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MESSES: Software for Transforming Messy Research Datasets into Clean Submissions to Metabolomics Workbench for Public Sharing

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Abstract: In recent years, the FAIR guiding principles and the broader concept of open science has grown in importance in academic research, especially as funding entities have aggressively promoted public sharing of research products. Key to public research sharing is deposition of datasets into online data repositories, but it can be a chore to transform messy unstructured data into the forms required by these repositories. To help generate Metabolomics Workbench depositions, we have developed the MESSES (Metadata from Experimental SpreadSheets Extraction System) software package, implemented in the Python 3 programming language and supported on Linux, Windows, and Mac operating systems. MESSES helps transform tabular data from multiple sources into a Metabolomics Workbench specific deposition format. The package provides three commands, extract, validate, and convert, that implement a natural data transformation workflow. Moreover, MESSES facilitates richer metadata capture than is typically attempted by manual efforts. The source code and extensive documentation is hosted on GitHub and is also available on the Python Package Index for easy installation.

Keywords: data sharing; dataset deposition; metadata capture; data transformation; Python programming language; Metabolomics Workbench

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1. Introduction

Open science is both a concept and movement to make all research data, products, and knowledge openly accessible by anyone, both promoting collaborative research efforts which can involve professionals, trainees, and non-professionals and improving the evaluation, reproducibility, and ultimately the rigor of the science [1,2]. A fundamental part of open science is the FAIR guiding principles for data management and stewardship, which focuses on making research data Findable, Accessible, Interoperable, and Reusable [3]. And the adoption of FAIR across the scientific community has spearheaded the growth of open science. Within the context of biological and biomedical research involving metabolomics and lipidomics experiments, a major goal of open science is for the resulting metabolomics and lipidomics datasets be deposited in an open data repository like Metabolomics Workbench [4] or MetaboLights [5]. Moreover, new funding agency policies are requiring deposition of research data into open scientific repositories, for example, the new National Institutes of Health (NIH) Data Management and Sharing (DMS) Policy that went into effect 25 January 2023 [6]. This new NIH DMS policy strongly promotes the deposition of "scientific data" into the most appropriate scientific repository, especially NIH-supported repositories like the Metabolomics Workbench.

While deposition of metabolomics and lipidomics datasets has become essential to satisfy both funding agency and publication requirements, there is less focus on the quality of deposition. This is partly due to the significant effort required to produce a high-quality deposition from whichever formats the data and related metadata are currently in. While metabolomics deposition reporting standards exist [7], historically, data repositories have used low deposition requirements and developed their own deposition tools with web interfaces in order to encourage deposition [4,8–11]. Moreover, these deposition tools and web interfaces were developed with the final deposition format in mind rather than the initial formats of the data and related metadata. In most cases, the data and metadata start in a tabular format within one or more spreadsheets, often with minimal organization, which must be converted into an organized format that can be handled by a given deposition system. Thus, the effort to generate a high-quality deposition is often manually intensive and quite demanding.

MESSES stands for Metadata from Experimental SpreadSheets Extraction System and originally was developed as part of a laboratory information management system (LIMS). A LIMS is essentially a database and user interface for storing, organizing, and accessing information needed to manage and document the activities in a lab. This can be inventory information, personnel information, experiment information, etc. Initially, a predecessor of MESSES was created to capture experimental data and related metadata that would go into the relational database of a LIMS. Transforming messy semi- and unstructured experiment data into a form that can be inserted into a relational database faces many of the same challenges as uploading experimental data into an online repository. Over several years, MESSES was improved, expanded, and re-implemented as a standalone package to handle this new use case.

As illustrated in Figure 1, the MESSES package enables the overall capture, validation, and conversion process using three major commands: 'extract', 'validate', and 'convert'. The MESSES 'extract' command is used to transform tabular data into a representative JavaScript Object Notation (JSON) file format using a tagging system. Users provide descriptive 'tags' above data columns that allow MESSES to extract and interpret the data. Once extracted, the data is organized into a JSON representation. Tags can be added manually, but MESSES provides tagging automation methods to easily add tags based on header names present in the tabular data. There are also facilities to modify the data, such as changing names or removing data not needed for a particular deposition.

The 'validate' command evaluates whether the extracted MESSES JSON representation conforms to a specific data schema, i.e., a specific (nested) data structure with specific fieldnames and associated values with specific data types, that is needed for eventual conversion into a deposition format. The command includes sub-commands to assist with creating and validating the schema(s) used for the actual validation.

The 'convert' command is used to convert the MESSES JSON representation into the mwTab JSON and tab-delimited formats. MESSES can handle the heterogeneous mwTab deposition format designed for both nuclear magnetic resonance (NMR) and mass spectrometry generated (MS) datasets. Detailed documentation for installing and using MESSES is available on GitHub and package installation is straight-forward via the Python Package Index.

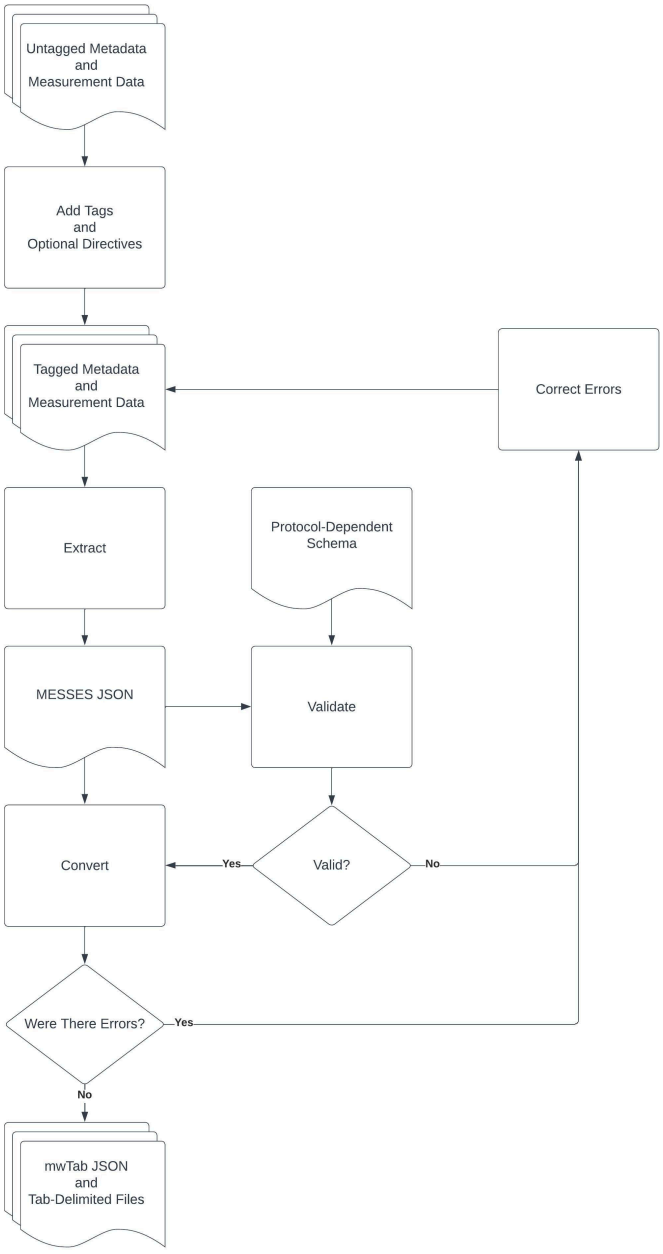


Figure 1. MESSES Overall Workflow Diagram. This includes each of the major steps: Extract, Validate, and Convert, along with error and warning correction steps represented by Correct Errors.

2. Materials and Methods

Figure 1 provides an overview of the data extraction, validation, and conversion workflow enabled by MESSES. This workflow starts with metadata and data in tabular format that is extracted into an intermediate MESSES JSON format which is further converted into the final mwTab deposition formats. However, the process is not expected to be error free in the beginning and MESSES provides warning and error feedback for the user at each step, especially the validation step, enabling an error correcting workflow.

2.1. Third Party Packages

MESSES leverages many third-party Python libraries and packages to accomplish its major tasks. MESSES uses the docopt library [12] to implement a command line interface (CLI) from a Python docstring description. Next, MESSES uses the jsonschema library to validate user JSON input against an expected schema generated by MESSES in JSON Schema format. JSON Schema is a declarative schema language for describing an

expected data schema for the purpose of validating and annotating JSON representations of structured data [13,14]. JSON Schema is developed under an OpenJS Foundation [15] project with incubation status and an active growing community of users. MESSES uses the jsonschema library to perform the lion's share of the validate command as well as to validate user input in the convert command. The submodules validate_schema.py and convert_schema.py include specific subschemas and schema templates used to generate final schemas for validation. The Protocol Dependent Schema (PD schema) and Experiment Description Specification base schema (EDS base schema) provide the bulk of the final integrated schema in JSON Schema format that is used for validation via the jsonschema library.

MESSES uses a collection of packages to work with tabular data. Specifically, pandas [16], numpy [17], and openpyxl [18] are all used to work with tabular data. The pandas package is used for reading and writing, numpy is used for optimized data access, and openpyxl and xlsxwriter are used by pandas to write Excel files. To implement matching by Levenshtein distance, the jellyfish package is used. The Cython package [19] is used to optimize and speed up some algorithms implemented with Cython language extensions that enable translation to C++ code and compilation to a compiled importable submodule. The mwtab package [8,20] is used to convert mwTab JSON format to the mwTab tab-delimited format, both developed by the Metabolomics Workbench. A list of packages and their versions are in Table 1.

Table 1. Library dependencies for MESSES.

Package	Version	Utilization	PyPI URL [a]
docopt	0.6.2	Implement CLI.	https://pypi.org/project/docopt/
jsonschema	3.0.1	Validate JSON files.	https://pypi.org/project/jsonschema/
pandas	0.24.2	Read and write tabular files.	https://pypi.org/project/pandas/
numpy	1.22.4	Optimize tabular data algorithms.	https://pypi.org/project/numpy/
openpyxl	2.6.2	Write Excel files.	https://pypi.org/project/openpyxl/
xlsxwriter	3.0.3	Write Excel files.	https://pypi.org/project/xlsxwriter/
jellyfish	0.9.0	Calculate Levenshtein distance.	https://pypi.org/project/jellyfish/
Cython	3.0.0a11	Optimize algorithms.	https://pypi.org/project/Cython/
mwtab	1.2.5	Create mwTab formatted files.	https://pypi.org/project/mwtab/

[a] Accessed on 1 January 2023.

2.2. Package Organization and Module Description

Although MESSES is primarily designed to be a command line tool, it does provide an equivalent application programming interface (API), which can be utilized if so desired. A high-level CLI that serves as an entry-point to each command is implemented in the __main__.py submodule, but each command implements its own CLI as well. Each command, extract, validate, and convert, are in their own module. The extract module contains the extract.py submodule that implements the entire extract command, with the addition of a cythonized submodule that optimizes a part of the code for the extract command. The heart of the extract module is a tag parser that identifies pound-delimited tags which direct the extraction of data from tabular files as tags and associated data are parsed.

