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Similarity to SAR - Interactive navigation of similarity relationships to guide optimization

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Overview

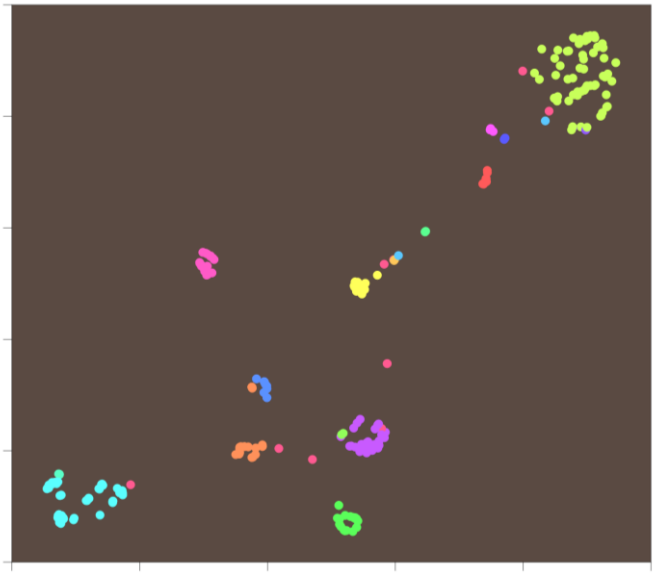
- Measures of similarity
- Applications of similarity to understand structure-activity relationships (SAR)
  - Clustering
  - Activity cliffs/landscapes
  - Matched pair analysis
- Interactive exploration of compound relationships
  - Card View™
- Example applications
- Conclusions

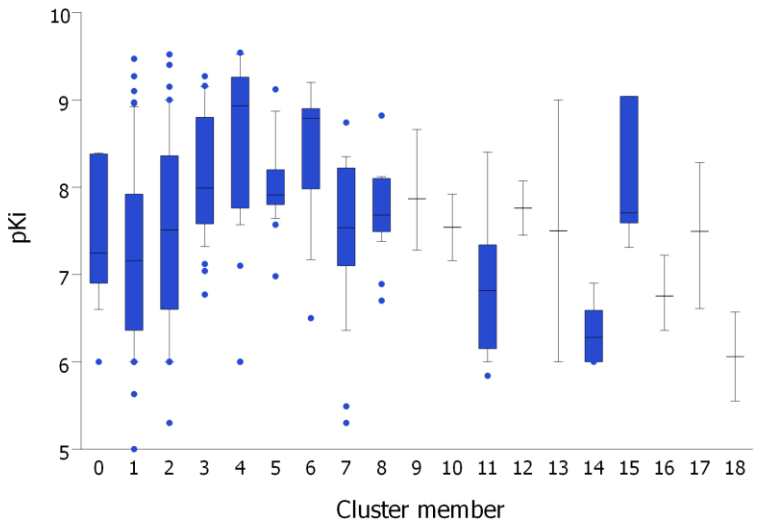
Measures of Compound Similarity

- Fingerprint similarity
  - Path-based, MACCS, circular…
  - Tanimoto (or similar) index
- Similarity in properties
  - Euclidean distance in descriptor space
- Common substructure
- Matched-pairs
  - Compounds that differ by one small substitution
- (Not explicitly discussing 3D similarity in this talk)

Applications of Similarity to SAR
Clustering

- Group together ‘similar’ compounds
- Objective:
  - Identify groups with good properties or interesting SAR
- Challenge:
  - Clusters often do not correspond with chemists’ interpretation of chemical series

