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## MathIOmica: An Integrative Platform for Dynamic Omics

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Multiple omics data are rapidly becoming available, necessitating the use of new methods to integrate different technologies and interpret the results arising from multimodal assaying. The MathIOmica package for *Mathematica* provides one of the first extensive introductions to the use of the Wolfram Language to tackle such problems in bioinformatics. The package particularly addresses the necessity to integrate multiple omics information arising from dynamic profiling in a personalized medicine approach. It provides multiple tools to facilitate bioinformatics analysis, including importing data, annotating datasets, tracking missing values, normalizing data, clustering and visualizing the classification of data, carrying out annotation and enumeration of ontology memberships and pathway analysis. We anticipate MathIOmica to not only help in the creation of new bioinformatics tools, but also in promoting interdisciplinary investigations, particularly from researchers in mathematical, physical science and engineering fields transitioning into genomics, bioinformatics and omics data integration.

With the advent of readily available omics technologies that will greatly aid the advancement of the emerging field of precision medicine, the need to integrate information from these disparate omics technologies<sup>1–6</sup> (genomics, transcriptomics, proteomics, metabolomics, etc.) is becoming more apparent. The role of bioinformatics in analyzing such high throughput omics data is unquestionable, and evident in major projects, such as the ENCODE Project<sup>7</sup>, 1000 Genomes<sup>8</sup>, UK10K<sup>9</sup> project, and will be indispensable in the Precision Medicine Initiative<sup>10</sup> (PMI) now underway. In particular, novel medical insights are expected through the integration of genomic information with the global monitoring of molecular components and physiological states in a coherent fashion, and the modeling of the integrated complex systems and associated dynamic pathways. The molecular component interactions are central in all biological processes and have contributed to our rudimentary understanding of disease onset, progression and treatment. Large-scale efforts to globally follow all such omics components in systems and in individuals are currently underway, including genomic and pharmacogenomic considerations<sup>11–16</sup>. One of the first such examples was the integrative Personal Omics Project (iPOP)<sup>16–18</sup>, profiling multiple omics datasets from a single individual over multiple time points. These studies provide a plethora of data and more are on the way. However, the studies show that the methodology for integrating such information is underdeveloped, especially in terms of dynamical analyses that directly address the complexities of biological experimentation, such as uniform normalization procedures across time course omics data and uneven time sampling.

Great progress has been made in the area of development of bioinformatics tools and platforms, towards data integration<sup>19–21</sup>. Notable examples include Bioconductor<sup>22,23</sup> and BioPython<sup>24</sup>, Galaxy<sup>25</sup>, GenePattern<sup>26</sup>, DAVID<sup>27</sup>, QIAGEN's Ingenuity Pathways (IPA, QIAGEN Redwood City, [www.qiagen.com/ingenuity](http://www.qiagen.com/ingenuity)), Cytoscape<sup>28</sup> and many more. Bioinformatics is now an essential tool for the modern geneticist, and intertwined with every aspect of genomics research. The practicing bioinformatician typically uses a combination of programs for the job at hand, and their language of choice for development includes high-level languages such as R<sup>29</sup> and Matlab by Mathworks, scripting languages such as Python and Perl, Unix shell scripts (e.g. Bash), as well as coding tools written in C, C++, Java, etc. Bioinformatics tools are continuously being developed and improved to address the increasing demand for sophisticated analysis tools. However there has not been as much development for bioinformatics in the Wolfram Language and Mathematica<sup>30</sup>. Mathematica, which was released in 1988<sup>31</sup>, has been widely used by mathematical and physical scientists and students and has extensive symbolic, statistical and computational capabilities. Furthermore, it is used widely in introductory and advanced mathematics courses, including first college courses in calculus. There have been a few packages for bioinformatics in Mathematica<sup>32–36</sup>,

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## MathIOmica Function Guide

### Data Importing

**DataImporter** — graphical interface to import data from files  
**DataImporterDirect** — import data as an OmicsObject directly from files  
**OmicsObjectCreator** — create an OmicsObject for use with MathIOmica  
**OmicsObject** — structured data used by MathIOmica  
**DataImporterDirect.Labeled . FileSelector**

### Data Processing of an OmicsObject

**Applier** — apply functions to an OmicsObject  
**ApplierList** — apply a function to a list of lists from the values across an OmicsObject  
**EnlargeInnerAssociation** — combining a list of OmicsObject elements by enlarging the inner associations  
**EnlargeOuterAssociation** — combine a list of OmicsObject elements by enlarging the outer associations  
**FilteringFunction** — filters an OmicsObject's data by a chosen comparison to a cutoff  
**FilterMissing** — filters out data from OmicsObject if across the datasets a percentage of data points is missing.  
**LowValueTag** — tag low values in an OmicsObject and tag values in specified position as Missing[] based on a provided value cutoff.  
**Returner** — substitute data in an OmicsObject  
**MeasurementApplier . ConstantAssociator . OmicsObjectUniqueMassConverter**

