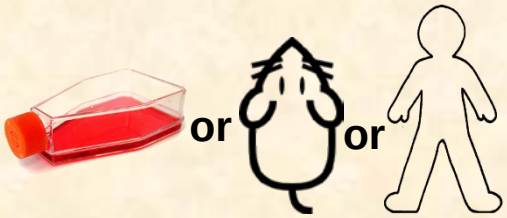
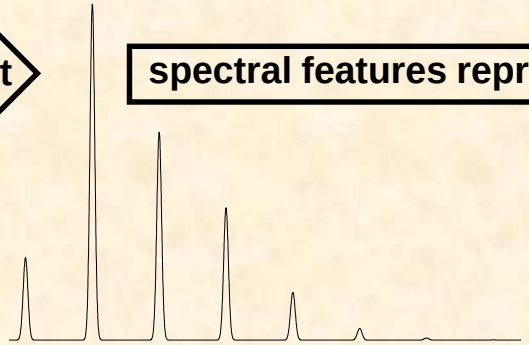
The Spectral Feature Annotation Problem



or or or ???

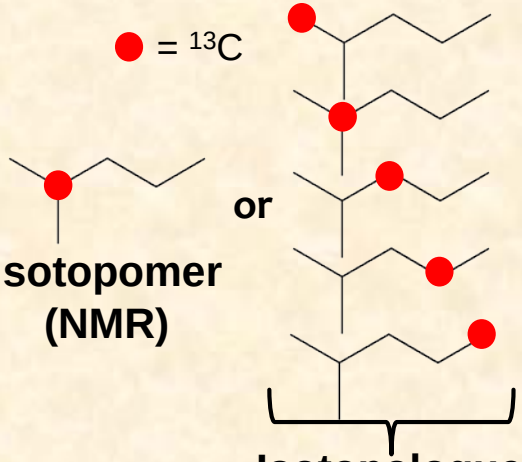
Stable Isotope Tracing Experiment

collect



Analytical Data

spectral features represent



Isotopomer (NMR)

or

Isotopologue (MS)

annotate

What should this annotation representation be?

Compact Annotation Representation

download

Metabolomics Workbench
MetaboLights
another public repository

deposit

Compact Annotation Representation

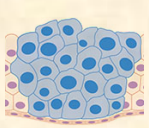
convert

```
C 1 0 0 0 0
1 C 1 1 0 0
0 1 C 0 0 0
0 1 0 C 1 0
0 0 0 1 C 1
0 0 0 0 1 C
```

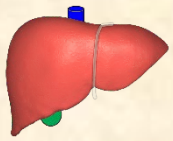
Isotope-Resolved Molecular Representation

reanalyze

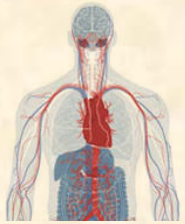
derive



or



or



New Biological Interpretation

Restating the Problem

How do we annotate spectral features so that computers can accurately represent them as isotopically-resolved chemical entities?

A Solution

Extend the current International Chemical Identifier (InChI) standard for this purpose.

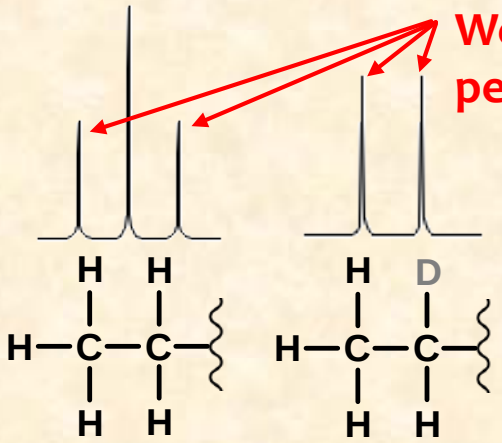
Justification

- **InChI is an open IUPAC standard for representing chemical entities that is widely used, with support from multiple software packages.**
- **Software exists that can convert between InChI and molecular representations like CT/MOL/SDF format.**

Isotopomer Definitions

- **Isotopomer – molecules with identical isotopic composition but differing by the position of isotope.**
  - **Examples:**

