The knapsack algorithm in analytical chemistry

Myriam Guillevic, *Aurore Guillevic*, Martin K. Vollmer, Paul Schlauri, Matthias Hill, Lukas Emmenegger, Stefan Reimann

Laboratory for Air Pollution /Environmental Technology,
Empa, Swiss Federal Laboratories for Materials Science and Technology
Dübendorf, Switzerland
Université de Lorraine, CNRS, Inria, LORIA, Nancy, France

September 23, 2021

https://members.loria.fr/AGuillevic/files/talks/21-Aarhus.pdf
https://members.loria.fr/AGuillevic/files/talks/knapsack.py

The software development team, 2018–2021

- Myriam Guillevic, PhD in Climate Sciences, LSCE France & U. of Copenhagen
  2019–2021 at Group for Climate Gases, EMPA, ETH, Dübendorf, Switzerland
  `https://www.empa.ch/web/s503/climate-gases`
- Aurore Guillevic, computer scientist, Inria Nancy since 2016,
  2017–2020: adjunct assistant professor, École Polytechnique, France
  Introduction to algorithms and programming in Java, Python

Aims

Trace gases: 0.066% of the (dry) atmosphere, gases other than nitrogen (78.1%), oxygen (20.9%) and argon (0.934%) (i.e. 99.934%, water vapor excluded).

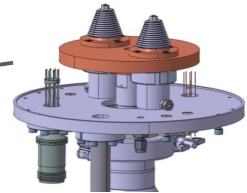
- Measuring trace gases known to be present (e.g. CO_2, CH_4, $CFCl_3$):
  target screening (mass spectra in databases)
  e.g. banned or regulated substances (Montreal protocol)
- Searching for expected/potential pollutants (known to be used in industry) and start monitoring them before emissions to the atmosphere is rising:
  suspect screening (chemical compound known, e.g. HFO-1234yf)
- Searching for unexpected pollutants or unknown unknowns:
  non-target screening (detecting new subtances in the air)
  e.g. industrial disaster (Lubrizol fire in Rouen, France in 2019, Beirut (Beyrouth) harbour explosion in 2020, Leverkusen, Germany, July 27)

How to search for unknown unknowns?

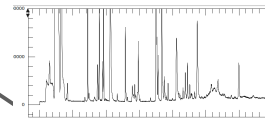
Empa
Materials Science and Technology

Target screening : Aprecon – GC – ToF-MS

Empa
Materials Science and Technology



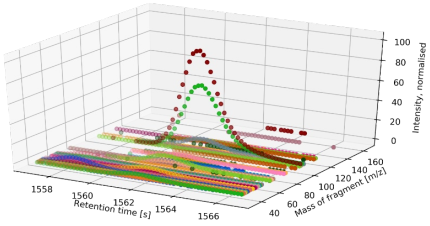
Pre-concentration (APRECON)

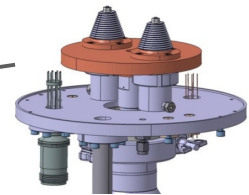


Gas Chromatography GasPro column

Target screening : Aprecon – GC – ToF-MS

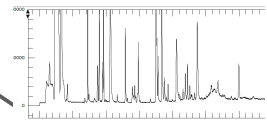
Empa
Materials Science and Technology





Pre-concentration (APRECON)

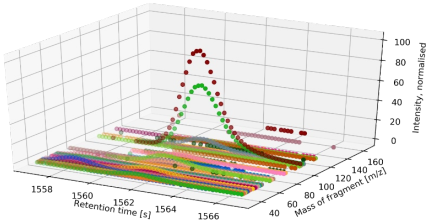
Electron impact (EI)
Time-of-Flight
Mass spectrometer
Tofwerk AG

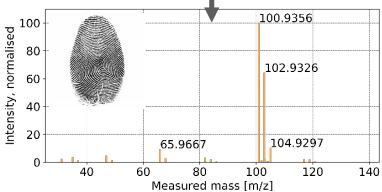


Gas Chromatography
GasPro column

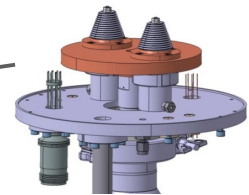
Target screening : Aprecon – GC – ToF-MS

Empa
Materials Science and Technology

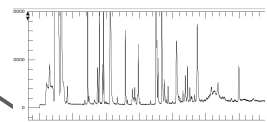




Electron impact (EI)
Time-of-Flight
Mass spectrometer
Tofwerk AG

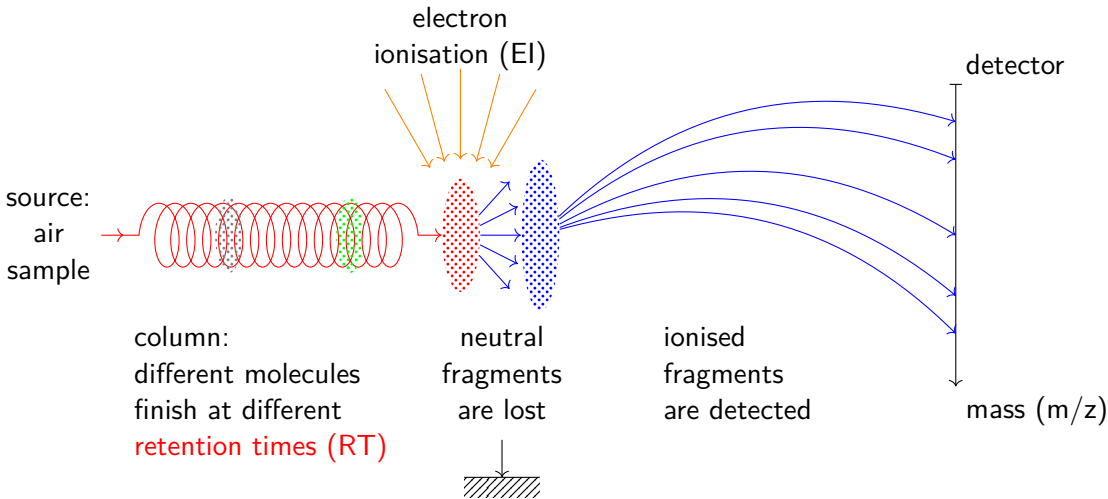


Pre-concentration
(APRECON)

