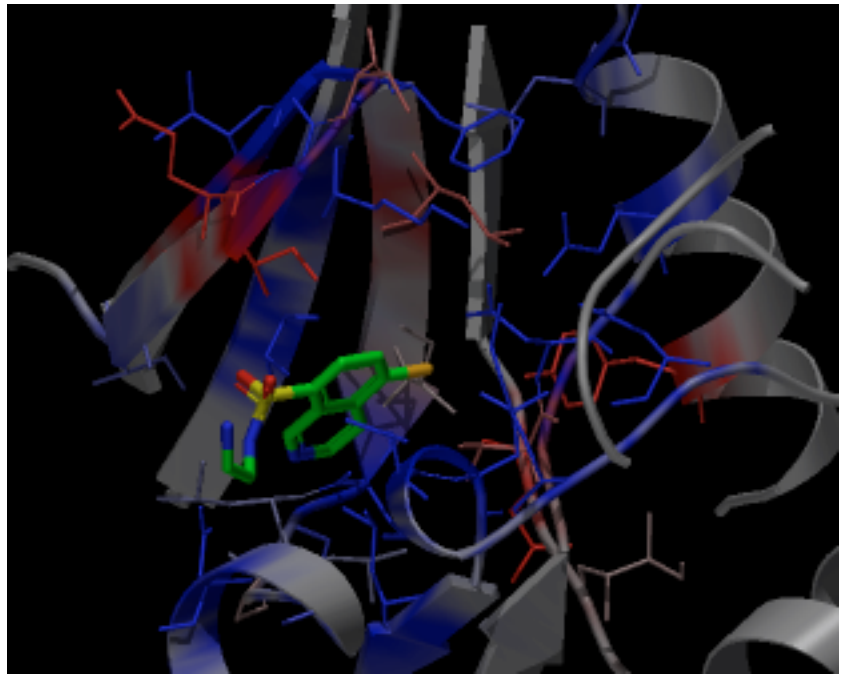
Coloring capabilities

- Via residue probability
  - for each gene family we've residue probabilities for all 20 residues at active site positions across that family
- Via electrostatics
- Via lipophilicity



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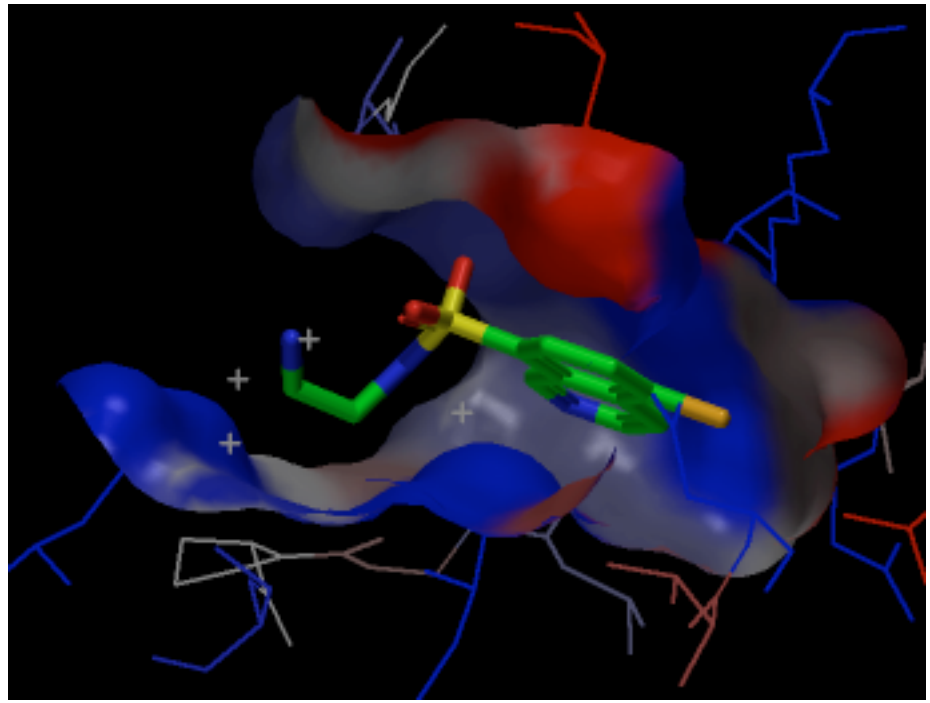
Clipping

