Hierarchical clustering of chemical structures by maximum common substructures

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•*Solutions for Cheminformatics*

Clustering made human

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Why do we cluster?

to reduce the number of objects to deal with

- group subsets together
- represent each group by one member of it

Conventional approaches

Similarity based

- fingerprints or other molecular descriptors
- high dimensional artificial abstract chemical spaces
- similarity measures

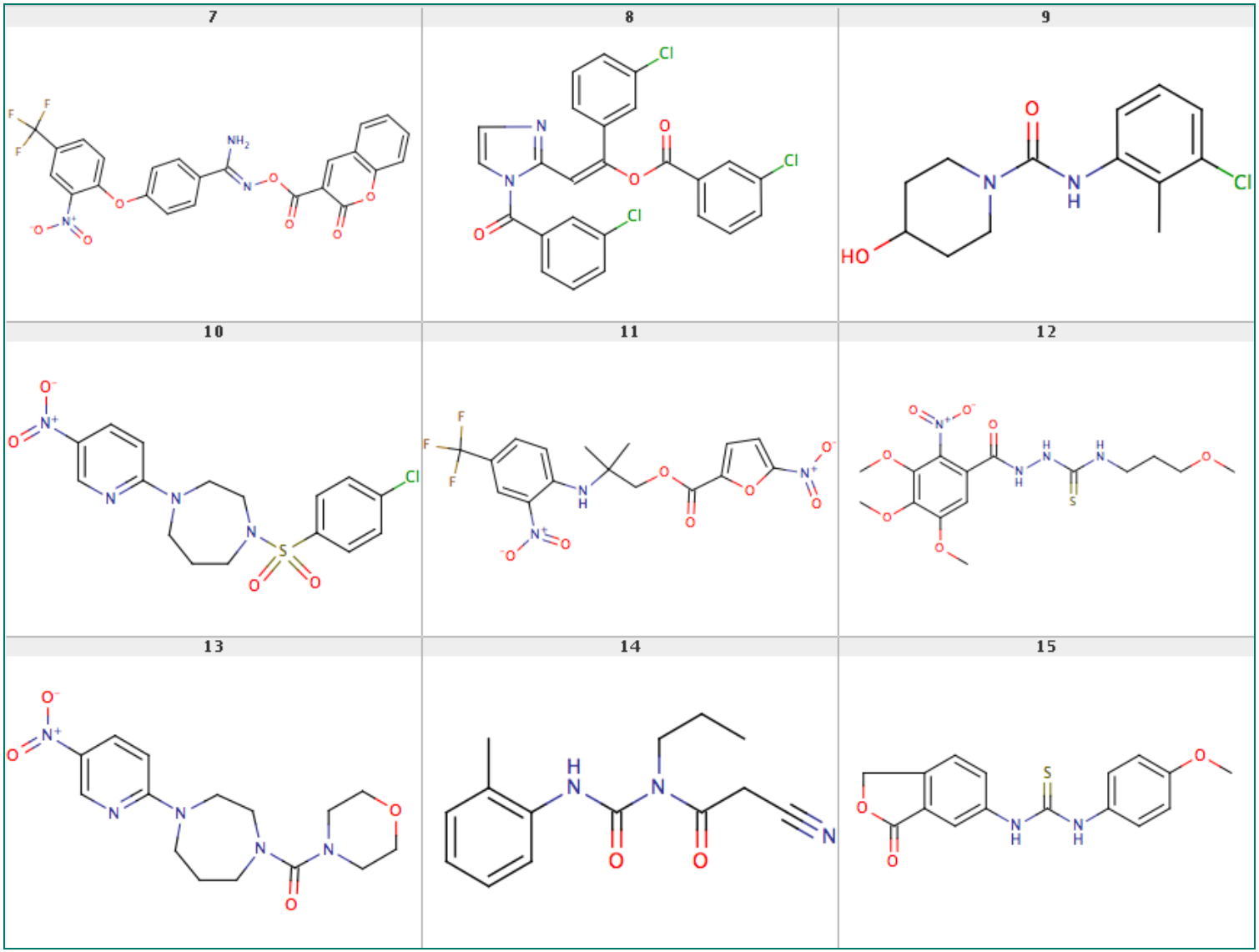
Jarvis-Patrick clustering

```
jarp -i SC1000.cfp -m 0 -f 1024 -t 0.6 -c 0.1
      -y -z -o SC1000.jarp.t0.6.c0.1 –g

Number of objects = 999
Number of clusters (without singletons) = 2
Number of singletons = 8

Average dissimilarity = 0.66208726
Minimum dissimilarity = 0.0
Maximum dissimilarity = 0.9411765
```

Parameter tuning

t	c	clusters	singletons
0.6	0.1	2	8
0.3	0.1	179	248
0.5	0.1	7	36
0.5	0.5	10	37
0.5	0.8	81	115

The most populated cluster



What's the matter with that?

- tedious
  - parameter tuning in a trial-and-error fashion
- lack of interpretability
  - the algorithm does not provide explanation
- often do not meet chemists' expectation