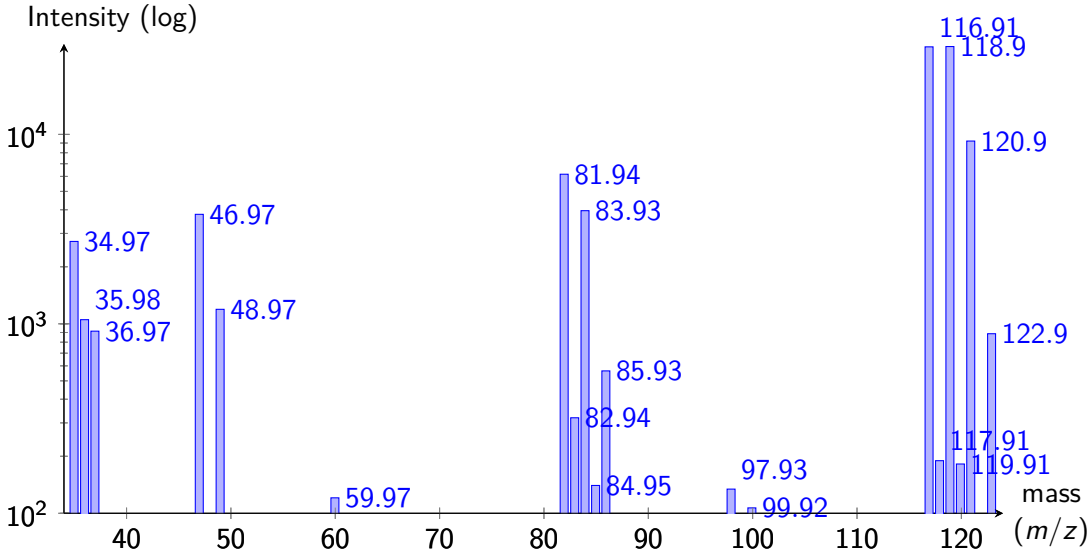


Gas Chromatography
GasPro column

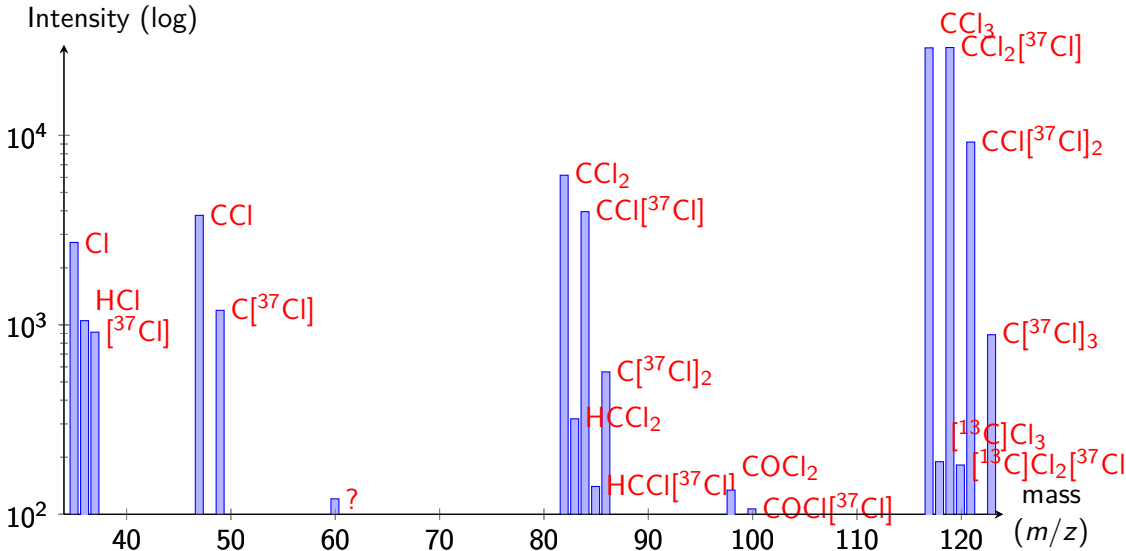
EI ToF MS: Electron Ionisation Time-of-Flight Mass Spectrometer



Input data: mass spectrum

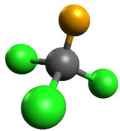


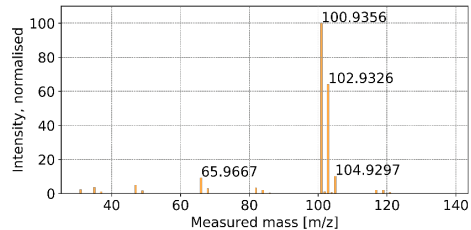
Aim: annotate the figure



Target vs non-target screening

Target screening:





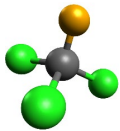
CFC-11
$CFCl_3$

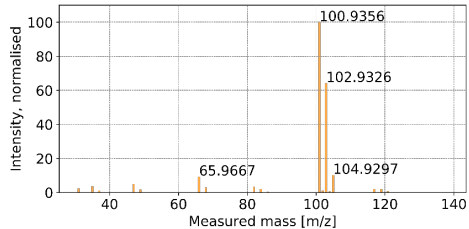
Instrumental fingerprint

Target vs non-target screening

Empa
Materials Science and Technology

Target screening:





CFC-11
$CFCl_3$

Instrumental fingerprint

Non-target screening

Workflow: Knapsack algorithm

Weight: 100.936 ± 0.0002 g/mol
(U = 2 ppm)

Which **atoms** can be packed together to match the measured masses, ± u?

9 atoms: H, C, N, O, S, F, Cl, Br, I

The knapsack algorithm

Inputs:

- measured mass intervals, e.g.
  $[34.96751071, 34.97006625]$
  $[84.92634272, 84.97112964]$
  $[116.90200574, 116.90847942]$
- IUPAC masses of atoms $\rightarrow$

Run the knapsack on each interval, list all solutions.

H	1.0078250319
B	11.00930536
C	12.
N	14.0030740074
O	15.9949146223
F	18.99840316
P	30.973762
S	31.97207073
Cl	34.96885271
Br	78.9183376
I	126.9044719

Knapsack Problem in Combinatorics

In a usual context:

- knapsack of limited capacity
- want to maximize the total value of items

Enumeration + dynamic programming

Knapsack Problem in Combinatorics

In a usual context:

- knapsack of limited capacity
- want to maximize the total value of items

Enumeration + dynamic programming

In chemistry:
Mass interval $\leftrightarrow$ knapsack with lower and upper capacity
No optimisation: list all solutions.
$I = [116.90200574, 116.90847942]$ has 2 solutions:
CCl_3 mass $116.90655813 \in I$,
H_{116} mass $116.9077037004 \in I$

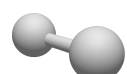
Knapsack Problem in Combinatorics

In a usual context:

- knapsack of limited capacity
- want to maximize the total value of items

Enumeration + dynamic programming

In chemistry:
Mass interval $\leftrightarrow$ knapsack with lower and upper capacity
No optimisation: list all solutions.
$I = [116.90200574, 116.90847942]$ has 2 solutions:
CCl_3 mass $116.90655813 \in I$,
H_{116} mass $116.9077037004 \in I$