### Data Processing of a (Time) Series

**CreateTimeSeries** — creates a time series list across an OmicsObject using outer keys  
**TimeExtractor** — extract a list of sorted times from an OmicsObject's outer keys  
**ConstantSeriesClean** — removes constant list series from an association of lists  
**SeriesApplier** — apply a function to an association of lists, masking for Missing values  
**SeriesCompare** — merges the values of two associations of series by pointwise operation on the values of each matching pair of keys  
**SeriesInternalCompare** — compare each value in each list of an association of lists to an internal reference value in the list

### Miscellaneous Data Processing

**JoinNestedAssociations** — merges a nested association list by joining inner associations  
**MissingDataCreator** — fill in Missing tags in a paired dataset for which the first component is not a member of a given sample list  
**StandardizeExtended** — standardize data that may include Missing values

### Spectral Analysis

**Autocorrelation** — calculate the normalized autocorrelation for a time series using a Lomb-Scargle based approach  
**LombScargle** — calculate the Lomb-Scargle power spectrum for time series data  
**InverseAutocovariance**

### Classification and Clustering

**BootstrapGeneral** — perform a resampling of an OmicsObject's data with replacement  
**QuantileEstimator** — obtain the quantile estimator following bootstrap for time series  
**TimeSeriesClassification** — identify classes of temporal behavior in time series  
**TimeSeriesClusters** — perform two-tiered clustering of time series data  
**MatrixClusters** — perform hierarchical clustering in both dimensions a matrix  
**TimeSeriesSingleClusters**

### Annotation and Enrichment

**GetGeneDictionary** — creates an ID/accession dictionary from a UCSC search  
**GeneTranslation** — Convert gene identities across different annotations/accessions  
**GOAnalysis** — Gene Ontology (GO) enrichment analysis  
**KEGGAnalysis** — KEGG: Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis  
**KEGGDictionary** — create a dictionary from KEGG: Kyoto Encyclopedia of Genes and Genomes terms  
**OBOGODictionary** — create an Open Biomedical Ontologies (OBO) Gene Ontology (GO) vocabulary dictionary  
**GOAnalysisAssigner . KEGGAnalysisAssigner . EnrichmentReportExport . MassDictionary . MassMatcher . UCSCBrowserSQL**

### Multiple Hypothesis Testing

**BenjaminiHochbergFDR** — calculate the Benjamini Hochberg approach false discovery rates (FDR) from a list of p-values

### Visualization

**MatrixDendrogramHeatmap** — generate dendrograms and heatmap plot for a matrix  
**MatrixDendrogramsHeatmaps** — generate multiple dendrograms and heatmap plots for a matrix with many classifications  
**TimeSeriesDendrogramHeatmap** — generate a dendrogram and heatmap plot for time series data clusters  
**TimeSeriesDendrogramsHeatmaps** — generate multiple dendrograms and heatmap plots for multiple classified classes of time series data clusters  
**KEGGPathwayVisual** — representation for a KEGG: Kyoto Encyclopedia of Genes and Genomes pathway  
**MSViewer** — view spectra for mass spectrometry from .mzXML or .mzML files  
**Heatmapper . TimeSeriesSingleDendrogramHeatmap . TimeSeriesSingleDendrogramsHeatmaps**

**Figure 1. MathIOmica Guide.** MathIOmica introduces multiple new functions to assist with bioinformatic analysis. The brief guide provides a short description for main functionality, and is available in the MathIOmica in-built documentation, providing a version with links pointing to each function's detailed description and example usage. MathIOmica's full documentation is integrated with Mathematica's native documentation upon installation and can be evaluated in place by the user.