The validate module contains the validate.py submodule that implements the validate command and the validate_schema.py submodule that simply holds the built-in schemas and schema templates in JSON Schema format for the command. The convert module is broken into more pieces. The convert.py submodule implements the convert command, the convert_schema.py submodule holds the schemas and schema templates in JSON Schema format for the command, the user_input_checking.py submodule validates conversion directives, and there are submodules for the built-in conversion directives and specific code for each supported conversion format. Table 2 lists the submodules of MESSES, Figure 2 shows a module diagram, and Figure A1 shows a directory tree of the source code.

Table 2. Submodules of MESSES.

Submodule	Description
__main__.py	Contains the top-most CLI.
extract.py	Implements the extract command and CLI.
cythonized_tagSheet.pyx	Cythonized version of the tagSheet method for extract.
validate.py	Implements the validate command and CLI.
validate_schema.py	Contains the JSON Schema schemas used by the validate command.
convert.py	Implements the convert command and CLI.
convert_schema.py	Contains the JSON Schema schemas used by the convert command.
user_input_checking.py	Validates conversion directives for the convert command.
mwtab_conversion_directives.py	Contains the built-in conversion directives for the mwTab format.
mwtab_functions.py	Contains functions specific to creating the mwTab format.

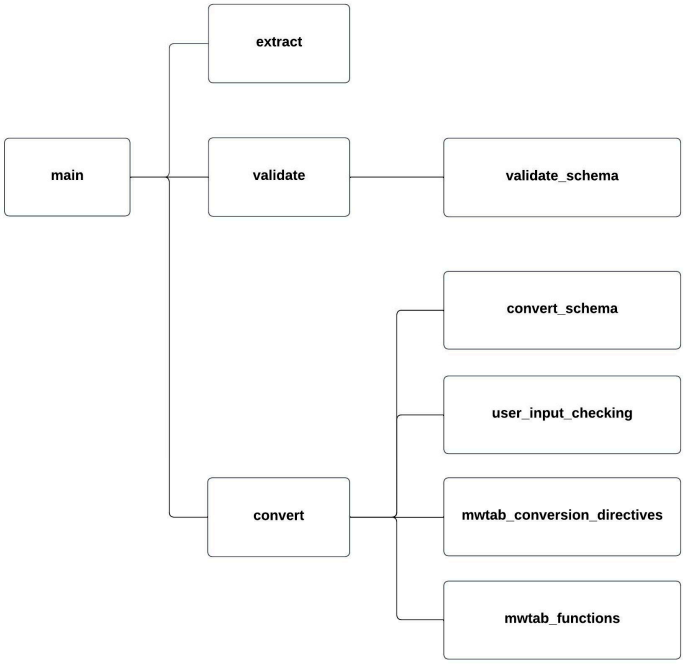


Figure 2. MESSES Module Diagram. Submodule and module dependencies are illustrated by connecting lines.

2.3. Tagging System

In order to extract organized data from arbitrarily placed and organized data tables within a spreadsheet in a programmatic way, some kind of system has to be devised. This could be something as simple as requiring a given data table be on the very first sheet row and for the starting row to have column names for every column or columns in a certain order; however, this type of implementation would be very fragile. Therefore, we decided to create a more robust system that could handle more complicated and/or arbitrary data arrangements and reduce the verbosity to a minimum. The system we devised uses an extra layer of tags inserted into an existing data spreadsheet at specific locations that tell the extract command how to transform the data sections of the sheet (i.e., data tables) into key-based records representable in both JSON format and a relational database.

This initial system served its function well, but it became clear that more functionality was sorely needed: (i) a way to programmatically add tags to sections of tabular data within a sheet and (ii) a way to modify field values. So, the system was expanded to provide facilities to do both. Ultimately, there are three parts to the tagging system that are distinct from one another but have similar syntax and ideas. The "export" part involves "export" tags that are directly inserted into an existing sheet before a section of tabular data. It is the base system that must be used for the extraction to work at all. The "automation" part

is used to automate adding "export" tags to tabular data. Based on the header values in your data, you can use "automation" tags to insert (add) the "export" tags automatically. A good use case for automation is when you have data generated by a program in a consistent way. Instead of manually adding export tags to the program output each time, you can create an "automation" spreadsheet that will add the "export" tags for you. The last "modification" part is used to modify record values. It can be used to prepend, append, delete, overwrite, or regex substitute values. An example use-case would be to update old naming conventions. Validly tagged files in their tabular or JSON form can be referred to as directives as they direct the extraction (automate, export, and modify) actions of MESSES. To reduce confusion between tags and directives, "tags" generally refer to the extra text added above a specific table, while "directives" are the tags and the associated table taken as a whole. Each row of a tagged table is an individual directive.

Each part of the tagging system must be in their own sheet or file for the extract command. By default, export tags are expected in a sheet named '#export', if given an Excel file without specifying a sheet name. If given a CSV file, then this file is expected to have export tags. Modification tags are expected in a sheet named '#modify' by default but can be specified using the --modify option. The option is very flexible and can be used to specify either a different sheet name in the given Excel file, a different Excel file, a different Excel file with a different sheet name, a Google Sheets file, a Google Sheets file with a different sheet name, a JSON file, or a CSV file. Automation tags are similarly specified using the --automate option or otherwise expected in a sheet named '#automate' by default. More detailed descriptions and examples of the tagging system can be found in the package documentation.

2.4. MESSES JSONized Data and Metadata Representation

The data schema developed for MESSES was designed to capture generalized experimental descriptions and data in an abstract way. To handle the arbitrary number of fields that widely varying experimental datasets would have, the schema supports multiple integrated entity–attribute–value (EAV) models. It is organized into several tables with a unique record identifier and a flexible collection of fields, with certain fields having a descriptive attribute relationship with another field. Note that we use the term "table" to refer to the JSON object of the same name. A "record" would be a named element inside a "table", which would normally correspond to a row in a spreadsheet table. A "field" would be a named element inside a "record", which would normally correspond to a column in a spreadsheet table.

There are 6 tables: project, study, protocol, entity, measurement, and factor.

- A project generally refers to a research project with multiple analytical datasets derived from one or more experimental designs.
    - The project table entries would have information about the project, such as PI contact information and a description of the project.
- A study is generally one experimental design or analytical experiment inside of the project.
    - The study table entries would have information about each study, such as PI contact information and a description of the study.
- A protocol describes an operation or set of operations done on a subject or sample entity.
    - The protocol table entries would have information about each protocol, such as a description of the procedure and details about the equipment used.
- Entities are either subjects or samples that were collected or experimented on.
    - The entity table entries would have information about each entity, such as sex and age of a subject or weight and units of weight of a sample. These latter examples demonstrate a descriptive attribute relationship between the weight

field and the units of weight field typically indicated by 'weight%unit' used as the field name for units of weight.

- A measurement is typically the results acquired after putting a sample through an assay or analytical instrument such as a mass spectrometer or nuclear magnetic resonance spectrometer as well as any data calculation steps applied to raw measurements to generate usable processed results for downstream analysis.
  - The measurement table entries would have information about each measurement, such as intensity, peak area, or compound assignment.
- A factor is a controlled independent variable of the experimental design. Experimental factors are conditions set in the experiment. Other factors may be other classifications such as male or female gender.
  - The factor table entries would have information about each factor, such as the name of the factor and the allowed values of the factor.

Figure 3 shows a lean example MESSES JSON with all of the tables, and Table 3 summarizes the descriptions and entry information for table entries.



Figure 3. MESSES JSON Tables Example. Ellipses indicate that there could be more fields or records, while arrows point to records or fields that a field is referencing.

Table 3. MESSES JSON Table Entry Summary. The "Entry Information" column is not exhaustive and simply presents examples of what kinds of information could be associated with each entry.

Table	Entry Description	Entry Information
project	A research project with multiple analytical datasets derived from one or more experimental designs.	PI Name PI Contact Information Institution Name Address Department Description Title

Table 3. *Cont.*

Table	Entry Description	Entry Information
protocol	An operation or set of operations done on a subject or sample entity.	Description Type Instrument Settings Instrument Information Software Settings Software Information Data Files Generated File Detailing Protocol
entity	Either subjects or samples that were collected or experimented on.	Type Weight Sex Protocols Underwent Parent Entity Experimental Factor
measurement	The results acquired after putting a sample through an assay or analytical instrument such as a mass spectrometer or nuclear magnetic resonance spectrometer as well as any data calculation steps applied to raw measurements to generate usable processed results for downstream analysis.	Measurement Protocol Measurements Acquired Associated Entity Calculations or Statistics Labels Obtained from Measurements
factor	A controlled independent variable of the experimental design. Conditions set in the experiment. May be other classifications such as male or female gender.	Discrete Values of the Factor Units of the Values Name of Factor Field Name of Factor

There are additional constraints within the tables. Protocols must be one of five types: treatment, collection, sample_prep, measurement, or storage.

- A treatment protocol describes the experimental factors performed on subject entities.
    - For example, if a cell line is given 2 different media solutions to observe the different growth behavior between the 2, then this would be a treatment type protocol.
- A collection protocol describes how samples are collected from subject entities.
    - For example, if media is taken out of a cell culture at various time points, this would be a collection protocol.
- A sample_prep protocol describes operations performed on sample entities.
    - For example, once the cells in a culture are collected, they may be spun in a centrifuge or have solvents added to separate out protein, lipids, etc.
- A measurement protocol describes operations performed on samples to measure features about them.
    - For example, if a sample is put through a mass spectrometer or into an NMR.
- A storage protocol describes where and/or how things (mainly samples) are stored.
    - This was created mostly to help keep track of where samples were physically stored in freezers or where measurement data files were located on a share drive.

Another constraint involves how subjects and samples inherit or derive from each other.

- If a sample comes from a sample, it must have a sample_prep type protocol.
- If a sample comes from a subject, it must have a collection type protocol.
- Subjects should have a treatment type protocol associated with it.

2.5. Testing

The MESSES package was originally developed in a Linux operating system (OS) environment but has been directly tested on Linux, Windows, and MacOS operating systems. Each module and submodule include unit-tests that test all critical functions. Every function in every module is tested to make sure it gives the expected output when it should and errors when it should. Every command and associated command line option are tested, for example, the update and override options for the convert command. Testing is automated using GitHub Actions. Total testing code coverage for the MESSES package is above 90%.

3. Results

3.1. The Command Line Interface and Overall Metabolomics Workbench Deposition Workflow

The MESSES CLI has a delegated implementation. In other words, there are four separate CLIs, one for each command and one main CLI. The main CLI serves as a gateway to the three commands that perform the bulk of the work and have their own CLIs. Once installed, a call to "messes --help" in the system terminal will show the gateway CLI, and calls to "messes [command] --help" will show the CLI for the selected command. Figures 4, A2–A4 show the main CLI, the extract CLI, the validate CLI, and the convert CLI, respectively.

```
MESSES Command-Line Interface
  The MESSES package has functionality to extract data, validate data, and convert data to other formats for deposition into public
repositories.

Online Documentation: https://moseleybioinformaticslab.github.io/messes/

Usage:
  messes -h | --help     print this screen.
  messes --full-help     help documentation on all commands.
  messes --version       print the version.
  messes extract ...     extract data from Excel workbooks, csv files, and JSON.
  messes validate ...    validate JSON files.
  messes convert ...     convert JSON to other file formats.

For help on a specific command, use the command option -h or --help.
For example:
  messes extract --help   for help documentation about the extract command.
```

Figure 4. MESSES main Command Line Interface (CLI). The extract, validate, and convert commands represent distinct steps in the overall MESSES workflow.