Astronomers' job is easier

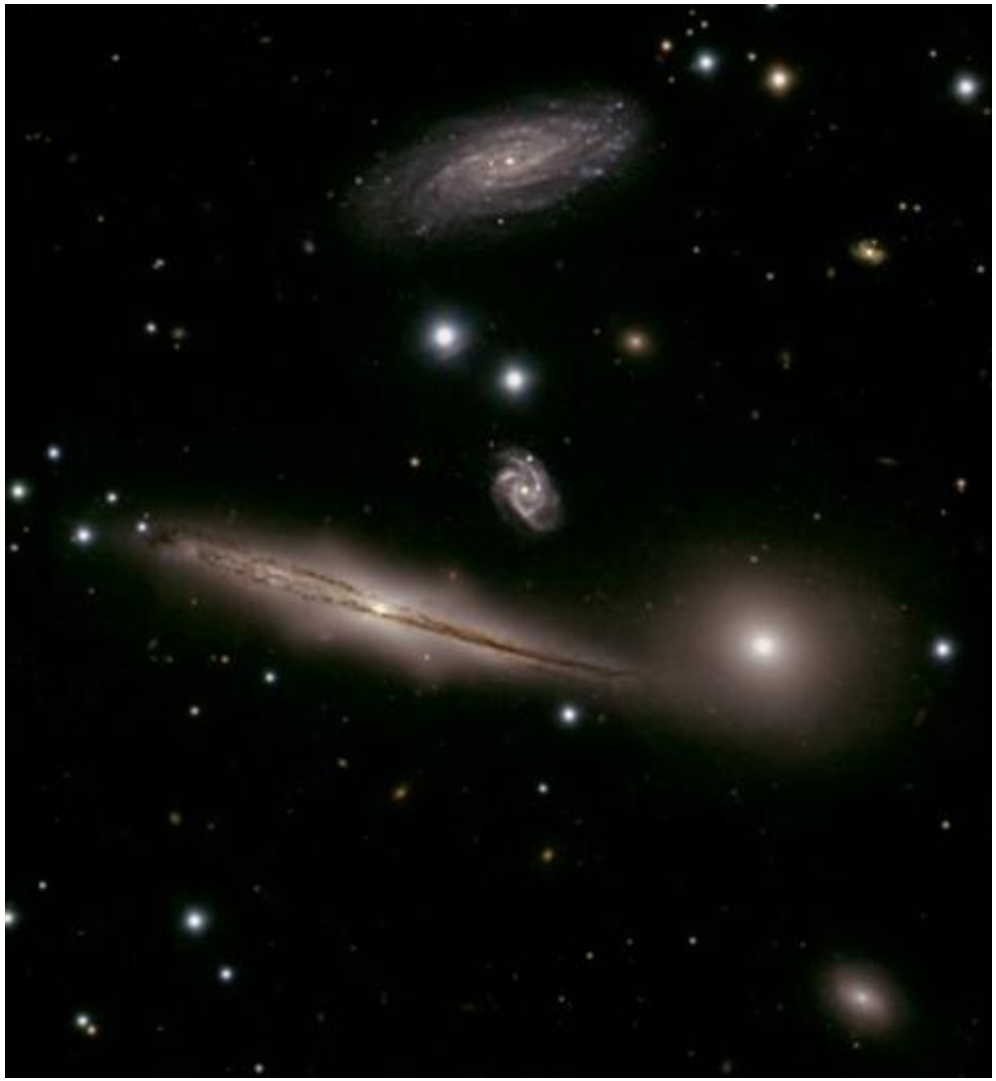
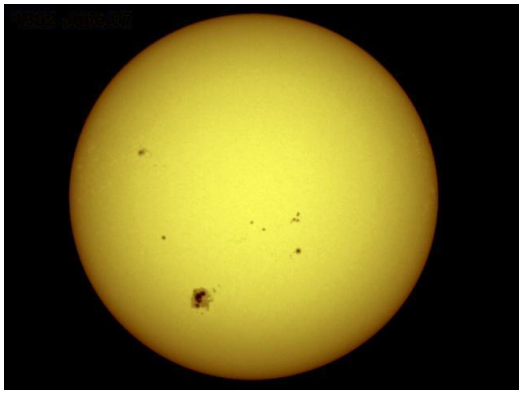
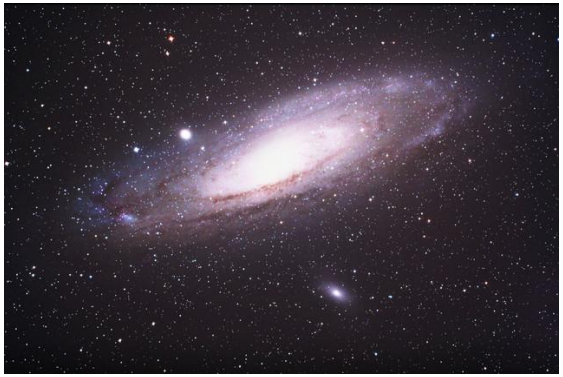


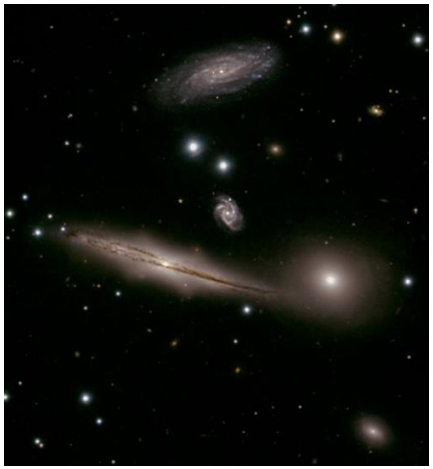
Image from Wikipedia, the free encyclopedia

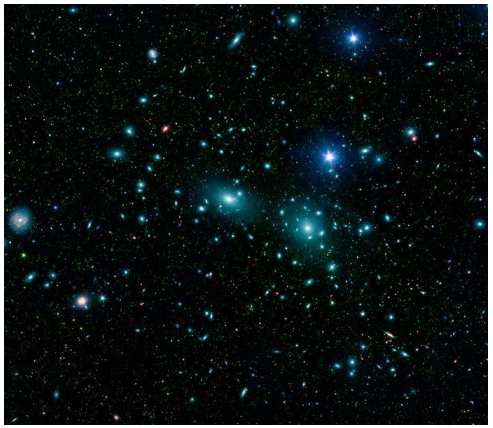
Why is clustering stars easy?

- stars have visible spatial arrangement
- distance between stars defines clusters, galaxies, …









Images from Wikipedia, the free encyclopedia

Why is clustering molecules hard?

lack of innate spatial arrangement

- artificial arrangement
  - infinite types of chemical spaces
  - various ‘distance metrics’
  - usually high dimensionality (hard to visualize)
- various approaches, no superior one
  - “best method” depends on application area, and on actual data

What do we need?

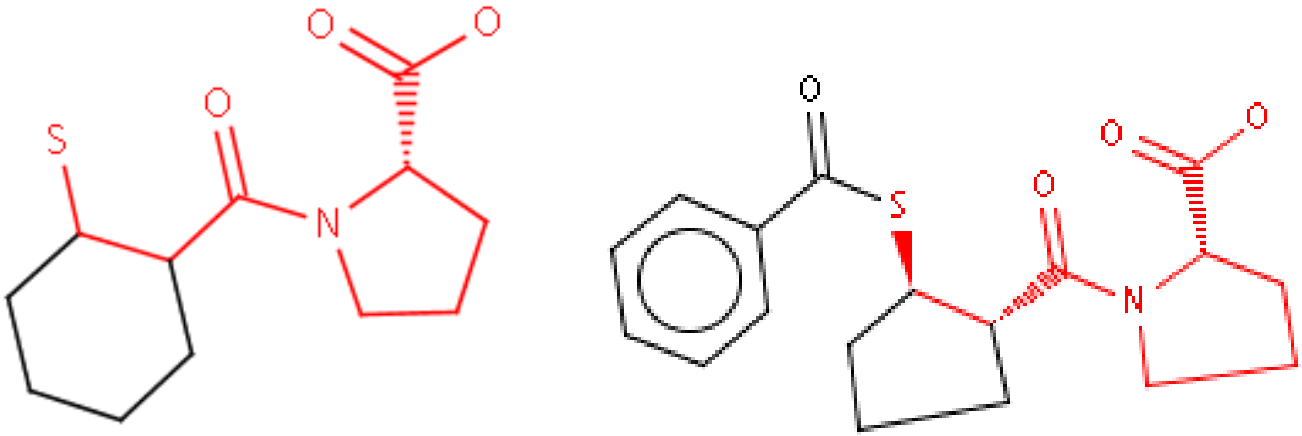
- no/few tuning
- easy to understand simple “explanation”

novel approach

- structure based clustering
- Maximum Common Substructure

Maximum Common Substructure

largest substructure shared by two molecules



Simple concept! More “human”, visual.

Yet hard (= expensive (= slow)) to compute.