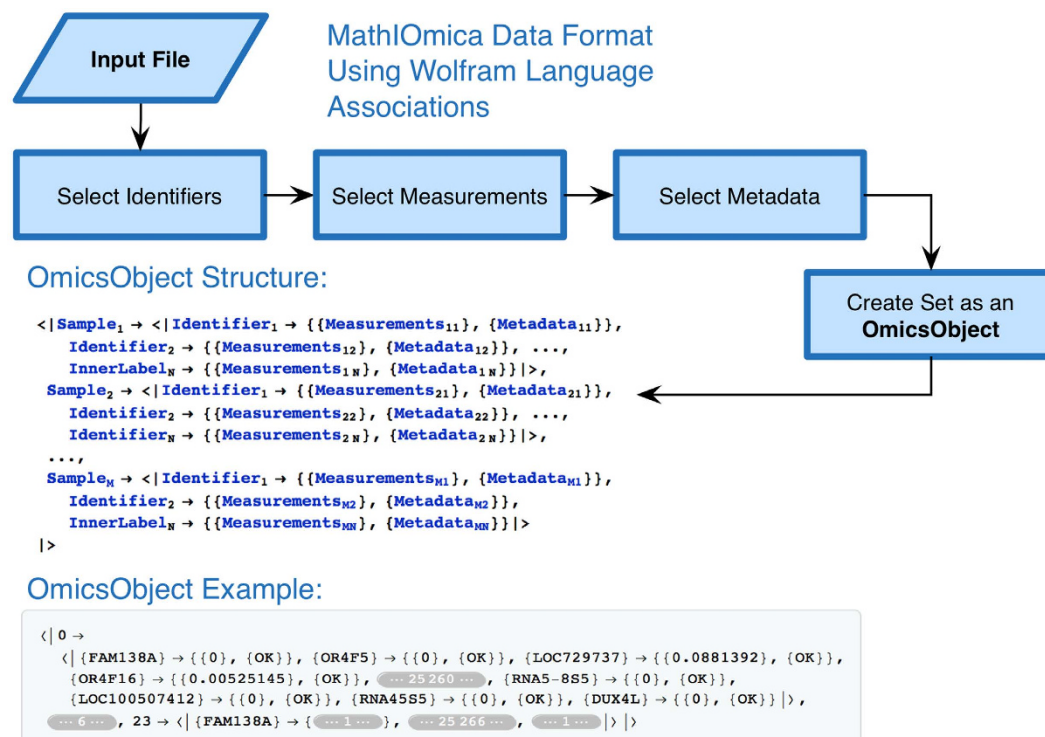
but a general approach and package, incorporating standard tools used in data exploration by biologists, has not been implemented systematically. We believe that the availability of bioinformatics packages in Mathematica will not only provide additional tools for current bioinformatics users, but additionally encourage interdisciplinary research from mathematical and physical science investigators that want to enter the field of applied bioinformatics.

In this work we present MathIOmica, an open source software package written in the Wolfram Language for Mathematica that provides a framework for the analysis and interpretation of (dynamic) multi-omics data. The package is one of the first steps towards the development of new universal methods and tools to integrate biological omics data in the Wolfram language. It supplements Mathematica with multiple new functions that facilitate the analysis and development of new analysis methods for dynamical omics data. MathIOmica provides a framework for importing datasets in a structured way, including methods for processing such data, addresses time series analysis of omics data (including considerations for missing values), and includes annotation capabilities using known databases (such as UCSC Browser Tables<sup>37,38</sup>, Gene Ontology<sup>39,40</sup> and KEGG pathways<sup>41,42</sup>). A particular feature of MathIOmica is the extensive documentation with over 1000 pages total of tutorials and input/output examples for functions, including the options for each function, that have been inbuilt into the package and are readily available through Mathematica's native help system upon installation. Two fully worked examples are also in the documentation based on dynamic data from the pilot iPOP project to provide additional real data examples of using the framework. MathIOmica was created with an outlook to become an extensible framework, to enable bioinformatics development in the Wolfram language, and use the considerable computational capabilities already available in Mathematica.

MathIOmica is available to download at <https://github.com/gmiaslab/mathiomica> and has a dedicated page found at <https://mathiomica.org>.

## MathIOmica's Framework

**Overview and Workflow.** We have been developing an integrative framework, MathIOmica, with multiple modules for omics downstream statistical analysis now completed. MathIOmica has multiple functions, Fig. 1, utilizes a flexible data format, Fig. 2, can implement multi-omics analyses, as shown in the example workflow in