The MESSES CLI was designed with a great deal of flexibility, anticipating users' desire to use the software in unpredictable ways. However, Figure 1 illustrates the overall workflow, using the three main commands with the intention of creating a deposition to Metabolomics Workbench. Starting from the assumption that all data files are untagged, the first step would be to add tags to the data so it will be exported into the MESSES JSON format correctly. Tags can be added manually or with automation directives used by the extract command (i.e, tagging step). Modification directives can also be used to modify the data as necessary for tasks such as renaming. Once tagged, the extract command extracts and exports the (meta)data into a MESSES JSON file. You may have to fix some errors if you have malformed tags or directives. Next, take the exported MESSES JSON file and deliver it to the validate command. It is recommended to use the --format option and specify "mwtab". It is also recommended to create a protocol-dependent schema and use the --pds option with the schema to perform additional validation. A protocol-dependent schema is provided in the Supplementary Materials. There will likely be warnings and errors after running the validate command, and they should be corrected in the data. After

correcting the errors and warnings, re-export the MESSES JSON with the extract command and re-validate with the validate command until there are no more errors or warnings of concern. Once the MESSES JSON file validates with no errors or warnings, deliver it to the convert command. Use the mwtab sub-command and select the appropriate machine type for your data, ms, nmr, or nmr_binned. The convert command should output a mwTab JSON and tab-delimited file. But even with a clean validation, it is still possible to have some errors that prevent conversion. If there are errors, correct them and start from the extraction step again.

3.2. Creation of an Example Mass Spectrometry Deposition

We demonstrate the capabilities of MESSES with a paired down example based on an ion chromatography Fourier transform mass spectrometry (IC-FTMS)-targeted metabolomics dataset of mouse colon tissue already deposited into Metabolomics Workbench Study ST001447 [21] using an earlier prototype of MESSES. Although this dataset was previously uploaded using an earlier version of MESSES, what is demonstrated here is using the latest version. This demonstration walks through the (meta)data extraction from Excel spreadsheets, JSON validation, and conversion steps to produce a deposition-compliant dataset in both the mwTab JSON and tab-delimited formats. Note that the figures below are general truncated examples. There are full examples with package commands and description that transform real datasets, available in the supplemental materials and in the examples directory of the GitHub repository.

3.2.1. Extraction from Spreadsheets

Figure 5 shows screenshots of the executed command and directory of files when running the extract command. The metadata Excel spreadsheet has metadata for several tissues besides colon, which are removed with the '--delete' option. Likewise, certain unrelated protocols (acetone_extraction and lipid_extraction) involving other related analytical measurements are likewise removed. Figures 6 and 7 show screenshots of the metadata and measurement data Excel files used with the extract command, respectively. Note that the "#export" sheet is what the command will use by default. Figure 6 shows the original sheet with its formatting and tags added, but the "#export" sheet is a copy that removes formatting. Figures 8 and 9 show screenshots of the automation and modification tags for the measurement data in separate '#automate' and '#modify' sheets, respectively. The automation tags are used to add export tags internally and the "#export" spreadsheet created can be saved out using the --save-export option. The modification tags are used to modify the data after it has been extracted from the spreadsheet to a JSONized form. Figure 10 shows portions of the extracted JSON organized in separate JSON objects which are represented as dictionaries in Python. The 'entity' dictionary describes individual subjects (mice in this instance) and individual samples derived from the subjects. The 'factor' dictionary describes the experimental design in terms of individual experimental factors. The 'protocol' dictionary describes individual protocols used in the experiment. The 'measurement' dictionary describes individual peak measurements derived from an IC-FTMS spectrum collected per sample. The 'project' and 'study' dictionaries describe the research project and specific study performed, including the contact and institution that the deposition comes from.

Command Line Interface:

```
C:\extract>messes extract mouse_experiment_metadata.xlsx MS_colon_measurements.xlsx --output extracted_result --silent --delete "entity,r'^(?!.*(-ICMS_A|-protein|\d$))|.*Plasma|Liver|Spleen|SI|Lung.*'" --delete "protocol,acetone_extraction" --delete "protocol,lipid_extraction"
```

Output Directory:

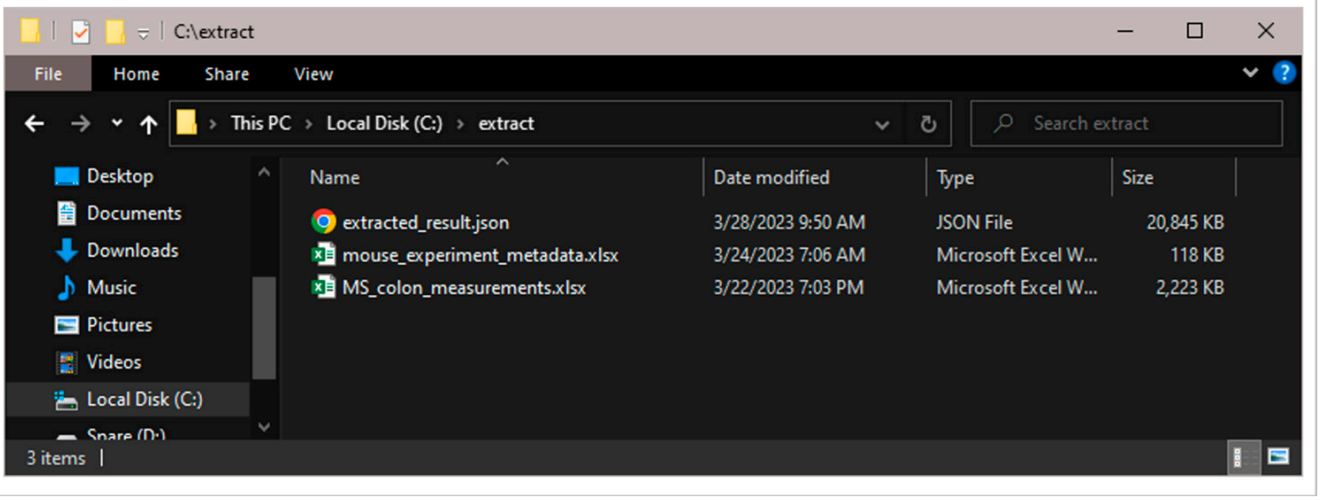


Figure 5. Example execution of the extract command in a Windows Command Prompt. The resulting output directory is shown in the Windows folder at the bottom.

