MALTAOMICS SUMMER SCHOOL

INTRODUCTION TO COMPUTER-AIDED DRUG DESIGN

DAY 4 – 10:40-11:30

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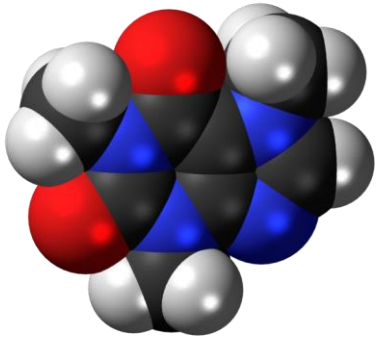
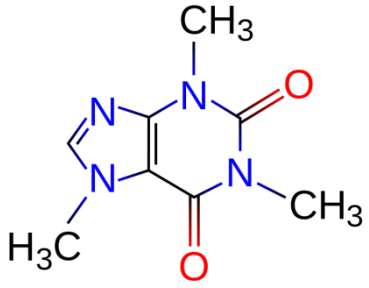
WHAT DOES A DRUG LOOK LIKE?

- Various ways how to represent the same compound (molecule)
- An Example: **Caffeine** (or 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione if you prefer)
- Chemical formula (1D): $C_8H_{10}N_4O_2$
- SMILES String (1D): Cn1cnc2c1c(=O)n(c(=O)n2C)C
- 2D Representation in 3D (Graph)





HOW DO WE REPRESENT MOLECULES IN COMPUTER SYSTEMS?

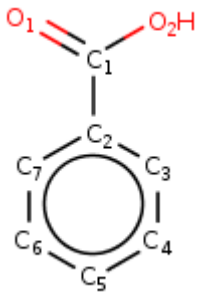
- Any representation of the molecules (which is not the molecule itself) is called a “Descriptor”
  - As the name implies, describes a molecule
- We can represent molecules as a vector
  - E.g. <Molecular Mass, Number of +ve charges, Volume, Log P>
- Countless different representations exist; computed on 1D (properties), 2D (topology; adjacency information), and 3D (geometry) properties of the molecule
- How do we represent connectivity of atoms?

MOLECULAR GRAPHS

- 2D information of a molecule represented by a graph (mathematical notation)
- A graph is made of:
  - A set of vertices which represent atoms ($v \in V$)
  - A set of edges connecting two nodes which represent edges ($e \in E$)
  - Therefore a graph is a tuple G = (V, E)
- Edges have no direction; so graph is said to be undirected
- Nodes and Edges contain information such as atom types, bond order, etc.
- Allows us to use graph theory on molecules; substructure searching etc.
- Only about connectivity

REPRESENTING A MOLECULAR GRAPH

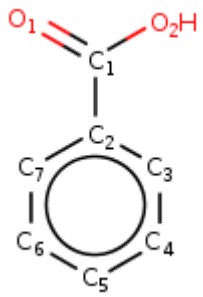
- Using Matrices!
- A molecule with n heavy atoms, may be represented with an n x n matrix
  - Hydrogens often considered “implicit” and omitted
- Adjacency Matrix (indicates which atoms are bonded)



	O1	O2	C1	C2	C3	C4	C5	C6	C7
O1	0	0	1	0	0	0	0	0	0
O2	0	0	1	0	0	0	0	0	0
C1	1	1	0	1	0	0	0	0	0
C2	0	0	1	0	1	0	0	0	1
C3	0	0	0	1	0	1	0	0	0
C4	0	0	0	0	1	0	1	0	0
C5	0	0	0	0	0	1	0	1	0
C6	0	0	0	0	0	0	1	0	1
C7	0	0	0	1	0	0	0	1	0

Can you think of some optimizations?

OPTIMIZATIONS



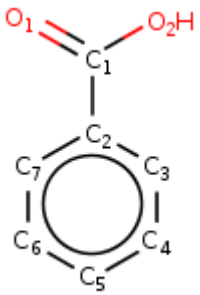
	O1	O2	C1	C2	C3	C4	C5	C6	C7
O1	0	0	1	0	0	0	0	0	0
O2	0	0	1	0	0	0	0	0	0
C1	1	1	0	1	0	0	0	0	0
C2	0	0	1	0	1	0	0	0	1
C3	0	0	0	1	0	1	0	0	0
C4	0	0	0	0	1	0	1	0	0
C5	0	0	0	0	0	1	0	1	0
C6	0	0	0	0	0	0	1	0	1
C7	0	0	0	1	0	0	0	1	0

	O1	O2	C1	C2	C3	C4	C5	C6	C7
O1			1						
O2			1						
C1				1					
C2					1				1
C3						1			
C4							1		
C5								1	
C6									1
C7									

- Matrix is symmetrical
- No need to store 0s
- Each row (or column) must have at least a 1 (otherwise it is not connected to anything!)