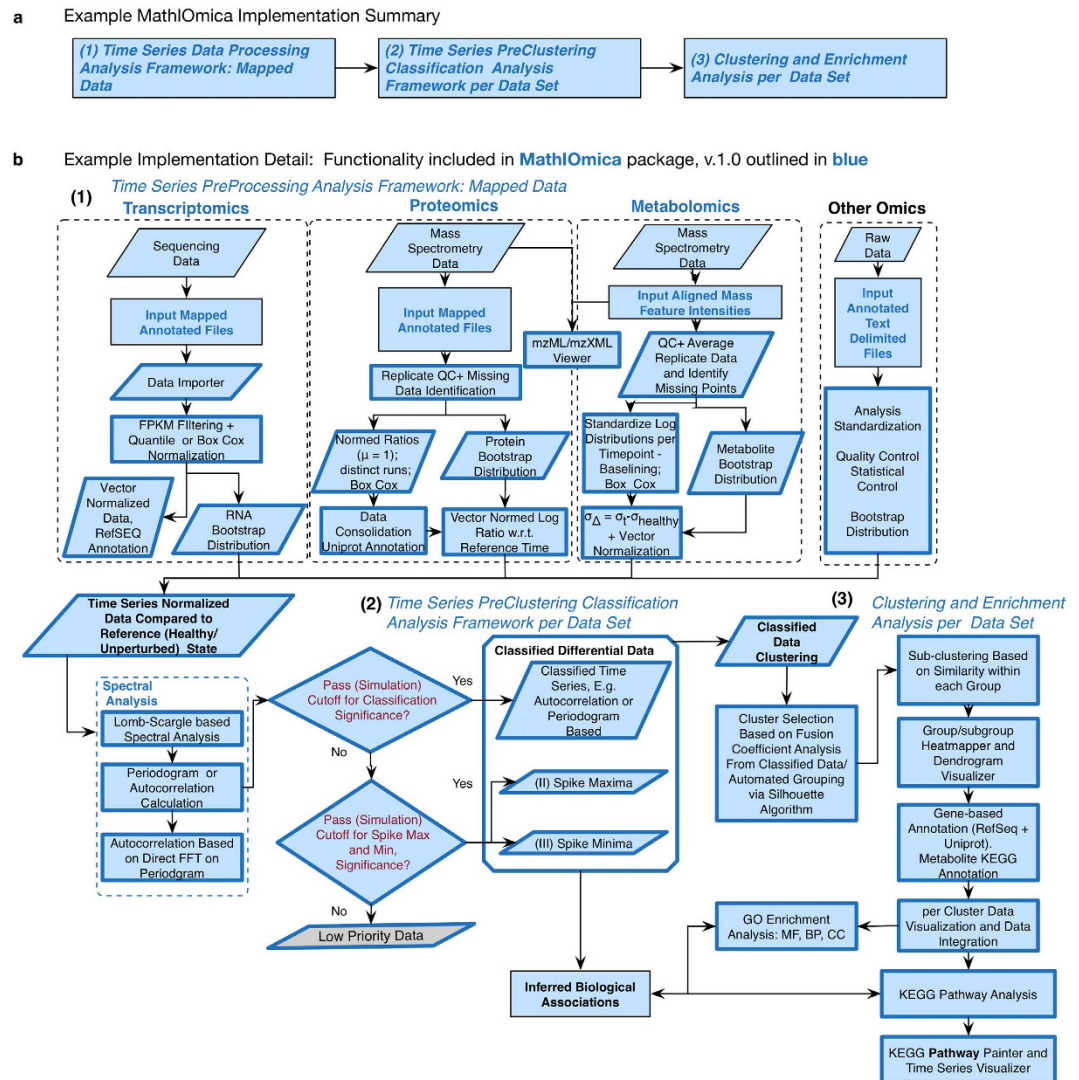
**Figure 2. MathIOmica OmicsObject Format.** The MathIOmica v.1 input format was redesigned to implement the 10.3+ Wolfram Language improvements to use associations (cf. dictionaries in Python). The data format is termed an OmicsObject, and is an association of associations with common identifiers as inner association keys across multiple samples. It addresses rapid sample identification, measurement and metadata all maintained for user accessibility and additionally accommodates missing values. In addition to the user having control of all aspects of the input data via Query commands on the OmicsObject representing the data, MathIOmica includes specialized functions designed specifically for creating and manipulating an OmicsObject.

Fig. 3, and provides various graphical interfaces and result visualizations, Fig. 4. MathIOmica integrates multiple omics information starting from mapped experimental omics data - typically RNA-Sequencing expression levels, mapped protein intensities, and small molecules intensities. Using this framework we can analyze different omics data (genome, transcriptome and proteome) individually, based on each technology's requirements, perform quality control (accounting for experimental and technical limitations) and set all the different technologies on common ground (statistical transformations). MathIOmica provides classification methods to identify patterns in the data, as well as annotation capabilities as discussed briefly below. Finally, extensive documentation is provided for every function and its option set.