MCS complexity

Sub-structure searching

- *query* structure is known, it “only” have to be found as part of the *target* structure (subgraph isomorphism)
- graph isomorphism is even “simpler” yet NP-hard
  - finding the answer can take long (scales exponentially with respect to the number graph vertexes) in the worst case
  - validating an answer is fast

MCS

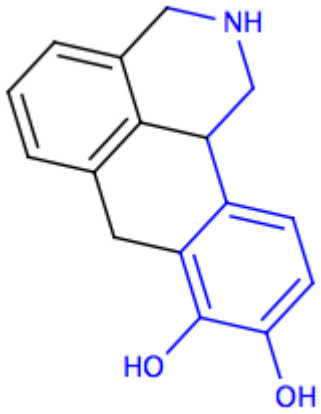
- “query” structure is not known
- all possible substructures need to be checked
  - even the number of substructures is exponential!

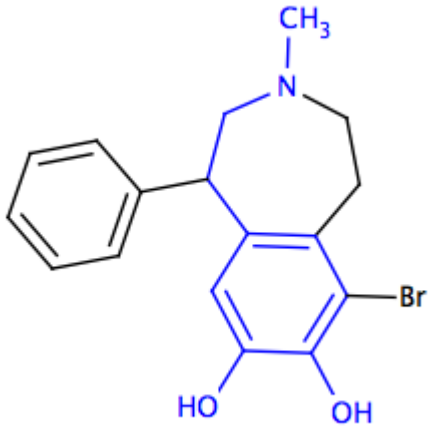
MCS algorithms

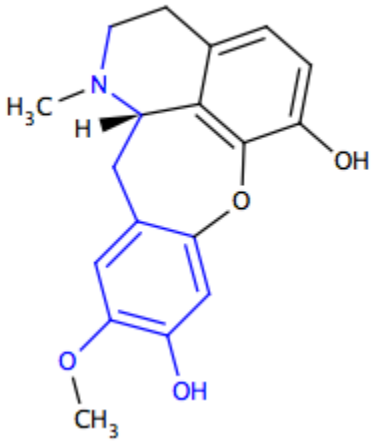
two camps

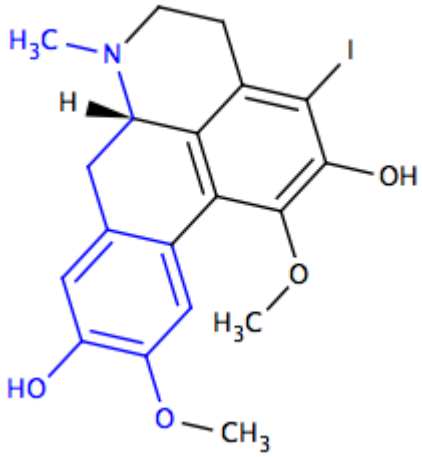
backtracking	clique detection
ad hoc	high mathematical elegance
average complexity is better than worst case	average complexity is same as worst case
dynamic heuristics	static (initial) heuristics
coloring is easy	coloring is hard
fuzzy matching	fussy matching

