Chemical Reaction Databases
Computer-Aided Synthesis Design
Reaction Prediction
Synthetic Feasibility

Dr. Wendy A. Warr

http://www.warr.com

Warr, W. A. A Short Review of Chemical Reaction Database Systems, Computer-aided Synthesis Design, Reaction Prediction and Synthetic Feasibility. *Mol. Inf.* **2014**, *33*, 469-476

Representation

- rxnfile
- RDfile
- SMILES/SMARTS/SMIRKS
- RInChI

Warr, W. A. Representation of chemical structures. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*(4), 557-579.

Reaction Queries

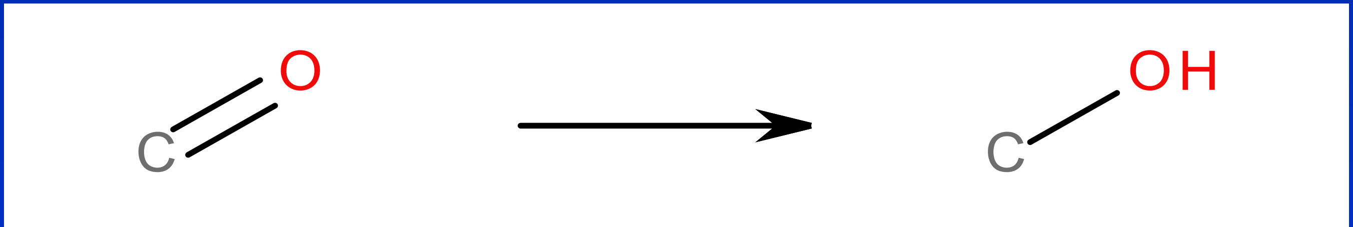
$$A \rightarrow C$$

$$A + B \rightarrow ?$$

$$? \rightarrow C$$

Reaction Queries

$$A \xrightarrow{?} C$$

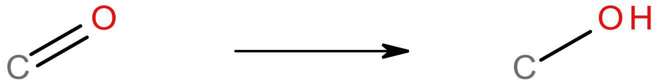


Reaction Queries

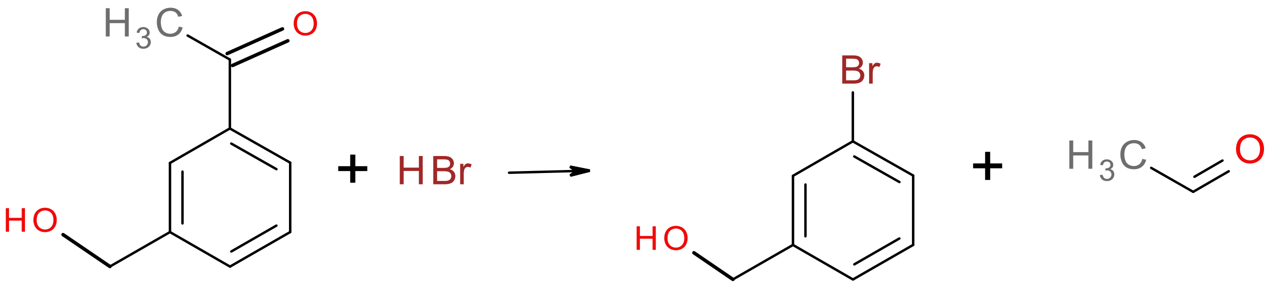
- “Name” reaction (e.g., Diels – Alder)
- Reduction of functional group A in presence of group B
- Stereoselectivity
- etc.