But H_{116} is not a molecule: Hydrogen has valence 1
$\rightarrow$ remove non-chemical solutions

mass min	mass max
34.96751071	34.97006625
35.97413780	35.97778836
36.96406557	36.96750599
46.96648952	46.97028744
48.96255817	48.96840119
59.96022019	59.97131577
81.93308641	81.93953315
82.93831759	82.95111397
83.93024931	83.93724265
84.92634272	84.97112964
85.92419323	85.93924313
97.92364853	97.93896563
99.90729357	99.94127719
116.90200574	116.90847942
117.89455759	117.92205637
118.89897942	118.90567754
119.89648859	119.91785117
120.89523104	120.90302932
122.88755350	122.90537266

mass min	mass max	knapsack
34.96751071	34.97006625	Cl
35.97413780	35.97778836	HCl
36.96406557	36.96750599	–
46.96648952	46.97028744	CCl
48.96255817	48.96840119	–
59.96022019	59.97131577	COS
81.93308641	81.93953315	CCl_2
82.93831759	82.95111397	S_2F, $HCCl_2$, H_4Br
83.93024931	83.93724265	–
84.92634272	84.97112964	H_2S_2F, H_2OSCl, $HNCl_2$, CF_2Cl, H_6Br, H_3CCl_2, H_2O_3Cl
85.92419323	85.93924313	OCl_2
97.92364853	97.93896563	H_2S_3, $COCl_2$, H_3OBr
99.90729357	99.94127719	HS_2Cl, HO_2SCl, $NOCl_2$, H_2FBr
116.90200574	116.90847942	CCl_3, H_{116}
117.89455759	117.92205637	S_2FCl, $OSCl_2$, $HCCl_3$, H_4ClBr, H_{117}
118.89897942	118.90567754	–
119.89648859	119.91785117	C_2S_3, $HNCl_3$
120.89523104	120.90302932	OCl_3
122.88755350	122.90537266	CSBr

mass min	mass max	knapsack	answer
34.96751071	34.97006625	Cl	Cl
35.97413780	35.97778836	HCl	HCl
36.96406557	36.96750599	–	$[^{37}Cl]$
46.96648952	46.97028744	CCl	CCl
48.96255817	48.96840119	–	$C[^{37}Cl]$
59.96022019	59.97131577	COS	–
81.93308641	81.93953315	CCl_2	CCl_2
82.93831759	82.95111397	S_2F, $HCCl_2$, H_4Br	$HCCl_2$
83.93024931	83.93724265	–	$CCl[^{37}Cl]$
84.92634272	84.97112964	H_2S_2F, H_2OSCl, $HNCl_2$, CF_2Cl, H_6Br, H_3CCl_2, H_2O_3Cl	$HCCl[^{37}Cl]$
85.92419323	85.93924313	OCl_2	$C[^{37}Cl]_2$
97.92364853	97.93896563	H_2S_3, $COCl_2$, H_3OBr	$COCl_2$
99.90729357	99.94127719	HS_2Cl, HO_2SCl, $NOCl_2$, H_2FBr	$COCl[^{37}Cl]$
116.90200574	116.90847942	CCl_3, H_{116}	CCl_3
117.89455759	117.92205637	S_2FCl, $OSCl_2$, $HCCl_3$, H_4ClBr, H_{117}	$[^{13}C]Cl_3$
118.89897942	118.90567754	–	$CCl_2[^{37}Cl]$
119.89648859	119.91785117	C_2S_3, $HNCl_3$	$[13C]Cl_2[^{37}Cl]$
120.89523104	120.90302932	OCl_3	$CCl[^{37}Cl]_2$
122.88755350	122.90537266	CSBr	$C[^{37}Cl]_3$

The knapsack algorithm in cryptography

Richard Schroeppel and Adi Shamir.
A $T = O(2^{n/2})$, $S = O(2^{n/4})$ Algorithm for Certain NP-Complete Problems.
SIAM Journal on Computing, 10(3):456–464, 1981.

A. M. Odlyzko.
The rise and fall of knapsack cryptosystems.
In Carl Pomerance, editor, *Cryptology and Computational Number Theory*, volume 42 of *Proceedings of Symposia in Applied Mathematics, August 6–7, 1989, Boulder, Colorado*, pages 75–88, Providence, Rhode Island, 1991. AMS.
`http://www.dtc.umn.edu/~odlyzko/doc/arch/knapsack.survey.pdf`.

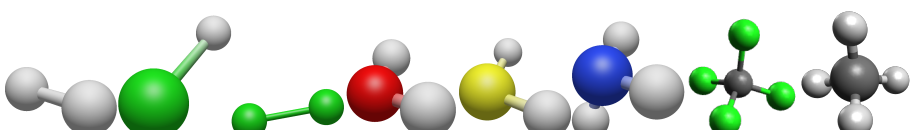
The knapsack algorithm in computer science

Divide-and-conquer method, target $[m_{\min}, m_{\max}]$:
(Thanks to Paul Zimmermann for pointing out the method)

1. Divide the element masses in two *balanced* sets A and B
2. In parallel:
   - List all possible sums in $[0, m_{\max}]$ of masses from set A, sort in increasing order $\rightarrow S_A$
   - List all possible sums in $[0, m_{\max}]$ of masses from set B, sort in increasing order $\rightarrow S_B$
3. Read onwards the masses from S_A and downwards the masses from S_B,
   find matches $m_{A,i} + m_{B,j} \in [m_{\min}, m_{\max}]$
   Linear complexity in $\text{length}(S_A) + \text{length}(S_B)$

Our knapsack algorithm in chemistry

Set A: masses of multi-valent atoms C (4), N (3), O (2), S (6)
Set B: masses of mono-valent atoms H, F, Cl, Br, I
$\text{valence}_{\max} = 1 + 0.5 \sum_{e_i \in \{\text{H,C,N, O,...,I}\}} n_i(v_i - 2)$



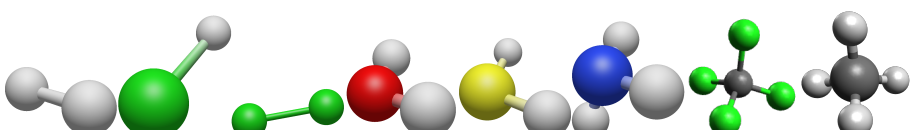
Our knapsack algorithm in chemistry

Set A: masses of multi-valent atoms C (4), N (3), O (2), S (6)

Set B: masses of mono-valent atoms H, F, Cl, Br, I

$\text{valence}_{\text{max}} = 1 + 0.5 \sum_{e_i \in \{\text{H,C,N, O,...,I}\}} n_i(v_i - 2)$

1. List all sums in $[0, m_{\text{max}}]$ of masses from set A, sort in increasing order $\rightarrow S_A$
2. Compute maximum valence of each solution of $S_A \rightarrow \text{valence}_{\text{max}}$