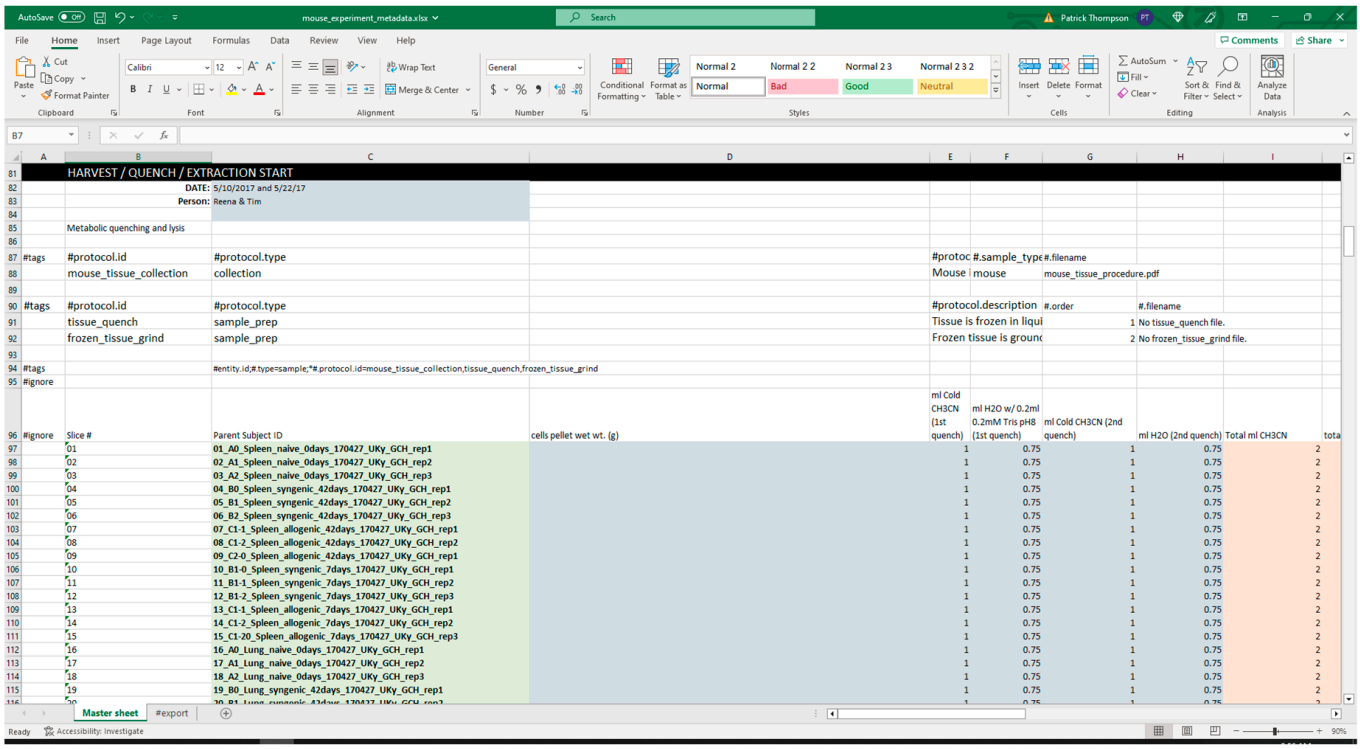
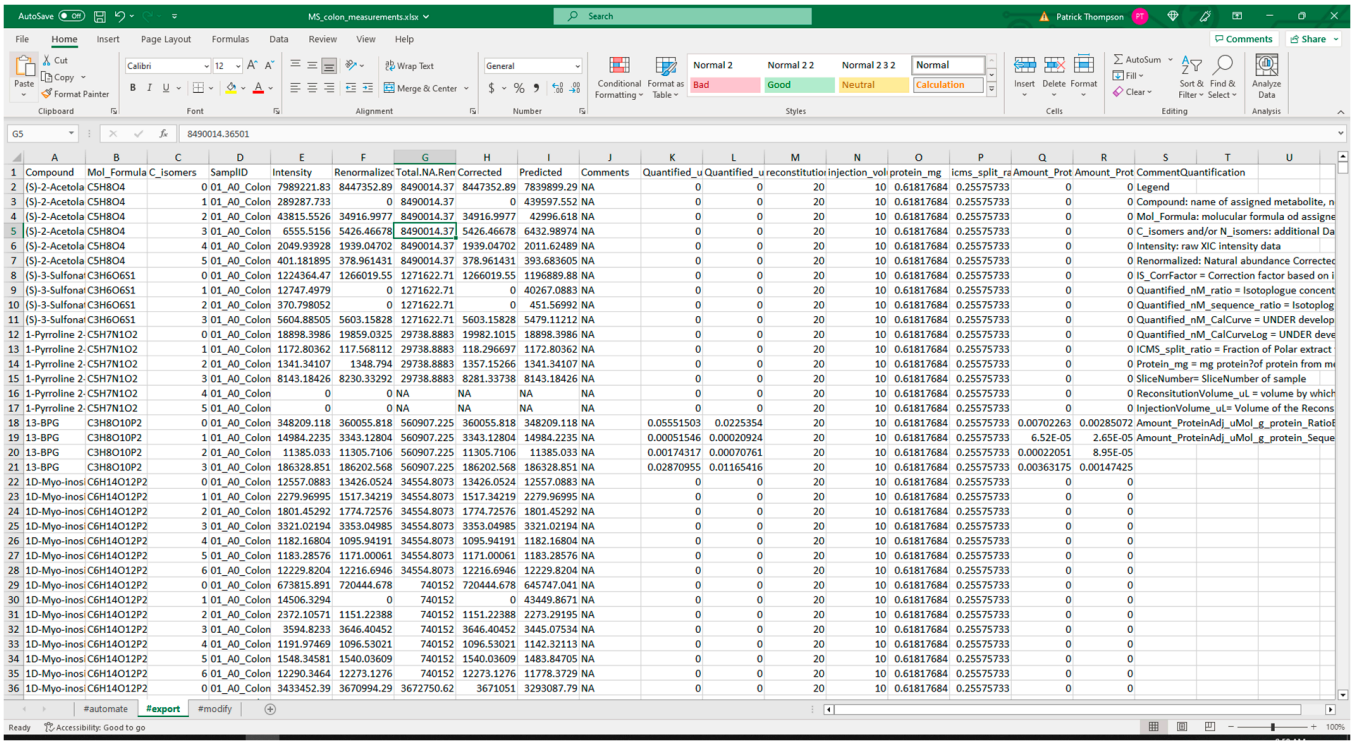
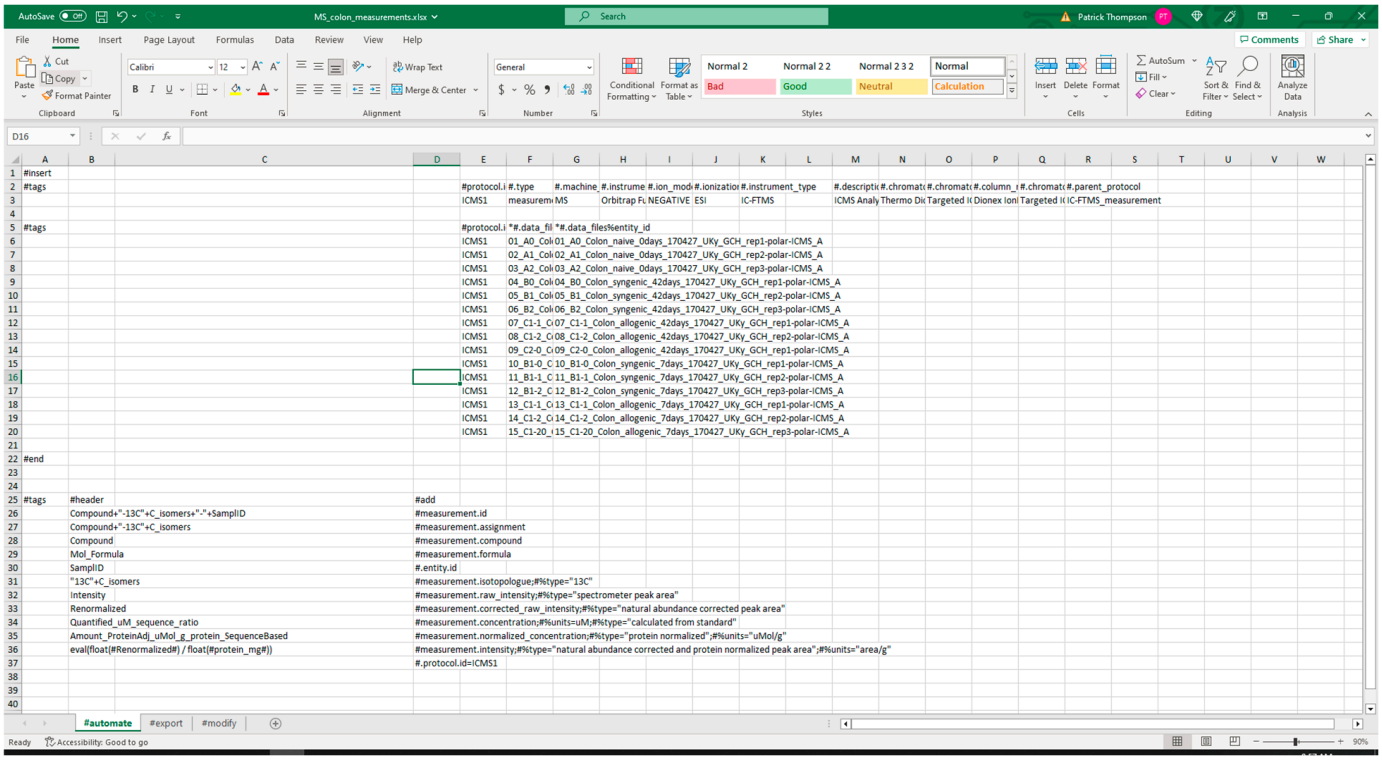


Figure 6. Screenshot of a portion of the metadata spreadsheet used with the extract command.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
1	Compound	Mol_Formula	C_isomers	SamplID	Intensity	Renormalizec	Total.NA.Rem	Corrected	Predicted	Comments	Quantified_u	Quantified_u	reconstitutior	injection_vol	protein_mg	icms_split_ra	Amount_Prot	Amount_Prot	CommentQuantification		
2	(S)-2-Acetola	C5H8O4	0	01_A0_Colon	7989221.83	8447352.89	8490014.37	8447352.89	7839899.29	NA	0	0	20	10	0.61817684	0.25575733	0	0	Legend		
3	(S)-2-Acetola	C5H8O4	1	01_A0_Colon	289287.733	0	8490014.37	0	439597.552	NA	0	0	20	10	0.61817684	0.25575733	0	0	Compound: name of assigned metabolite, n		
4	(S)-2-Acetola	C5H8O4	2	01_A0_Colon	43815.5526	34916.9977	8490014.37	34916.9977	42996.618	NA	0	0	20	10	0.61817684	0.25575733	0	0	Mol_Formula: molucular formula od assigne		
5	(S)-2-Acetola	C5H8O4	3	01_A0_Colon	6555.5156	5426.46678	8490014.37	5426.46678	6432.98974	NA	0	0	20	10	0.61817684	0.25575733	0	0	C_isomers and/or N_isomers: additional Da		
6	(S)-2-Acetola	C5H8O4	4	01_A0_Colon	2049.93928	1939.04702	8490014.37	1939.04702	2011.62489	NA	0	0	20	10	0.61817684	0.25575733	0	0	Intensity: raw XIC intensity data		
7	(S)-2-Acetola	C5H8O4	5	01_A0_Colon	401.181895	378.961431	8490014.37	378.961431	393.683605	NA	0	0	20	10	0.61817684	0.25575733	0	0	Renormalized: Natural abundance Correctec		
8	(S)-3-Sulfona	C3H6O6S1	0	01_A0_Colon	1224364.47	1266019.55	1271622.71	1266019.55	1196889.88	NA	0	0	20	10	0.61817684	0.25575733	0	0	IS_CorrFactor = Correction factor based on i		
9	(S)-3-Sulfona	C3H6O6S1	1	01_A0_Colon	12747.4979	0	1271622.71	0	40267.0883	NA	0	0	20	10	0.61817684	0.25575733	0	0	Quantified_nM_ratio = Isotoplogue concent		
10	(S)-3-Sulfona	C3H6O6S1	2	01_A0_Colon	370.798052	0	1271622.71	0	451.56992	NA	0	0	20	10	0.61817684	0.25575733	0	0	Quantified_nM_sequence_ratio = Isotoplog		
11	(S)-3-Sulfona	C3H6O6S1	3	01_A0_Colon	5604.88505	5603.15828	1271622.71	5603.15828	5479.11212	NA	0	0	20	10	0.61817684	0.25575733	0	0	Quantified_nM_CalCurve = UNDER develop		
12	1-Pyrroline 2	C5H7N1O2	0	01_A0_Colon	18898.3986	19859.0325	29738.8883	19982.1015	18898.3986	NA	0	0	20	10	0.61817684	0.25575733	0	0	Quantified_nM_CalCurveLog = UNDER deve		
13	1-Pyrroline 2	C5H7N1O2	1	01_A0_Colon	1172.80362	117.568112	29738.8883	118.296697	1172.80362	NA	0	0	20	10	0.61817684	0.25575733	0	0	ICMS_split_ratio = Fraction of Polar extract		
14	1-Pyrroline 2	C5H7N1O2	2	01_A0_Colon	1341.34107	1348.794	29738.8883	1357.15266	1341.34107	NA	0	0	20	10	0.61817684	0.25575733	0	0	Protein_mg = mg protein?of protein from me		
15	1-Pyrroline 2	C5H7N1O2	3	01_A0_Colon	8143.18426	8230.33292	29738.8883	8281.33738	8143.18426	NA	0	0	20	10	0.61817684	0.25575733	0	0	SliceNumber= SliceNumber of sample		
16	1-Pyrroline 2	C5H7N1O2	4	01_A0_Colon	0	0	NA	NA	NA	NA	0	0	20	10	0.61817684	0.25575733	0	0	ReconsitutionVolume_uL = volume by which		
17	1-Pyrroline 2	C5H7N1O2	5	01_A0_Colon	0	0	NA	NA	NA	NA	0	0	20	10	0.61817684	0.25575733	0	0	InjectionVolume_uL= Volume of the Recons		
18	13-BPG	C3H8O10P2	0	01_A0_Colon	348209.118	360055.818	560907.225	360055.818	348209.118	NA	0.05551503	0.0225354	20	10	0.61817684	0.25575733	0.00702263	0.00285072	Amount_ProteinAdj_uMol_g_protein_RatioB		
19	13-BPG	C3H8O10P2	1	01_A0_Colon	14984.2235	3343.12804	560907.225	3343.12804	14984.2235	NA	0.00051546	0.00020924	20	10	0.61817684	0.25575733	6.52E-05	2.65E-05	Amount_ProteinAdj_uMol_g_protein_Seque		
20	13-BPG	C3H8O10P2	2	01_A0_Colon	11385.033	11305.7106	560907.225	11305.7106	11385.033	NA	0.00174317	0.00070761	20	10	0.61817684	0.25575733	0.00022051	8.95E-05			
21	13-BPG	C3H8O10P2	3	01_A0_Colon	186328.851	186202.568	560907.225	186202.568	186328.851	NA	0.02870955	0.01165416	20	10	0.61817684	0.25575733	0.00363175	0.00147425			
22	1D-Myo-inos	C6H14O12P2	0	01_A0_Colon	12557.0883	13426.0524	34554.8073	13426.0524	12557.0883	NA	0	0	20	10	0.61817684	0.25575733	0	0			
23	1D-Myo-inos	C6H14O12P2	1	01_A0_Colon	2279.96995	1517.34219	34554.8073	1517.34219	2279.96995	NA	0	0	20	10	0.61817684	0.25575733	0	0			
24	1D-Myo-inos	C6H14O12P2	2	01_A0_Colon	1801.45292	1774.72576	34554.8073	1774.72576	1801.45292	NA	0	0	20	10	0.61817684	0.25575733	0	0			
25	1D-Myo-inos	C6H14O12P2	3	01_A0_Colon	3321.02194	3353.04985	34554.8073	3353.04985	3321.02194	NA	0	0	20	10	0.61817684	0.25575733	0	0			
26	1D-Myo-inos	C6H14O12P2	4	01_A0_Colon	1182.16804	1095.94191	34554.8073	1095.94191	1182.16804	NA	0	0	20	10	0.61817684	0.25575733	0	0			
27	1D-Myo-inos	C6H14O12P2	5	01_A0_Colon	1183.28576	1171.00061	34554.8073	1171.00061	1183.28576	NA	0	0	20	10	0.61817684	0.25575733	0	0			
28	1D-Myo-inos	C6H14O12P2	6	01_A0_Colon	12229.8204	12216.6946	34554.8073	12216.6946	12229.8204	NA	0	0	20	10	0.61817684	0.25575733	0	0			
29	1D-Myo-inos	C6H14O12P2	0	01_A0_Colon	673815.891	720444.678	740152	720444.678	645747.041	NA	0	0	20	10	0.61817684	0.25575733	0	0			
30	1D-Myo-inos	C6H14O12P2	1	01_A0_Colon	14506.3294	0	740152	0	43449.8671	NA	0	0	20	10	0.61817684	0.25575733	0	0			
31	1D-Myo-inos	C6H14O12P2	2	01_A0_Colon	2372.10571	1151.22388	740152	1151.22388	2273.29195	NA	0	0	20	10	0.61817684	0.25575733	0	0			
32	1D-Myo-inos	C6H14O12P2	3	01_A0_Colon	3594.8233	3646.40452	740152	3646.40452	3445.07534	NA	0	0	20	10	0.61817684	0.25575733	0	0			
33	1D-Myo-inos	C6H14O12P2	4	01_A0_Colon	1191.97469	1096.53021	740152	1096.53021	1142.32113	NA	0	0	20	10	0.61817684	0.25575733	0	0			
34	1D-Myo-inos	C6H14O12P2	5	01_A0_Colon	1548.34581	1540.03609	740152	1540.03609	1483.84705	NA	0	0	20	10	0.61817684	0.25575733	0	0			
35	1D-Myo-inos	C6H14O12P2	6	01_A0_Colon	12290.3464	12273.1276	740152	12273.1276	11778.3729	NA	0	0	20	10	0.61817684	0.25575733	0	0			
36	1D-Myo-inos	C6H14O12P2	0	01_A0_Colon	3433452.39	3670994.29	3672750.62	3671051	3293087.79	NA	0	0	20	10	0.61817684	0.25575733	0	0			