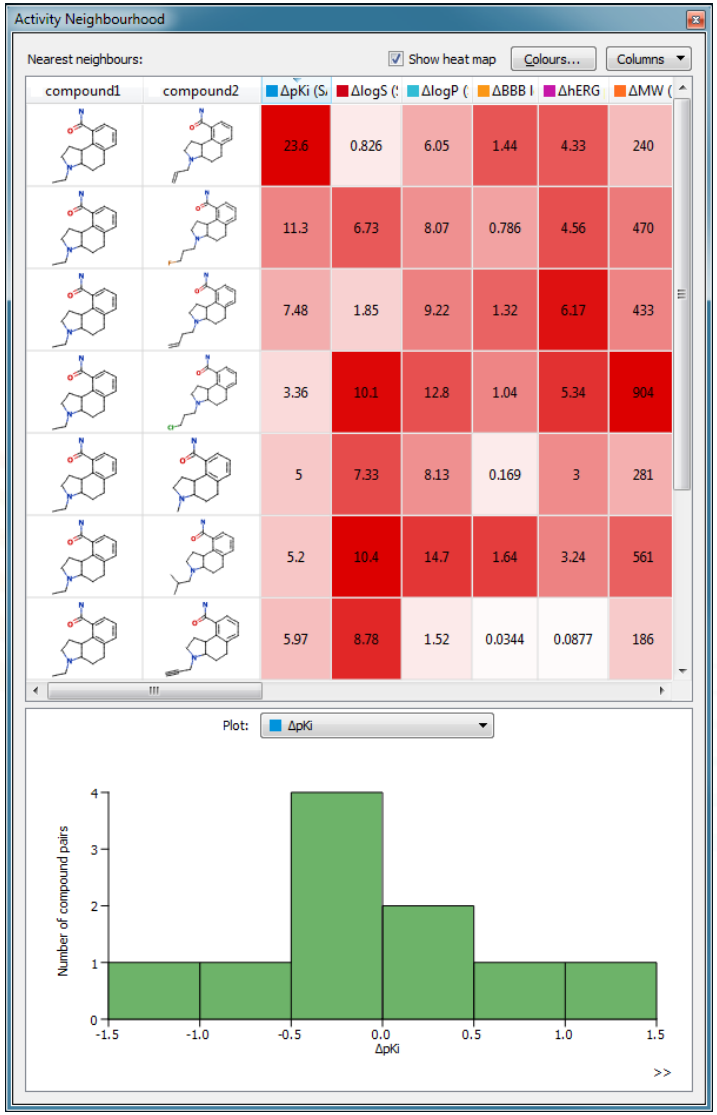




Applications of Similarity to SAR
Activity Cliff Detection

- Objective
  - Find small structural changes that result in a large change in activity
- Explore nearest neighbours to a reference compound
- Structure-activity landscape index (SALI)

$$SALI_{i,j} = \frac{|A_i - A_j|}{1 - sim(i,j)}$$



Applications of Similarity to SAR
Activity Landscapes

- All-by-all comparison
- ‘Rough’ regions
  - large changes in activity result from small changes in structure
  - Interesting SAR
- ‘Flat spots’
  - Limited opportunity for optimisation of activity
  - Opportunity to optimise different property without having negative impact on activity