Our knapsack algorithm in chemistry

Set A: masses of multi-valent atoms C (4), N (3), O (2), S (6)
Set B: masses of mono-valent atoms H, F, Cl, Br, I
$\text{valence}_{\max} = 1 + 0.5 \sum_{e_i \in \{\text{H,C,N, O,...,I}\}} n_i(v_i - 2)$

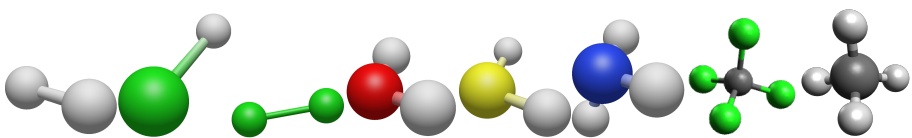
1. List all sums in $[0, m_{\max}]$ of masses from set A, sort in increasing order $\rightarrow S_A$
2. Compute maximum valence of each solution of $S_A \rightarrow \text{valence}_{\max}$
3. List all sums in $[0, m_{\max}]$ of at most $\text{valence}_{\max}$ masses from set B, sort in increasing order $\rightarrow S_B$
4. Read onwards the masses from S_A and downwards the masses from S_B, find matches $m_{A,i} + m_{B,j} \in [m_{\min}, m_{\max}]$ and check DBE ≥ 0
   Linear complexity in $\text{length}(S_A) + \text{length}(S_B)$

Our knapsack algorithm in chemistry

Observe that:

- atoms in A are heavy (lightest one C of 12.0 m/z)
- lightest atom H $\in B$ of mass 1.0078250319, but #H bounded by $\text{valence}_{\text{max}}$

$\rightarrow$ in average, reduce the length of S_B by a factor 2



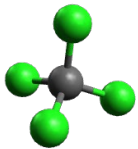
Other knapsack algorithm in analytical chemistry

SIRIUS software, AGPL `https://github.com/boecker-lab/sirius`
`https://bio.informatik.uni-jena.de`
Universität Jena, Germany, Bio-informatic group

Sebastian Böcker and Zsuzsanna Liptak.
A fast and simple algorithm for the money changing problem.
Algorithmica, 48:413–432, 2007.

Kai Dührkop, Marcus Ludwig, Marvin Meusel, and Sebastian Böcker.
Faster mass decomposition.
In Aaron Darling and Jens Stoye, editors, *Algorithms in Bioinformatics*, pages 45–58, Berlin, Heidelberg, 2013. Springer Berlin Heidelberg.

Workflow: mimick fragmentation process



Molecular ion

CCl_4

e- e- e- e- e-

CCl_3^+

CCl^+

CCl_2^+

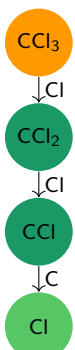
Cl^+

Measured fragments

More about graph algorithms: CCl_4

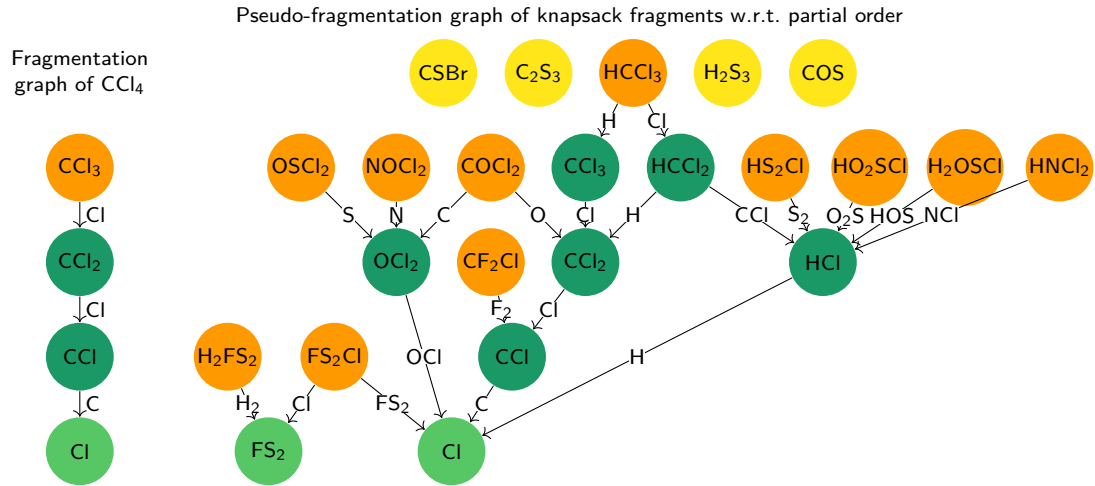
Singleton, Maximal, Node, Leaf.

Fragmentation graph of CCl_4



More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



More about graph algorithms: CCl_4

Ouput of knapsack: a list of candidate fragment formulas

Define a partial order on the fragment formulas

$Cl \leq CCl \leq CCl2 \leq CCl3 \leq HCCl3$, but COS incomparable

Build a Directed Acyclic Graph according to the ordering

Setting edges has quadratic complexity in the number of vertices (nodes)

More about graph algorithms: CCl_4

Ouput of knapsack: a list of candidate fragment formulas
Define a partial order on the fragment formulas
$Cl \leq CCl \leq CCl2 \leq CCl3 \leq HCCl3$, but COS incomparable
Build a Directed Acyclic Graph according to the ordering
Setting edges has quadratic complexity in the number of vertices (nodes)

- Fragments in batches, per target interval mass, decreasing mass
- All fragments in one batch are incomparable (mass diff $\ll 1$)

More about graph algorithms: CCl_4

Ouput of knapsack: a list of candidate fragment formulas
Define a partial order on the fragment formulas
$Cl \leq CCl \leq CCl2 \leq CCl3 \leq HCCl3$, but COS incomparable
Build a Directed Acyclic Graph according to the ordering
Setting edges has quadratic complexity in the number of vertices (nodes)

- Fragments in batches, per target interval mass, decreasing mass
- All fragments in one batch are incomparable (mass diff $\ll 1$)

Much faster complexity, starting with the heaviest target mass

1. First batch: roots (maximal elements)

More about graph algorithms: CCl_4

Ouput of knapsack: a list of candidate fragment formulas
Define a partial order on the fragment formulas
$Cl \leq CCl \leq CCl2 \leq CCl3 \leq HCCl3$, but COS incomparable
Build a Directed Acyclic Graph according to the ordering
Setting edges has quadratic complexity in the number of vertices (nodes)

- Fragments in batches, per target interval mass, decreasing mass
- All fragments in one batch are incomparable (mass diff $\ll 1$)

Much faster complexity, starting with the heaviest target mass

1. First batch: roots (maximal elements)
2. Process one batch of fragments as a whole
   - 2.1 Compare each fragment to the roots
   - 2.2 If a subfragment, recursively visit the children until it is a leaf, set a new edge from the parent node
   - 2.3 if incomparable to any root, keep it aside