Figure 7. Screenshot of a portion of the measurement spreadsheet data used with the extract command.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	#insert																						
2	#tags				#protocol.i	#.type	#.machine	#.instrume	#.ion_mod	#.ionizatio	#.instrument_type		#.descriptic	#.chromat	#.chromat	#.column_t	#.chromat	#.parent_protocol					
3					ICMS1	measurem	MS	Orbitrap Fu	NEGATIVE	ESI	IC-FTMS		ICMS Analy	Thermo Dic	Targeted I	Dionex Ion	Targeted I	IC-FTMS_measurement					
4																							
5	#tags				#protocol.i	*#.data_fil	*#.data_files%entity_id																
6					ICMS1	01_A0_Col	01_A0_Colon_naive_0days_170427_UKy_GCH_rep1-polar-ICMS_A																
7					ICMS1	02_A1_Col	02_A1_Colon_naive_0days_170427_UKy_GCH_rep2-polar-ICMS_A																
8					ICMS1	03_A2_Col	03_A2_Colon_naive_0days_170427_UKy_GCH_rep3-polar-ICMS_A																
9					ICMS1	04_B0_Col	04_B0_Colon_syngenic_42days_170427_UKy_GCH_rep1-polar-ICMS_A																
10					ICMS1	05_B1_Col	05_B1_Colon_syngenic_42days_170427_UKy_GCH_rep2-polar-ICMS_A																
11					ICMS1	06_B2_Col	06_B2_Colon_syngenic_42days_170427_UKy_GCH_rep3-polar-ICMS_A																
12					ICMS1	07_C1-1_C	07_C1-1_Colon_allogenic_42days_170427_UKy_GCH_rep1-polar-ICMS_A																
13					ICMS1	08_C1-2_C	08_C1-2_Colon_allogenic_42days_170427_UKy_GCH_rep2-polar-ICMS_A																
14					ICMS1	09_C2-0_C	09_C2-0_Colon_allogenic_42days_170427_UKy_GCH_rep1-polar-ICMS_A																
15					ICMS1	10_B1-0_C	10_B1-0_Colon_syngenic_7days_170427_UKy_GCH_rep1-polar-ICMS_A																
16					ICMS1	11_B1-1_C	11_B1-1_Colon_syngenic_7days_170427_UKy_GCH_rep2-polar-ICMS_A																
17					ICMS1	12_B1-2_C	12_B1-2_Colon_syngenic_7days_170427_UKy_GCH_rep3-polar-ICMS_A																
18					ICMS1	13_C1-1_C	13_C1-1_Colon_allogenic_7days_170427_UKy_GCH_rep1-polar-ICMS_A																
19					ICMS1	14_C1-2_C	14_C1-2_Colon_allogenic_7days_170427_UKy_GCH_rep2-polar-ICMS_A																
20					ICMS1	15_C1-20_	15_C1-20_Colon_allogenic_7days_170427_UKy_GCH_rep3-polar-ICMS_A																
21																							
22	#end																						
23																							
24																							
25	#tags	#header		#add																			
26		Compound+"-13C"+C_isomers+"-"+SamplID		#measurement.id																			
27		Compound+"-13C"+C_isomers		#measurement.assignment																			
28		Compound		#measurement.compound																			
29		Mol_Formula		#measurement.formula																			
30		SamplID		#.entity.id																			
31		"13C"+C_isomers		#measurement.isotopologue;#%type="13C"																			
32		Intensity		#measurement.raw_intensity;#%type="spectrometer peak area"																			
33		Renormalized		#measurement.corrected_raw_intensity;#%type="natural abundance corrected peak area"																			
34		Quantified_uM_sequence_ratio		#measurement.concentration;#%units=uM;#%type="calculated from standard"																			
35		Amount_ProteinAdj_uMol_g_protein_SequenceBased		#measurement.normalized_concentration;#%type="protein normalized";#%units="uMol/g"																			
36		eval(float(#Renormalized#) / float(#protein_mg#))		#measurement.intensity;#%type="natural abundance corrected and protein normalized peak area";#%units="area/g"																			
37				#.protocol.id=ICMS1																			
38																							
39																							
40																							

Figure 8. Screenshot of the automation tags used with the measurement data when executing the extract command.

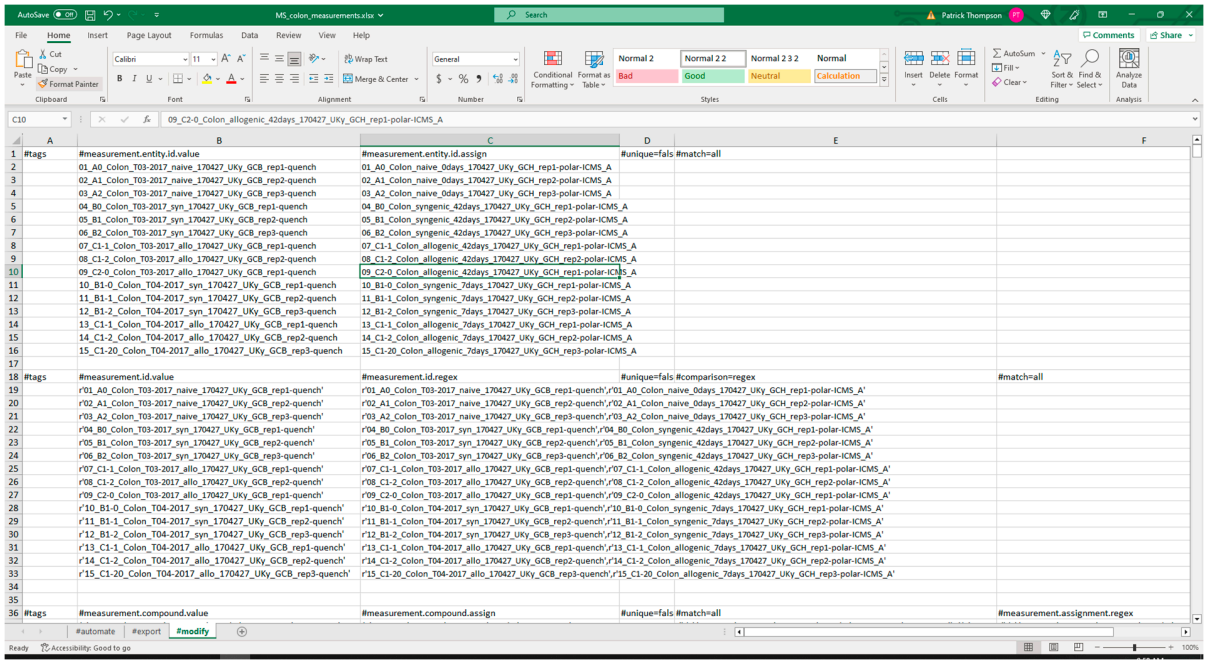


Figure 9. Screenshot of a portion of the modification tags used with the measurement data when executing the extract command.



Figure 10. Portions of each table in the MESSES JSON file output generated by the extract command.

3.2.2. Validation of Extracted Data and Metadata

After extraction, a user should use the validate command on the (JSON) output to validate the result. Typically, both the extract and validate commands will be used iteratively with dataset revision until no more errors or warnings are detected during validation, creating a combined extraction and validation process. If extraction involves datasets generated in a consistent format from other programs, this could essentially become an automated process; however, given the nature of most analytical labs and core facilities, a semi-automated process is expected in most cases. But by following Good Laboratory Practice (GLP) on Data Integrity [22], this semi-automated process should approach a fully automated process, especially if tagged spreadsheet templates are used for manual data collection steps. Figure 11 shows screenshots of the executed command and directory of files when running the validate command. The json subcommand identifies the extracted_result.json as being in JSON format. The '--pds' option identifies the specific (protocol-dependent) PD schema to validate against. The '--format mwtab' option indicates the conversion format specific schema to validate against. The '--silent nuisance' option

ignores common warnings that most often can be ignored. Figure 12 shows a portion of this PD schema used here, and Figure A5 shows a portion of this PD schema transformed into JSON Schema. This example is clean and complete and thus does not show any warnings or errors during validation. However, Figures A6 and A7 demonstrate common warnings and errors that often occur.

