PyKrev: A Python Library for the Analysis of Complex Mixture FT-MS Data

PyKrev: A Python library for the analysis of complex mixture FT-MS data.

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ABSTRACT: In this paper we present PyKrev, a Python library for the analysis of complex mixture FT-MS data. PyKrev is a comprehensive suite of tools for analysis and visualisation of FT-MS data after formula assignment has been performed. These comprise: formula manipulation and calculation of chemical properties, intersection analysis between multiple lists of formulas, calculation of chemical diversity, assignment of compound classes to formulas, multivariate analysis and a variety of visualisation tools producing van Krevelen diagrams, class histograms, PCA score and loading plots, biplots, scree plots and UpSet plots. The library is showcased through analysis of hot water green tea extracts and Scotch whisky FT-ICR-MS datasets. PyKrev addresses the lack of a single, cohesive toolset for researchers to perform FT-MS analysis in the Python programming environment encompassing the most recent data analysis techniques used in the field.

INTRODUCTION

Fourier-transform mass spectrometry (FT-MS) offers the resolution and mass accuracy necessary for the molecular characterisation of chemical species contained within complex mixtures[1–3]. It is routinely used in the analysis of natural organic matter[4, 5], food and beverages[6, 7] or petroleum fractions[8].

Interrogation of large datasets produced by FT-MS necessitates the use of advanced chemoinformatic tools. Several such tools have already been developed. Most of these are web based[9, 10], or command line based programs[11, 12] allowing users to analyse their data with little to no programming experience.

However, oftentimes these rigid products do not fulfil all research needs. Performing data analysis within a programming environment allows more flexibility and capacity for customisation compared to using software with a fixed user interface. In the field of FT-MS data analysis, there is generally a lack of tools for users who wish to perform their analyses in a programming environment. Notably, to address such needs, an R package, *ftmsRanalysis,* was recently published[13].

Here we present PyKrev, a Python library that provides a comprehensive set of tools for the analysis of processed FT-MS data. Our library is designed to be used after formula assignment has been performed, and performs subsequent data analysis, statistical inquiry and data visualisation. PyKrev does not include tools for raw FT-MS data processing, however other tools for this exist, including the open source libraries SPIKE[14] and CoreMS[15]. Both support signal processing and peak picking, and CoreMS includes formula assignment. A complete, Python-based programmatic data analysis workflow may couple CoreMS to PyKrev.

A primary advantage of data analysis in Python is access to well documented libraries that provide sophisticated tools for numerical[16] and scientific[17] computation, including machine learning[18]. Novel aspects of the PyKrev library include mass filtering, intersection analysis and advanced visualisation, analysis of chemical diversity, statistical ordination and the ability to generate and quantitatively compare different compound classifications. Whilst many of these functions exist in disparate packages, or are accessible to skilled programmers, PyKrev brings together this combination of tools in an accessible, but flexible, library for the first time.

METHODS

PyKrev is available to install through the Python Package Index; its full documentation can be found on the GitHub page: https://github.com/Kzra/pykrev. PyKrev was written in Python 3.6 and requires the following Python dependencies to be available: NumPy[16], SciPy[17], pandas[19] and Matplotlib[20]. Specific versions of dependencies are detailed in the online documentation.

PyKrev contains a collection of modules defining functions for processing and visualizing FT-MS data, grouped into three packages: “Formula”, “Diversity” and “Plotting”. A description of the module organisation is given in S.I. Table 1, and, where applicable, each function can be tested against provided literature data; these tests are available in the “Tests” package.

For input data, most functions in PyKrev require lists of molecular formula with corresponding arrays of monoisotopic peak intensities and *m/z* values. PyKrev does not perform formula assignment routines as there already exists powerful open access algorithms to perform this[21–23]. Input data can be parsed directly from the .csv output of formula assignment with *Formularity* software[22] using *read_formularity.py* or *read_batch_formularity.py* in the Formula package, or manually imported into a Python environment. While the library was designed with FT-ICR or Orbitrap instruments in mind, the library is analyser independent and will work, in principle, on any assigned mass list.