MCS of a structure set

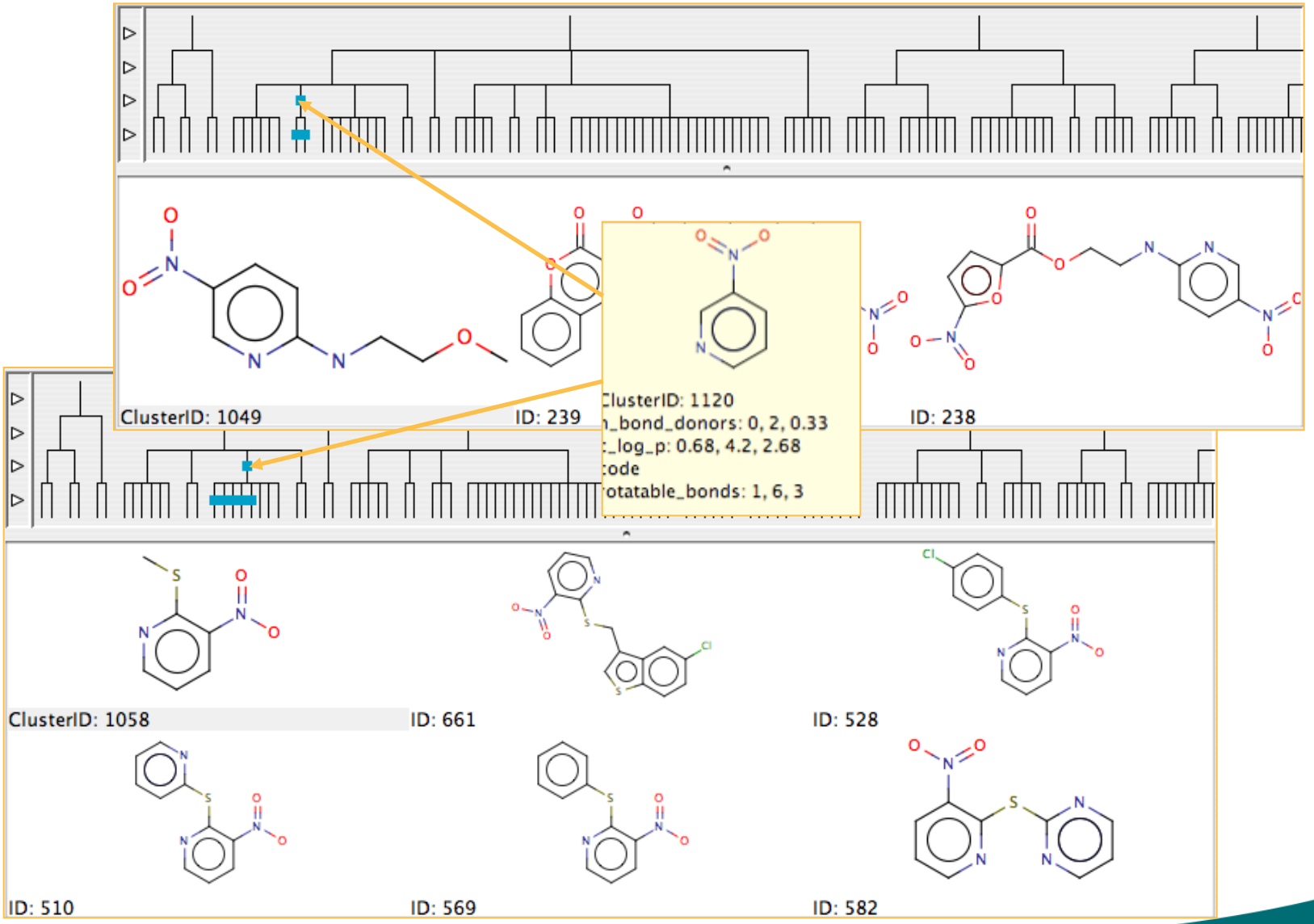




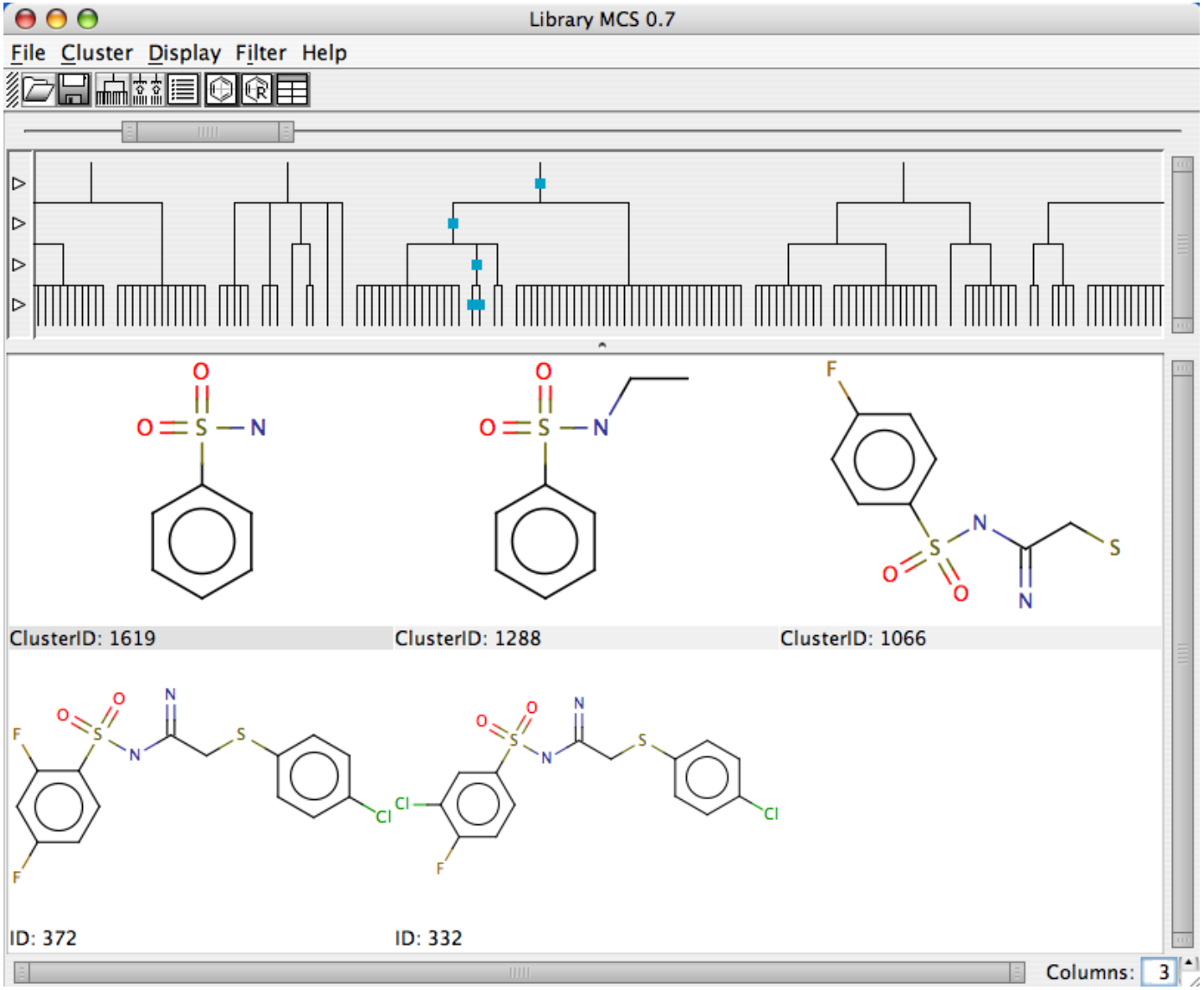




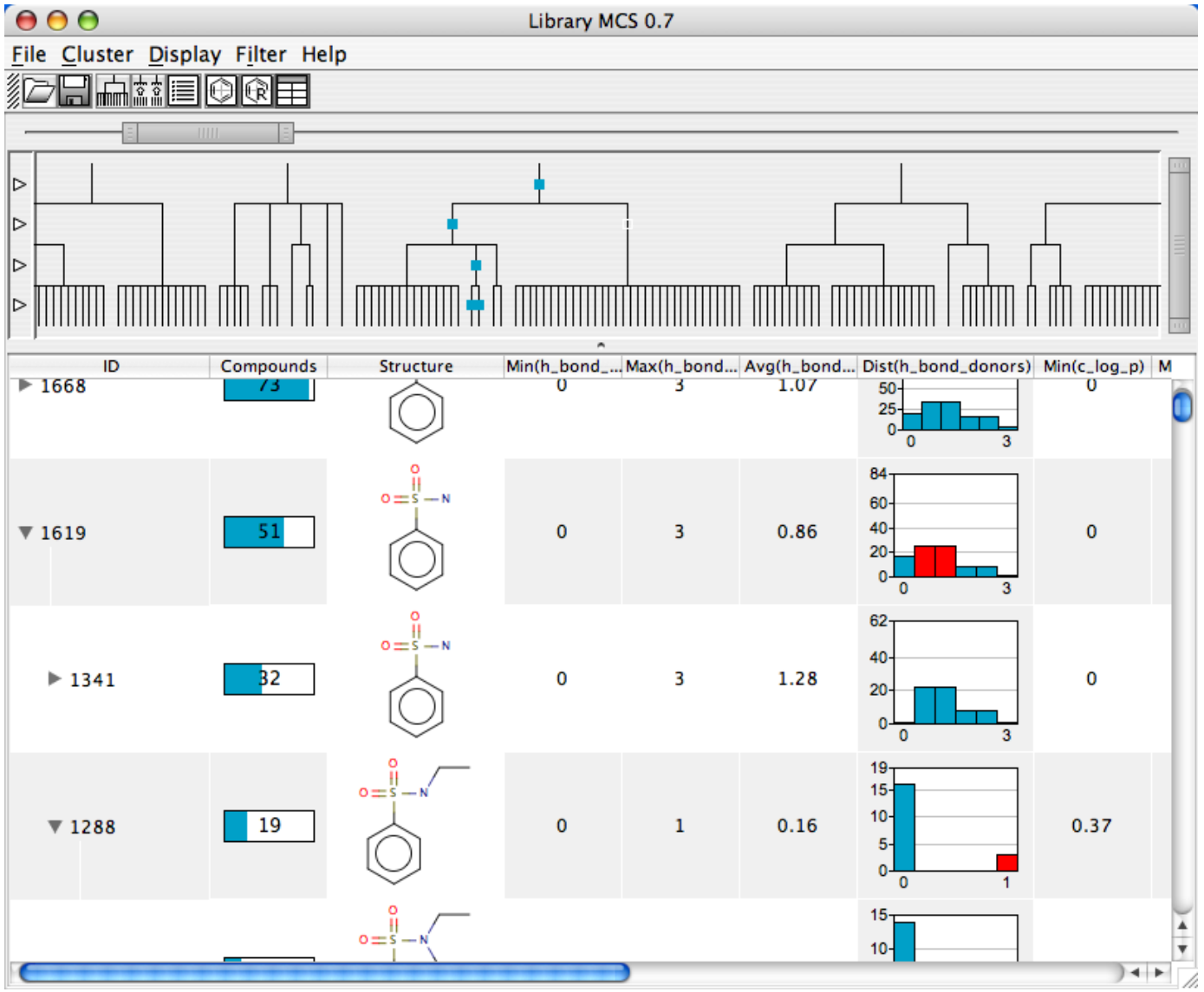
LibraryMCS: Hierarchical MCS



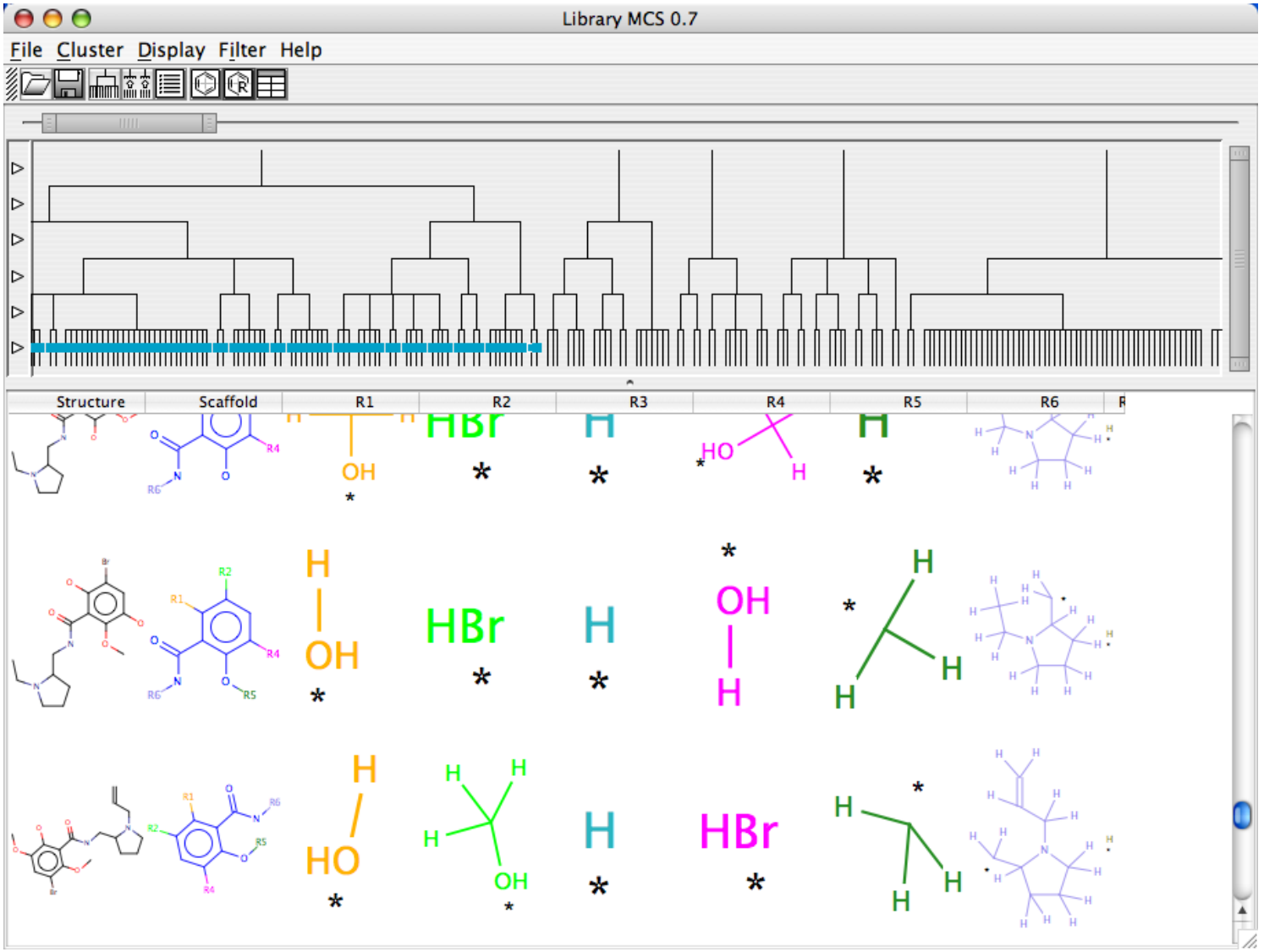
Intuitive visualization