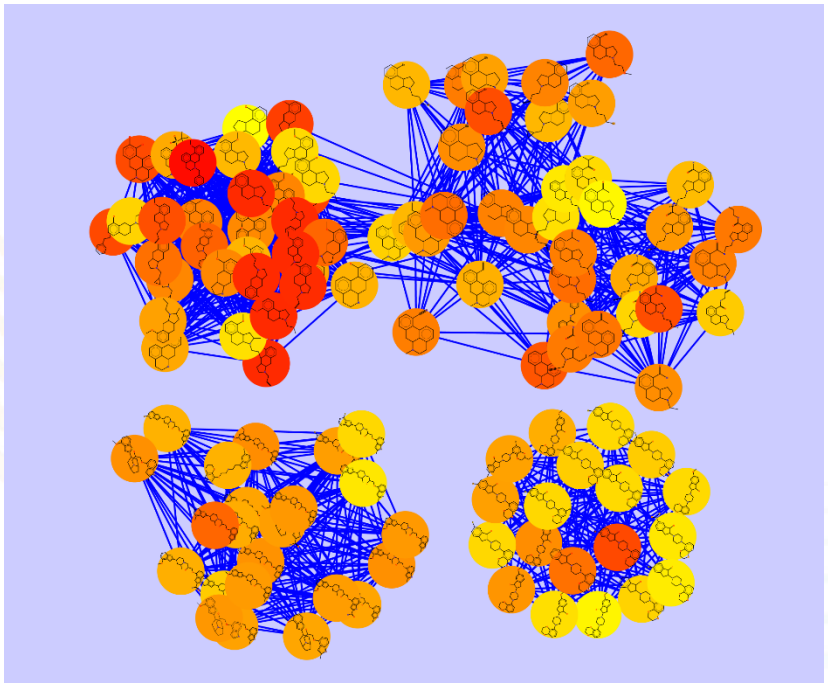
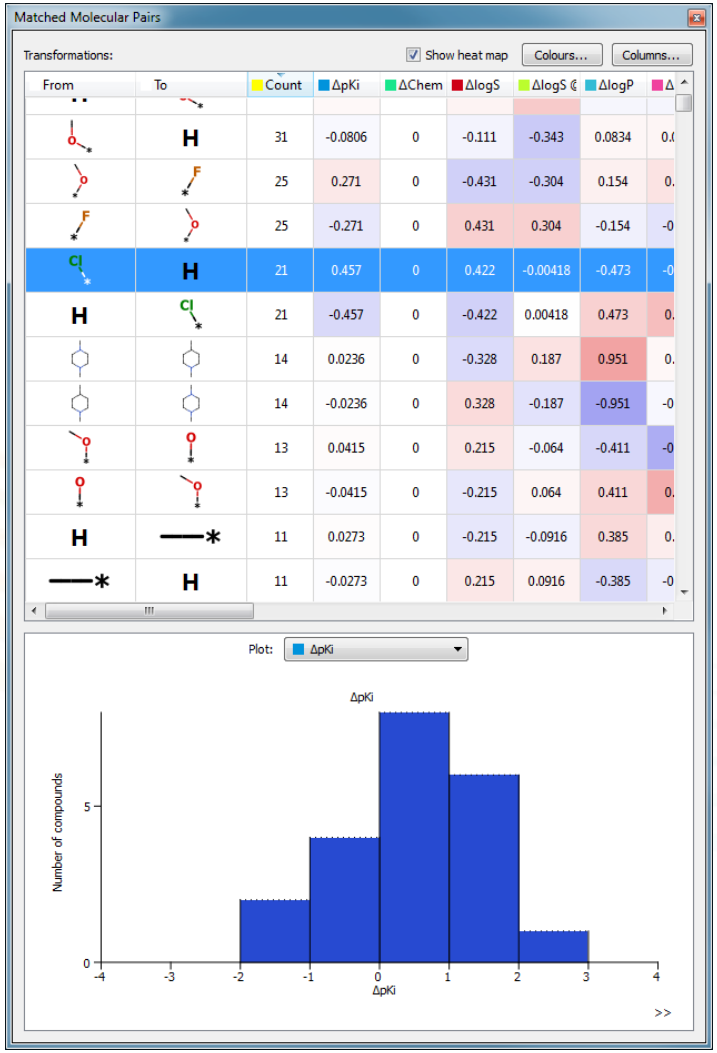


Image generated with Chemviz and Cytoscape www.cgl.ucsf.edu/cytoscape/chemViz/

Applications of Similarity to SAR
Matched Molecular Pair Analysis (MMPA)

- Compare compounds that differ only by one, small substitution
- Objective:
  - Find replacements (transformations) with a consistent, significant impact on activity
- Challenge:
  - Often context-dependent, particularly for target activity
  - Where does transformation apply?