RESULTS/DISCUSSION

The capabilities of PyKrev are demonstrated using FT-ICR-MS datasets obtained on (i) hot water extracts of green tea bags buried in peatland soils. Teabags were buried at a depth of 8 cm in three different peatlands, referred to a 'A', 'B' and 'C'; (ii) Four different Scotch whisky samples labelled 'W1 – 'W4' analysed using four complementary ionization techniques. A full description of the acquisition parameters of the green tea and whisky MS data have been published[6, 7]. Formula were assigned to calibrated lists of *m/z* values using *Formularity* software[22] with the following elemental rules (green tea: O > 0, N <= 8, P & S = 0, Scotch whisky: O>0, N<2, S<=2, P<1); all the subsequent analysis was performed using PyKrev.

FORMULA

PyKrev can be used to perform a variety of formula manipulation such as stoichiometric analysis, mass analysis and intersection analysis (S.I. Table 1). This includes the ability to filter out suspected interference from high molecular weight doubly charged ions[24], calculation of double bond equivalent[25], two forms of the aromaticity index[25, 26], nominal oxidation state of carbon[27] and Kendrick mass defect[28].

PLOTTING

Plotting in PyKrev is based on the Application Programming Interface (API) of the Matplotlib[20] library. PyKrev can create a range of van Krevelen style diagrams (i.e. O/C *vs* H/C scatter plots). It is also possible to plot centroid mass spectra, histograms of atomic class, mass and mass error, bar charts of compound class assignments and Kendrick mass defect plots[28]. Figure 1 shows a subset of available plots.

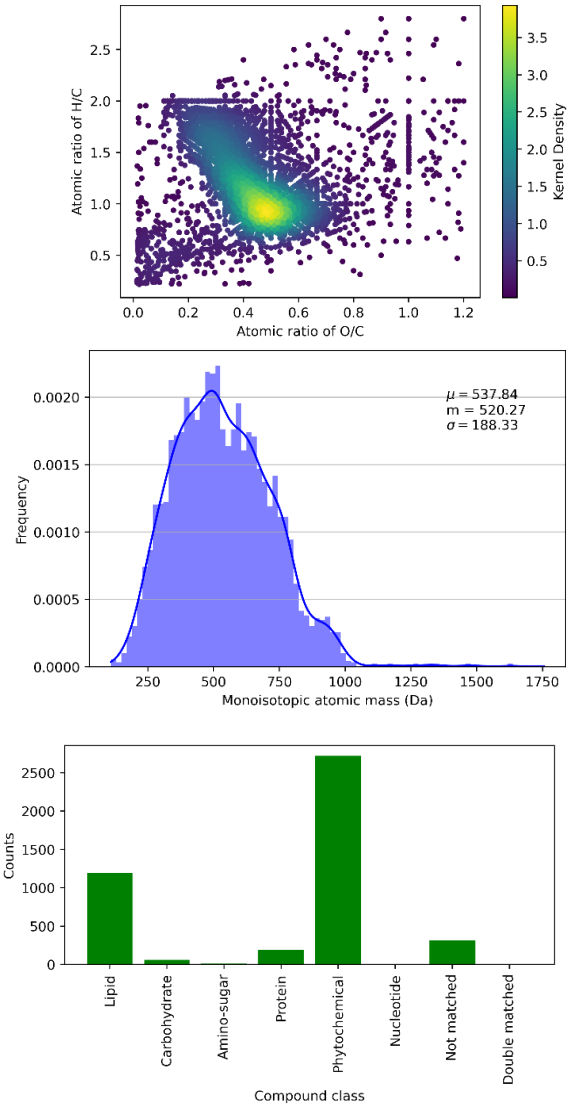

Figure 1. A selection of plots made in PyKrev on the green tea dataset. Top: van Krevelen scatter plot with formulas coloured by Gaussian kernel density estimation using SciPy[17]. *Middle: histogram of monoisotopic masses with an overlaid line depicting the probability density function estimated via Gaussian kernel density. Bottom: compound classes assigned to formulas using the 'MSCC' algorithm (not matched: formula was not assigned a compound class, double matched: formula was assigned to two compound classes)*[29].