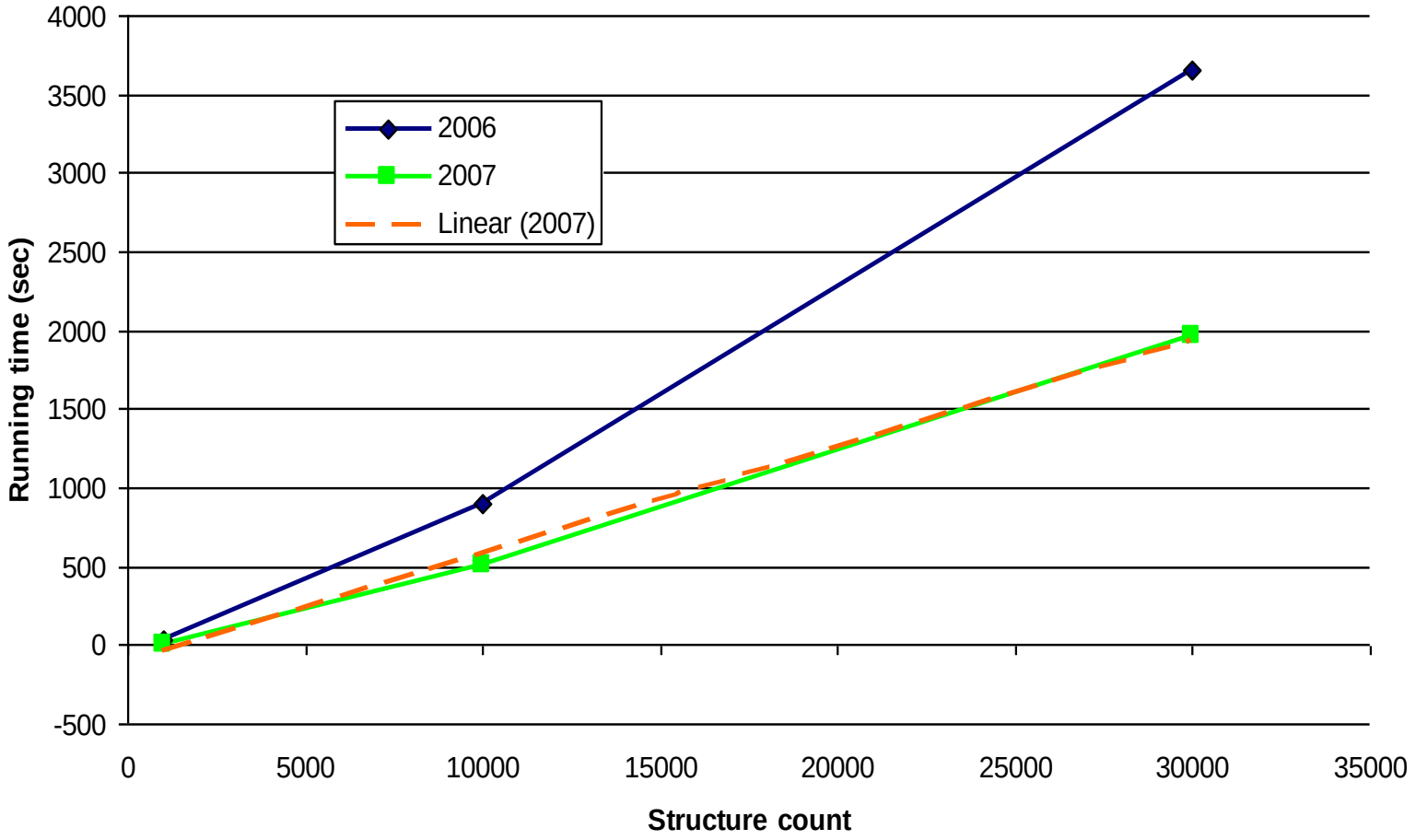
SAR table view



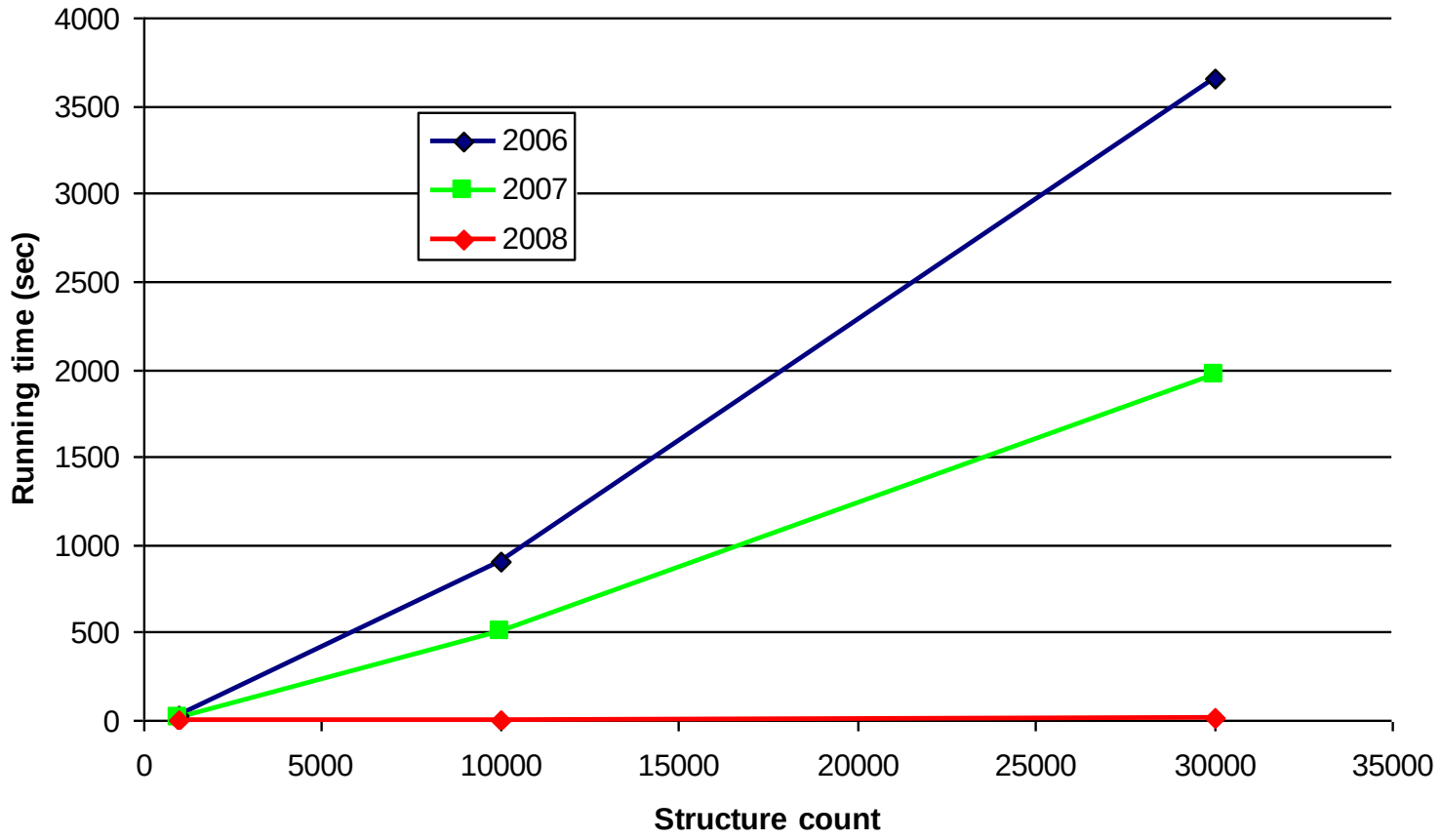
R-group decomposition



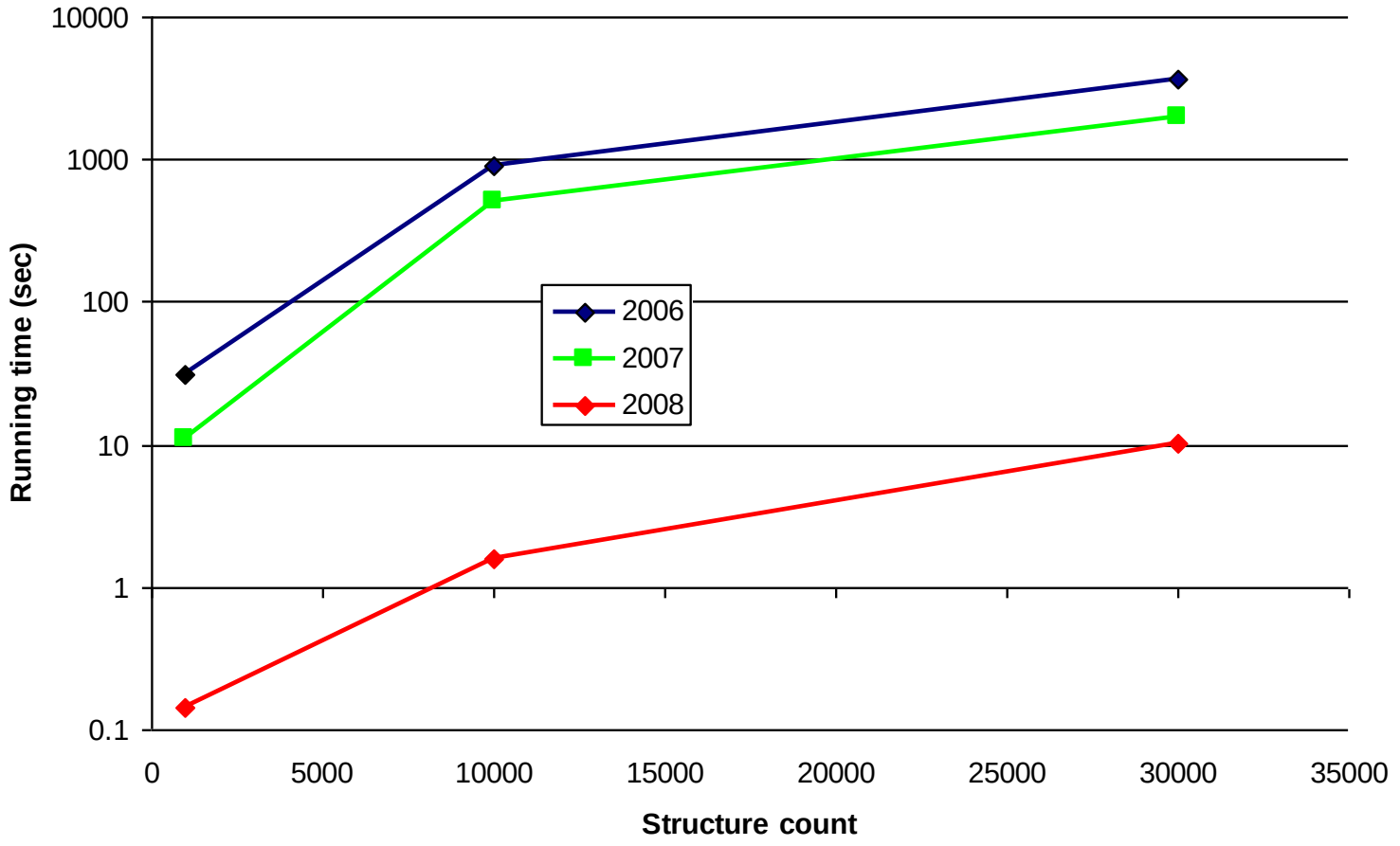
LibraryMCS scales linearly



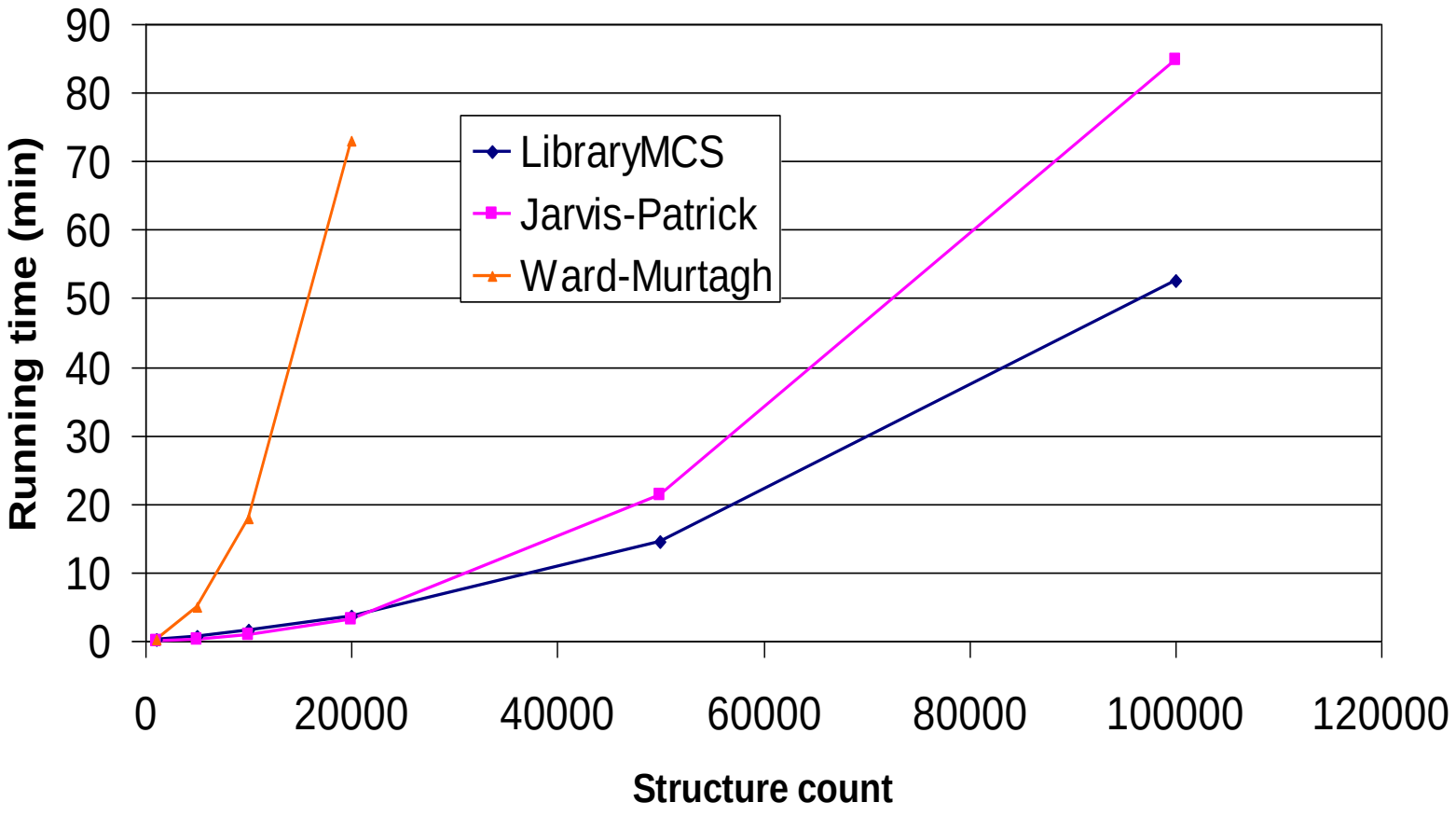
Speed-up achieved this year



Speed-up this year



Clustering performance comparison



Live demonstration

Clustering various types of structure sets

- VHTS hit sets
- focused libraries
- combi-chem libraries
- diverse sets
- corporate libraries

Behind performance

MCS search

- exhaustive
- heuristics
  - exact
  - inexact

Predictive MCS coupling in clustering

- all pairs are not feasible
- rich fingerprinting

Live demonstration

Affect of use of heuristics

- on average < 10% misclassifications
- useful for obtaining birds-eye-view of a larger/diverse sets