DISTANCE MATRIX

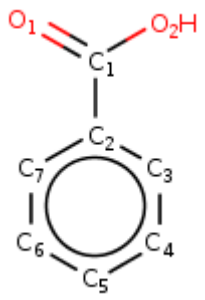
- Encodes distance between atoms
  - Number of bonds between atoms using shortest path
  - Could be 3D distance (in Å)



	O1	O2	C1	C2	C3	C4	C5	C6	C7
O1	0	2	1	2	3	4	5	4	3
O2	2	0	1	2	3	4	5	4	3
C1	1	1	0	1	2	3	4	3	2
C2	2	2	1	0	1	2	3	2	1
C3	3	3	2	1	0	1	2	3	2
C4	4	4	3	2	1	0	1	2	3
C5	5	5	4	3	2	1	0	1	2
C6	4	4	3	2	3	2	1	0	1
C7	3	3	2	1	2	3	2	1	0

BOND MATRIX

- Indicates which atoms are bonded and the corresponding bond orders



	O1	O2	C1	C2	C3	C4	C5	C6	C7
O1	0	0	2	0	0	0	0	0	0
O2	0	0	1	0	0	0	0	0	0
C1	2	1	0	1	0	0	0	0	0
C2	0	0	1	0	1	0	0	0	1
C3	0	0	0	1	0	1	0	0	0
C4	0	0	0	0	1	0	1	0	0
C5	0	0	0	0	0	1	0	1	0
C6	0	0	0	0	0	0	1	0	1
C7	0	0	0	1	0	0	0	1	0

WHY USE MATRICES?

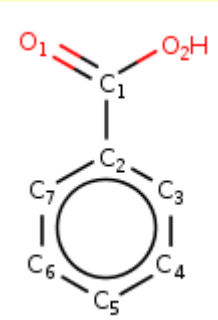
- Advantages
  - Use of Matrix Algebra for comparison etc.
  - Complete representation of graph
- Disadvantages
  - Quadratic size (n^2)
  - Sparsely populated

SOLUTION

- Use of adjacency list (a.k.a. the connection table)
- Linear size
- E.g. MDL SDF (Structure Data File)

```
Benzoic Acid
  Mrv1903 04071910542D

  9  9  0  0  0  0            999 V2000
    0.3348    5.3339    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.3796    4.9214    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.3796    4.0964    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.3348    3.6839    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.0493    4.0964    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.0493    4.9214    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.3348    2.8589    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.0493    2.4464    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   -0.3796    2.4464    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
  1  2  4  0  0  0  0
  2  3  4  0  0  0  0
  3  4  4  0  0  0  0
  4  5  4  0  0  0  0
  5  6  4  0  0  0  0
  1  6  4  0  0  0  0
  4  7  1  0  0  0  0
  7  8  2  0  0  0  0
  7  9  1  0  0  0  0
M  END
$$$$
```



A LINEAR NOTATION TO REPRESENT MOLECULES

- Simplified Molecular Input Line Specification (SMILES)
- Developed by David Weininger, 1988

SMILES, a Chemical Language and Information System. 1. Introduction to Methodology and Encoding Rules

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Received June 17, 1987

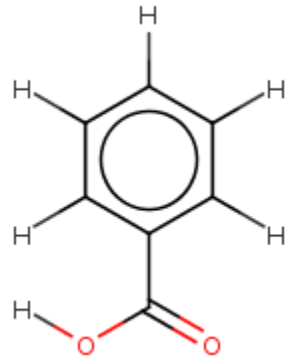
SMILES (Simplified Molecular Input Line Entry System) is a chemical notation system designed for modern chemical information processing. Based on principles of molecular graph theory, SMILES allows rigorous structure specification by use of a very small and natural grammar. The SMILES notation system is also well suited for high-speed machine processing. The resulting ease of usage by the chemist and machine compatability allow many highly efficient chemical computer applications to be designed including generation of a unique notation, constant-speed (zeroeth order) database retrieval, flexible substructure searching, and property prediction models.