Atom-to-atom Mapping

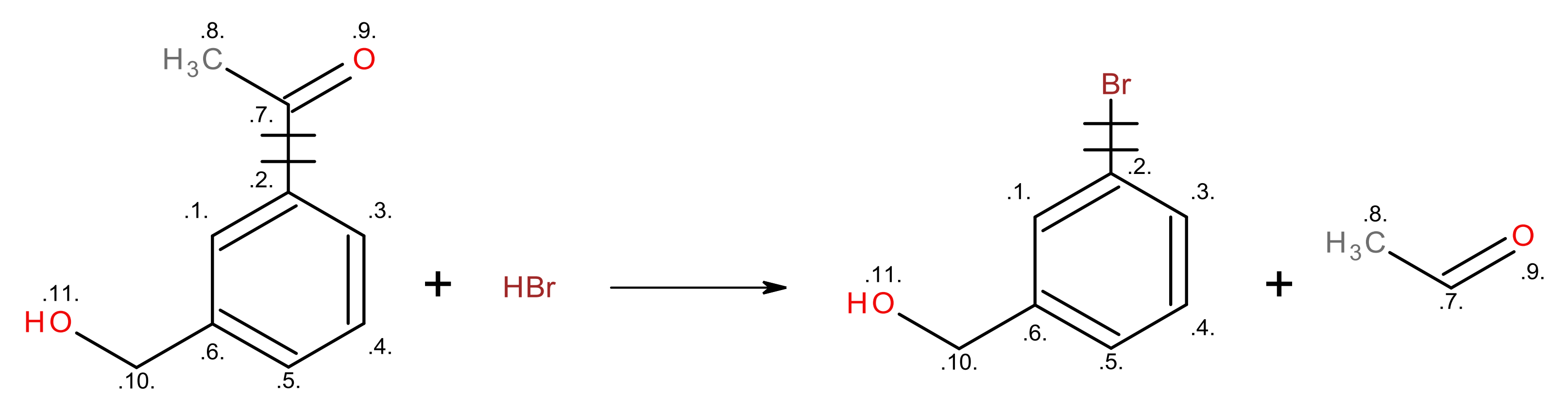
Query:



"Hit":



Atom-to-atom Mapping



Atom-to-atom mapping

- Automatic mapping is not perfect
- Authors publish incomplete equations
- Takes no account of reaction mechanism

Approaches to Mapping

- Maximum common substructure (MCS)
- Optimization approach
  - Fujita’s imaginary transition state (ITS)
  - Gasteiger ITS
  - Varnek condensed graph of reaction (CGR). Pseudomolecules
    - ISIDA descriptors calculated based on graph
    - similarity search
- Baldi MCS and optimization

MCS Approach

- M. F. Lynch, P. Willett, *J. Chem. Inf. Comput. Sci.* **1978**, *18*, 154-159.
- P. Willett, *J. Chem. Inf. Comput. Sci.* **1980**, *20*, 93-96.
- J. J. McGregor, P. Willett, *J. Chem. Inf. Comput. Sci.* **1981**, *21*, 137-140.
- J. W. Raymond, P. Willett, *J. Comput.-Aided Mol. Des.* **2002**, *16*, 521-533.

Reaction Database Systems

- MDL’s REACCS
  - later ISIS, Isentris
- CASREACT
  - now in SciFinder
- Beilstein CrossFire
  - superseded by Elsevier’s Reaxys

Reaction Databases

- SPRESI and ChemReact
- Theilheimer
- ChemInform
- Science of Synthesis
- Current Chemical Reactions
- Methods in Organic Synthesis
- Catalysts and Catalysed Reactions
- Organic Syntheses
- Selected Organic Reactions Database
- In-house ELNs

Reaction Classification: Uses (1)

- Teaching similarity of reactions
- Indexing reactions
- Browsing in databases
- Management of large hit lists
- Simplification of query generation
- Linking reactions from different sources