LibraryMCS roadmap

In the dev pipeline

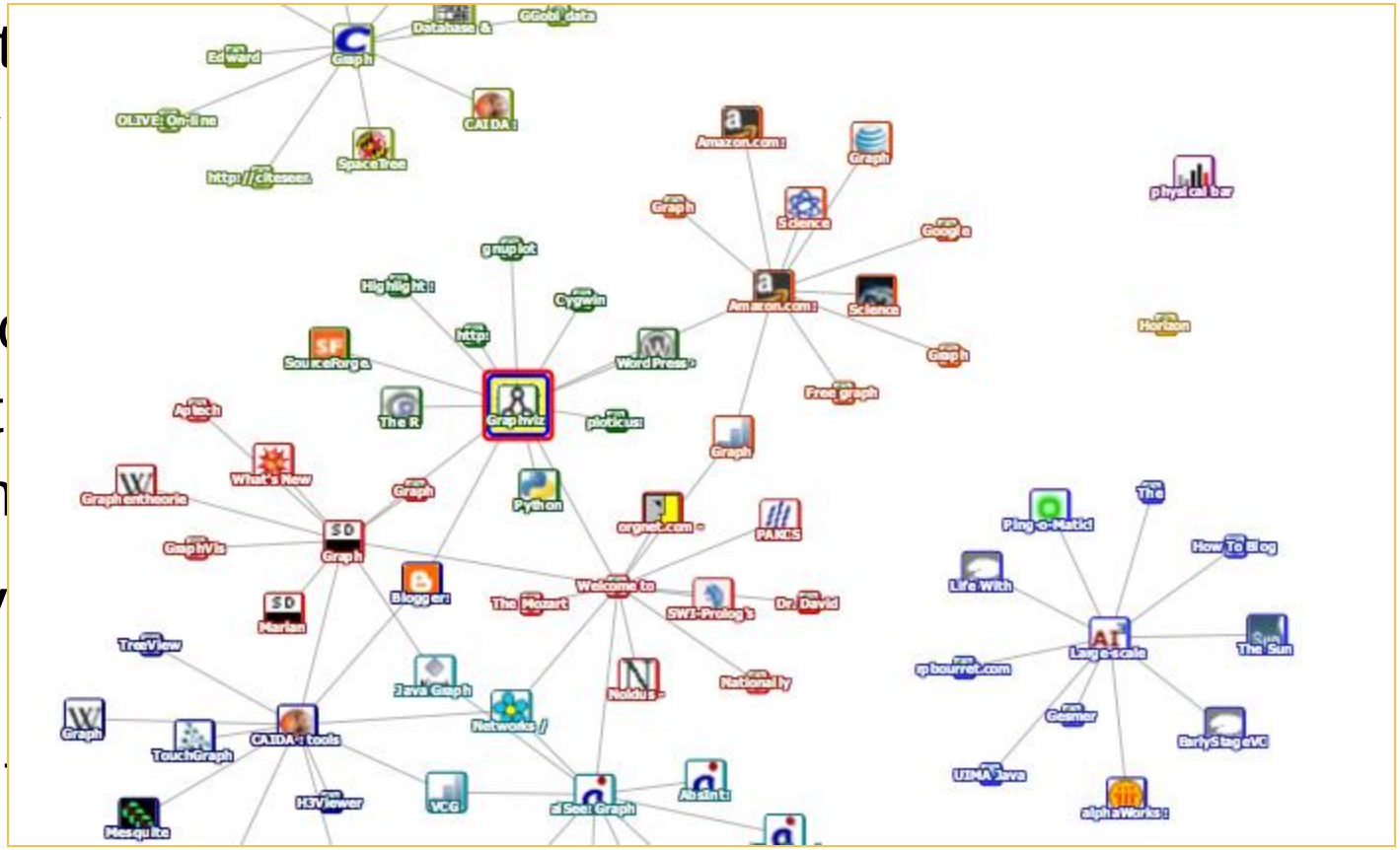
- IJC integration
- Spot
- new

Planned

- disc
- mult
- Bem

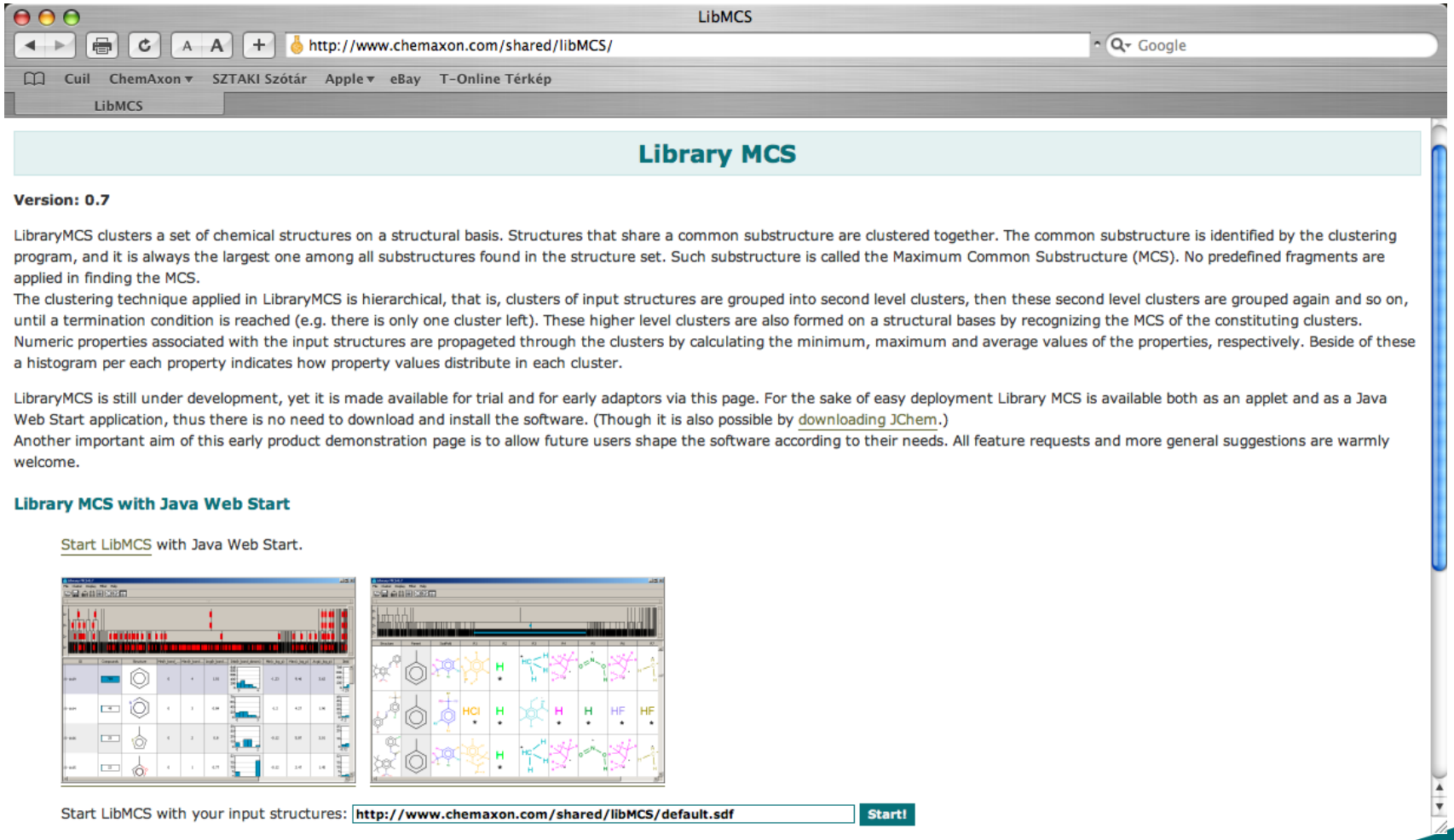
Blue sky

- 1M l
- addi



Try it on-line

www.chemaxon.com/shared/libMCS



Acknowledgements

Péter Vadász

Judit Vaskó-Szedlár

Gábor Imre