**Wolfram Language Code Base.** MathIOmica was written exclusively in the Wolfram Language<sup>31</sup>. The language provides a robust, fully tested, cross-platform environment (Mac OS, Windows and Linux have been tested). The Wolfram Language already leverages symbolic, statistical, computational and database capabilities that are utilized by MathIOmica. The functions were written using the recently available association constructs (akin to dictionaries in other languages, e.g. Python), in Mathematica 10.4+<sup>30</sup>, and with a functional approach in mind. The source code is provided with the package, and adheres to standard Wolfram Language conventions with respect to capitalization and definitions of functions. All documentation and data files necessary are also provided with the code. In implementing the package in Mathematica, we find the standard Mathematica notebook interface provides a balance of detailed note taking, and rationale interweaved with code, commenting and results, and believe this feature to be particularly attractive for sharing executable code, and for documenting analysis extensively for reproducibility.

**Data Format.** MathIOmica uses standard Mathematica expressions. In addition we created a simple structured data format termed an OmicsObject, Fig. 2. This OmicsObject input format was created to facilitate data organization, with an eye for multiple datasets with different information included, such as identifiers to samples, identifiers to entities in the sample (e.g. gene names), measurements for the entities (e.g. intensities or gene expression), and any metadata the user may wish to keep or use in their analysis. The main format is two levels of associations, with outer keys matching sample labels, inner keys matching identifiers for the components, and values for each inner key taking two lists, one for measurements and another for metadata, as shown in Fig. 2. The OmicsObject was designed to utilize 10.3+ Wolfram Language improvements to use associations (cf. dictionaries in Python). This data format allows rapid sample identification, measurement and metadata all maintained