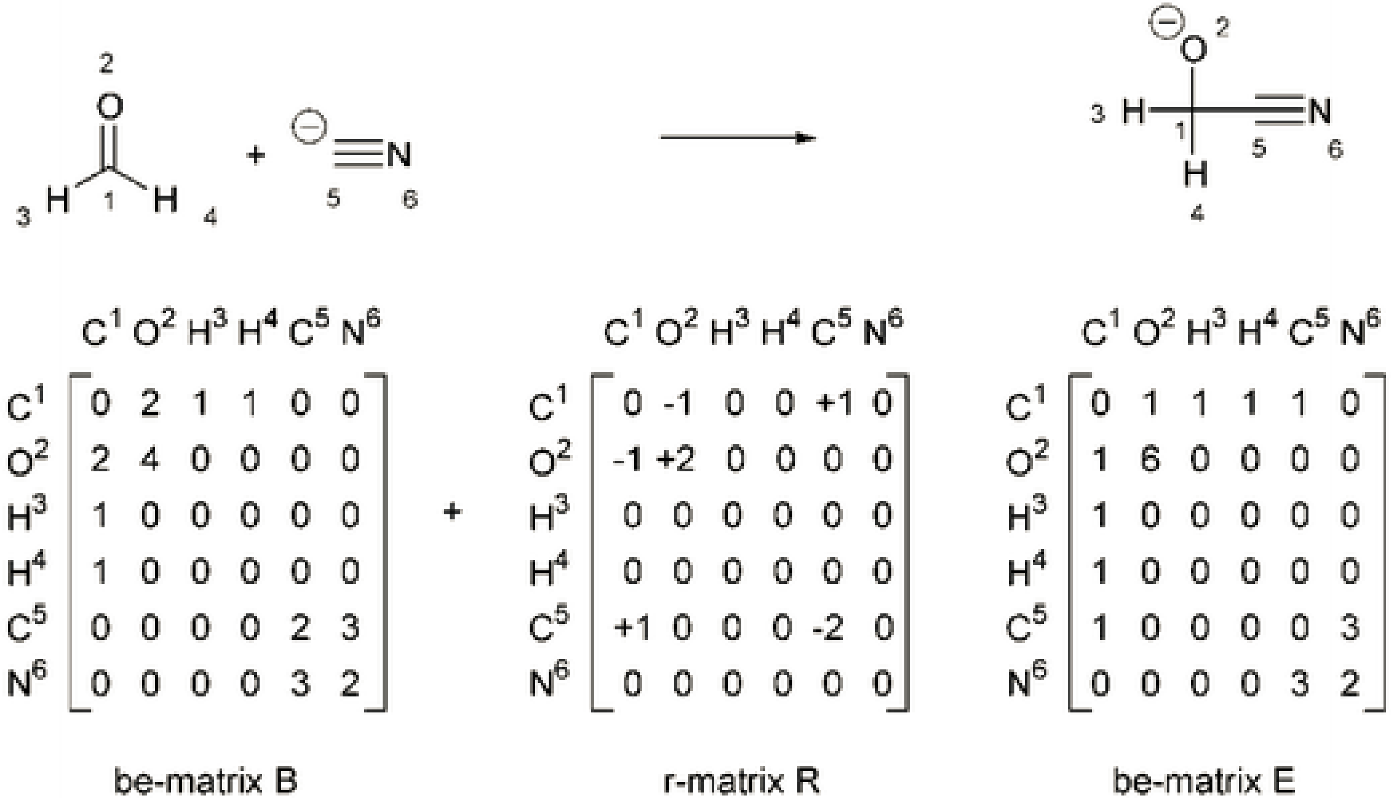
Reaction Classification: Uses (2)

- Access to generic type of information
- Deriving knowledge bases
  - for synthesis design
  - for reaction prediction
- Prediction of new reactions
- Automatic procedures for analysis
- Quality control of databases
- Overlap studies of databases

Reaction Classification Methods

- Model-driven
  - manual
  - computerized
    - Balaban, Hendrickson, Arens, Zefirov, Fujita
    - Dugundji-Ugi
- Data-driven

