Friedrich-Alexander-Universität
Naturwissenschaftliche Fakultät

43384 – Digital Alchemy

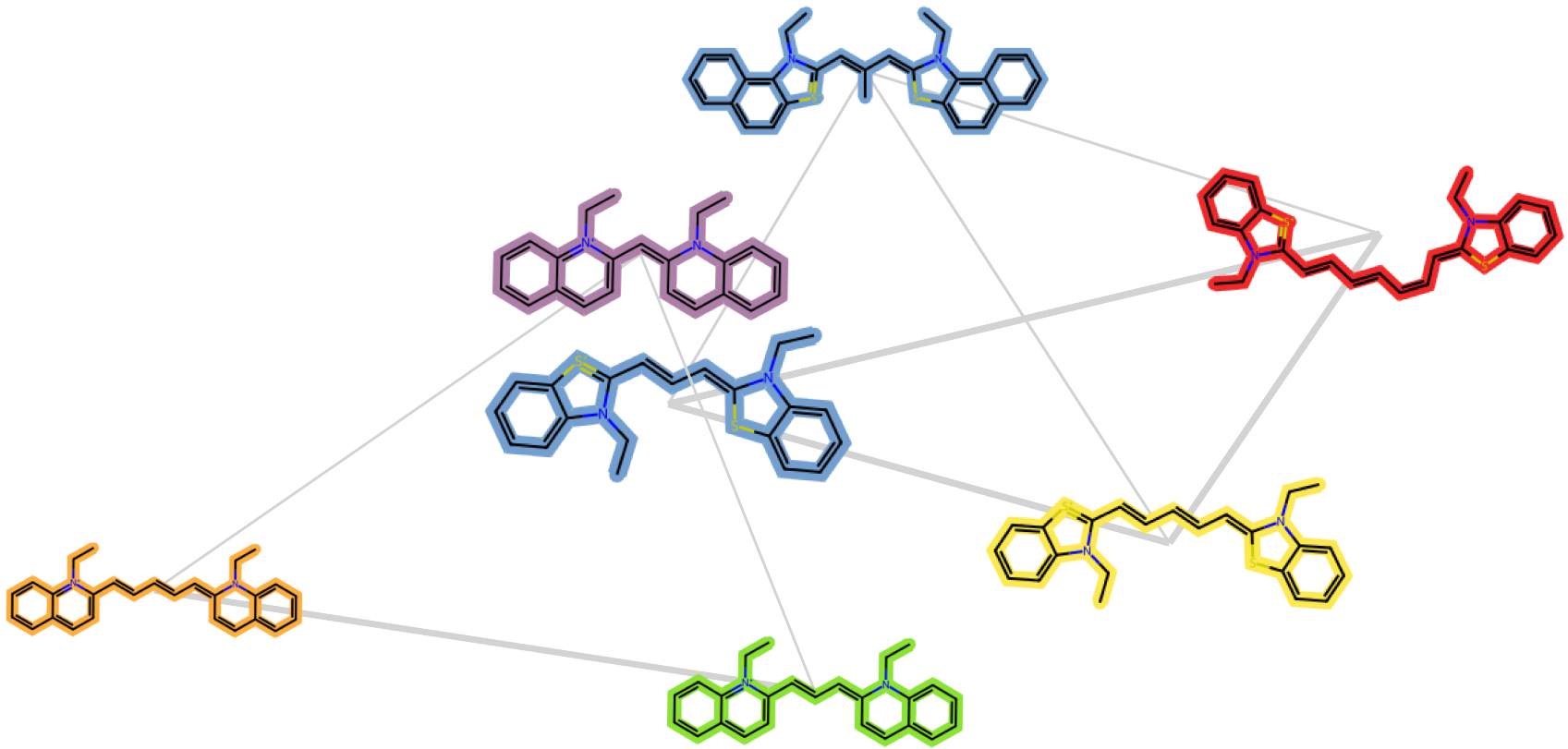
Unit 04 – Searching Chemical Structures

Prof. Dr. Carolin Müller

November 04, 2025

Searching Chemical Structures

Substructure and Similarity Relation of Molecules

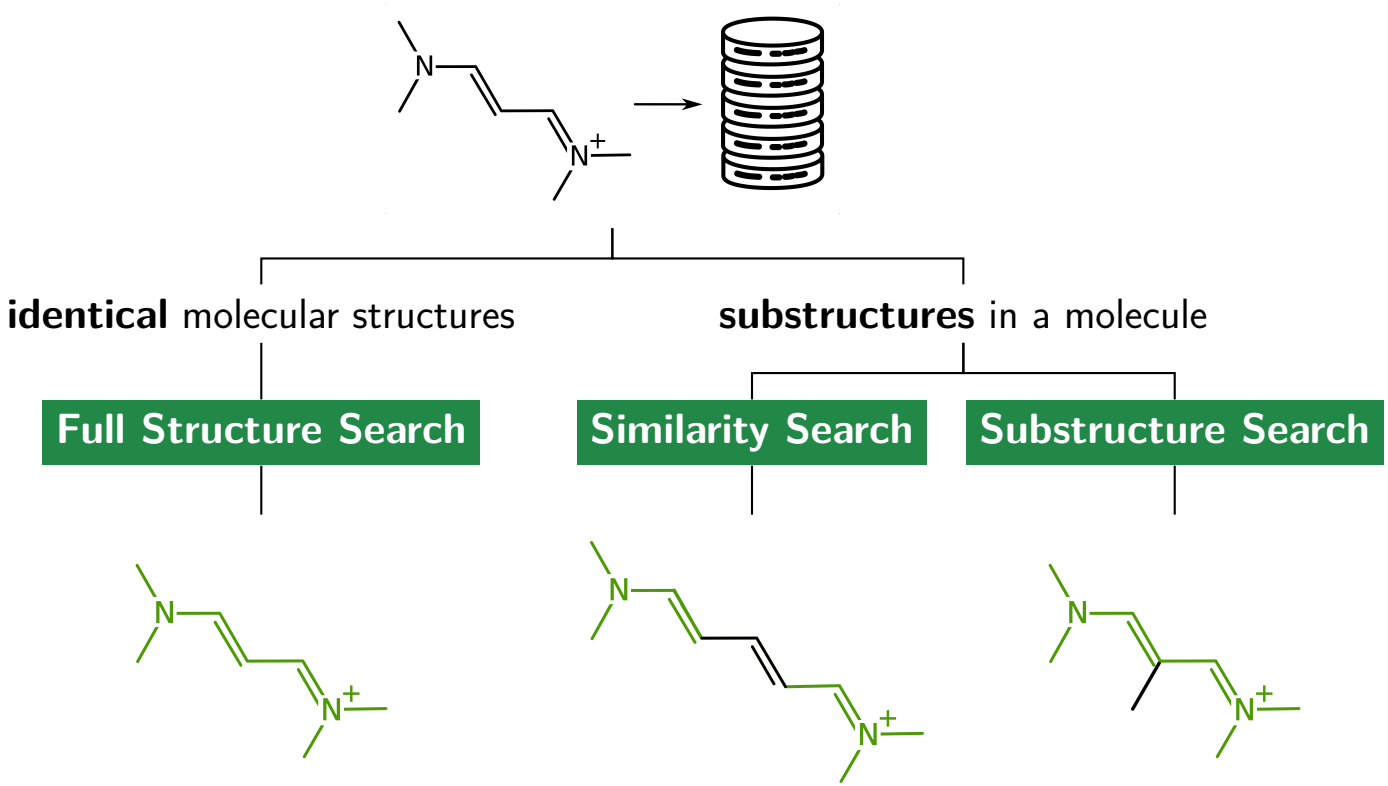


Searching Chemical Structures

Classical Algorithmic Chemoinformatics Problems

Searching Chemical Structures

Databases are indispensable tools in modern chemical research. Thus, the search of structural information in these databases is an important task, *e.g.*, for *molecular design* and *property prediction*.



Identification of Molecules

Classical Algorithmic Chemoinformatics Problems

- Identifying **identical** molecular structures

- Identifying **substructures** in a molecule

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Two graphs are isomorphic (the same) if there is an edge-preserving one-to-one correspondence between their vertices.