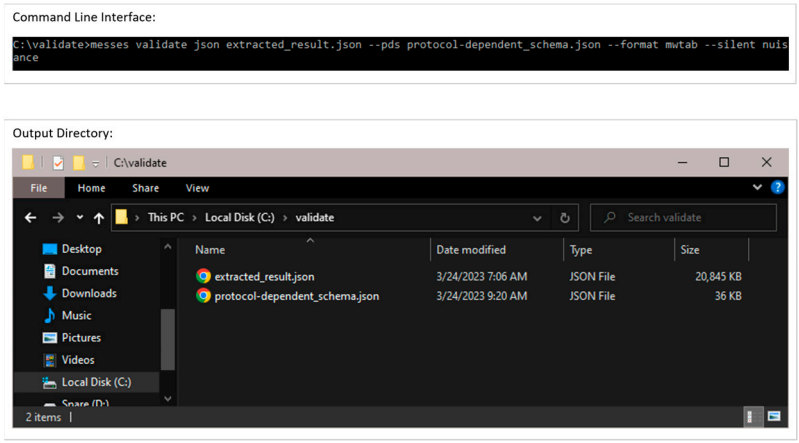


Figure 11. Example execution of the validate command in a Windows Command Prompt. The resulting output directory is shown in the Windows folder at the bottom.

(A)


```
"parent_protocol": {
  "master_measurement": {
   "description": "master measurement protocol",
   "filename": "",
   "id": "master_measurement",
   "type": "measurement"
  },
  "MS_measurement": {
   "description": "Measurements made using mass spec",
   "filename": "",
   "id": "MS_measurement",
   "parent_id": "master_measurement",
   "type": "measurement"
  },
  "Chromatography_MS_measurement": {
   "description": "Measurements made using mass spec with chromatography",
   "filename": "",
   "id": "Chromatography_MS_measurement",
   "parent_id": "MS_measurement",
   "type": "measurement"
  },
  "IC-FTMS_measurement": {
   "description": "Measurements made using ion chromatoraphy FTMS",
   "filename": "",
   "id": "IC-FTMS_measurement",
   "parent_id": "Chromatography_MS_measurement",
   "type": "measurement"
  },
...
}
```

```
"Chromatography_MS_measurement": {
  "chromatography_description": {
   "minLength": "1",
   "table": "protocol",
   "type": "string"
  },
  "chromatography_instrument_name": {
   "minLength": "1",
   "required": "True",
   "table": "protocol",
   "type": "string"
  },
  "chromatography_type": {
   "minLength": "1",
   "required": "True",
   "table": "protocol",
   "type": "string"
  },
  "column_name": {
   "minLength": "1",
   "required": "True",
   "table": "protocol",
   "type": "string"
  },
  "retention_time": {
   "format": "numeric",
   "table": "measurement",
   "type": "number"
  },
  "retention_time%units": {
   "minLength": "1",
   "table": "measurement",
   "type": "string"
  }
 }
...
```


(B)

#tags	#parent_protocol.id	#.description	#.filename	#.parent_id	#.type
	Chromatography_MS_measurement	Measurements made using mass spec with chromatography		MS_measurement	measurement
	IC-FTMS_measurement	Measurements made using ion chromatoraphy FTMS		Chromatography_MS_measurement	measurement
	MS_measurement	Measurements made using mass spec		master_measurement	measurement

#tags	#parent_protocol.id	#.description	#.filename	#.type
	master_measurement	master measurement protocol		measurement

#tags	#Chromatography_MS_measurement.id	#.minLength	#.table	#.type
	chromatography_description	1	protocol	string
	retention_time%units	1	measurement	string

#tags	#Chromatography_MS_measurement.id	#.minLength	#.required	#.table	#.type
	chromatography_instrument_name	1	True	protocol	string
	chromatography_type	1	True	protocol	string
	column_name	1	True	protocol	string

#tags	#Chromatography_MS_measurement.id	#.format	#.table	#.type
	retention_time	numeric	measurement	number

Figure 12. A portion of the parent_protocol table and protocols in the protocol-dependent schema. (**A**) is in JSON format and (**B**) is in tagged tabular format.

3.2.3. Conversion into mwTab Formats

Once the extracted MESSES JSON is validated, it can be converted into the mwTab JSON and tab-delimited formats. Figure 13 shows screenshots of the executed command and directory of files when running the convert command. The 'mwtab ms' subcommand identifies the output type, which is followed by the input extracted_results.json filename and the output filename without file extension. Two separate output files are generated in mwTab JSON (output.json) and tab-delimited (output.txt) formats. Technically, the mwTab JSON format is generated first and then the mwtab library is used to convert it further into the mwTab tab-delimited format. Figures 14 and 15 show screenshots of portions of the mwTab JSON and tab-delimited text outputs, respectively. Note that the ANALYSIS_ID and STUDY_ID default to 000000. Before submission to the Metabolomics Workbench these need to be updated manually with the IDs they give you, or they can be updated by using the --update option to update that portion of the conversion directives.

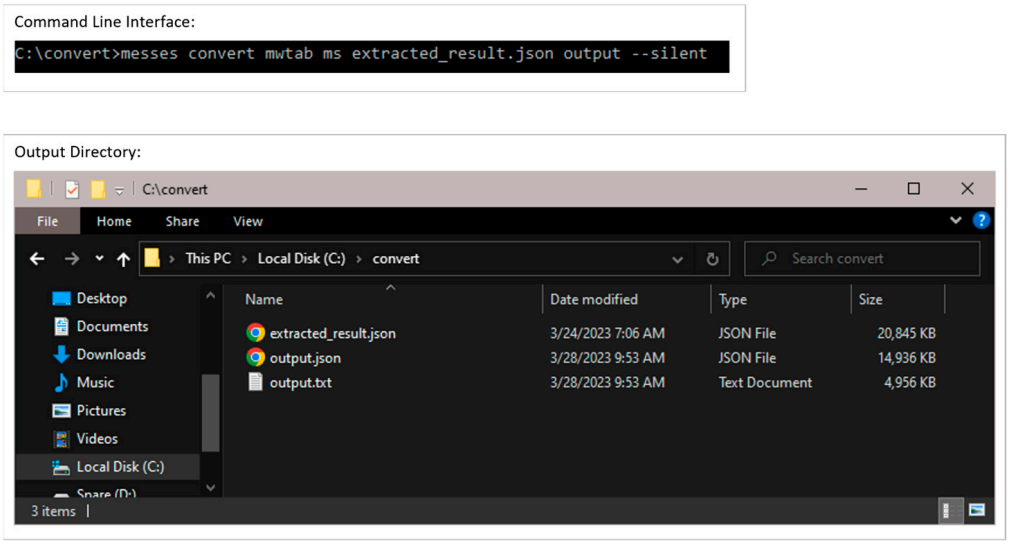


Figure 13. Example execution of the convert command in a Windows Command Prompt. The resulting output directory is shown in the Windows folder at the bottom.


```
{
 "ANALYSIS": {
  "ANALYSIS_TYPE": "MS"
 },
 "CHROMATOGRAPHY": {
  "CHROMATOGRAPHY_SUMMARY": "Targeted IC",
  "CHROMATOGRAPHY_TYPE": "Targeted IC",
  "COLUMN_NAME": "Dionex IonPac AS11-HC-4um 2 mm i.d. x 250 mm",
  "INSTRUMENT_NAME": "Thermo Dionex ICS-5000+"
 },
 "COLLECTION": {
  "COLLECTION_PROTOCOL_FILENAME": "mouse_tissue_procedure.pdf",
  "COLLECTION_PROTOCOL_ID": "mouse_tissue_collection",
  "COLLECTION_SUMMARY": "Mouse is sacrificed and tissues are harvested.",
  "SAMPLE_TYPE": "mouse"
 },
 "METABOLOMICS WORKBENCH": {
  "ANALYSIS_ID": "AN000000",
  "CREATED_ON": "2023-03-28",
  "STUDY_ID": "ST000000",
  "VERSION": "1"
 },
...
}
```


Figure 14. A portion of the mwTab JSON output generated by the convert command.

```
#ANALYSIS
AN:ANALYSIS_TYPE                MS
#CHROMATOGRAPHY
CH:CHROMATOGRAPHY_SUMMARY               Targeted IC
CH:CHROMATOGRAPHY_TYPE                  Targeted IC
CH:COLUMN_NAME                  Dionex IonPac AS11-HC-4um 2 mm i.d. x 250 mm
CH:INSTRUMENT_NAME                      Thermo Dionex ICS-5000+
#COLLECTION
CO:COLLECTION_PROTOCOL_FILENAME         mouse_tissue_procedure.pdf
CO:COLLECTION_PROTOCOL_ID               mouse_tissue_collection
CO:COLLECTION_SUMMARY                   Mouse is sacrificed and tissues are harvested.
CO:SAMPLE_TYPE                  mouse
#METABOLOMICS WORKBENCH ANALYSIS_ID:AN000000 STUDY_ID:ST000000
CREATED_ON                      2023-03-28
VERSION                         1
#MS
MS:INSTRUMENT_NAME                      Orbitrap Fusion
MS:INSTRUMENT_TYPE              IC-FTMS
MS:ION_MODE                     NEGATIVE
MS:MS_COMMENTS                  ICMS Analytical Experiment with detection of compounds by comparison to
MS:MS_COMMENTS                  standards.
```

Figure 15. A portion of the mwTab tab-delimited text output generated by the convert command.

4. Discussion

MESSES is a useful tool for turning messy, disorganized data and metadata into the proper format for deposition into Metabolomics Workbench. MESSES and its prior prototypes have been used to deposit over 40 studies into Metabolomics Workbench (see Table A1), many of which provide the richest level of metadata demonstrated so far in dataset deposition into Metabolomics Workbench. MESSES was designed to improve deposition quality and metadata consistency, which are known issues in scientific repositories like Metabolomics Workbench [8,9]. The package provides a way to organize, filter, and modify data so that it can be put into the proper form, and its automation support makes adding MESSES into workflows much easier. Although a significant amount of time and effort went into refining the package so that it is as easy to use and understand as possible, there is some intellectual overhead required to initially setup all the tags, validation schemas, and conversion directives. Additional supportive sub-commands are included where applicable to make learning and troubleshooting the tool easier for new users. Also, there is extensive documentation available to help with the learning curve: https://moseleybioinformaticslab.github.io/MESSES/ (accessed on 30 June 2023). In addition, when installed via the Python package management system pip, a console script "messes" is created automatically for the user, providing easy access to the CLI.