Dugundji-Ugi Model



$$\begin{array}{c|cccccc|}
 & C^1 & O^2 & H^3 & H^4 & C^5 & N^6 \\
C^1 & 0 & 2 & 1 & 1 & 0 & 0 \\
O^2 & 2 & 4 & 0 & 0 & 0 & 0 \\
H^3 & 1 & 0 & 0 & 0 & 0 & 0 \\
H^4 & 1 & 0 & 0 & 0 & 0 & 0 \\
C^5 & 0 & 0 & 0 & 0 & 2 & 3 \\
N^6 & 0 & 0 & 0 & 0 & 3 & 2
\end{array}
\quad + \quad
\begin{array}{c|cccccc|}
 & C^1 & O^2 & H^3 & H^4 & C^5 & N^6 \\
C^1 & 0 & -1 & 0 & 0 & +1 & 0 \\
O^2 & -1 & +2 & 0 & 0 & 0 & 0 \\
H^3 & 0 & 0 & 0 & 0 & 0 & 0 \\
H^4 & 0 & 0 & 0 & 0 & 0 & 0 \\
C^5 & +1 & 0 & 0 & 0 & -2 & 0 \\
N^6 & 0 & 0 & 0 & 0 & 0 & 0
\end{array}
\quad
\begin{array}{c|cccccc|}
 & C^1 & O^2 & H^3 & H^4 & C^5 & N^6 \\
C^1 & 0 & 1 & 1 & 1 & 1 & 0 \\
O^2 & 1 & 6 & 0 & 0 & 0 & 0 \\
H^3 & 1 & 0 & 0 & 0 & 0 & 0 \\
H^4 & 1 & 0 & 0 & 0 & 0 & 0 \\
C^5 & 1 & 0 & 0 & 0 & 0 & 3 \\
N^6 & 0 & 0 & 0 & 0 & 3 & 2
\end{array}$$

be-matrix B

r-matrix R

be-matrix E

Dugundji-Ugi Model

- WODCA
- EROS
- IGOR
- RAIN

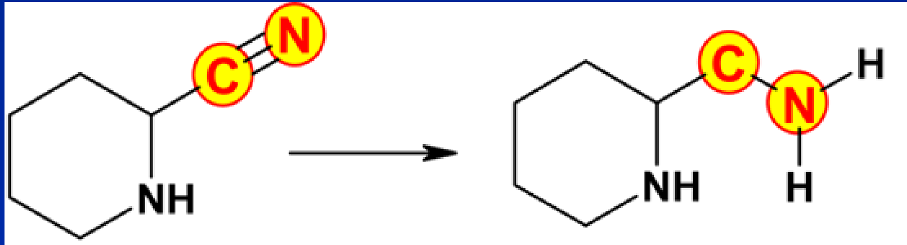
Data-driven Classification

- Goes beyond the reaction center
- Allows sub-classes
- Wilcox and Levinson, Blurock, Gelernter, Sello
- InfoChem CLASSIFY

CLASSIFY

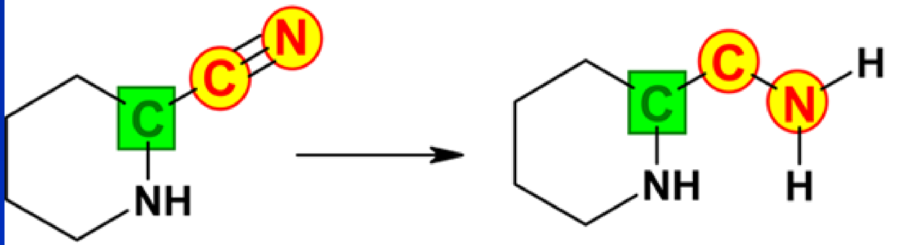
- Based on IC_{MAP}
  - extension of Willett and Funatsu’s work
  - maximum common substructure
  - minimum chemical distance
- Atom hash codes calculated for reaction center
  - uses modified Morgan algorithm
- Sum all hash codes of all reactants and one product → unique Reaction Classification Code (15 digit number)

CLASSIFY



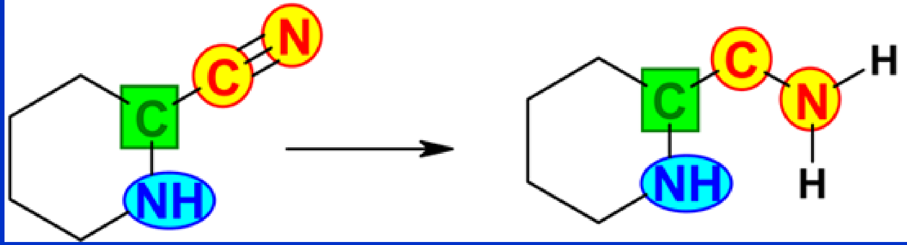
0-Sphere (BROAD)