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- Identifying **identical** molecular structures
  - **Graph isomorphism** problem: Two molecules are considered the same if they have the same molecular graph
- Identifying **substructures** in a molecule
  - **Subgraph isomorphism** problem: A fragment is part of a molecule (graph G) if it corresponds to a subset of atoms and their corresponding bonds, *i.e.*, if the fragment graph F is a subgraph of G, *i.e.*, if F is isomorphic to a subgraph of G

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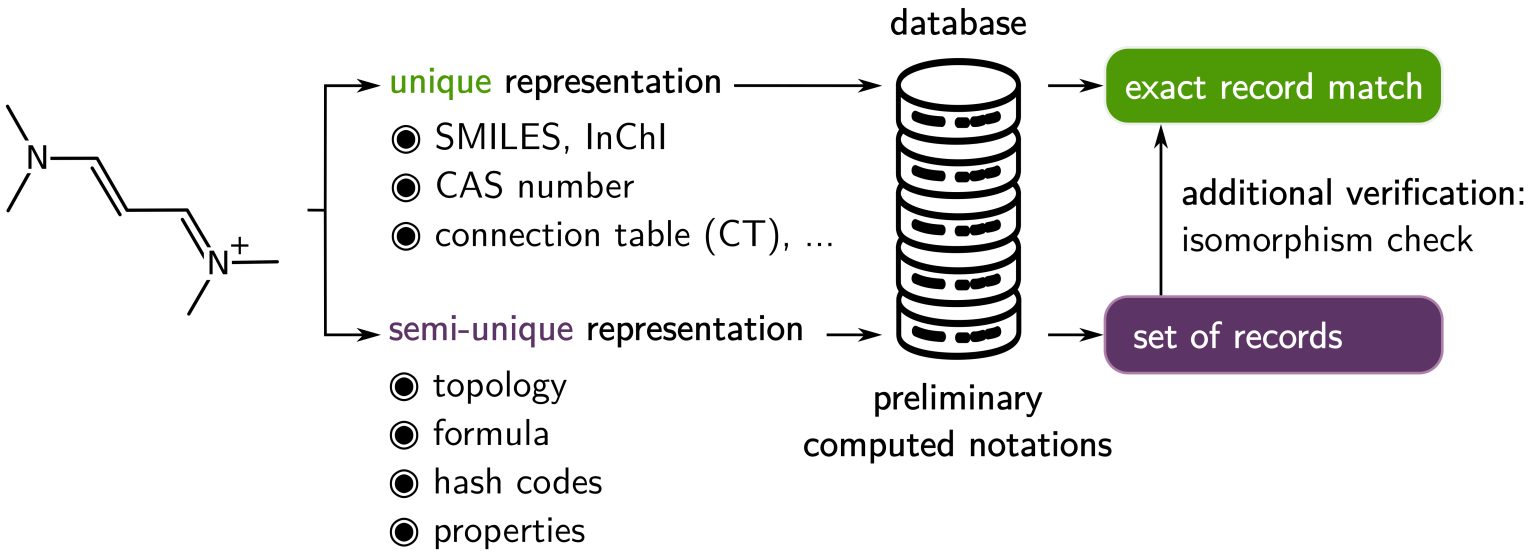
Full Structure Search

Perception of complete chemical structures

The perception of **complete structures** is dependent on their representation. Structures must be **represented uniquely** and usually compactly by an indexing key or may only be used for indexing purposes in order to retrieve the exact database record number.



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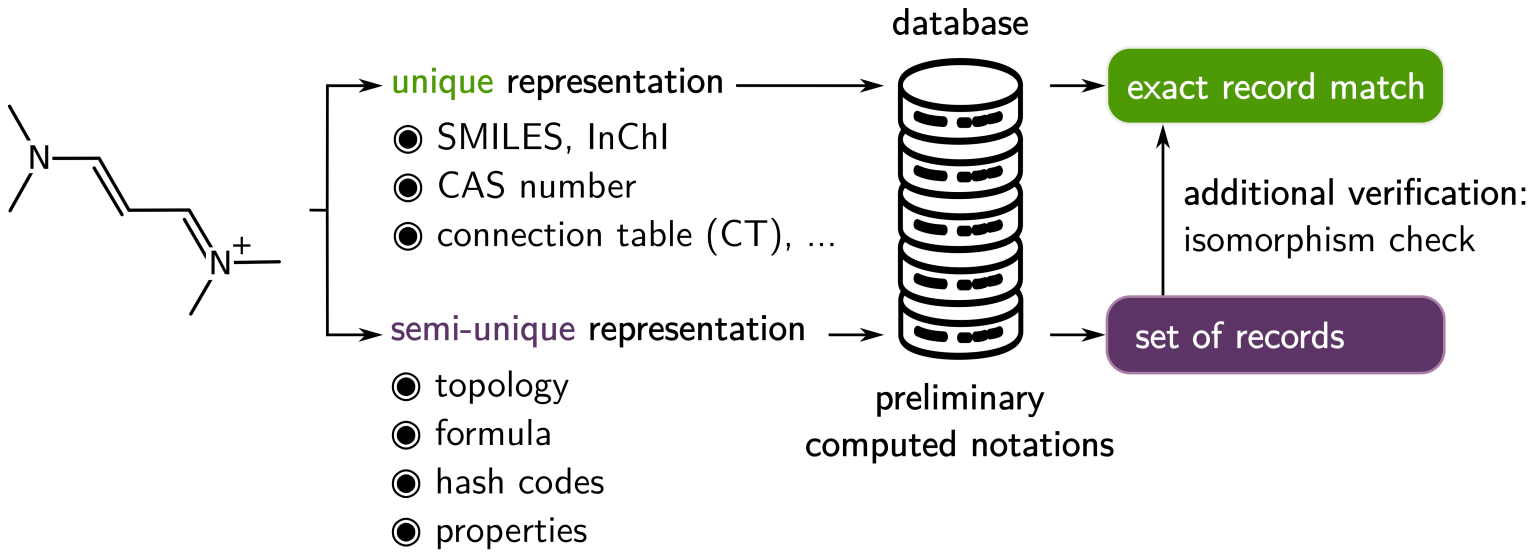

Problem: How to uniquely identify molecular structures?

a) Canonical Representations

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In principal, a structure with n atoms can be labeled in $n!$ different ways
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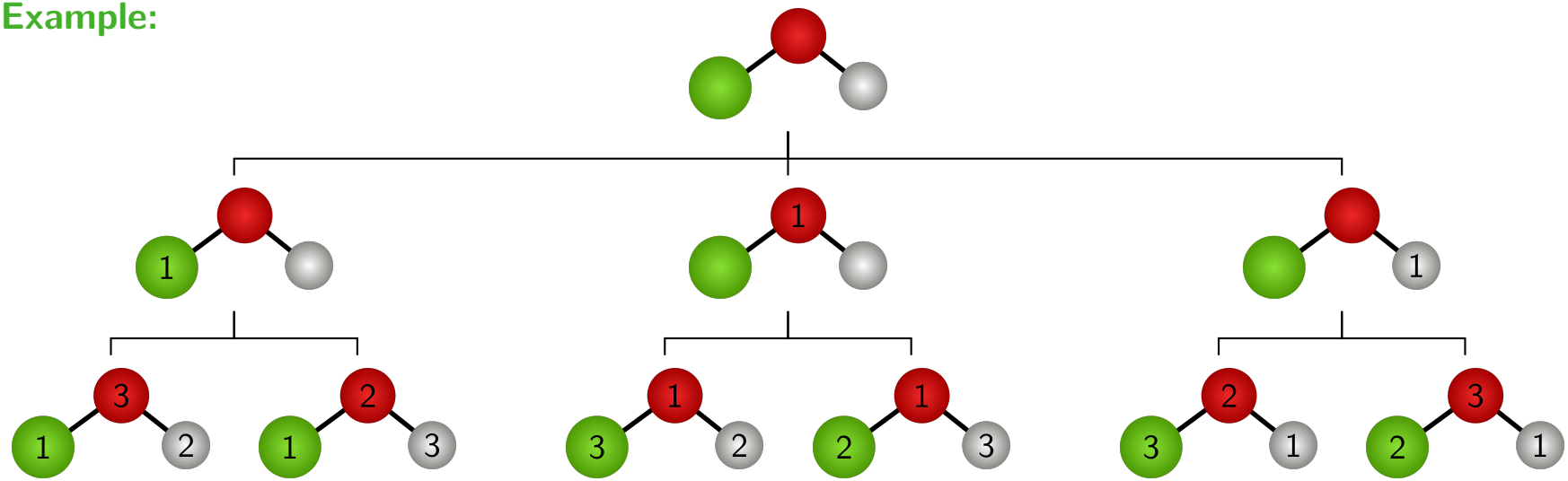

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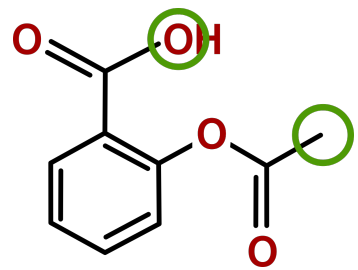
Idea of canonicalization

- Representations like Smiles and InChI depend on the order of traversal of atoms, *i.e.*
  - **What** is the first atom of the representation?