PyKrev can visualise set analysis between multiple lists of formulas, by plotting the missing or unique formula in each list on a van Krevelen diagram or creating an UpSet plot[30] using the UpSetPlot Python library[31] (Figure 2).

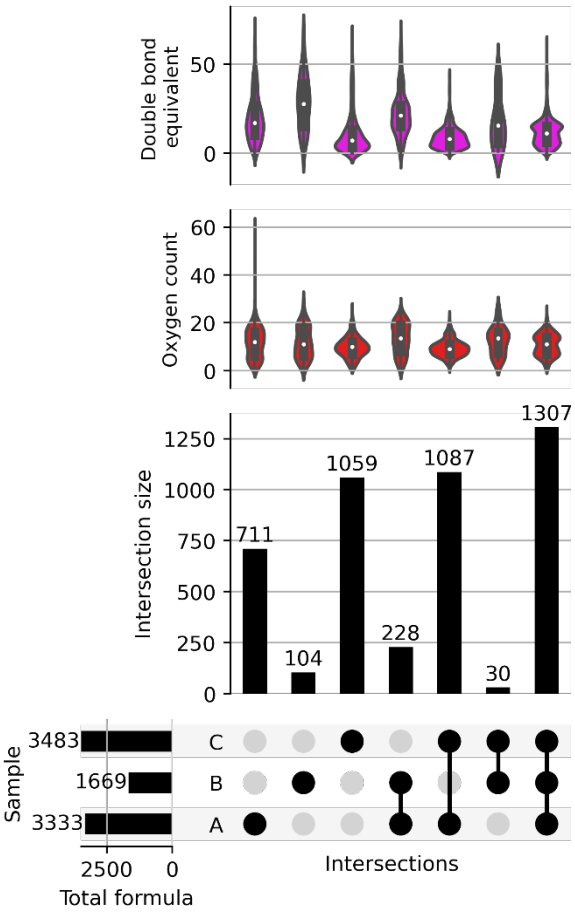

Figure 2 UpSet plot comparing intersections of three green tea samples made with PyKrev and UpSetPlot. The distribution of double bond equivalent and oxygen count of the formula in each inter section are provided in corresponding violin plots above. The violin plot combines a box plot (grey interior) with a mirrored kernel density estimate of the parameter distribution (coloured edge).

DIVERSITY

PyKrev can calculate a range of diversity metrics (akin to biological diversity metrics) based on lists of molecular formula and peak intensities. This technique has been applied previously in the study of dissolved organic matter (DOM)[32, 33]. Alpha diversity metrics such as Shannon-Wiener diversity[34] and Gini-Simpson diversity[35] are based on the number (richness) and relative intensity of a set of formulas in a sample, and compute diversity irrespective of the atomic composition of the formula present.

Functional diversity, computed using Rao's quadratic entropy[36][37], accounts for chemical properties by measuring the expected difference of a property (e.g. C number, double bond equivalent) if two formulas in a list were to be sampled with replacement.

PyKrev can be used to assign a putative compound class to formulas using the following classifications: multi-dimensional stoichiometry[29], aromaticity index[38], H/C and O/C ratios[22] and compound matching to the KEGG compound database[39].

Finally, PyKrev can assist with multivariate analysis when comparing multiple lists of formula. It is possible to create an ordination matrix in which the rows are a set of all formulas across all samples and the column values are the reported peak intensities of formulas in a given sample. Users can impute a custom value in place of compounds that are absent. A variety of peak intensity normalisation techniques can be computed on the ordination matrix (e.g. z-score standardization, sum relative intensity, unit vector relative intensity[40]), including the ability to subset data prior to generating normalization factors [41, 42]. Principal component analysis (PCA) can then be performed using the algorithm implemented in Scikit-learn[18].

Following PCA, it is possible to visualise PCA results using score and scree plots, biplots and loading plots. Figure 3 shows a selection of loading plots created with PyKrev and Matplotlib[20] on the Scotch whisky dataset. Loadings describe how much each feature in the model, in this case each molecular formula, contributes to each principal component. In Figure 3, the plots on the left show the loadings based on mass, oxygen class or compound class (in the latter two cases the loadings of all formula within a class are summed). The plots on the right show the scores of the samples, with randomly jittered x-axis positions, on the first two principal axis. This layout makes it easier to ascertain the relative contribution of a chemical property to the sample separation produced by PCA.