The package has been developed in a way such that additional formats can be added into the list of inherently supported formats. But the package is also generalized enough that anyone should be able to use it to convert to whatever arbitrary format is desired, as long as it has a JSON representation. Going from the JSON representation to another non-JSON representation would have to be done using another tool if the format is not supported in MESSES. Currently, only the mwTab format is directly supported, but as the tool is used to create more diverse depositions, it is likely that more formats will be added. Another notable limitation is that deeply nested JSON structures cannot be created using MESSES without supplying your own Python code for the convert command. This is due to a desire to keep tags and directives simple enough to be in a tabular form, but if there is enough demand or need for deeper nesting, the tags and directives can be expanded.

5. Conclusions

The MESSES Python package enables a straight-forward mwTab deposition creation process that involves iterative extraction-validation steps followed by a final conversion step. MESSES was developed to help solve the specific deposition problems we faced in

helping collaborators deposit their data, and we believe it can help many others with their depositions. While there is an initial learning curve, once a user sets up the needed tagging directives and validation schemas, repetitive generation of mwTab formatted depositions should be much easier. Moreover, MESSES enables a more comprehensive extraction of metadata to promote FAIRer depositions into Metabolomics Workbench.

Supplementary Materials: The following supporting information can be downloaded at: https://figshare.com/articles/dataset/MESSES_Supplemental_Material/23148224, DOI: https://doi.org/10.6084/m9.figshare.23148224.

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Data Availability Statement: The Python package is available on the Python Package Index (https://pypi.org/project/messes accessed on 30 June 2023) and on GitHub (https://github.com/MoseleyBioinformaticsLab/MESSES accessed on 30 June 2023), along with extensive end-user documentation (https://moseleybioinformaticslab.github.io/MESSES/ accessed on 30 June 2023). Examples of dataset capture, validation, and conversion into mwTab deposition format are available on Figshare: https://figshare.com/articles/dataset/MESSES_Supplemental_Material/23148224 (accessed on 30 June 2023).

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Abbreviations

FAIR	Findable, Accessible, Interoperable, Reusable.
NIH	National Institutes of Health
DMS	Data Management Sharing
MESSES	Metadata from Experimental SpreadSheets Extraction System
LIMS	Laboratory Information Management System
JSON	JavaScript Object Notation
mwTab	Metabolomics Workbench Tabular format
NMR	Nuclear Magnetic Resonance
MS	Mass Spectrometry
PyPi	Python Package Index
CLI	Command Line Interface
API	Application Programming Interface
PD schema	Protocol-Dependent schema
EDS	Experiment Description Schema
CSV	Comma Separated Values

Appendix A

```
src\messes
|   _version.py
|   __init__.py
|   __main__.py
|
+---convert
|       convert.py
|       convert_schema.py
|       mwtab_conversion_directives.py
|       mwtab_functions.py
|       user_input_checking.py
|       __init__.py
|
+---extract
|       cythonized_tagSheet.c
|       cythonized_tagSheet.cp310-win_amd64.pyd
|       cythonized_tagSheet.pyx
|       extract.py
|       tagSheet.py
|       __init__.py
|
+---validate
|       validate.py
|       validate_schema.py
|       __init__.py
```

Figure A1. MESSES Source Code Directory Structure. The convert, extract, and validate subdirectories represent submodules for each major section of the codebase.

```
Extract data from Excel workbooks, csv files, and JSON files.

 Usage:
   messes extract <metadata_source>... [--delete <metadata_section>...] [options]
   messes extract --help

   <metadata_source> - tagged input metadata source as csv/json filename or
                       xlsx_filename[:worksheet_name|regular_expression] or
                       google_sheets_url[:worksheet_name|regular_expression]
                       "#export" worksheet name is the default.

 Options:
   -h, --help                    - show this help documentation.
   -v, --version                 - show the version.
   --silent                      - print no warning messages.
   --output <filename_json>          - output json filename.
   --compare <filename_json>         - compare extracted metadata to given JSONized metadata.
   --modify <source>             - modification directives worksheet name, regular expression, csv/json filename, or
                                   xlsx_filename:[worksheet_name|regular_expression] or
                                   google_sheets_url[:worksheet_name|regular_expression]
                                   [default: #modify].
   --end-modify <source>             - apply modification directives after all metadata merging. Requires csv/json filename or
                                   xlsx_filename:[worksheet_name|regular_expression] or
                                   google_sheets_url[:worksheet_name|regular_expression].
   --automate <source>           - automation directives worksheet name, regular expression, csv/json filename, or
                                   xlsx_filename:[worksheet_name|regular_expression] or
                                   google_sheets_url[:worksheet_name|regular_expression]
                                   [default: #automate].
   --save-directives <filename_json>   - output filename with modification and automation directives in JSON format.
   --save-export <filetype>          - output export worksheet with suffix "_export" and with the indicated xlsx/csv format extension.
   --show <show_option>              - show a part of the metadata. See options below.
   --delete <metadata_section>...    - delete a section of the JSONized metadata. Section format is tableKey or tableKey,IDKey or tableKey,IDKey,fieldName. These can be regular expressions.
   --keep <metadata_tables>          - only keep the selected tables.  Delete the rest.  Table format is tableKey,tableKey,... The tableKey can be a regular expression.
   --file-cleaning <remove_regex>    - a string or regular expression to remove characters in input files, removes unicode and \r characters by default, enter "None" to disable [default: _x([0-9a-fA-
F]{4})_|\r].

 Show Options:
   tables    - show tables in the extracted metadata.
   lineage   - show parent-child lineages per table.
   all       - show every option.

 Regular Expression Format:
   Regular expressions have the form "r'...'" on the command line.
   The re.match function is used, which matches from the beginning of a string, meaning that a regular expression matches as if it starts with a "^".

   Directives JSON Format:
     {
     "modification" : { table : { field :  { "(exact|regex|levenshtein)\-(first|first\-nowarn|unique|all)" :
                     { field_value : { "assign" : { field : value,... }, "append" : { field : value,... }, "prepend" : { field : value,... },
                                       "regex" : { field : regex_pair,... }, "delete" : [ field,... ], "rename" : { old_field : new_field } } } } } }
     "automation" : [ { "header_tag_descriptions" : [ { "header" : column_description, "tag" : tag_description, "required" : true|false } ],   "exclusion_test" : exclusion_value, "insert" : [ [ cell_content, ... ] ] } ]
```

Figure A2. MESSES extract CLI. This command enables extraction of (meta)data from spreadsheets into a MESSES JSON representation.

```
Validate JSON files.

Usage:
  messes validate json <input_JSON> [--pds=<pds> [--csv | --xlsx | --json | --gs] | --no_base_schema]
                        [--no_extra_checks]
                        [--additional=<add_schema>...]
                        [--format=<format>]
                        [--silent=<level>]
  messes validate save-schema <output_schema> [--input=<input_JSON>]
                              [--pds=<pds> [--csv | --xlsx | --json | --gs]]
                              [--format=<format>]
                              [--silent=<level>]
  messes validate schema <input_schema>
  messes validate pds <pds> [--csv | --xlsx | --json | --gs] [--silent=<level>] [--save=<output_name>]
  messes validate pds-to-table <pds_json> <output_name> [<output_filetype>]
  messes validate pds-to-json <pds_tabular> [--csv | --xlsx | --gs] <output_name>
  messes validate cd-to-json-schema <conversion_directives> [--csv | --xlsx | --json | --gs] <output_schema>
  messes validate --help

  <input_JSON> - if '-' read from standard input.
  <pds> - can be a JSON, csv, xlsx, or Google Sheets file. If xlsx or Google Sheets, the default sheet name to read in is #validate,
      to specify a different sheet name separate it from the file name with a colon ex: file_name.xlsx:sheet_name.
      If '-' read from standard input.
  <input_schema> - must be a valid JSON Schema file. If '-' read from standard input.
  <output_schema> - if '-' save to standard output.
  <output_name> - path to save tabular pds to, if '-' save to standard output as CSV.
  <output_filetype> - "xlsx" or "csv", defaults to "csv".
  <conversion_directives> - can be a JSON, csv, xlsx, or Google Sheets file. If xlsx or Google Sheets,
                    the default sheet name to read in is #convert, to specify a different
                    sheet name separate it from the file name with a colon ex: file_name.xlsx:sheet_name.
                    If '-' read from standard input.

Options:
  -h, --help                    - show this screen.
  -v, --version                  - show version.
  --silent <level>                - if "full" silence all warnings,
                            if "nuisance" silence warnings that are more likely to be a nuisance,
                            if "none" do not silence warnings [default: none].
  --pds <pds>                       - a protocol-dependent schema file, can be a JSON, csv, or xlsx file.
                            If xlsx the default sheet name to read in is #validate, to specify
                            a different sheet name separate it from the file name with a colon
                            ex: file_name.xlsx:sheet_name.
  --csv                      - indicates that the protocol-dependent schema file is a csv (comma delimited) file.
  --xlsx                     - indicates that the protocol-dependent schema file is an xlsx (Excel) file.
  --json                      - indicates that the protocol-dependent schema file is a JSON file.
  --gs                       - indicates that the protocol-dependent schema file is a Google Sheets file.
                            If a file type is not given then it will be guessed from the file extension.
  --additional <add_schema>          - an additional JSON Schema file that will be used to validate <input_JSON>.
  --format <format>                - additional validation done for the desired supported format.
                            Current supported formats:
                              mwtab
  --no_base_schema                - don't validate with the base JSON schema.
  --no_extra_checks               - only do JSON Schema validation and nothing else.
  --input <input_JSON>             - optionally give an input JSON file to save-schema to reproduce the
                            schema used to validate in the json command.
  --save <output_name>              - save the JSON Schema created from the protocol-dependent schema.


The "json" command will validate the <input_JSON> against the internal base_schema, and optional schema provided
by the --pds and --additional options. To validate only against a provided schema, use the --additional and --no_base_schema options.

The "save-schema" command will save the internal base_schema to the <output_schema> location. If --pds is given
then it will be parsed and placed into the base_schema. If --input is given, the protocols table will be added
in with the PDS to reproduce what happens in the json command. If --format is used, then that format schema is
saved instead of the base_schema.

The "schema" command will validate the <input_schema> against the JSON Schema meta schema.

The "pds" command will validate that the <pds> file is a valid protocol-dependent schema file.
If the --save option is given, then save the built JSON Schema.

The "pds-to-table" command will read in a protocol-dependent schema in JSON form and save it out in a tabular form.

The "pds-to-json" command will read in a protocol-dependent schema in tabular form and save it out in a JSON form.

The "cd-to-json-schema" command will read in conversion directives and create a JSON Schema
template file that can be filled in and used to validate files that will be converted using those directives.
```