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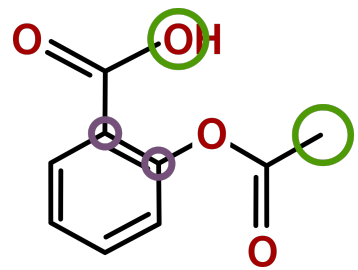

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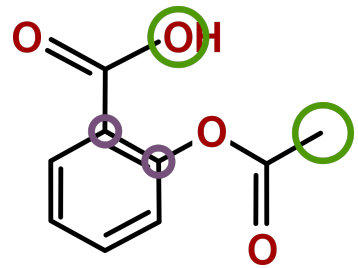

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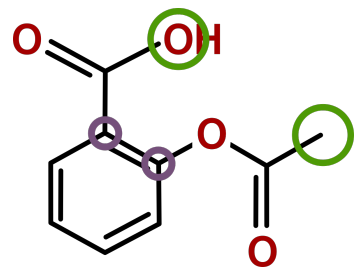

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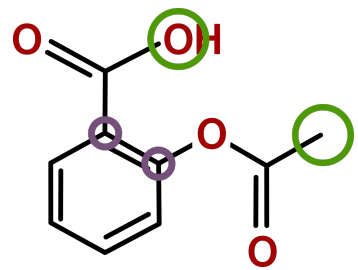

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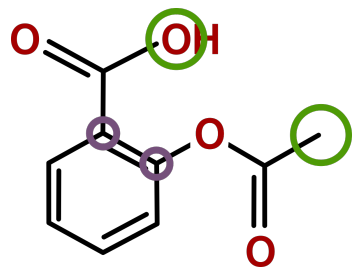

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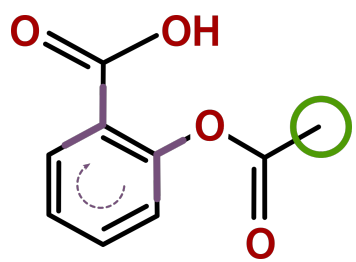

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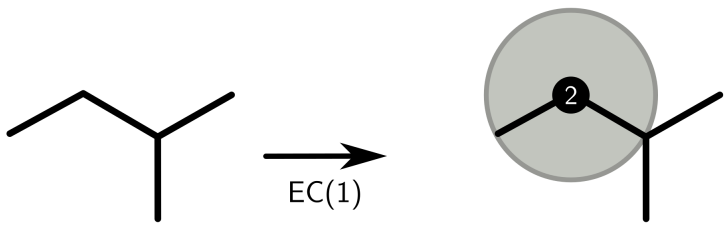

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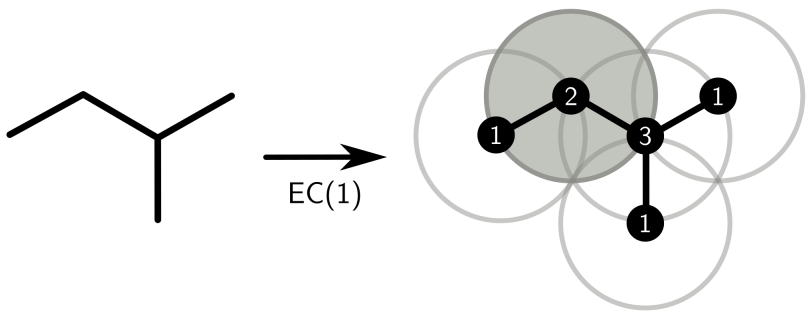

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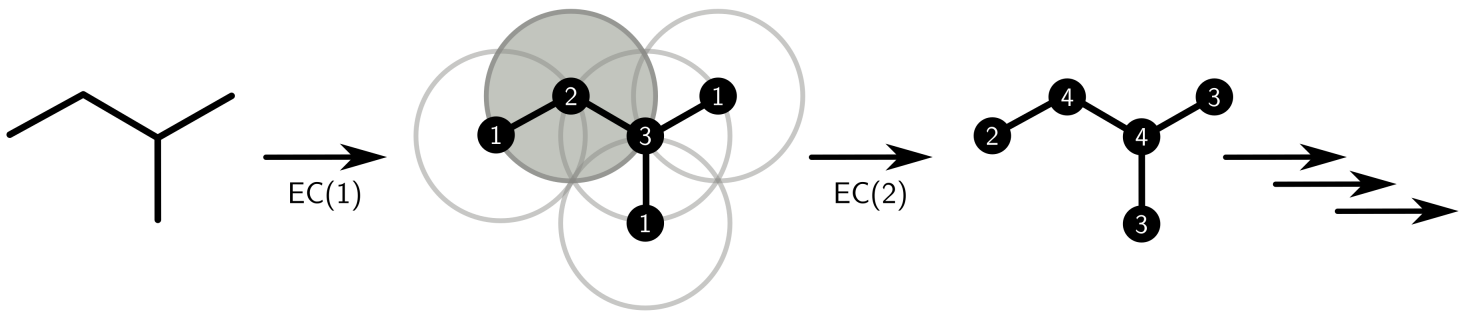

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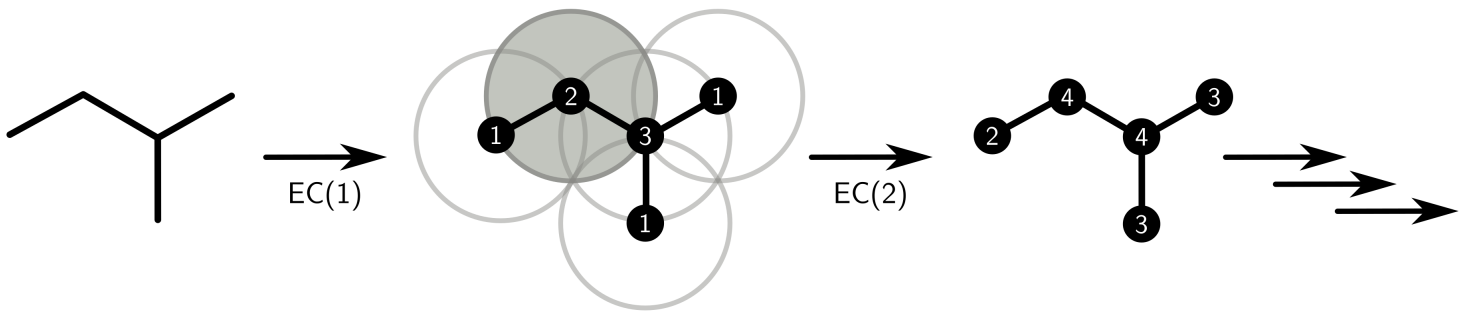