More about graph algorithms: CCl_4

Ouput of knapsack: a list of candidate fragment formulas
Define a partial order on the fragment formulas
$Cl \leq CCl \leq CCl2 \leq CCl3 \leq HCCl3$, but COS incomparable
Build a Directed Acyclic Graph according to the ordering
Setting edges has quadratic complexity in the number of vertices (nodes)

- Fragments in batches, per target interval mass, decreasing mass
- All fragments in one batch are incomparable (mass diff $\ll 1$)

Much faster complexity, starting with the heaviest target mass

1. First batch: roots (maximal elements)
2. Process one batch of fragments as a whole
   - 2.1 Compare each fragment to the roots
   - 2.2 If a subfragment, recursively visit the children until it is a leaf, set a new edge from the parent node
   - 2.3 if incomparable to any root, keep it aside
3. update the list of roots with the incomparable fragments of the batch

More about graph algorithms: CCl_4

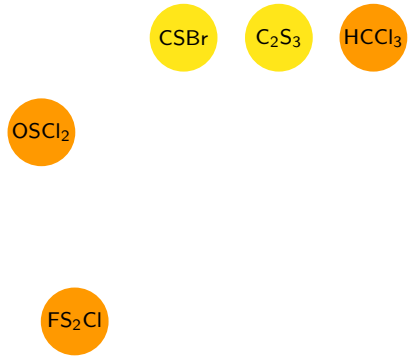
Singleton, Maximal, Node, Leaf.

More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.

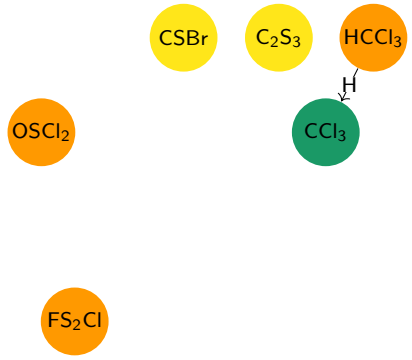
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



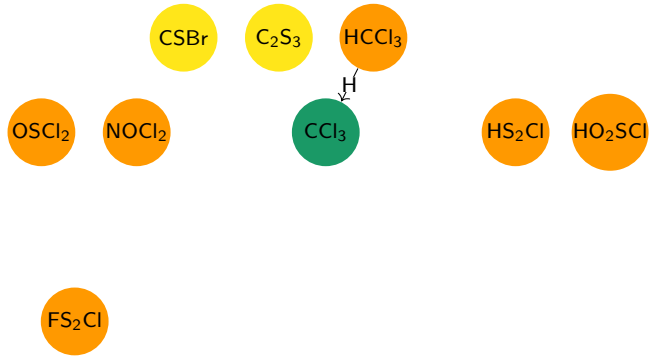
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



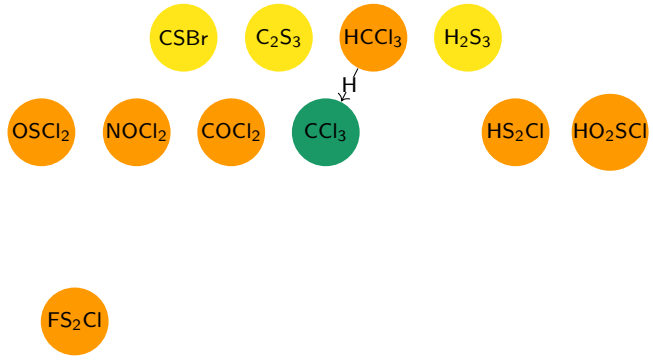
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



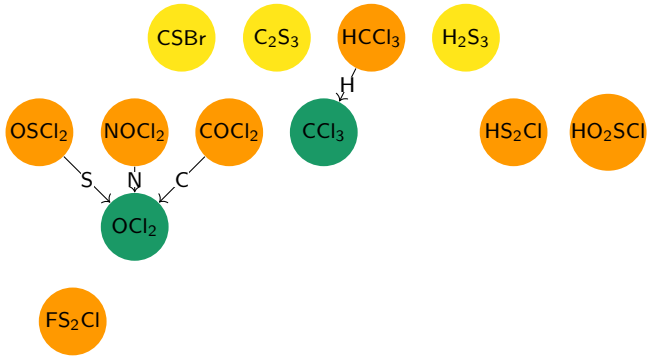
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



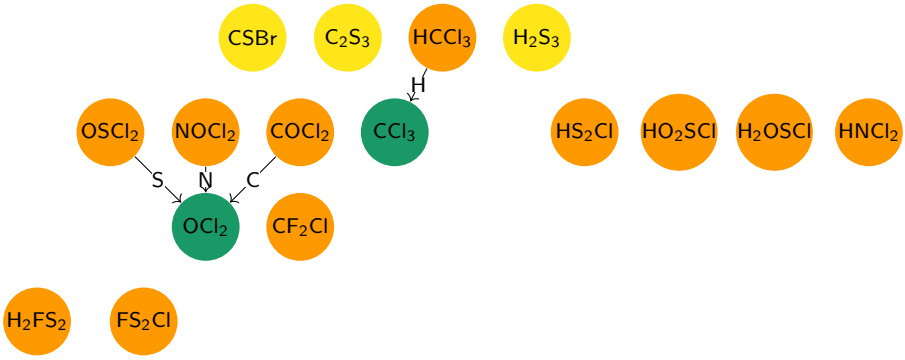
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



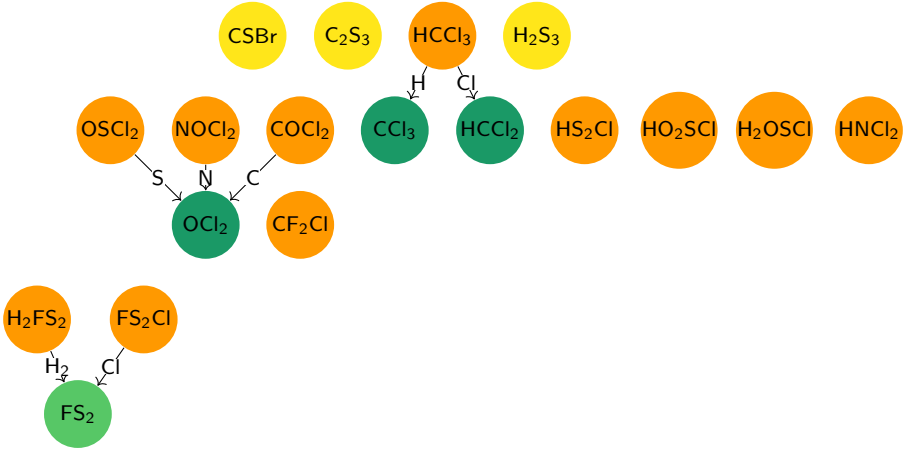
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



