Making a hash of it
The advantage of selectively leaving out structural information

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NextMove Software
INTRODUCTION
WHAT DO THESE MOLECULES HAVE IN COMMON?

Lunularic acid
Xanthoxyletin
Menbutone
Peucedanin
Yangonin
Menadiol diacetate
WHAT DO THESE MOLECULES HAVE IN COMMON?

Lunularic acid

Xanthoxyletin

Menbutone

Peucedanin

Menadiol diacetate

Yangonin

MOLECULAR FORMULA

• A representation of the molecular structure that discards connectivity and stereochemistry
  – Sufficient to calculate the molecular weight
  – The simplest molecular hash

• Can be used to index chemical structures
  – Invariant to differences in bond representation (e.g. inorganic complexes), tautomeric form

• Can be used to identify isomers
  – Constitutional isomers and stereoisomers
HASH FUNCTION

- A function (or procedure) that maps a set of inputs to a smaller set of outputs
  - Inputs with the same hashed value ("hash") are equivalent (in some respect)
- Can be used to find/eliminate duplicates (with respect to some property)
HASHING WORDS VS MOLECULES
FIND ALL ANAGRAMS IN A SET: ENUMERATION

• For all pairs of words (A, B) of the same length in the set, generate all possible orderings of the letters of A and compare to B

• Drawbacks:
  – The number of pairs of words increases with \( \sim N^2 \)
  – Enumerating all possible orders of a word of length N may take a while
    • E.g. 13! is 62270208

• Is there a more efficient way?
  – (Hint: enumeration is rarely a good idea)
Find all Anagrams in a List of Words

- For each word, create a hash of the letters in sorted order, for example:
  - “noboyle” → belnooy
  - “boloney” → belnooy

- Collate words that hash to the same value
  - belnooy: [noboyle, boloney]

- Efficient process, future queries just need a lookup

- General points
  - We need a hash that is only shared by the items of interest
    - All anagrams of “noboyle” have the hash belnooy
    - Only anagrams of “noboyle” have the hash belnooy
  - Hashes discard some features of the original data
    - Here we discard information on the original letter order
<table>
<thead>
<tr>
<th>Find anagrams</th>
<th>Find duplicate molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set of words</td>
<td>Set of molecules (e.g. SMILES strings)</td>
</tr>
<tr>
<td>Sort letters in alphabetical order</td>
<td>Sort atoms in canonical order</td>
</tr>
<tr>
<td>Generate hash (sorted text)</td>
<td>Generate hash (canonical SMILES)</td>
</tr>
<tr>
<td>Find duplicates based on hash</td>
<td>Find duplicates based on hash</td>
</tr>
<tr>
<td>Original words are anagrams of each other</td>
<td>Original SMILES represent the same molecule</td>
</tr>
</tbody>
</table>
Find words that differ by a single letter

- For each word, create hashes where each letter in turn is replaced by an asterisk

- isotropic
  - *sotropic (also esotropic)
  - i*otropic (also inotropic)
  - is*tropic
  - iso*rpic (also isorropic)
  - isot*opic
  - isotr*pic
  - isotro*ic (also isotronic)
  - isotrop*c
  - isotropi* (also isotropil)
FIND MOLECULES THAT DIFFER BY A SINGLE ATOM

For each atom in turn, create a hash as follows:

1. Set to zero the atomic number, charge, isotope, and implicit hydrogen count
2. Generate the canonical SMILES

Molecules with the same hash differ by single atom replacement

- CHEMBL464806
- CHEMBL511860

C\text{c1ccc2(c(=O)[nH]1)C(=O)*/C2=C\text{c1ccc(C)oc1}}
<table>
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<tr>
<th>Words that differ by a single letter</th>
<th>Molecules that differ by a single atom</th>
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<td>Find duplicates based on hash</td>
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<td>Original words have one letter replaced</td>
<td>Original molecules have one atom replaced</td>
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</table>
IDENTIFY MATCHED PAIRS IN A SET

- Replace each R group in turn by an asterisk, and generate the canonical SMILES
- Matched pairs share the same hash
- References:
  - Wagener and Lommerse (*JCIM*, **2006**, *36*, 677) used Cactvs hash codes
  - Popularised by Hussain and Rea (*JCIM*, **2010**, *50*, 339) using canonical SMILES

Fc1cc(0)cc(c1)C(=O)c1ccc(*)cc1
MOLHASH

https://github.com/nextmovesoftware/molhash
The Murcko scaffold hash is the canonical SMILES after removing all substituents.