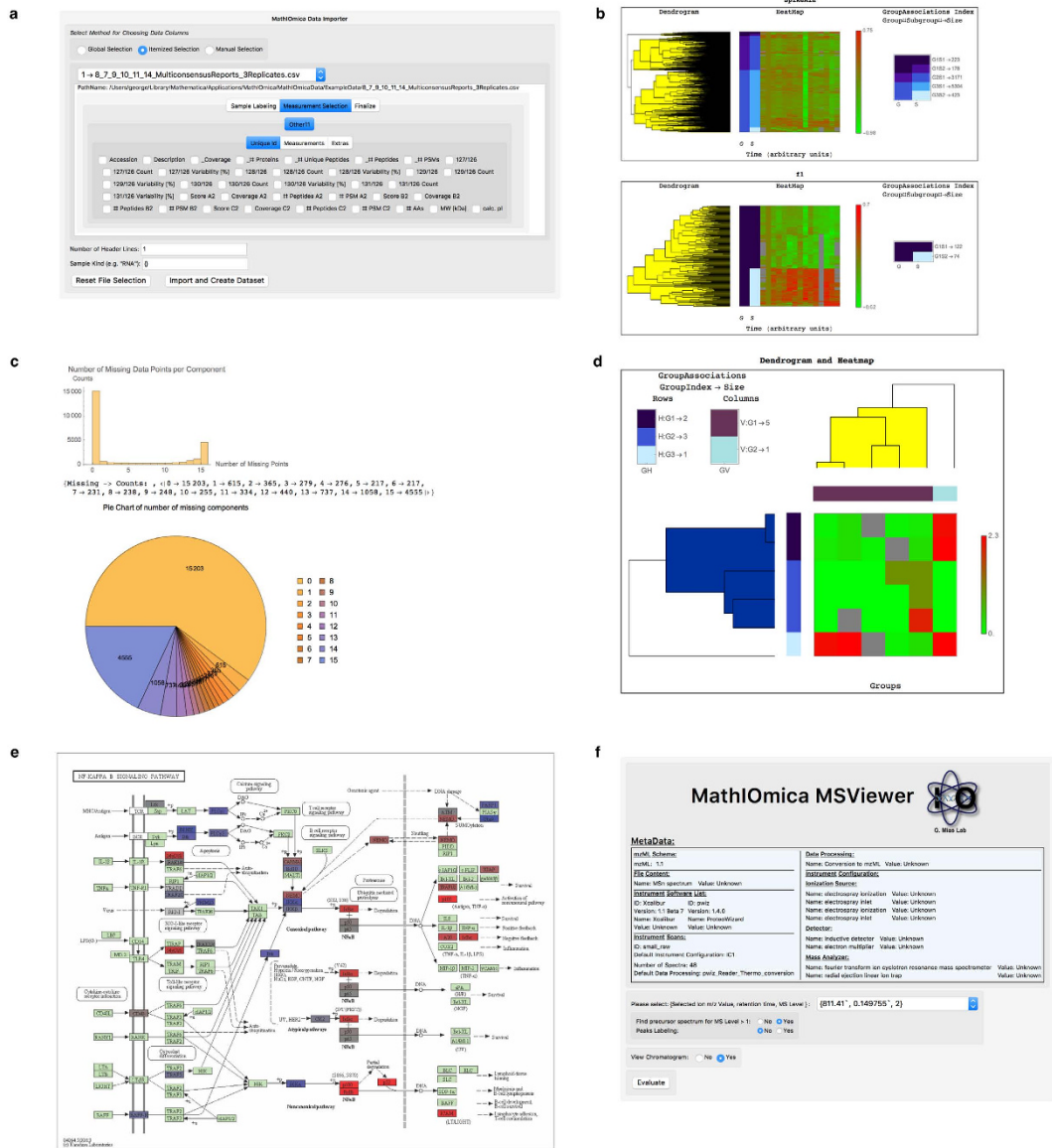




**Figure 3. MathIOmica Implementation Example.** MathIOmica allows the integration of multiple omics dynamic data. The generalized approach summarized in (a) first preprocesses each omics dataset according to its own considerations towards a common format of a time series. The time series can then be classified for temporal patterns using spectral analyses. Finally classes of temporal patterns are clustered, and the results can be visualized and further analyzed for Gene Ontology or KEGG pathway overrepresentation. A fully worked example with the various details shown in (b) is provided in the MathIOmica Tutorial as part of the in-built package documentation (see also Supplementary Note 1 for a printout version).

at various stages for user accessibility. MathIOmica includes specialized functions designed specifically for the OmicsObject data format to assist the user in controlling all aspects of the input data, Fig. 1. Furthermore, an OmicsObject is an association of associations, and so the inbuilt powerful Wolfram Language Query function can be used directly to access and manipulate components.

**Data Processing. OmicsObject creation and manipulation.** MathIOmica offers utilities to process mapped data and import them into an OmicsObject, Fig. 1, including a graphical interface, Fig. 4. The data format for the graphical interface importer can be any text delimited file, including files with comma separated values (csv), or tab delimited (tsv), as well as Excel spreadsheets (Microsoft), which are typical standard outputs in many computational applications or informatics software. Once the data has been imported or cast into an OmicsObject then the data may be processed as fit for each omics. This includes transformations such as quantile normalization, Box-Cox power transformations<sup>43</sup>, and filtering based on any field. Additionally the data can be tagged for low or missing values and filtered. For more customizable options the Applier function allows the user to apply any function of interest across the OmicsObject components. The workflow for the example multi-omics implementation in the documentation's tutorials is shown in Fig. 3 - we are also providing a printout version in Supplementary Note 1.



**Figure 4. MathIOMica Example Screenshots.** MathIOMica has various graphical interfaces and visualization capabilities, including: (a), a graphical importer, (b), time series clustering visualization, (c), missing data filtering summaries, (d), clustering of matrices, (e), visualization of KEGG pathways, and (f), a mass spectrometry viewer.

*Time Series.*

- *Time Series from an OmicsObject*. From an OmicsObject simple operations can create a time series for each component, e.g. each gene. MathIOmica provides functions to facilitate the process, such as CreateTimeSeries and TimeExtractor. The functions assume an OmicsObject as an input for which times have been used as the sample labels strings (outer keys). The time series can be unevenly sampled and contain missing values as well.
- *Spectral Analysis*. Time series spectral analysis for missing data has been implemented through various standard approaches in MathIOmica. The main functionality exists to use a Lomb-Scargle transformation to handle uneven sampling and/or missing data, an approach that has been adapted from astronomy and used in the analysis and classification of dynamics in biological systems<sup>17,44–56</sup>. Two main options are provided, the Lomb-Scargle function for reconstructing a periodogram directly, and additionally the Autocorrelation function for obtaining the autocorrelations through an inverse Fourier transform of the power spectrum for the data.
- *Classification and Clustering*. For sets of time series measurements, (e.g. gene expression levels, protein intensities, compound concentrations, temperature) we would like to identify groups of entities whose temporal behavior is similar. If we can classify temporal signals that show similar behavior into classes, then we can also look for associations/connections between the members of each class. The behavior of a given signal can

be considered in terms of time or frequency (if we can Fourier transform the signal). The structure of the signal can then be described through autocorrelations, or equivalently its power spectrum (periodogram). Additionally, a signal can also be modeled with a time series model that has certain structure, e.g. autoregressive (AR), moving-average (MA), autoregressive moving-average (ARMA) etc. In this version, MathIOMica provides five different methods for time series classification through its `TimeSeriesClassification` function: Three methods use statistical cutoffs generated typically through simulation and are provided by the user: (i) Classification based on a Lomb-Scargle periodogram, classifying data into classes for time-series showing the same dominant frequency in their spectra; Classification based on autocorrelation, either computed by (ii) an inverse Fourier transform on the Lomb-Scargle periodogram to address missing data/uneven sampling or (iii) autocorrelation using interpolation (by default cubic) to address missing data/uneven sampling if any. Additionally two methods classify time series data into appropriate models, either (iv) by model kind, or (v) into classes that correspond to same model and parameters for the model.