- Single click clipping of views based on distance from active site



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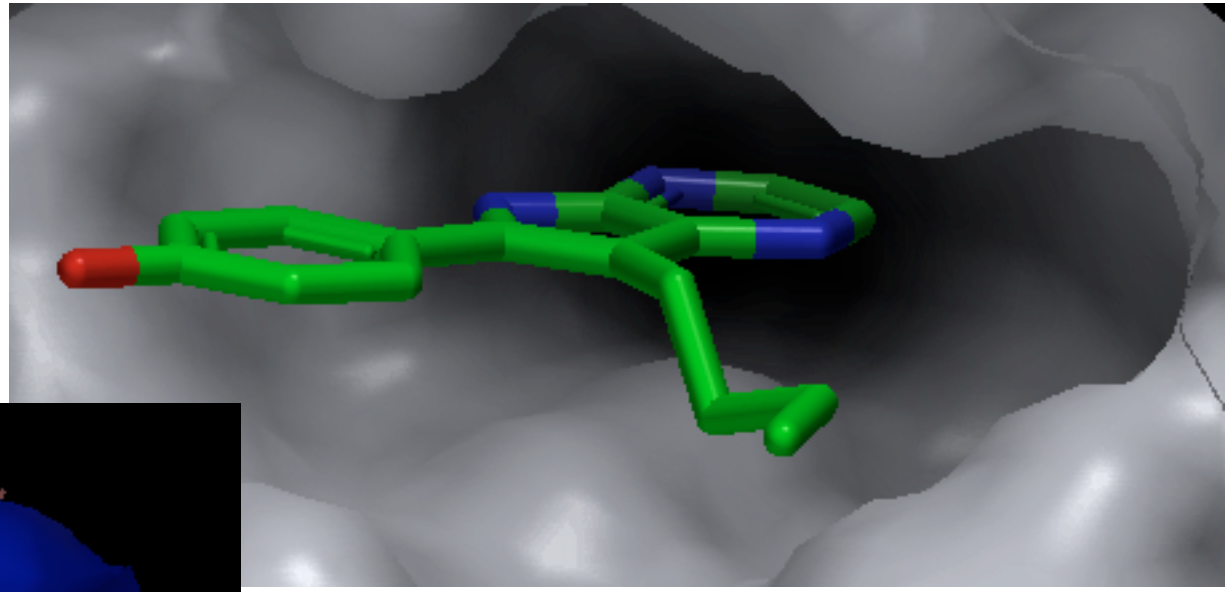
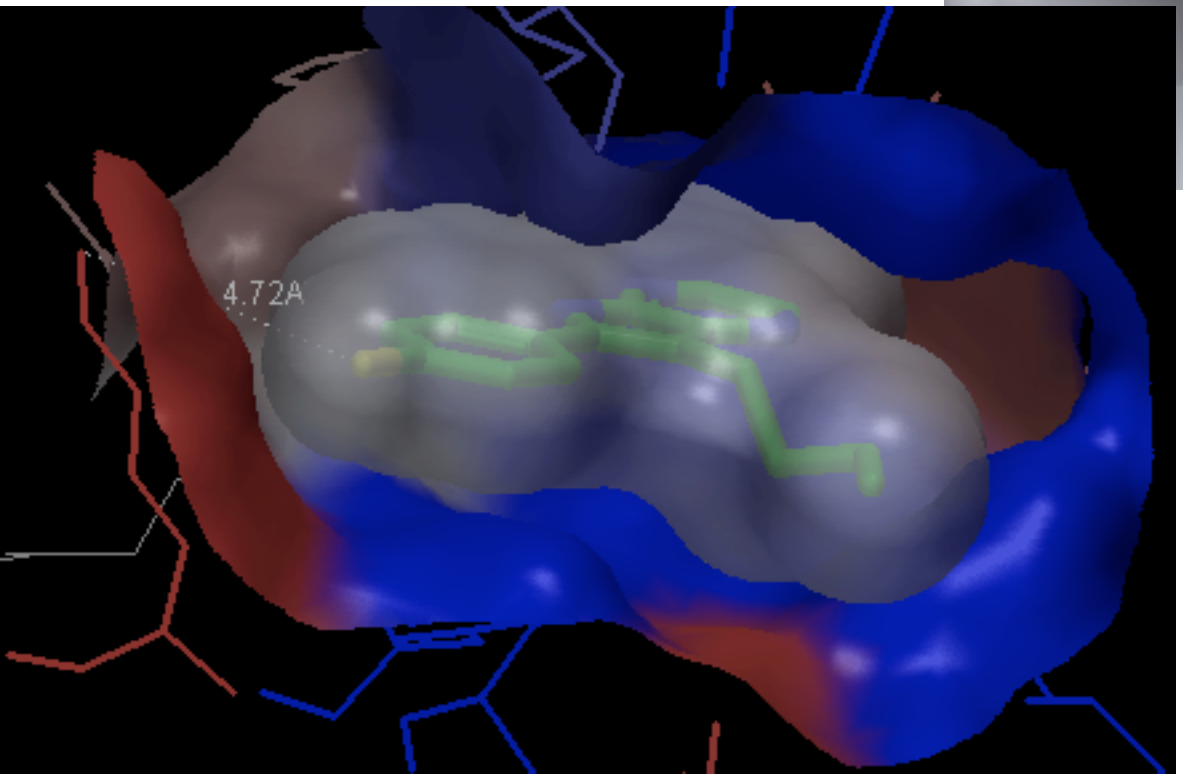
Docking to CDK5 molecule