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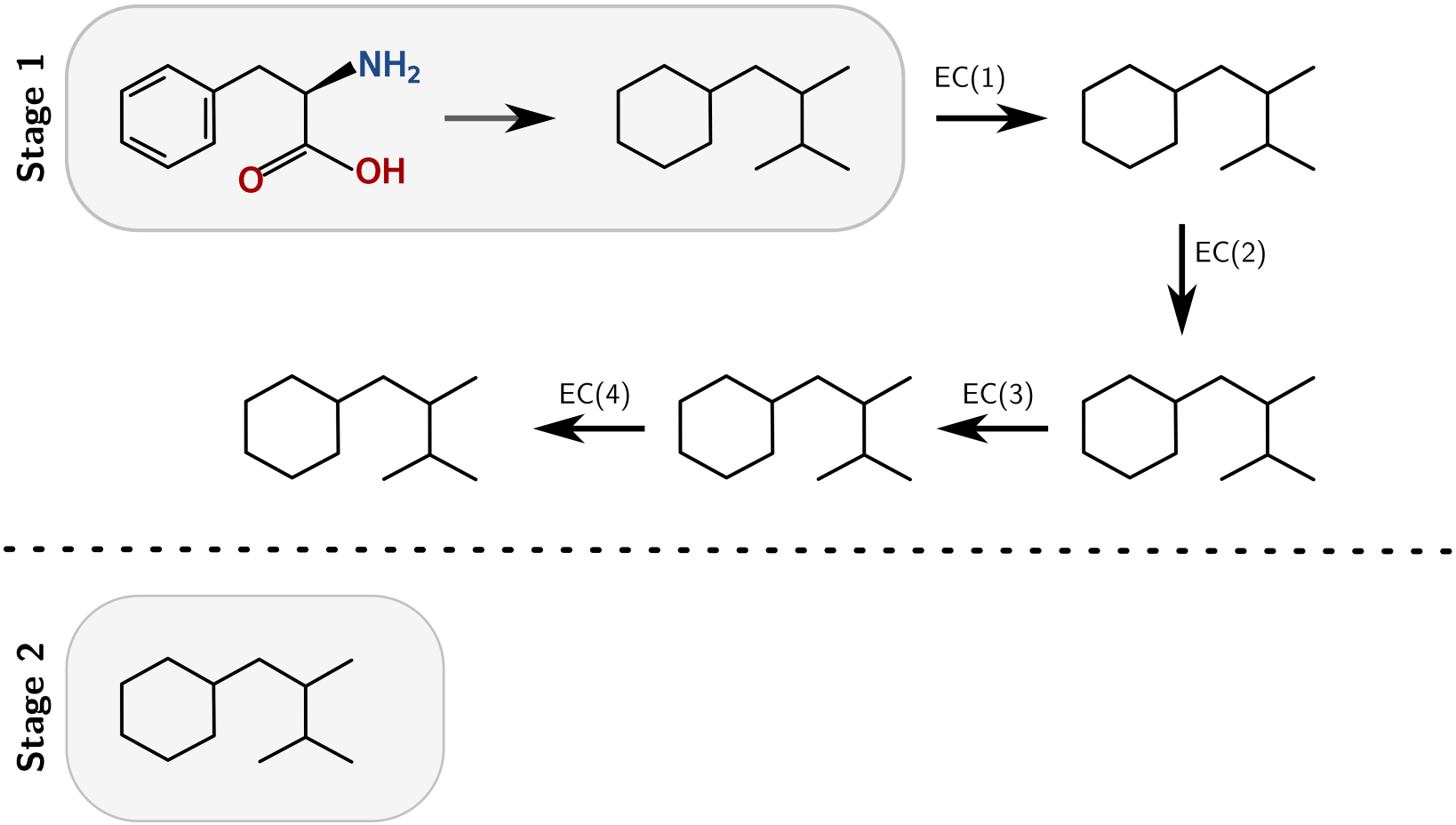
Morgan Algorithm – Example



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Molecular Bit Vectors (1D Descriptors)

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RDKit Example:

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- internal usage in software apps
- fast location of molecules in databases (full structure search), by generating structure hash-codes from:
  - molecular topology (graphs)
  - connection tables (foundation of CAS registry system)
  - ensemble (merge hash codes of atoms into bond and molecular hash codes)

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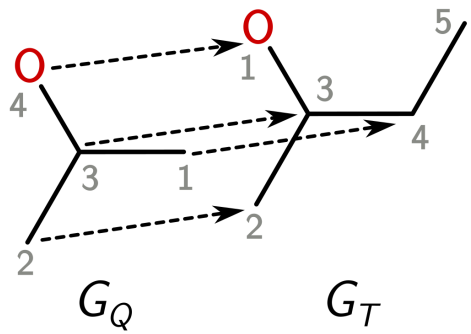

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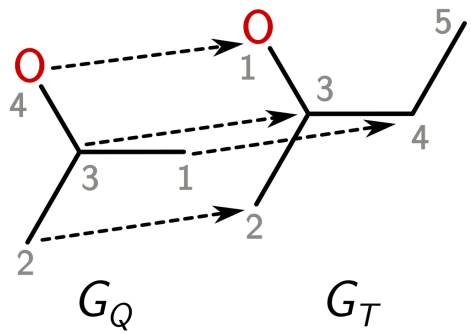

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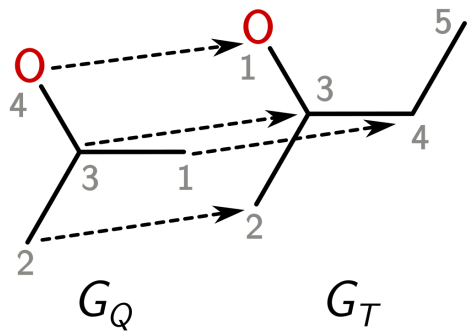

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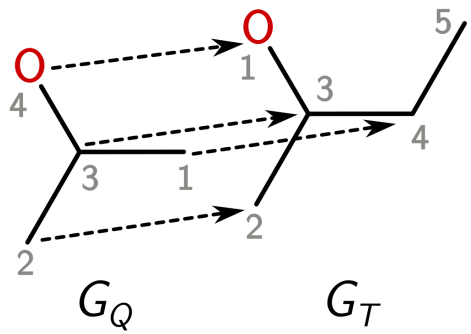
- search is non-polynomial-complete problem ($\mathcal{O}(2^n)$)



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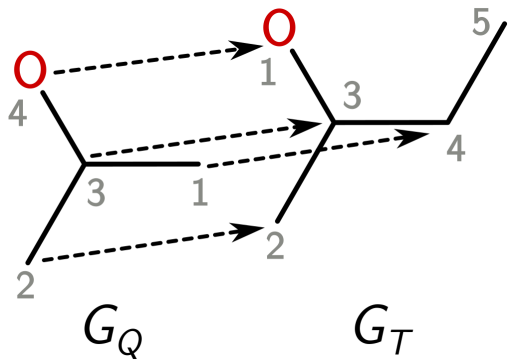

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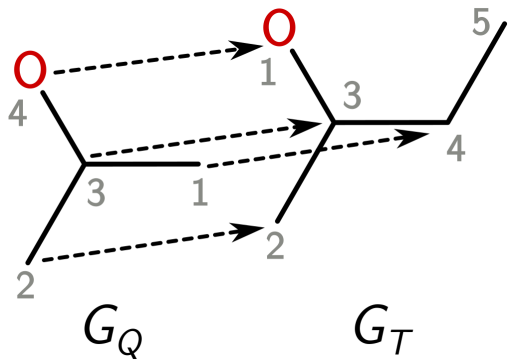
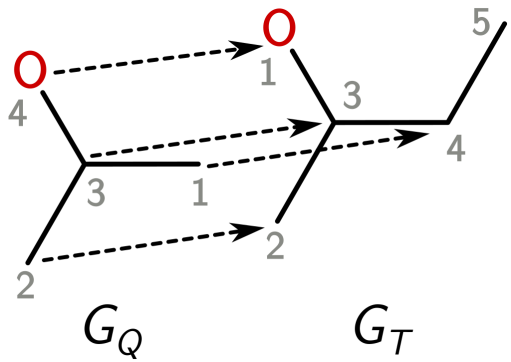


- **Task:** Find edge-preserving mapping between all atoms (vertices) of G_Q and some atoms of G_T, *i.e.*, so that if there is a bond between two atoms in G_Q there has to be a bond between the two corresponding atoms in G_T

Substructure Search

Basic Idea

- **Given:** substructure G_Q of $n = 4$ atoms and molecule G_T of $m = 5$ atoms.