Reaction centers only



1-Sphere (MEDIUM)

Reaction centers plus alpha atoms, excluding hydrogens



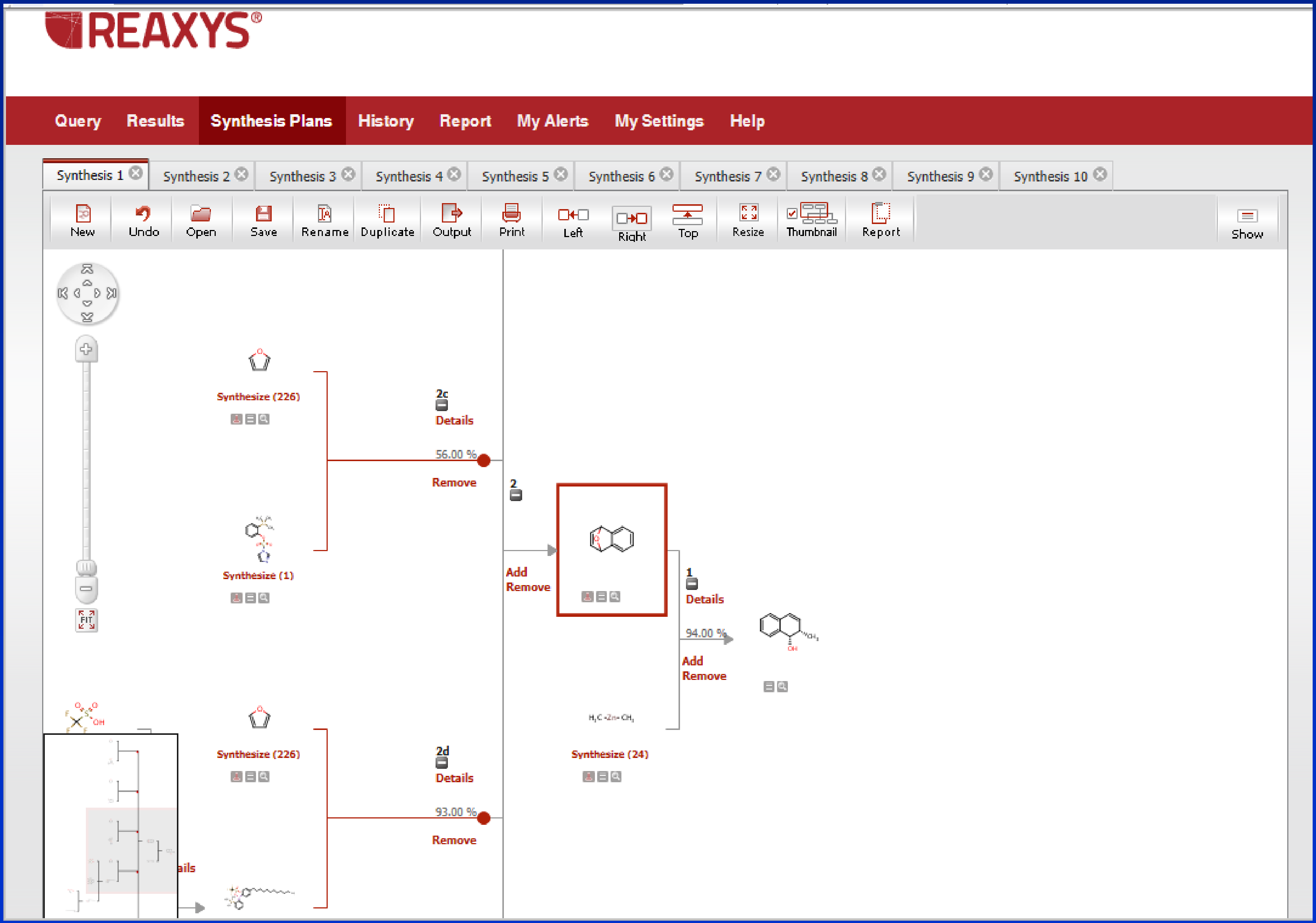
2-Sphere (NARROW)