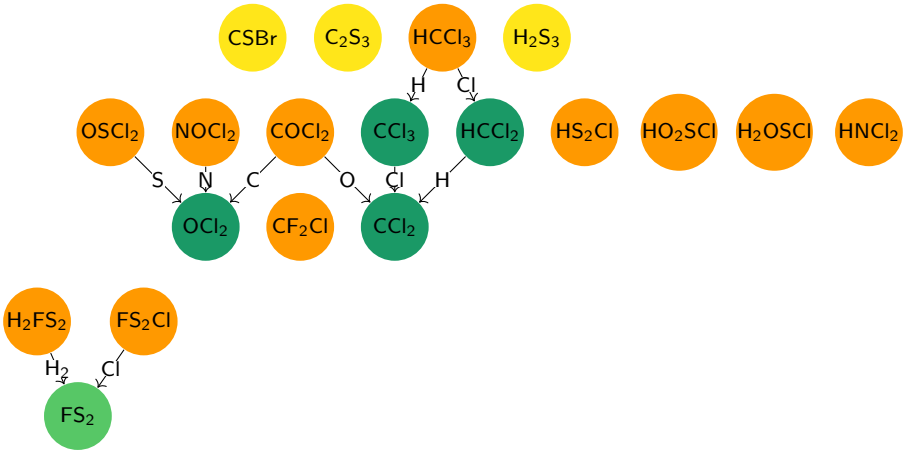
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



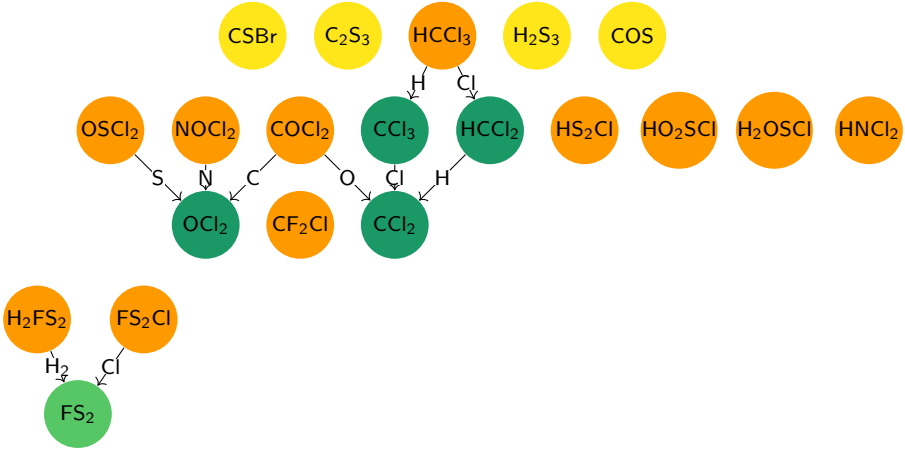
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



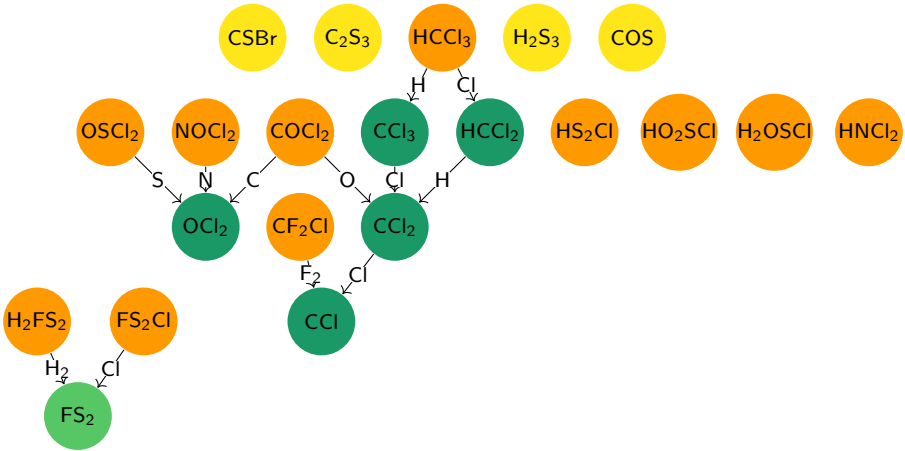
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



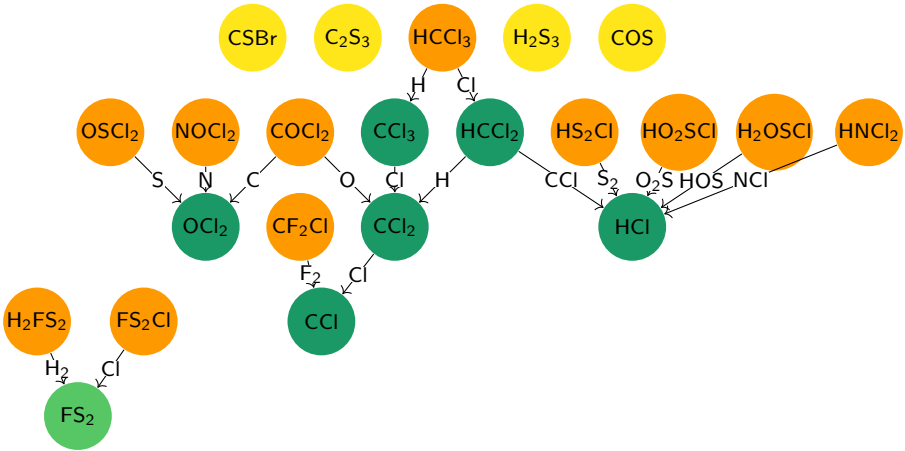
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



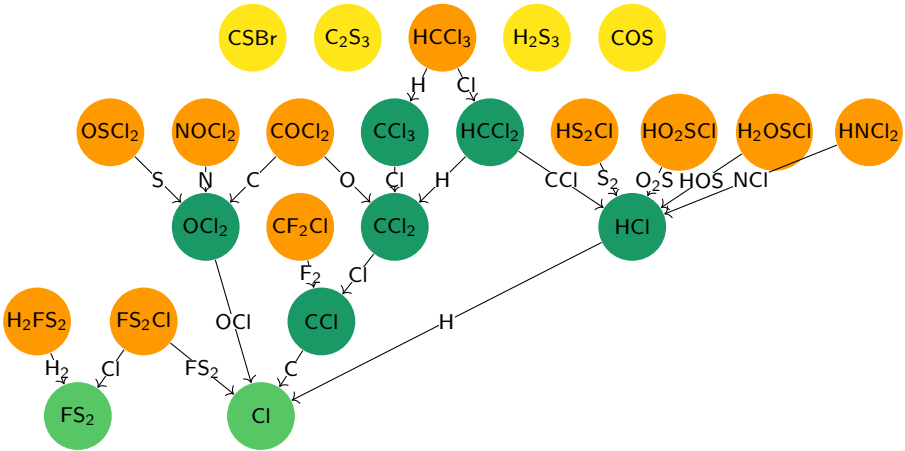
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