- **Task:** Find edge-preserving mapping between all atoms (vertices) of G_Q and some atoms of G_T, *i.e.*, so that if there is a bond between two atoms in G_Q there has to be a bond between the two corresponding atoms in G_T
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  - e.g., with $n = 30$ and $m = 7$ there are circa 10 billion possible mappings

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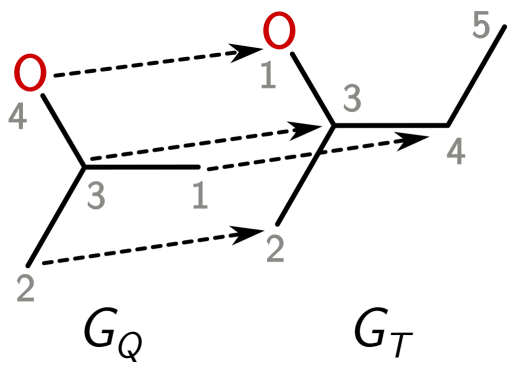

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- **Problem:** the number of possible mappings can be huge
  - e.g., with $n = 30$ and $m = 7$ there are circa 10 billion possible mappings
- **Approach:** *brute force* walk through all mappings is time-consuming and impracticable with $N_{at} > 10$
  - Standard algorithmic solution: **Backtracking**

Backtracking Algorithm

Basic Idea

Backtracking

Algorithm for fast search for isomorphism among all mappings ($G_q \to G_T$) with a search strategy that traverses a search tree in depth-first order. All searched mappings can be organized hierarchically as a tree. A search tree assigns atoms of G_Q to all possible atoms of G_T in a systematic way.

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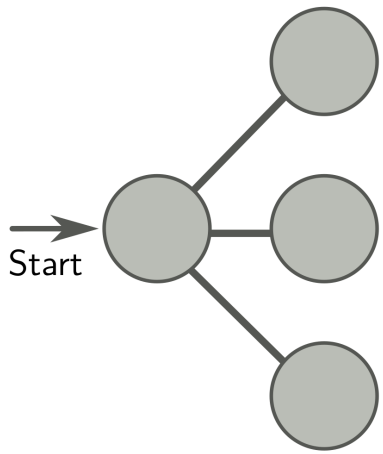

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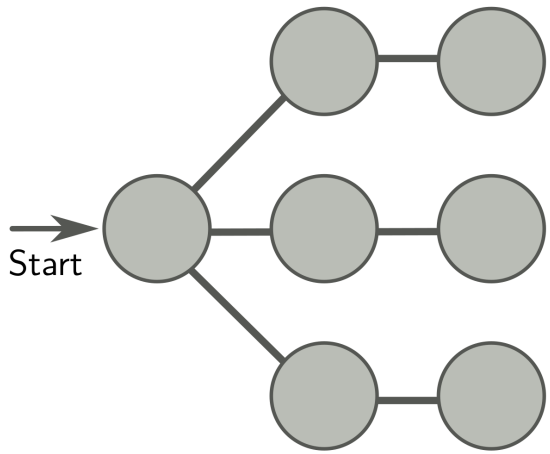

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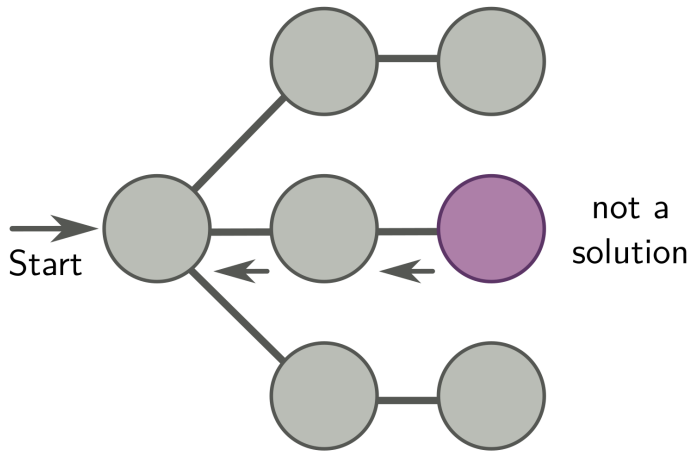

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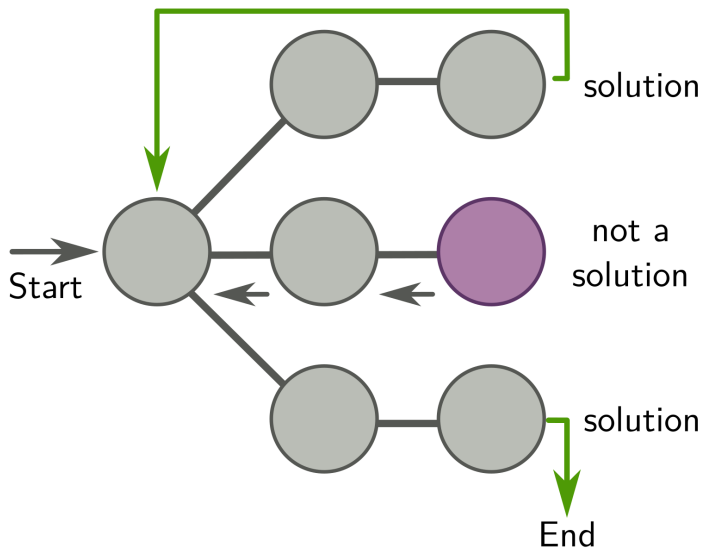
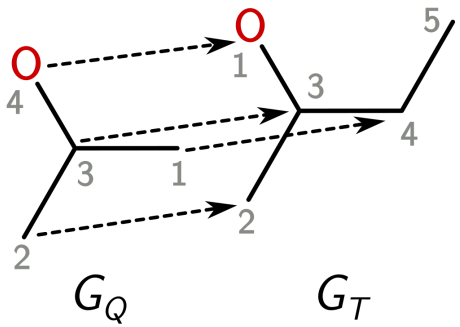


Backtracking Algorithm

Example



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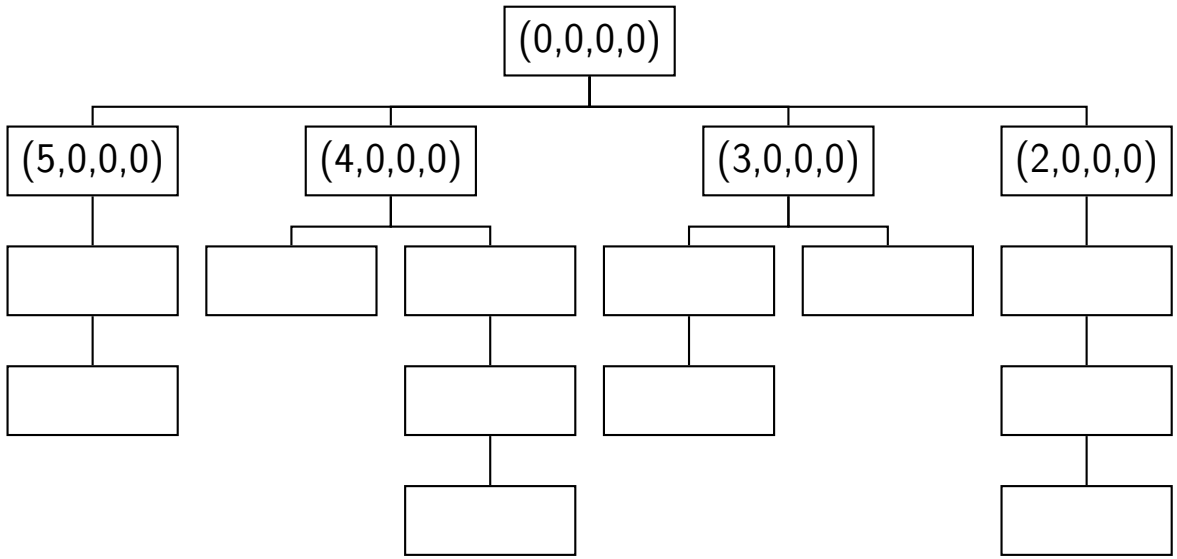