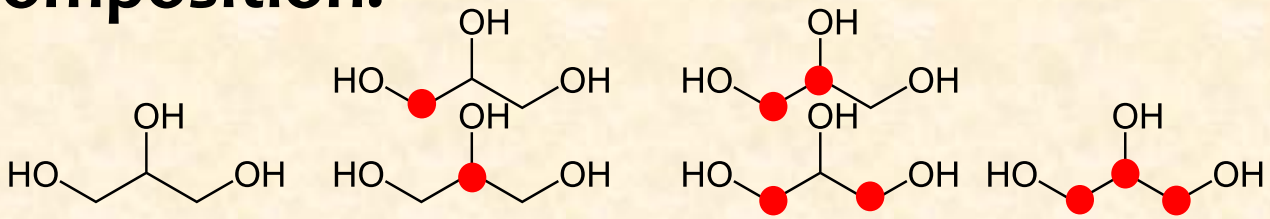
- **Partial Isotopomer - part of an isotopomer where the isotopic content of specific atoms is known.**
  - **In NMR, spin-spin coupling (J-coupling or scalar coupling) can produce peaks that indicate the isotopic status of neighboring atoms.**
  - **Example:**



We need the ability to annotate these peaks in an isotopic informative manner.

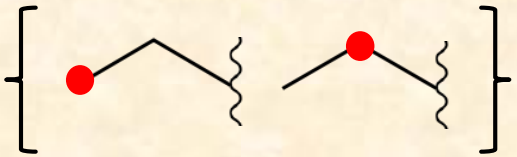
Isotopologue Definitions

- **Isotopologue – set of molecules that differ *only* in their isotopic composition.**

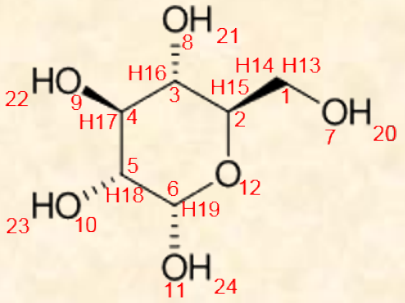


  - **Examples: $^{12}C_3{}^{1}H_8{}^{16}O_3$, $^{12}C_2{}^{13}C_1{}^{1}H_8{}^{16}O_3$, $^{12}C_1{}^{13}C_2{}^{1}H_8{}^{16}O_3$, $^{13}C_3{}^{1}H_8{}^{16}O_3$**

- **Isotopologue Fragment - a refined set of isotopomers where the ambiguity of isotope location is limited to a subset of the atoms.**
  - **Tandem mass spectrometry can provide spectral features that indicate where isotopes are localized within a chemical structure.**
  - **Example:**



The Proposal



alpha-D-glucopyranose

- **Full isotopomer with respect to carbon for alpha-D-glucopyranose with ^{13}C at the 4th carbon:**
  - InChI=1/C6H12O6/c7-1-2-3(8)4(9)5(10)6(11)12-2/h2-11H,1H2/t2-,3-,4+,5-,6+/m1/s1/i1+0,2+0,3+0,4+1,5+0,6+0
- **Partial isotopomer of alpha-D-glucopyranose with ^{13}C at the 1st and 2nd carbons:**
  - InChI=1S/C6H12O6/c7-1-2-3(8)4(9)5(10)6(11)12-2/h2-11H,1H2/t2-,3-,4+,5-,6+/m1/s1/i1+1,2+1
- **$^{13}C_2{}^{2}H_3$ isotopologue of alpha-D-glucopyranose:**
  - InChI=1/C6H12O6/c7-1-2-3(8)4(9)5(10)6(11)12-2/h2-11H,1H2/t2-,3-,4+,5-,6+/m1/s1/a(C2+1)
- **$^{13}C_2$ limited to atoms 4,5,6 isotopologue fragment of alpha-D-glucopyranose:**
  - InChI=1/C6H12O6/c7-1-2-3(8)4(9)5(10)6(11)12-2/h2-11H,1H2/t2-,3-,4+,5-,6+/m1/s1/a(C2+1,4,5,6)

How to Provide Feedback

There are three different ways:

1. Use the following Google Form:
   - https://goo.gl/forms/8lwvLJDae75bKobk2
2. Post an issue on the associated GitHub repository:
   - https://github.com/MSI-Metabolomics-Standards-Initiative/inchi-isotopologue-extension
3. Email the comments.
   - Create a PDF of the full InChI isotopologue proposal (see above links).
   - Mark up the PDF.
   - Email comments to hunter.moseley@gmail.com .

Development Team

- Hunter Moseley - hunter.moseley@gmail.com
- Philippe Rocca-Serra - proccaserra@gmail.com
- Reza Salek - r7salek@gmail.com
- Masanori Arita - masanori.arita@gmail.com
- Emma Schymanski - schymane@gmail.com