Interactive Exploration of Compound Relationships

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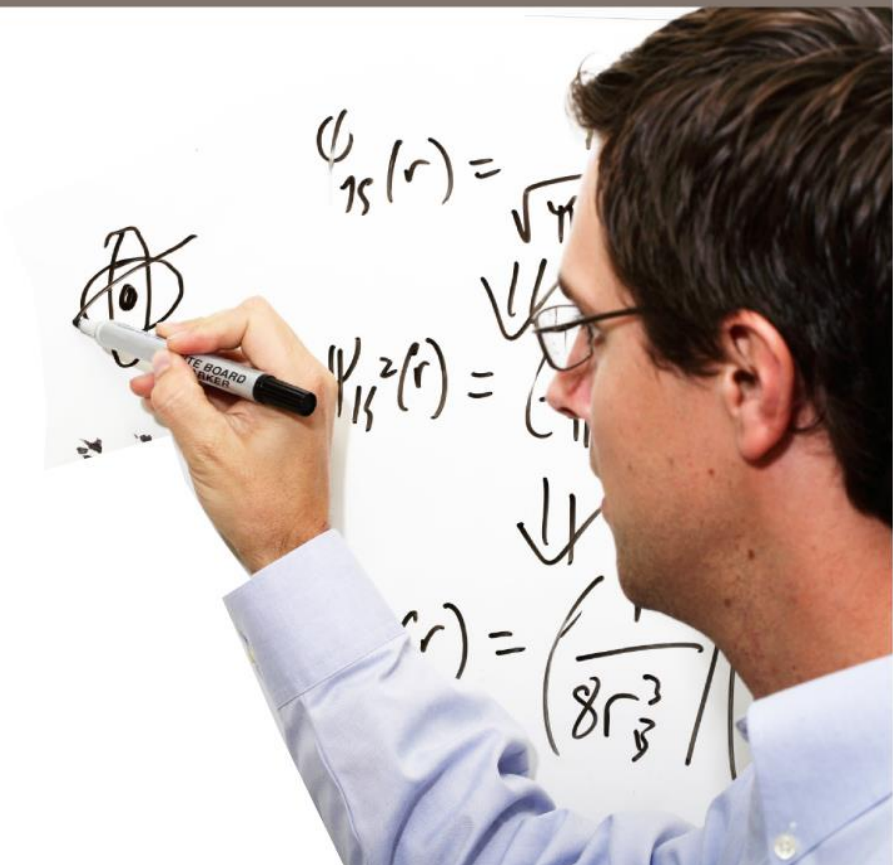
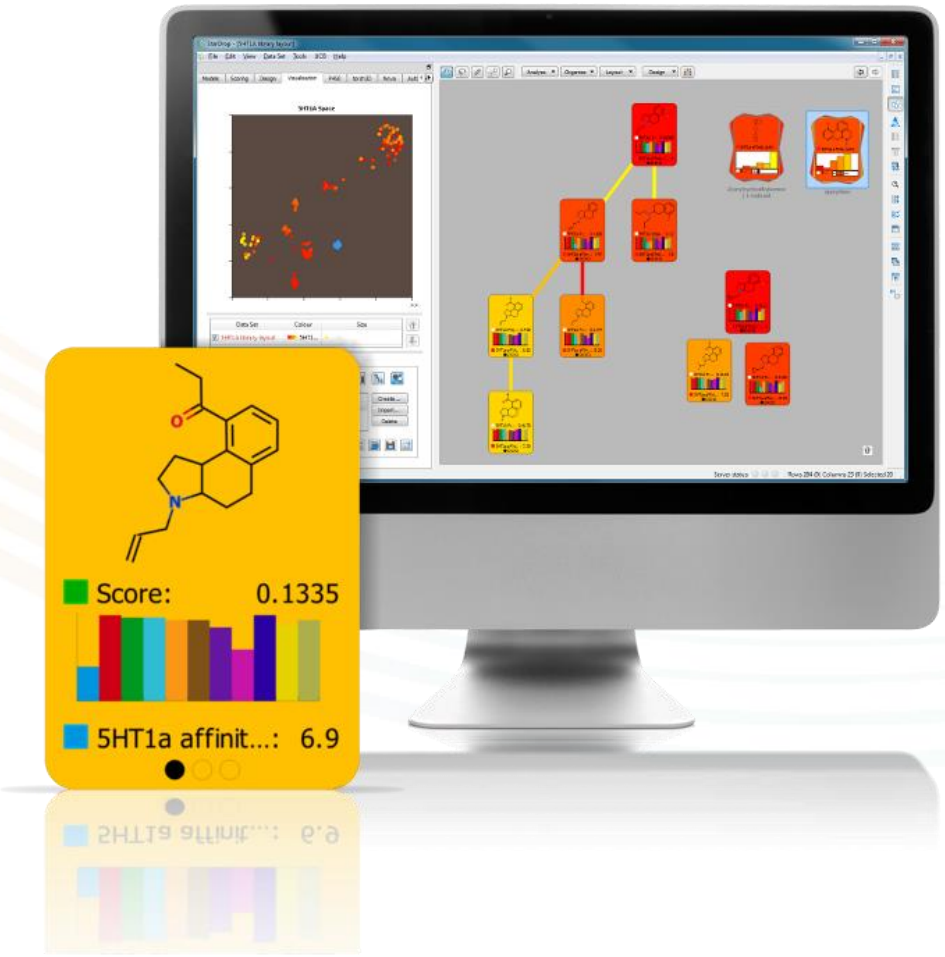