Backtracking Algorithm

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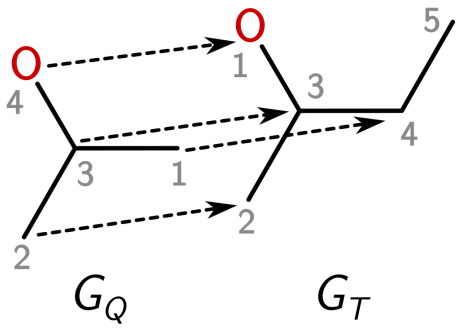

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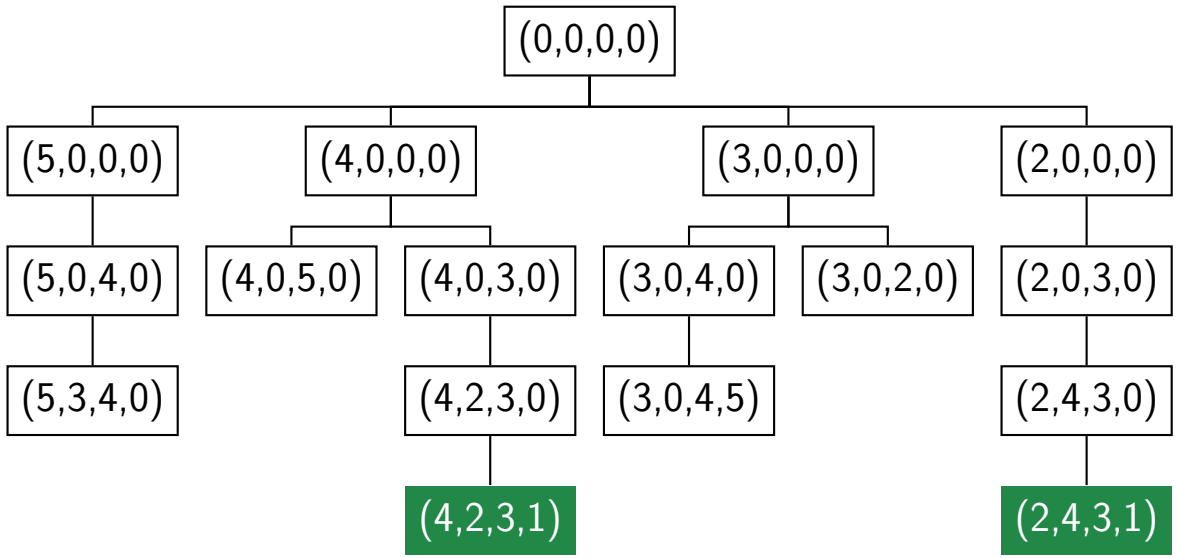

- **Backtracking:** 16 instead of 120 mappings

Backtracking Algorithm

Summary and refined backtracking

- Backtracking:
  - depth-first algorithm has exponential order of computational complexity ($m \cdot 1.141^n$)
  - the earlier search tree traversal fails, the better
  - The order in which substructure atoms are assigned is arbitrary
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- Refined backtracking: **Ullmann algorithm**
  - Backtracking only checks if currently mapped atom yields plausible assignment
  - idea:
    - In each step, keep track of all possible assignments for all substructure atoms
    - If no possible matches remain for any single substructure atom the branch can be skipped
    - Note, that the basic backtracking only check possibilities of the current atom to be assigned and not any later ones

Ullmann Algorithm

Feasibility Matrix for refined backtracking

Ullman Algorithm

The **Ullman algorithm** is a backtracking-based approach used to determine whether two graphs are isomorphic, efficiently exploring all possible mappings between their nodes while employing pruning strategies to minimize unnecessary exploration.

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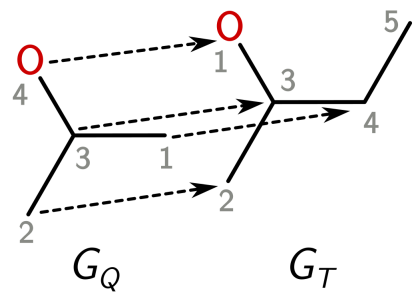

	1	2	3	4	5
1		x		x	x
2		x		x	x
3			x		
4	x				

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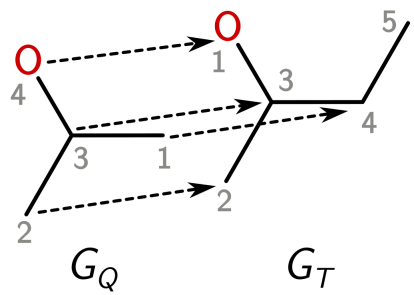
   - Thus, for $M(Q,T) = x$ check for all neighbors j of Q if $M(j,k) = x$ where k is neighbor of T. If no neighbor T can be found eliminate possibility $M(Q,k)$



	1	2	3	4	5
1		x		**x**	x
2		x		**x**	x
3			x		
4	x				

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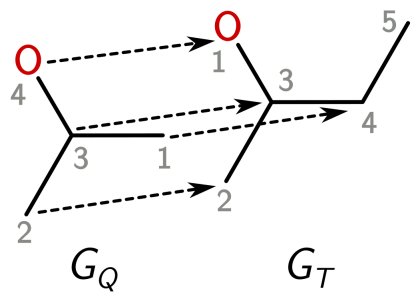
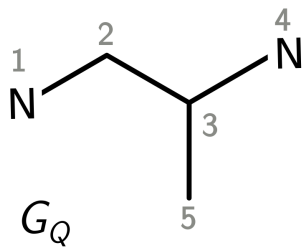
3. Perform standard backtracking

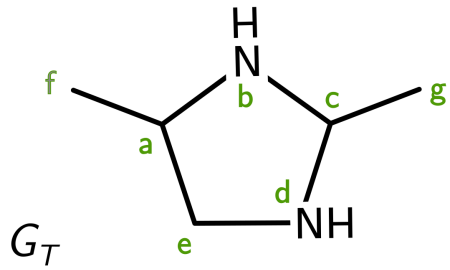


	1	2	3	4	5
1		x			x
2		x			x
3			x		
4	x				

Ullmann Algorithm

Example





- Initial feasibility matrix:

	a	b	c	d	e	f	g
1							
2							
3							
4							
5							

- Refined feasibility matrix:

	a	b	c	d	e	f	g
1							
2							
3							
4							
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Ullmann Algorithm