Following the classification, each class of time series can be clustered using hierarchical clustering using either `TimeSeriesClusters` or `TimeSeriesSingleClusters`. We should note here a subtlety when performing clustering of data series that are based on absolute values of intensity, (e.g. from a power spectrum/periodogram). In such cases, the sense (sign/phase) of the original time series cannot be detected directly from the intensity values. Therefore, such data vectors cannot distinguish correlated data from anti-correlated data that have the same periodogram structure. MathIOMica provides functionality to address this, through performing two tiers of clustering in `TimeSeriesClusters`, which can potentially distinguish the sense of each series, first clustering data using the periodograms to compute distances between components, and performing a secondary clustering on the results, using the original (non spectral) data for each time series that can assess the directionality of the data in real space.

**Matrix Data Clustering.** Standard clustering of data matrices can be performed by the function `MatrixClusters` in both the horizontal and vertical directions to identify groups based on similarities between the input series rows and columns.

**Annotation and Enumeration.** MathIOMica provides annotations and over-representation analysis for gene ontology (GO) and KEGG pathways: (i) For GO analysis, the `GOAnalysis` function uses annotations (default is for human data) obtained from the Gene Ontology consortium. The annotation by default uses human data annotated with UniProt<sup>57</sup> identifiers/accessions. Advanced function options also allow the user to use or directly download data for other species (examples with mouse and arabidopsis data are included in the documentation). An internal dictionary function can convert Gene Symbol and other identifiers obtained from the UCSC Browser<sup>38</sup> tables to UniProt. (ii) In terms of KEGG pathway analysis, MathIOMica provides the `KEGGAnalysis` function. This uses annotations (default is for human data obtained from KEGG and by default uses human data annotated with KEGG Gene IDs (advanced options can also be used to utilize data from other species). Again, an internal dictionary function can convert Gene Symbol and UniProt identifiers to KEGG Gene IDs. Additionally, a molecular analysis is implemented for querying compounds against KEGG maps for metabolomics considerations.

Both `GOAnalysis` and `KEGGAnalysis` functions perform an over-representation (ORA) analysis, providing a p-value assessed by a hypergeometric function for membership in term categories/pathways. Additionally, a false discovery rate (FDR) cutoff for reporting is implemented, where adjusted p-values are computed (q-values) by a Benjamini Hochberg method<sup>58</sup>. The method and cutoffs can be customized (e.g. Bonferroni) by advanced users.

As mentioned above, MathIOMica includes a gene dictionary translation function, `GeneTranslation`, to convert identifiers between multiple databases. Additionally dictionaries are generated to provide GO term and KEGG pathway term descriptions.

## Visualization.

- **Dendrograms and Heatmaps.** MathIOMica provides dendrogram/heatmap representations of clustering results. Separate functions are available to implement visualization for time series (with two-tier clustering [`TimeSeriesDendrogramHeatmap`] and single-tier clustering options [`TimeSeriesSingleDendrogramHeatmap`] available), as well as matrices [`MatrixDendrogramHeatmap`] that have been clustered. If classifications have been carried out, all classification output and graphs can be output simultaneously, e.g. by `TimeSeriesDendrogramsHeatmaps` (see Fig. 4 and the inbuilt documentation).
- **KEGG Pathways.** A visual representation for KEGG pathways is implemented through use internally of the KEGG API. The returned data output can be a URL pointing to the online version of the pathway, that may be used in a browser, a downloaded figure, or a sequence of figures that may be used to generate animations in the case of time series data. Specific genes/proteins can be highlighted in the pathways, as well as represented in terms of intensities.
- **Mass Spectrometry Spectra.** MathIOMica provides a mass spectrum viewer for viewing .mzXML or .mzML<sup>59,60</sup> raw data. The viewer provides MS<sup>n</sup> viewing capabilities, filtering searches based on mass to charge ratios as well as retention times, viewing of precursor spectra and additionally summarizes the file metadata.

**Documentation and Examples.** One distinct feature of MathIOMica is the utilization of Mathematica's inbuilt system for documentation. MathIOMica was compiled so that its documentation is directly available in the Mathematica help system. This includes autocompletion in the system, templates for function use and direct access to definitions while developing code. Every function has at least a working example that can be evaluated in place, and documentation of all option choices for a given function. In all, more than 1000 pages of

documentation and output are available. A printout of the function manual and tutorial are also available online at the MathIOmica websites.