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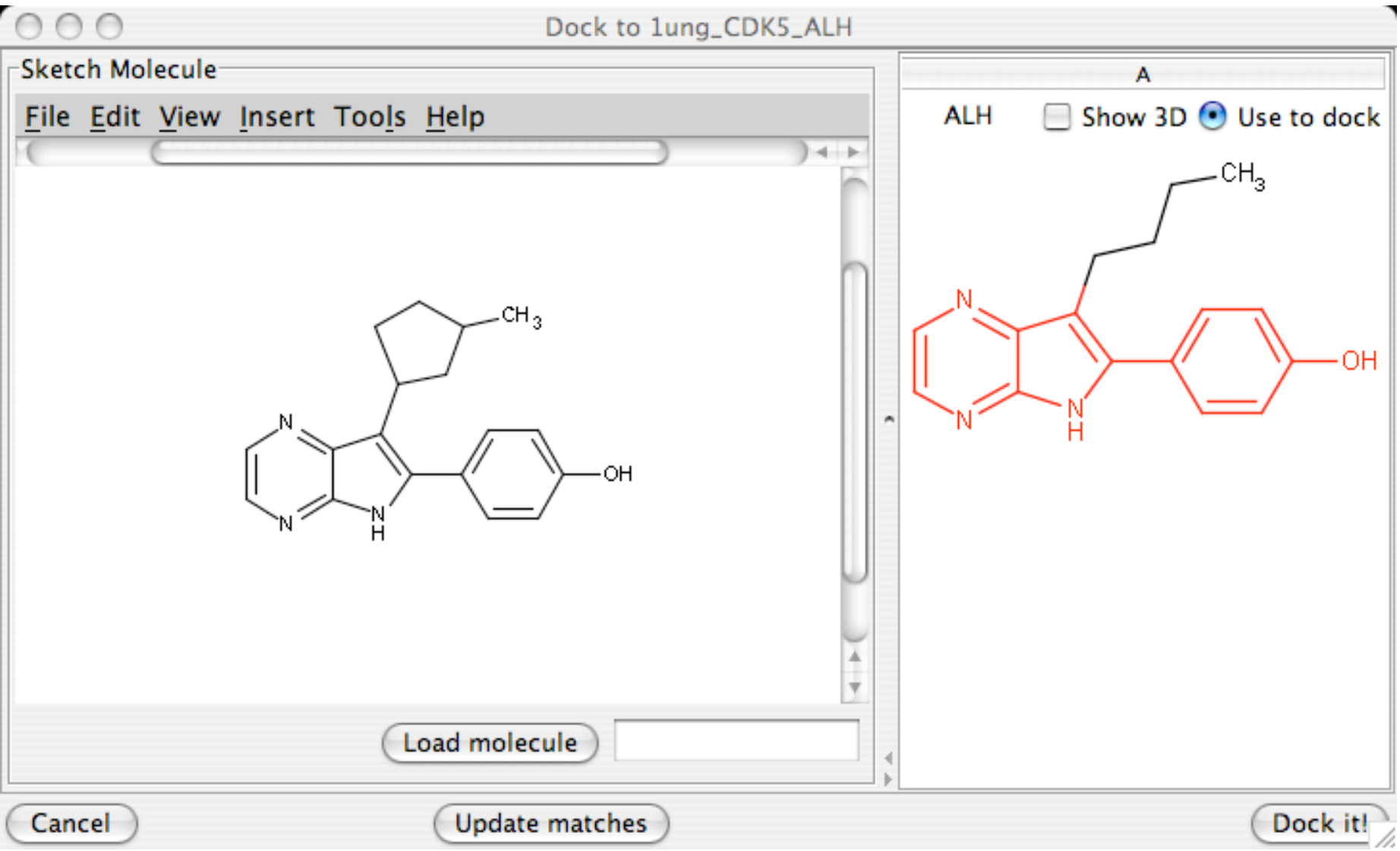
Docking to CDK5 molecule