Card View
Concepts

- Freedom from the constraints of ‘chemical spreadsheets’
  - Represent compound relationships
- Cards
  - Show relevant compound
  - Complete freedom to move
- Stacks
  - Group compounds
  - Summarise and compare data
- Links
  - Highlight compound relationships
- Intuitive visualisation of SAR
  - Clustering, activity landscapes, matched molecular pairs…



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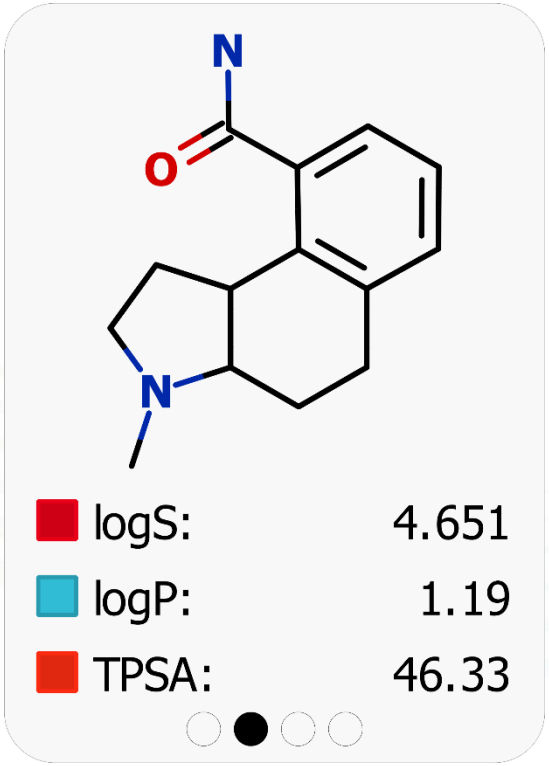