SMILES – MAIN POINTS

- Atoms represented by their chemical symbols
  - Uppercase for aliphatic
  - Lowercase for aromatic
- Implicit hydrogen atoms (but explicit definition possible)
- Implicit single bonds
- Greatly reduces complexity and redundancy

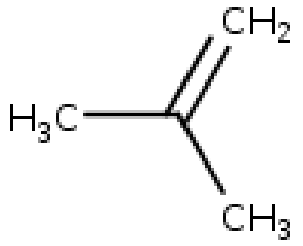

```
OC(=O)c1ccccc1
```

```
[H]OC(=O)c1c([H])c([H])c([H])c([H])c1[H]
```



SMILES (II)

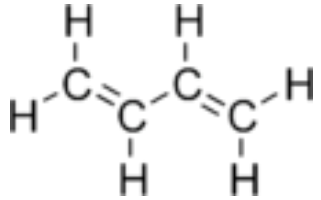
- Double and triple bonds represented with = and #
- Branches represented with parentheses



2-methylprop-1-ene
C=C(C)C

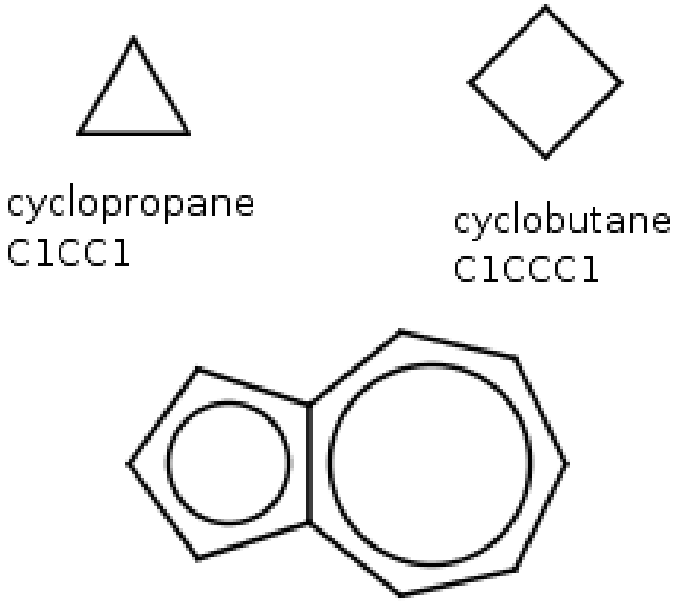
But-1-ene
C=CCC

What about 1,3-Butadiene?



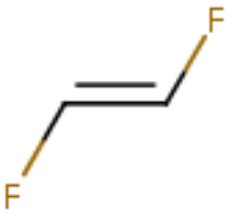
SMILES (III)

- Ring closure represented by numbers



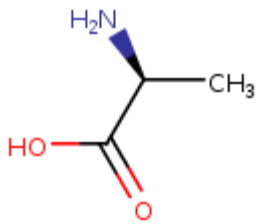
SMILES (IV)

- Stereochemistry at double bonds
  - Z, cis, zusammen, \/ or /\
  - E, trans, Entgegen, // or \\
- Chirality
  - @ counter-clockwise
  - @@ clockwise

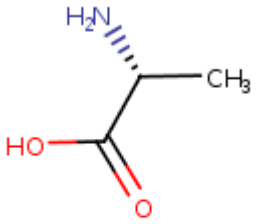


trans-difluoroethene
F/C=C/F

cis-difluoroethene
F/C=C\F



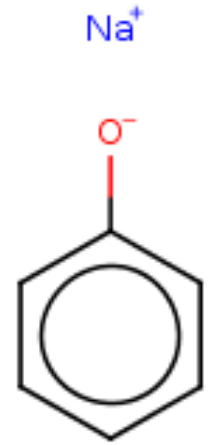
L-alanine
N[C@@H](C)C(=O)O



D-alanine
N[C@H](C)C(=O)O

SMILES (V)

- Atoms of rare elements (not B, C, N, S, P, F, Cl, Br, I) in square brackets; e.g. [Au]
- Charges – use + or -
- Disconnected structures separated by .



sodiumphenolate
[Na+].[O-]c1ccccc1

RECAP

- Limitless ways how to represent molecules in computer systems using notion of “Descriptors”
- Proteins usually stored in PDB file format
- Connectivity information (2D) may be represented using SMILES
- Small molecules may contain 3D information (e.g. SDF).
  - Large sizes


PRACTICAL