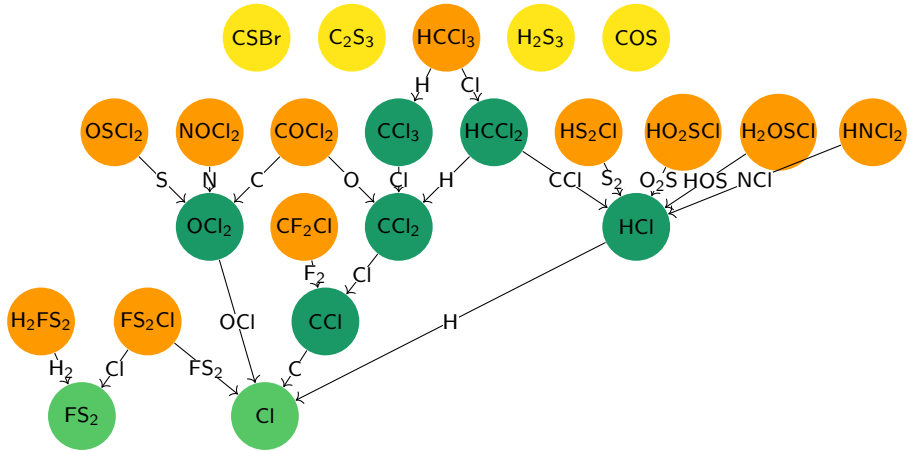
More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.



More about graph algorithms: CCl_4

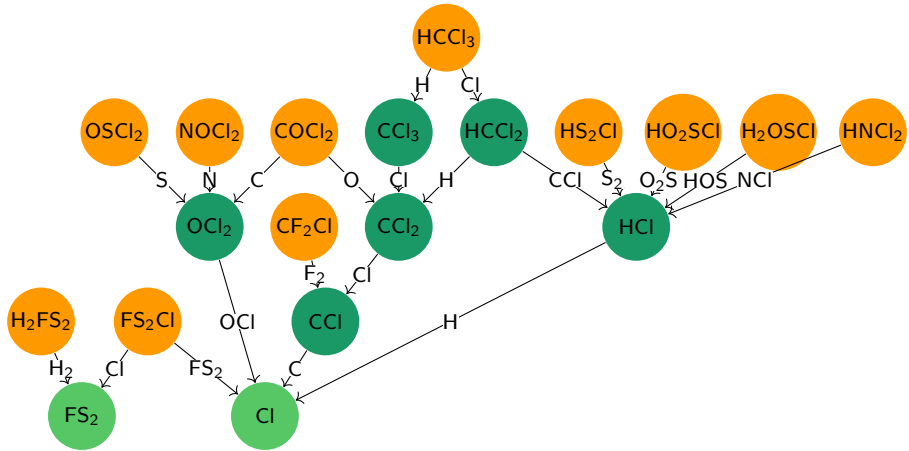
Singleton, Maximal, Node, Leaf.



Remove singletons

More about graph algorithms: CCl_4

Singleton, Maximal, Node, Leaf.

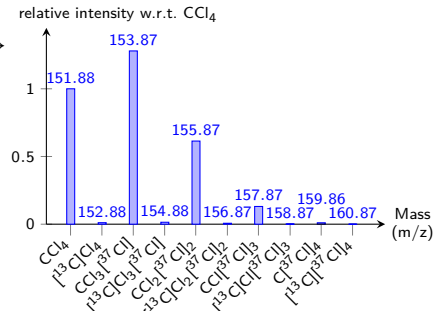


Remove singletons

Optimise isotopic profiles

Aim: eliminate all unlikely candidate formlas.

1. Compute the intensity profile of isotopocules →
2. Define a likelihood estimator
3. Fit the theoretic intensities to the measured signal (next slide)
4. Update pseudo-frag graph:
   Remove candidate formulas below LOD (limit of detection)
   Remove new singletons



Workflow: optimise isotopic ‘profiles’

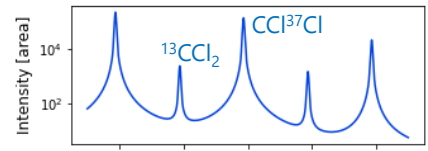
Empa
Materials Science and Technology

knapsack

Isotopologue profiles

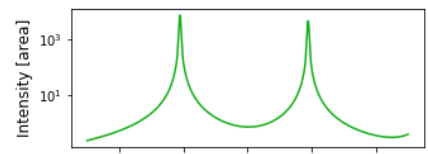
Python
lmfit

CCl_2^+



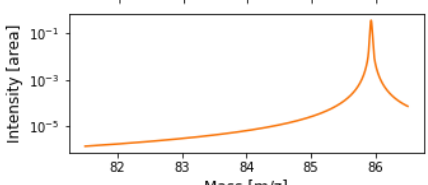
$\cdot k_1$

$HCCl_2^+$



$\cdot k_2$

OCl_2^+



$\cdot k_3$

Workflow: optimise isotopic ‘profiles’

Empa
Materials Science and Technology

knapsack

Isotopologue profiles

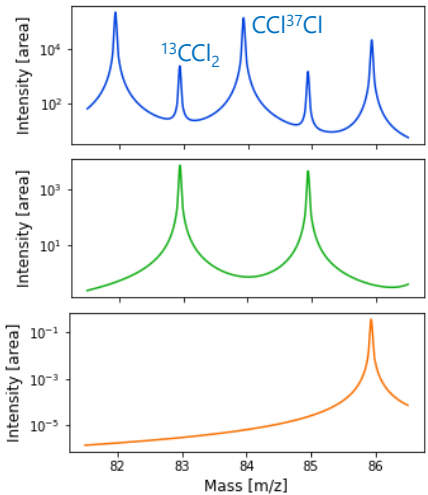
Python lmfit

Optimised contributions

CCl_2^+

$HCCl_2^+$

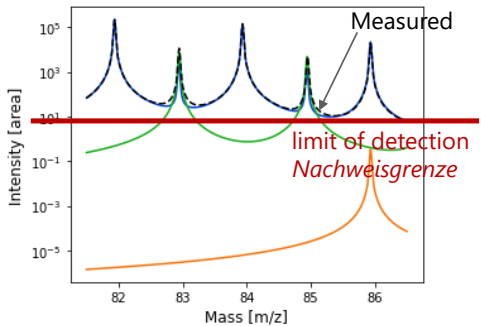
OCl_2^+



$\cdot k_1$

$\cdot k_2$

$\cdot k_3$



Workflow: optimise isotopic ‘profiles’