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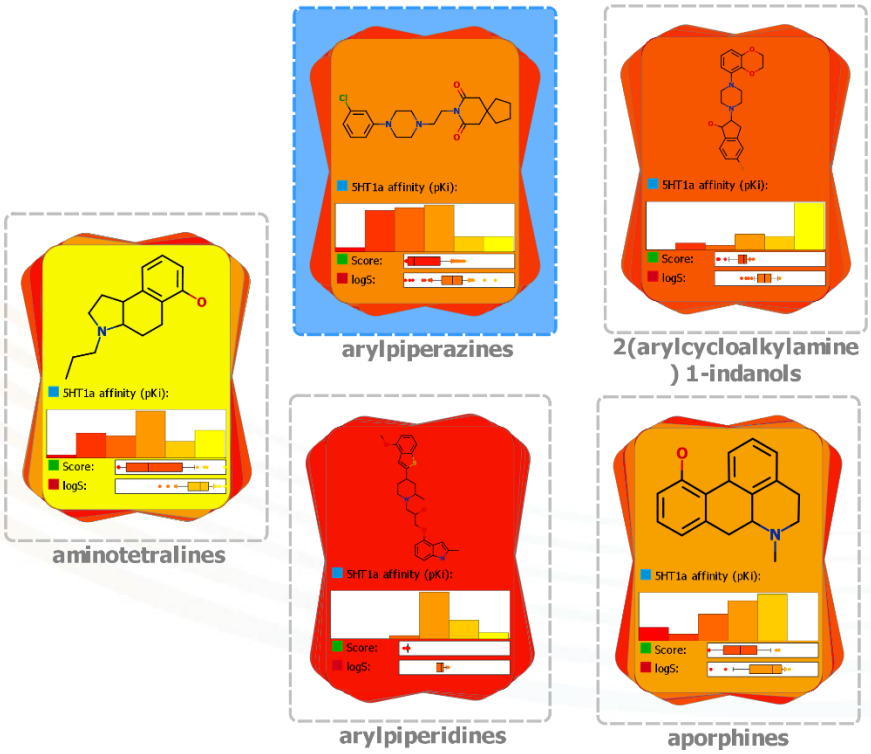

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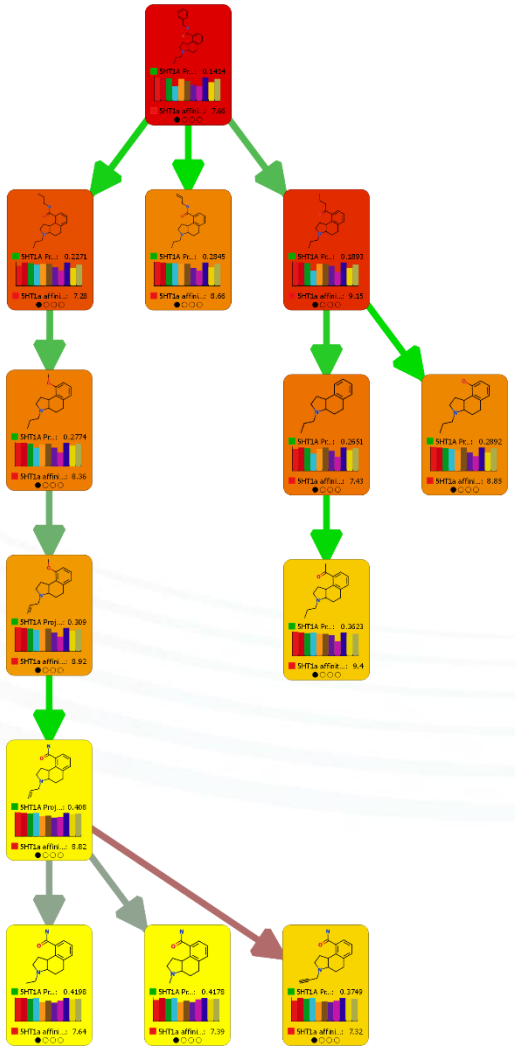