**iPOP examples.** Data from the first integrative Personal Omics Profiling<sup>16,17</sup> (iPOP) are used for inbuilt examples, comprised of dynamics from proteomics transcriptomics and metabolomics. Briefly, the data corresponds to a time series analysis of omics from blood components from a single individual. Different samples (from 7 to 21 included here) were obtained at different time points. The time points included here correspond to days ranging from 186th to the 400th day of the study. On day 289 the subject of the study had a respiratory syncytial virus (RSV) infection. Additionally, after day 301, the subject displayed high glucose levels and was eventually diagnosed with type 2 diabetes. The analyzed mapped data are used in these examples for illustrative purposes - these and additional dynamic omics data that will become available can also be accessed on MathIOmica's main website. Various analyzed portions of the data are used in the documentation examples.

Furthermore, two full simple analyses are presented for the integrated full omics and streamlined transcriptome analyses as documentation tutorials. The main steps are depicted in Fig. 3, and the tutorials are included as Supplemental Notes 1 (multiple omics) and 2 (transcriptome). Briefly, as shown in Fig. 3, this simplified analysis example shows how each omic component can be first analyzed according to its own considerations towards a normal distribution and a time series of normalized intensities, relative to a healthy reference point. For each omic dataset a Lomb-Scargle periodogram classification identifies dominant frequency classes addressing periodicity, as well as Spike Max and Spike Min classes that correspond to singular events of high or low intensity. Cutoffs for the classification are provided from a bootstrap distribution construction (sampling with replacement) to compare against simulated randomized measurements. Following classification, data is clustered directly based on their periodograms (agglomerative clustering). Groups and subgroups are identified, with automatic group identification performed through a standard silhouette algorithm. The groups and subgroups in the different pattern categories are then checked for biological significance, looking for enrichment in GO categories and KEGG pathways. KEGG pathways are finally visualized and can be color coded to create animations corresponding to the intensities at different time points.

## Discussion

We have created MathIOmica, one of the first open source packages in the Wolfram Language to perform bioinformatics analyses. MathIOmica provides a general framework that is extensible to enable current and future workflows for integrating multiple data. This includes analysis of data, classification, annotation and visualization modules. The extensive inbuilt documentation provides an interactive environment for users to learn function usage and implementation.

We must note that the current version of MathIOmica is based entirely on established algorithms, which are also already available and implemented in other platforms/languages used widely by practicing bioinformaticians, especially through Bioconductor<sup>22</sup>. MathIOmica's features are directed at an interdisciplinary audience, in addition to the practicing bioinformaticians, to include particularly mathematicians and physicists that use Mathematica in their research. It utilizes the high-level Wolfram language that is very familiar to quantitative scientists, and we believe this will facilitate novel development and introduce new algorithms into bioinformatics. Mathematica interfaces directly with R, Java and other languages, including the ability to work with C code, so it supplements other platforms and tools. The notebook interface is extremely attractive for prototyping, developing and sharing results, as well as a teaching platform.

We anticipate the next versions of MathIOmica to include further direct analysis of raw data, in addition to more advanced downstream classification and network analysis, as well as graphical user interfaces. We also plan to include a genome visualization, to locate differentially expressed genes in the genome, and merge structural and functional genomics in one package. All future versions and improvements will be provided for free at mathiomica.org and GitHub repositories.

## Methods

**Code Base.** MathIOmica was written exclusively in the Wolfram language. The package was built using Wolfram Workbench plugin for Eclipse (Mars) and built on Mathematica 10.4. It is also compatible with the newly released Mathematica 11. All source code is freely available and openly provided under an MIT open source license.

**Availability.** MathIOmica is available for download as a Mathematica package at:

- <https://mathiomica.org>
- <https://github.com/gmiaslab/mathiomica>

The package contains the full open source code and documentation, which is released under an MIT open source license. All example files and data used therein are included as part of the package.

**Tutorial Supplementary Notes.** MathIOmica's documentation tutorials for multiple omics and transcriptome are provided online as Supplementary Notes 1 and 2 respectively.

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## Author Contributions

G.I.M. conceived of and oversaw the study, carried out project planning, software design, tested and developed code, and wrote the manuscript. T.Y. was involved in computational work, wrote code and documentation, R.R. wrote code, L.R.K.B. wrote code and analyzed data, V.V.S. provided experimental data, C.C. designed and implemented the project website. G.I.M. is the senior author on this work. All authors reviewed the manuscript.

## Additional Information

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