Reaction centers plus beta atoms, excluding hydrogens and consecutive sp^3-atoms

Synthetic Analysis Programs

- Synthesis design (planning)
- Reaction prediction
- Mechanism elucidation
- Synthetic feasibility

Synthesis Planning



Synthesis Planning

- Reaxys Synthesis Planner
- SciFinder SciPlanner
- Chematica
  - Network of 7 million chemicals/reactions

Computer-aided Synthesis Design

- LHASA
  - expert system
  - knowledge base
    - reaction transforms (manual)
  - combinatorial explosion
    - so prune trees using heuristics
    - or user interaction

Computer-aided Synthesis Design

- SECS
- ARChem
- $\text{IC}_{\textit{SYNTH}}$

ARChem

- Rules automatically generated
- Uses large database to verify rules
- Core (reaction center) extended to *relevant* functionality
- Tries to use reaction mechanism

Computer-aided Synthesis Design

- HORACE
  - – mechanistic descriptors
    - inductive effect
    - resonance effect
    - charge distribution etc.
  - – topology based on Gelernter classification
  - – produces reaction hierarchy
  - – extended with Kohonen neural networks
    - Gasteiger and Chen, Funatsu

WODCA and EROS

- WODCA
  - retrosynthesis
  - similarity search in catalogs
  - break strategic bonds
    - charge distribution, and inductive, resonance, and polarizability effects
- EROS knowledge-based system
  - metabolic reactions
  - mass spectrometer reactions
  - with IR, in identification of degradation products

Reaction Prediction

- The reverse of retrosynthesis
- Approaches:
  - simulation of transition states
  - rule-based, expert systems
  - inductive learning methods

IGOR

- Generality of formal techniques
  - can generate new reaction mechanisms
- Dugundji-Ugi model
- Herges predicted and verified new reactions with IGOR
  - and did further work…

Reaction Prediction: More

- Gasteiger (compare WODCA)
- Gasteiger and Chen Kohonen neural networks
- Zefirov's Symbolic Equations (SYMBEQ)
  - another formal-logical approach
  - can also be used to generate Dugundji-Ugi matrices

ReactionPredictor

- Baldi, Chen *et al.* use multiple approaches:
  - – descriptors are MOs and topological and physical attributes (not graph rearrangements)
  - – rule-based system Reaction Explorer
  - – inductive machine learning

Varnek and Co-workers

- For atom mapping:
  - CGR (pseudomolecules)
  - calculate ISIDA descriptors
  - similarity search
- To model chemical reactivity maybe use ISIDA property-labeled fragment descriptors (IPLF)

Synthetic Feasibility

- Large number of compounds generated by:
  - combinatorial library design
  - *de novo* design
- Some of them will be hard to make
- CAESA
- SYLVIA

CAESA

- Rule-based system too slow for intermediate structures in *de novo* design
- Complexity analysis is more practical
- Matches structural motifs in designed structures with those in drugs and starting materials

SYLVIA

- Synthetic complexity score 1-10
- Adds scores from components
  - molecular graph, ring and stereochemistry
  - similarity to starting materials
  - frequency analysis of strategic bonds from reaction databases

Conclusions (1)

- Much research “complete” before 1990
  - but papers on atom-to-atom mapping are still appearing
- Computer-aided synthesis design programs preceded reaction retrieval systems
  - but have never achieved same levels of usage

Conclusions (2)

- Emphasis on “*aided*”
  - – chemist plus machine
- Regio- and stereo-selectivity, interfering functional groups are active fields of research
- Synthetic chemists not interested in reaction prediction?
- In-house systems *are* using synthetic feasibility