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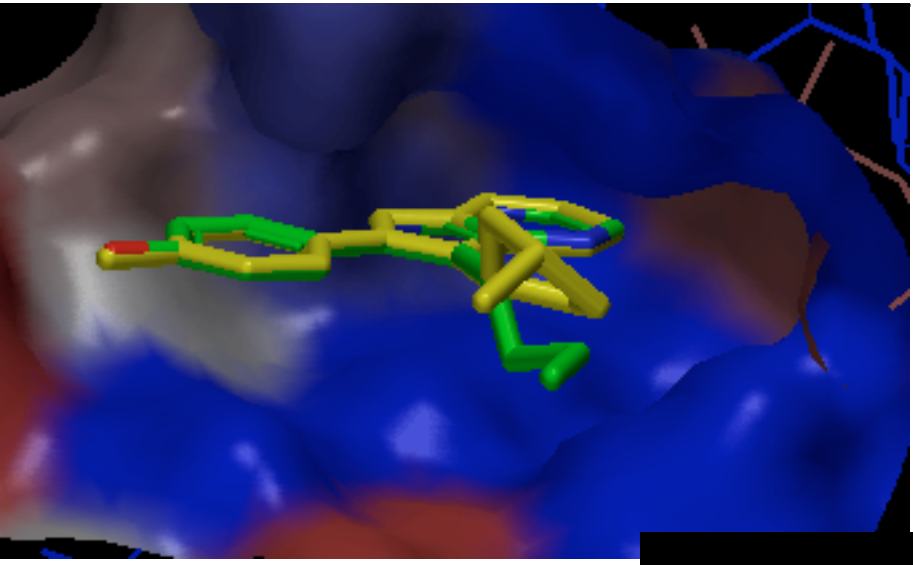
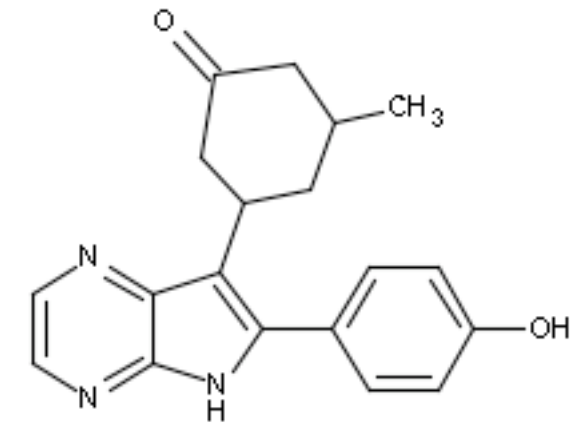
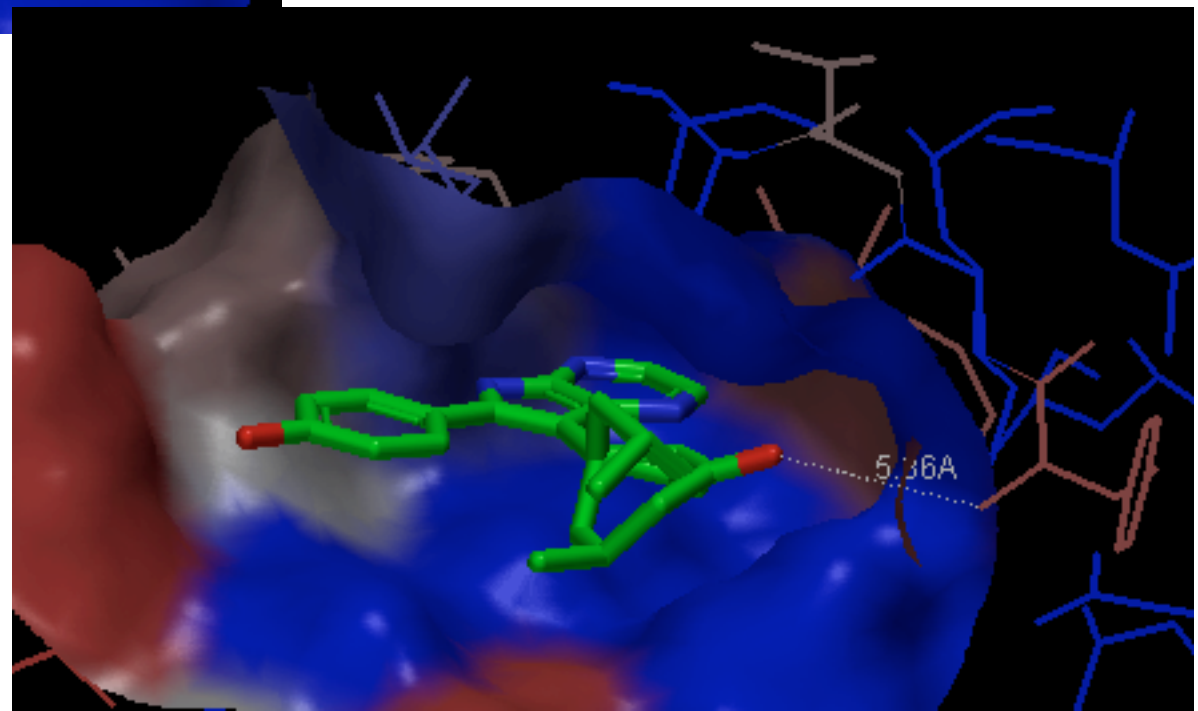
Docking to CDK5 molecule