The extended Murcko scaffold hash is the canonical SMILES after replacing all substituents with attachment points.
The canonical SMILES after breaking a subset of acyclic single bonds and replacing the connection by an asterisk or hydrogen.

Specifically, acyclic single bonds are cut if either end of the bond is involved in a ring or if the bond is between a non sp\textsuperscript{2}-hybridized carbon atom and a non-carbon atom.
**ANONYMOUS GRAPH**

- The canonical SMILES string after setting all atoms to asterisks and bonds to single bonds
- Can identify molecules that share the same graph structure independent of atom identity, bond order or hydrogen count
The canonical SMILES after setting all bonds to single bonds, and normalizing hydrogen counts

Identify molecules that share the same bonding arrangement but different bond order
**MESOMER_HASH**

- Two parts: a SMILES component and an integer
  - The canonical SMILES after setting all bonds to single bonds, all charges to zero
  - An integer: the total charge
- Identify duplicate structures independent of resonance form
**Redox Pair Hash**

- Two:
  - One part: a SMILES component and an integer
    - The canonical SMILES after setting all bonds to single bonds, all charges to zero
    - An integer: the total charge
- Identify redox pairs (same hash, different charge)
**HeteroAtom Tautomer Hash**

- Two parts: a SMILES component and two integers
  - The canonical SMILES after setting all bonds to single bonds, all charges to zero, and stripping hydrogens from heteroatoms
  - Two integers: the count of stripped hydrogens, and total charge
- Identify duplicate structures independent of tautomeric state or resonance form
HETEROATOM PROTOMER HASH

• Two parts: a SMILES component and an integer
  – The canonical SMILES after setting all bonds to single bonds, all charges to zero, and stripping hydrogens from heteroatoms
  – An integer: the count of stripped hydrogens minus total charge

• Identify duplicate structures independent of charge, tautomeric state or resonance form
APPLICATIONS
Identify matched pairs II

- Replace each R group in turn by an asterisk, and generate the canonical SMILES tautomer hash
- Matched pairs share the same hash, independent of tautomeric form
TAUTOMER NORMALIZATION BASED ON MEDICINAL CHEMISTS

• Need a source of structures exactly as drawn by chemists
  – US Patents - ChemDraw files
  – ChEMBL – those structures taken from journals (*)

* ChEMBL retains the first tautomeric form entered for any molecule. For structures taken from journals, the tautomer as present in the journal reference is used. However, ChEMBL also incorporates other data sources and structures from those sources may have been normalised.
Tautomer Normalization Based on Medicinal Chemists

- Need a source of structures exactly as drawn by chemists
- Identify all tautomeric regions* and generate the corresponding heteroatom protomer hash

TAUTOMER NORMALIZATION BASED ON MEDICINAL CHEMISTS

- Need a source of structures exactly as drawn by chemists
- Identify all tautomeric regions and generate the corresponding heteroatom protomer hash
- First the most popular form for each tautomeric substructure, and use to normalize databases (or flag up dubious structures)

CHEMBL464806
DATABASE SEARCHING

• Add hashes as columns to enable:
  – Tautomer independent searches
  – Searching for molecules with the same Murcko scaffold
  – Searching for matched pairs of a molecule
  – (...etc.)

• Exploit any subset relationship between hashes
  – E.g. all element graphs have the same anonymous graph (but not v.v.)
  – Similarly, extended Murcko/Murcko, regioisomer/MF, tautomer hash/protomer hash
  – Only store the more general form in a database column, and calculate the more specific one on-the-fly
Other Line Notations are Available

• InChI
  – A molecular hash independent of atom order and tautomeric form

• CACTVS Hash codes, and NCI/CADD structure identifiers

• Reduced graphs (Sheffield, plus others)
  – Text representation where similar ring systems have the same representation, is invariant to ring system locant (e.g. Birchall et al. *JCIM, 2009*, 49, 1330 and refs therein)

• Related work:
CONCLUSIONS
TAKE-HOME MESSAGE

• If the solution appears to require enumeration, think about whether a hashing approach is possible
• Molecular hashes can be used to efficiently investigate many problems in cheminformatics
• You just need the right hash!
  – What information to leave out?

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• John Mayfield
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ARTHOR SUBSTRUCTURE INDEX HASH

- A hash that can be used to sort a database to be searched
- Ensures that substructure search results will be returned in an order that approximates similarity to the query
  - Smallest molecules first
  - ‘Plain’ molecules first – no radicals, charges or isotopes