Summary

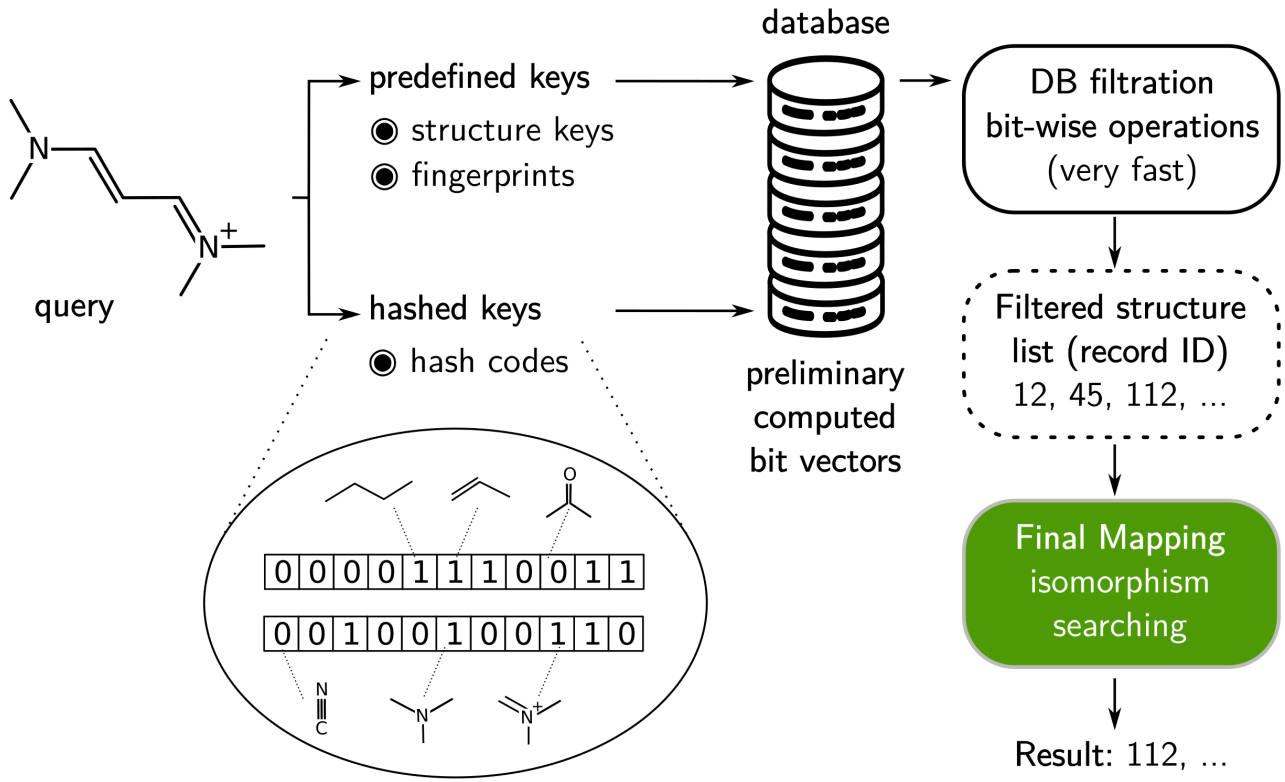
- Set up a feasibility matrix containing all possible assignments of substructure atoms to molecule atoms with respect to
  - atom type
  - bond order
- Refine the matrix
  - for each potential assignment check possible assignments of neighboring atoms
- Explore the search tree
  - choose assignment for current atom from feasibility matrix
  - update matrix & refine matrix
    - possibilities remain for every atom: continue exploration with next atom
    - no possibilities for at least one atom: choose different assignment & backtrack

Substructure Search

Screening

Screening

Screening is a process to filter structures that do not meet certain criteria or match specific patterns, namely predefined set of structural fragments (keys), reducing the set of structures being checked for isomorphism by means of backtracking.



c) Structural Keys

Perception of structural fragments

- idea: speed-up substructure search by filtering out molecules that do not contain a specified substructure

Structural Key

A structural key is a Boolean vector (represented by a bit vector) in which each element is *true* or *false* and denotes existence or absence of a corresponding structural feature.

Typical examples:

- absence/presence of certain elements
- existence of rings
- common functional groups

Procedure:

1. Construct key for searched substructure
2. reject molecules that do not contain fragments encoded in query key from further processing
3. isomorphism search on molecules that passed screening

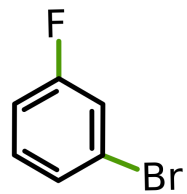
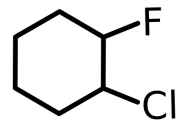
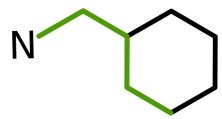
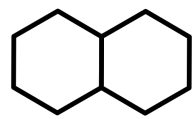
- approaches:
  - molecular formula (missing atoms)
  - structural keys
    - **M**olecular **ACC**ess **S**ystem (**MACCS**) keys: set of 166 keys (functional groups, rings, etc.)
    - **SMARTS**

c) Structural Keys

SMARTS

SMARTs (SMiles ARbitrary Target Specification)

Line notation used for the description of queries for substructure searching. While SMILES describe valid molecules, **SMARTS** describes a fragment that is searched against some other target molecules.

SMARTS	Match	No-match
`a[Cl,Br,F]` aromatic atom connected to a halogen		
`NC[C;R1;D3]` aliphatic carbon participating in 1 ring with 3 explicit connections		

d) Molecular Fingerprints

Molecular Bit Vectors (1D Descriptors)

Fingerprints (FPs)

A molecular **fingerprint** (FP) is a vectorized representation of molecules that captures precise details of the atomic configurations in them.

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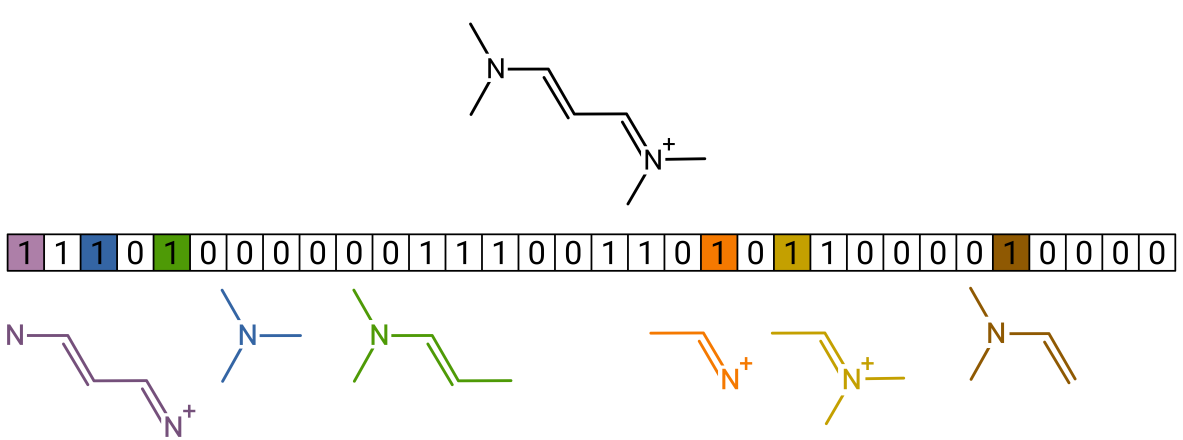

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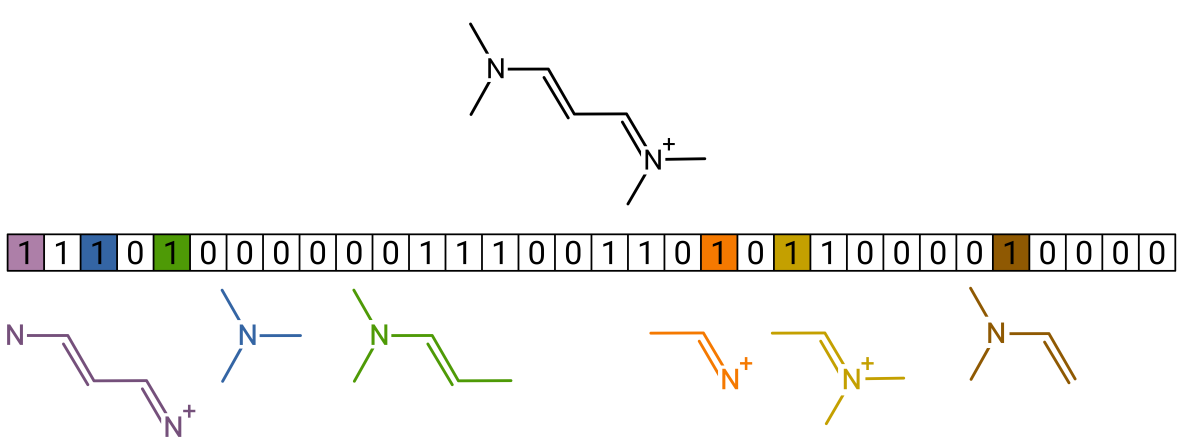

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- Examples (`rdkit` implementations):
  - RDKit FPs
  - Morgan/Circular FPs
  - Extended Connectivity FPs (ECFP)

1D Molecular Structure Descriptors

Morgan and Extended Connectivity Fingerprints

Idea

Morgan fingerprints (MFPs) are iteratively constructed by applying a hashing procedure to atom environments, considering their neighboring atoms up to a certain radius. **Extended Connectivity Fingerprints (ECFPs)** are a specific type of MFPs, where in every iteration features are hashed to generate identifiers for different substructures.