Figure A3. MESSES validate CLI. This command enables validation of the MESSES JSON representation against an expected schema(s).

```
Convert JSON data to another JSON format.

Usage:
  messes convert mwtab (ms | nmr | nmr_binned) <input_JSON> <output_name> [--update <conversion_directives> | --override <conversion_directives>] [--silent]
  messes convert save-directives mwtab (ms | nmr | nmr_binned) <output_filetype> [<output_name>]
  messes convert generic <input_JSON> <output_name> <conversion_directives> [--silent]
  messes convert --help

  <conversion_directives> - can be a JSON, csv, xlsx, or Google Sheets file. If xlsx or Google Sheets the default sheet name to read in is #convert,
                to specify a different sheet name separate it from the file name with a colon ex: file_name.xlsx:sheet_name.

  <output_filetype> - "json", "xlsx", or "csv"

Options:
  -h, --help                - show this screen.
  -v, --version             - show version.
  --silent                  - silence all warnings.
  --update <conversion_directives>    - conversion directives that will be used to update the built-in directives for the format.
                        This is intended to be used for simple changes such as updating the value of
                        the analysis ID. You only have to specify what needs to change, any values
                        that are left out of the update directives won't be changed. If you need to remove
                        directives then use the override option.
  --override <conversion_directives>  - conversion directives that will be used to override the built-in directives for the format.
                        The built-in directives will not be used and these will be used instead.


The general command structure for convert is convert <format> which will convert an input JSON file over to the supported format.
The outputs of these commands will save both the JSON conversion and the final format file.

The generic command is the same as the supported formats except the user is required to input conversion directives specifying how to
convert the input JSON to the desired output JSON. Only an output JSON is saved.

The save-directives command is used to print the default conversion directives used by convert for any of the supported formats. <output-filetype>
can be one of "json", "xlsx", or "csv". The file is saved as "format_conversion_directives.ext" where ".ext" is replaced with ".json", ".xlsx",
or ".csv" depending on the value of <output-format>, unless <output_name> is given.
```

Figure A4. MESSES convert CLI. This command enables conversion of a MESSES JSON representation into mwTab deposition format.



```
{
 "type": "object",
 "properties": {
  "protocol": {
    "type": "object",
    "minProperties":1,
    "additionalProperties": {
          "type":"object",
          "properties":{
            "id": {"type":"string", "minLength":1},
            "parent_id": {"type":"string"},
            "parent_protocol": {"type":"string"},
            "type": {"type":"string", "enum":["sample_prep", "treatment", "collection", "storage", "measurement"]},
            "description": {"type":"string"},
            "filename": {"type":["string", "array"], "items":{"type":"string", "minLength":1}}
            },
          "required": ["id", "type"],
          "allOf": [
           {
            "if": {
             "anyOf": [
              {
               "properties": {
                "id": {"const": "Chromatography_MS_measurement"}
               },
               "required": ["id"]
              },
              {
               "properties": {
                "parent_id": {
                 "anyOf": [
                  {"const": "Chromatography_MS_measurement"},
                  {"type": "array", "contains": {"const": "Chromatography_MS_measurement"}}
                 ]
                }
               },
               "required": ["parent_id"]
              }
             ]
            },
            "then": {
             "properties": {
              "instrument": {
               "id": "instrument",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "instrument_type": {
               "id": "instrument_type",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "ion_mode": {
               "id": "ion_mode",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "ionization": {
               "id": "ionization",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "description": {
               "id": "description",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "data_files": {
               "id": "data_files",
               "table": "protocol",
               "type": "array",
               "uniqueItems": true
              },
              "data_files%entity_id": {
               "id": "data_files%entity_id",
               "table": "protocol",
               "type": "array",
               "uniqueItems": true
              },
              "chromatography_description": {
               "id": "chromatography_description",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "chromatography_instrument_name": {
               "id": "chromatography_instrument_name",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "chromatography_type": {
               "id": "chromatography_type",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              },
              "column_name": {
               "id": "column_name",
               "minLength": 1,
               "table": "protocol",
               "type": "string"
              }
             },
             "required": [
              "instrument",
              "ion_mode",
              "ionization",
              "chromatography_instrument_name",
              "chromatography_type",
              "column_name"
             ]
            }
           },
           ...
          ]
         }
    }
  ...
  }
}
```


Figure A5. Section of the protocol-dependent schema transformed into JSON Schema and combined with the Experiment Description Specification base JSON Schema. The fields required for a protocol are shown, but Chromatography_MS_measurement has fields for a measurement as well.

```
Warning:  The allowed value, naive, for the factor, Treatment, in the factor table of the input JSON is not used by any of the entities.
Warning:  The protocol from the input JSON, ICMS1, does not have the same type as its parent_protocol, IC-FTMS_measurement, in the protocol-dependent schema.
Warning:  The protocol from the input JSON, allogenic, is not in the parent_protocol table of the protocol-dependent schema, nor does it have a parent_protocol in the protocol-dependent schema. Records with this protocol cannot have thier fields validated.
Warning: The protocols:

IC-FTMS_preparation
allogenic

have the exact same descriptions.
Warning:  The entity, 29_C1-2_Lung_allogenic_7days_170427_UKy_GCH_rep2, has no values in the field, protocol.id, that are in the allowed values of the factor, Treatment.
Warning:  The entity, 30_C1-20_Lung_allogenic_7days_170427_UKy_GCH_rep3-polar-ICMS_A, has a field, protocol.id, that is a field for the factor, Treatment, but it is not a string or list type.
Warning:  The factor, Time Point, was not used by any of the entities.
Warning:  The protocol, "qwer"," in the "parent_protocol" table does not itself have any fields to validate, nor do any of its ancestors.
Warning:  The parent protocol, "asdf", for the protocol "qwer" in the "parent_protocol" table is not itself in the protocol-dependent schema. Parent entities must be in the protocol-dependent schema as well.
Warning:  The protocol, "qwer" in the "parent_protocol" table is not in the protocol-dependent schema.
```

Figure A6. Example of warnings printed by the validate command.

```
Error:  The entity, 15_C1-20_allogenic_7days_UKy_GCH_rep3, has more than 1 value in the field, protocol.id, that is in the allowed values of the factor, Treatment. Entities can only have 1 value from each factor.
Error:  The entry ['factor']['Time Point'] is missing the required property 'allowed_values'.
Error:  In the measurement table of the input JSON, the record "dUMP-13C0-29_C1-2_Lung_allogenic_7days_170427_UKy_GCH_rep2-polar-ICMS_A" has a field, entity.id, that is an id to another table, entity, but that id, 29_C1-2_Lung_allogenic_7days_170427_UKy_GCH_rep2-polar-ICMS_, is not in the entity table.
Error:  The value for ['measurement']["AXP-1'_1-16_A0_Lung_naive_0days_170427_UKy_GCH_rep1-polar-NMR_A-NMR2"]['base_inchi'] cannot be empty.
Error:  The value for ['measurement']['dUMP-13C0-29_C1-2_Lung_allogenic_7days_170427_UKy_GCH_rep2-polar-ICMS_A']['concentration'] must be less than or equal to -1.
Error:  The value for ['measurement']['dUMP-13C0-29_C1-2_Lung_allogenic_7days_170427_UKy_GCH_rep2-polar-ICMS_A']['concentration'] is not of type "string".
Error:  The value for ['protocol']['ICMS1']['array1'] has non-unique elements.
Error:  The parent project, "asdf", for the project "GH_Spleen" in the "project" table is not itself in the "project" table. Parent entities must be in the table as well.
Error:  The protocol, "IC-FTMS_preparation", does not have the same type as its parent "ICMS1".
Error:  The entity, "30_C1-20_Lung_allogenic_7days_170427_UKy_GCH_rep3", in the "entity" table has a circular ancestry, i.e., somewhere in the lineage a entity has a "parent_id" to a child in the lineage.
Error:  In the project table of the input JSON, the record "GH_Spleen" has a field, asdf.id, that is an id to another table, asdf, but that table is not in the input JSON.
Error:  In the project table of the input JSON, the record "GH_Spleen" has a field, qwer.asdf, with a period in the name, but it is not an id.
Error:  In the project table of the input JSON, the record "GH_Spleen" has a field, entity.id, that has id's to another table, entity, but at least one of the id's are not in the entity table.
The id's are:
asdf
qwer
Error:  In the project table of the input JSON, the record "GH_Spleen" has a field, measurement.id, that is an id to another table, measurement, but that id, asdf, is not in the measurement table.
Error:  In the project table of the input JSON, the record "GH_Spleen" has a parent_id, asdf, but this parent is not in the project table.
Error:  The protocol, "ICMS1", does not have the same type as its parent "IC-FTMS_preparation".
```

Figure A7. Example of errors printed by the validate command.

Appendix B

Table A1. Studies deposited into Metabolomics Workbench with MESSES prototypes.

Study ID	Title
ST000076	A549 Cell Study
ST000110	SIRM Analysis of human P493 cells under hypoxia in [U-13C/15N] labeled Glutamine medium (Both positive and ion mode FTMS)
ST000111	Study of biological variation in PC9 cell culture
ST000113	SIRM Analysis of human P493 cells under hypoxia in [U-13C/15N] labeled Glutamine medium (Positive ion mode FTMS)
ST000114	SIRM Analysis of human P493 cells under hypoxia in [U-13C] labeled Glucose medium
ST000142	H1299 13C-labeled Cell Study
ST000148	A549 13C-labeled Cell Study
ST000367	Distinctly perturbed metabolic networks underlie differential tumor tissue damages induced by immune modulator b-glucan in a two-case ex vivo non-small cell lung cancer study
ST000949	Human NK vs. T cell metabolism using 13C-Glucose tracer (part I)
ST000950	Human NK vs. T cell metabolism using 13C-Glucose tracer with/out galactose (part II)
ST000951	Human NK vs. T cell metabolism using 13C-Glucose tracer with/out oligomycin (part III)
ST000952	Human NK vs. T cell metabolism using 13C-Glucose tracer with/out oligomycin and galactose (part IV)
ST001044	PGC1-A effect on TCA enzymes
ST001045	FASN effect on HCT116 metabolism probed by 13C6-glucose tracer (part I)
ST001046	FASN effect on HCT116 metabolism probed by 13C6-glucose tracer (part II)
ST001049	P4HA1 knockdown in the breast cell line MDA231 (part I)
ST001050	P4HA1 knockdown in the breast cell line MDA231 Gln metabolism (part II)
ST001129	P4HA1 knockdown in the breast cell line MDA231 (part III)
ST001138	P4HA1 knockdown in the breast cell line MDA231 Gln metabolism (part V)
ST001139	P4HA1 knockdown in the breast cell line MDA231 Gln metabolism (part VI)
ST001445	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Colon NMR 1D
ST001446	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Colon NMR HSQC
ST001447	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Colon ICMS
ST001449	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Colon DI-FTMS
ST001453	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Liver ICMS
ST001455	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Liver NMR 1D
ST001456	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Liver NMR HSQC
ST001459	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Lung NMR 1D
ST001460	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Lung NMR HSQC
ST001461	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Plasma NMR 1D
ST001462	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Plasma NMR HSQC
ST001463	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Small Intenstines NMR 1D
ST001465	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Spleen NMR 1D
ST001466	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation Spleen—NMR HSQC
ST001469	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Lung DI-FTMS
ST001470	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Lung ICMS

Table A1. *Cont.*

Study ID	Title
ST001471	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Small Intestines DI-FTMS
ST001472	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Small Intestines ICMS
ST001473	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Spleen DI-FTMS
ST001474	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Spleen ICMS
ST001475	Metabolomics of lung injury after allogeneic hematopoietic cell transplantation—Liver DI-FTMS

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