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BREED: an idea generator

- Automatically joins fragments of known ligands to breed new ones
  - Overlapping bonds found
  - fragments on each side of bond swapped
- Recursive application
  - entirely new scaffold sets
  - novel substituents on known scaffolds
- Fast and yields 3D coordinates for visual analysis
- Common medchem process automated

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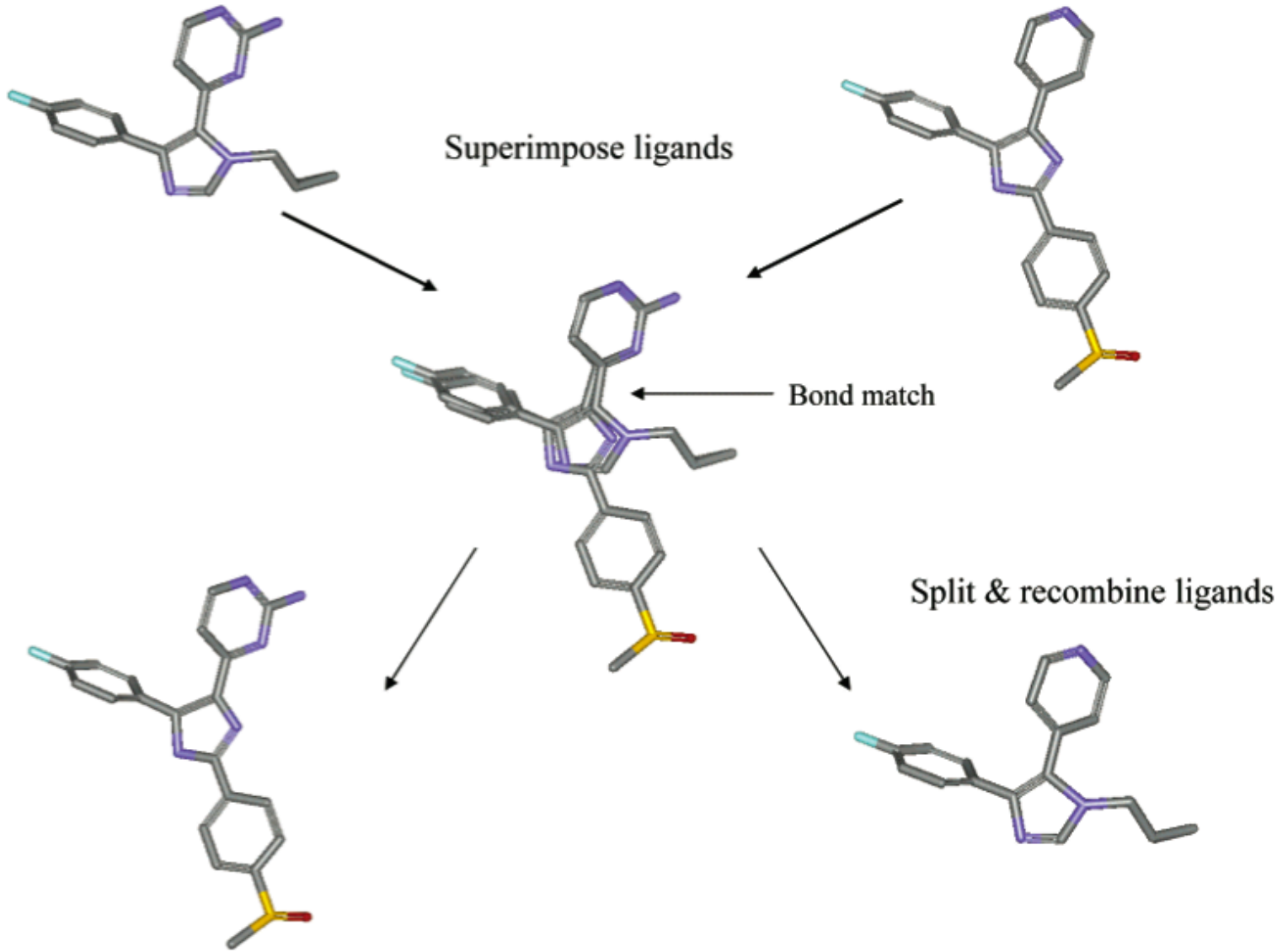
BREED: logic



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BREED: Usage

- (demo)

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Conclusion

- As comp. chem. tools get greater acceptance, bench chemists are now need access to features previously done via complex multi-step calculations
- We have developed an extensible collaborative solution to address this.
- With time we hope our tools will become as easy as using iTunes for a layman chemist.

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