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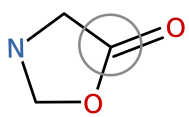

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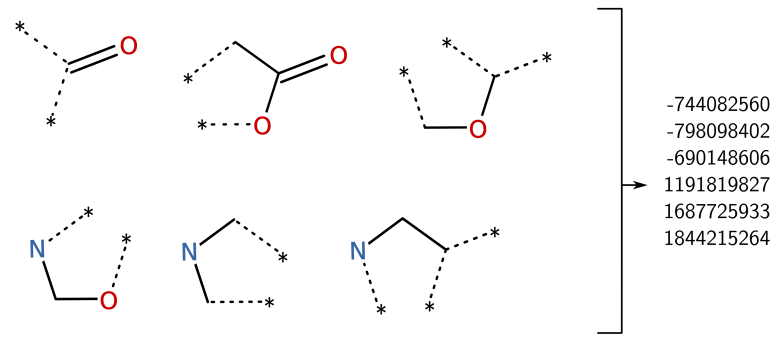

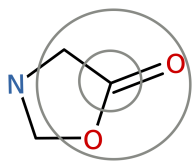

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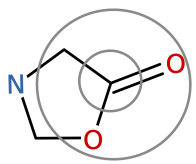
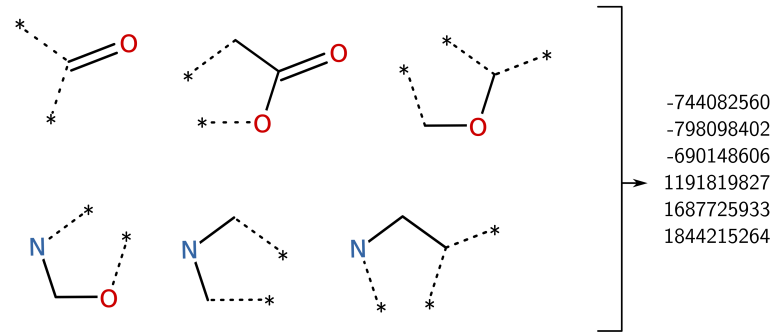
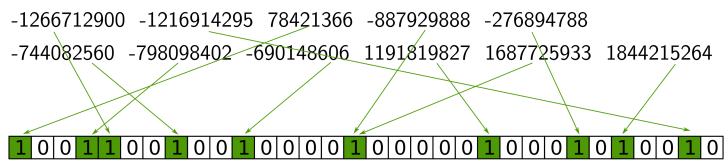
- **Final Hashing:** Hashing of final identifiers into a fixed-length bit vector (binary string, *i.e.*, molecular FP)



- Diameter 2:





Similarity Search

Perception of similar structures

- limits of substructure searching:
  - database structure must contain the entire query substructure (user must have a clear view of types of structure to be retrieved)
  - no control over size of produced output given a query (number of hits)
  - queries need to be engineered to obtain meaningful results (not too few or too many hits)
  - no ranking

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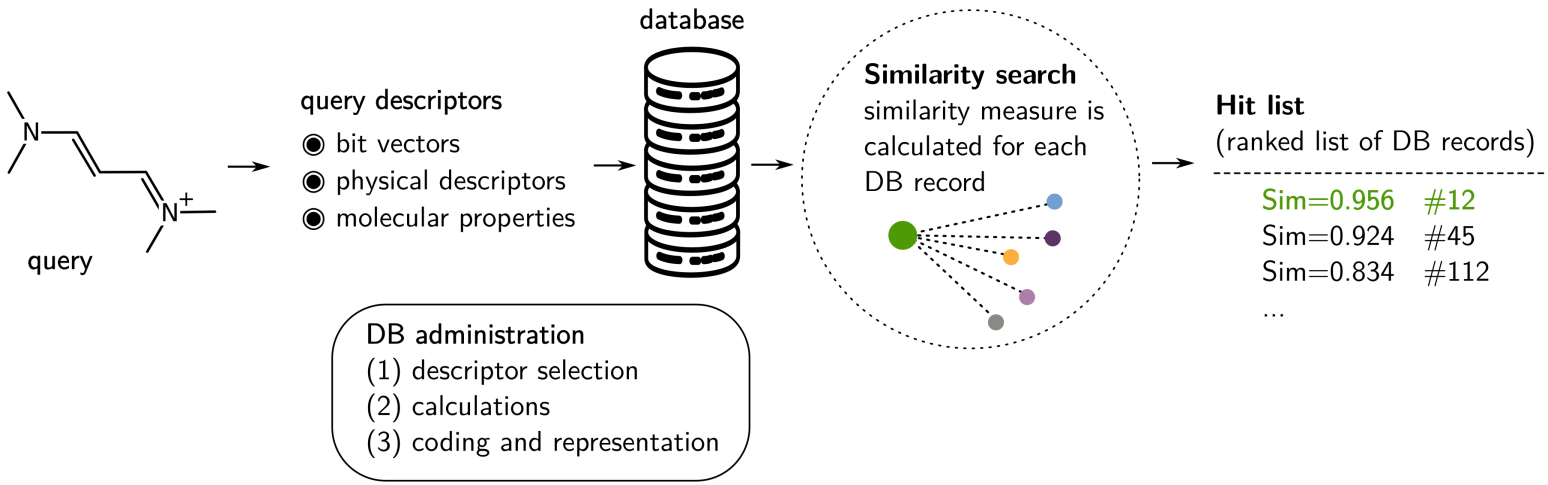
Similarity search is an alternative and complement to substructure searching. Similarity searching retrieves objects that are similar to a query, sorted in order of their decreasing similarity.



Similarity Search

Similarity measures

Similarity

Similarity concept can be applied in different chemical spaces, e.g., in the vector, property, descriptor or structure space, which can be formalized as vectors ($\{X_1, X_2, \ldots, X_n\}$) in the following way:

$$V_A\ V_B \Leftrightarrow P_A\ P_B \Leftrightarrow D_A\ D_B \Leftrightarrow S_A\ S_B \Leftrightarrow V_A\ V_B$$

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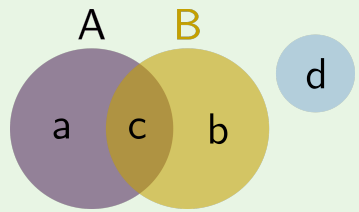
  - descriptor space:
    - *Correlation coefficients* – statistical analysis of the relationships between variables, *e.g.*, in the descriptor vectors D_A and D_B
    - *Probabilistic coefficients* – distribution of the frequencies of descriptor values over a particular database

Similarity Search

Association Coefficients

Simple matching coefficient

Lets consider objects A and B, where a is the number of features present in A and absent in B, b is the number of features absent in A but present in B, c is the number of features common to both objects, and d is the number of features absent in both.



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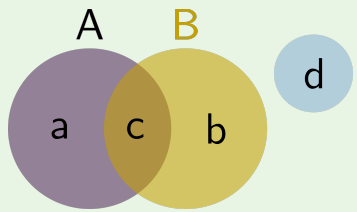

Similarity measure: all matches $c + d$ relative to all possibilities of matches and mismatches $(c + d) + (a + b)$, yields

$$S = \frac{c + d}{a + b + c + d},$$

which is called simple matching coefficient (equal weight to matches and mismatches).

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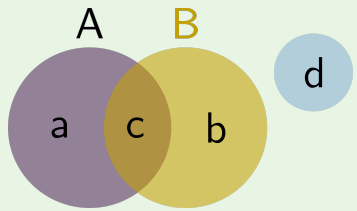

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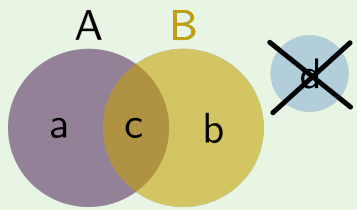
Tanimoto Similarity

Omitting d (features absent in both objects), when absent features convey no information, gives the Tanimoto similarity:

$$T = \frac{c}{a + b + c}$$



Similarity Searching

Practical course

- construct database comprising 3D-structures and absorption maxima (integer) of 19 cyanine dyes
- perform similarity search across this database
- visualize the molecular relations in form of a network