Example Applications

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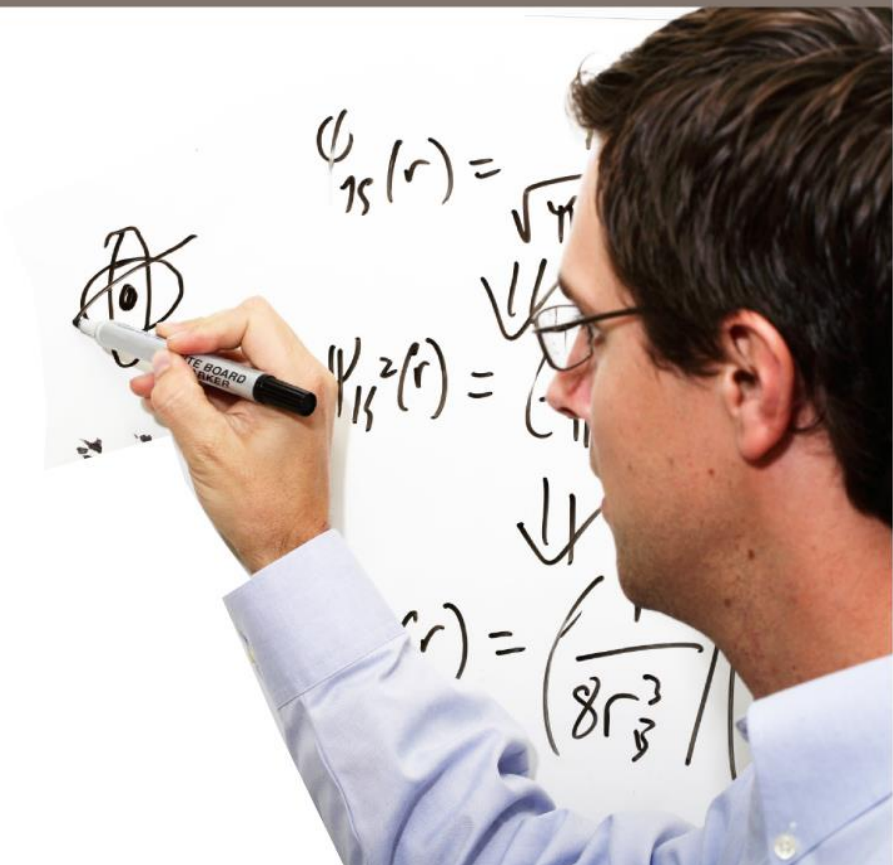
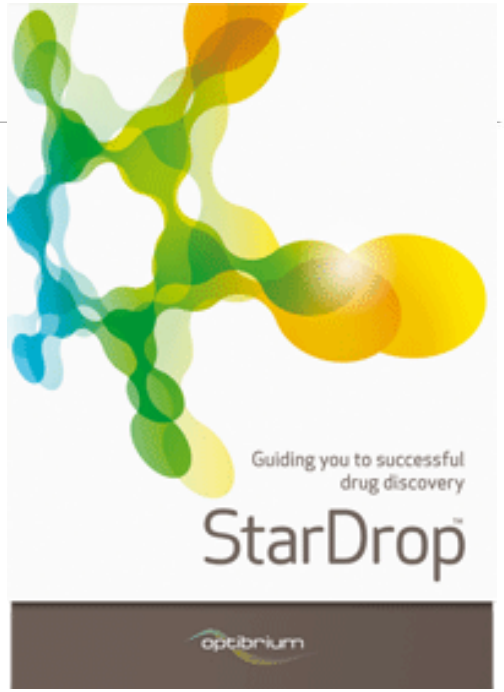


Conclusion



- Many different measures of ‘similarity’
- Similarity measures can help us to identify interesting chemistries and SAR
- Challenges:
  - ‘Similarity’ is in the eye of the beholder
  - When can SAR be transferred to guide further optimisation?
- Intuitive and interactive environments such as Card View provide synergy between:
  - Algorithms’ abilities to analyse complex data
  - Expert’s understanding of chemistry
- Segall *et al.* “Breaking Free from Chemical Spreadsheets” Drug Discov. Today (in press)
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