Empa
Materials Science and Technology

knapsack

Isotopologue profiles

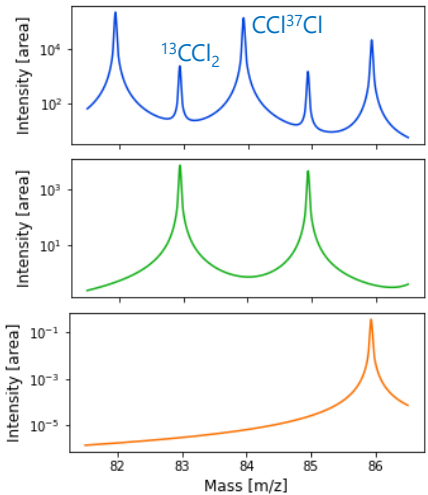
Python lmfit

Optimised contributions

CCl_2^+

$HCCl_2^+$

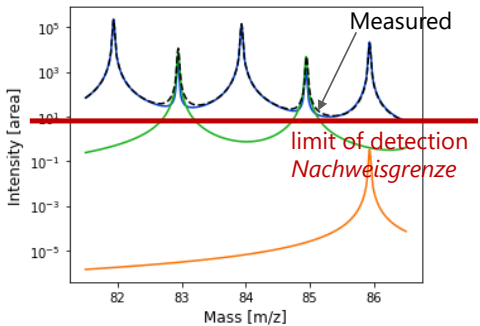
~~CCl_2^+~~



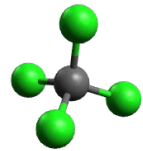
$\cdot k_1$

$\cdot k_2$

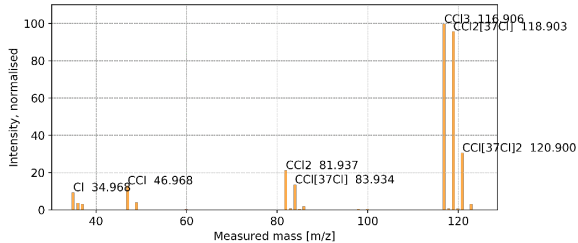
$\cdot k_3$



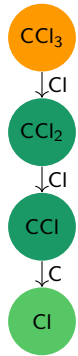
Results – example for CCl_4



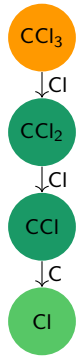
- 19 measured masses
- 23 knapsack solutions using C, H, N, O, S, F, Cl, Br, I
- 3 singletons removed
- 2 solutions < LOD
- 98% correctly assigned signal
- Runtime: 4 s on a laptop



Result: final graph for CCl_4

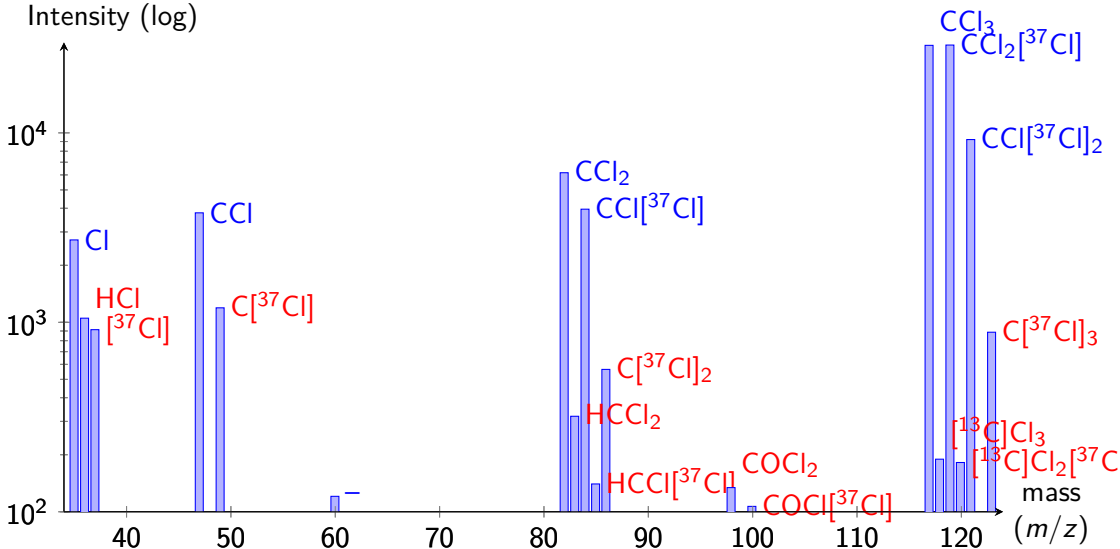


Result: final graph for CCl_4



Molecular Ion CCl_4 not in the graph!!!

In 40% of measured samples, the molecular ion is not measured (due to the Electron Ionisation technique)


Intensity (log)
10^4
10^3
10^2
Cl
HCl
$[^{37}Cl]$
CCl
$C[^{37}Cl]$
CCl_2
$CCl[^{37}Cl]$
$C[^{37}Cl]_2$
$HCCl_2$
$HCCl[^{37}Cl]$
$COCl_2$
$COCl[^{37}Cl]$
CCl_3
$CCl_2[^{37}Cl]$
$CCl[^{37}Cl]_2$
$C[^{37}Cl]_3$
$[^{13}C]Cl_3$
$[^{13}C]Cl_2[^{37}Cl]$
40
50
60
70
80
90
100
110
120
mass
(m/z)

Field work at Jungfraujoch, 3500m

https://www.empa.ch/web/s604/jungfraujoch-bauarbeiten

Validation of the results

More than 75 newly identified substances in Dübendorf air.

1. Buy the suspected substances on catalog
2. Measure with the same machine and same settings
3. Check Retention Time (RT), and mass spectra: peaks at same masses, same proprtion of peak intensities

24 subtances validated so far.

Issues:

- unavailable substances (exist, but cannot buy them on catalog)
- too toxic for shipping
- too costly ($1000/5g) (our threshold cost: $750/5g)
- all are banned substances
- special authorization from Ministry of Environment for customs department

Future Work

Solve the knapsack problem with LLL?

- François Morain says it will work
- Paul Zimmermann says it will work
- Léo Ducas says it will work

It's only a question of time and human resources...

Conclusion

Fruitful collaboration between computer-scientist and environmental science researchers and engineers

- learned about chemistry
- learned about how to teach CS to senior researchers and engineers
- co-authors learned about algorithms, Python programming, software architecture, and development tools (git)

Python source code released on June 30, 2021 with LGPL license at
`https://gitlab.inria.fr/guillevi/alpinac/`
Paper accepted at the Journal of Cheminformatics
Preprint at `https://hal.inria.fr/hal-03176025`

EMPA will be looking to hire a computer scientist.