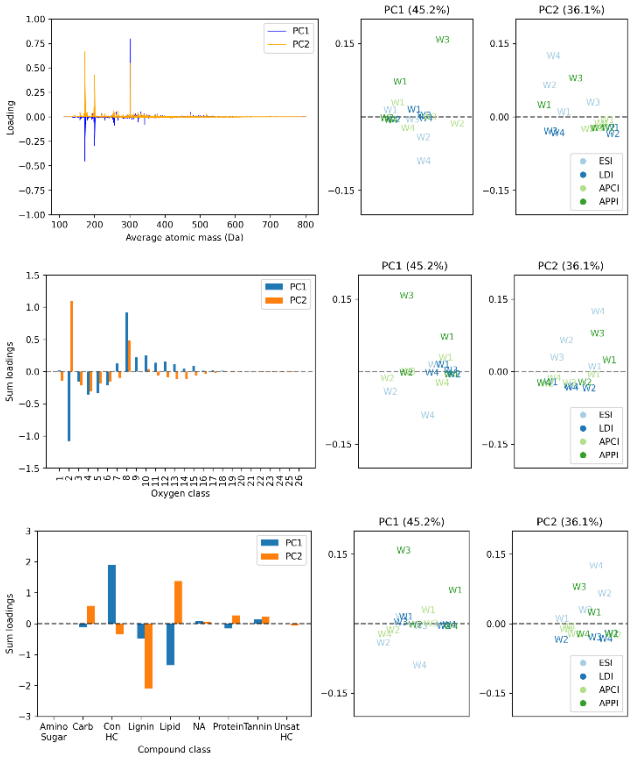

Figure 3 Loading plots for the first (PC1) and second (PC2) principal components from PCA of the Scotch whisky dataset. In each case the loading plot is shown on the left and the coordinates of the samples on the first two principal components are plotted on the right (coordinates on the y-axis, randomly selected x-axis positions to avoid point overlap). Four whisky samples (W1 -W4) were analysed using different ionization techniques, ESI: Electrospray ionization, LDI: Laser desorption ionization, APCI: Atmospheric pressure chemical ionization, APPI: Atmospheric pressure photoionization. Top: A mass spectrum of loadings across all formula. Middle: The sum of loadings for each oxygen class across all formula. Bottom: The sum of loadings in each compound class, assigned using H/C and O/C ratios[22] *based on Formularity classification.*

CONCLUSION

We believe that PyKrev is a useful and accessible tool for scientists who wish to work in Python with complex and rich datasets measured by FT-MS. PyKrev is one of a suite of emerging tools that enable researchers to make the most of FT-MS processed data without resorting to costly proprietary software whilst retaining a minimal number of components in a programmable workflow.

The open source nature and simple implementation of the PyKrev library provide a large capacity for updates capturing future advances in the field of FT-MS data analysis. We heartily encourage collaboration and contributions to the library by specialists working in this field.

ASSOCIATED CONTENT

Supporting Information

PyKrev is available at https://github.com/Kzra/pykrev alongside a user guide on how to use the library, and specific guides on performing PCA and creating UpSetPlots with PyKrev.
A description of PyKrev module organisation and core functionality is given in S.1. Table 1 (.pdf).

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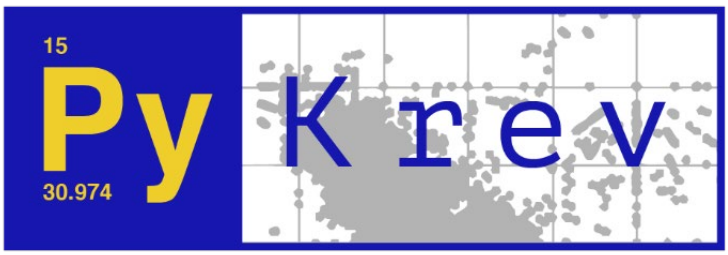
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