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Recent advances in mass spectrometry-based computational metabolomics

Timothy M. D. Ebbels[1], Justin J. J. van der Hooft[2,3], Haley Chatelaine[5], Corey Broeckling[4], Nicola Zamboni[8], Soha Hassoun[6,7] and Ewy A. Mathé[5]

Abstract

The computational metabolomics field brings together computer scientists, bioinformaticians, chemists, clinicians, and biologists to maximize the impact of metabolomics across a wide array of scientific and medical disciplines. The field continues to expand as modern instrumentation produces datasets with increasing complexity, resolution, and sensitivity. These datasets must be processed, annotated, modeled, and interpreted to enable biological insight. Techniques for visualization, integration (within or between omics), and interpretation of metabolomics data have evolved along with innovation in the databases and knowledge resources required to aid understanding. In this review, we highlight recent advances in the field and reflect on opportunities and innovations in response to the most pressing challenges. This review was compiled from discussions from the 2022 Dagstuhl seminar entitled "Computational Metabolomics: From Spectra to Knowledge".

Addresses

[1] Section of Bioinformatics, Department of Metabolism, Digestion & Reproduction, Imperial College London, Burlington Danes Building, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK
[2] Bioinformatics Group, Wageningen University & Research, Wageningen 6708 PB, the Netherlands
[3] Department of Biochemistry, University of Johannesburg, Auckland Park, Johannesburg 2006, South Africa
[4] Bioanalysis and Omics Center, Analytical Resources Core, Colorado State University, Fort Collins, CO, USA
[5] Informatics Core, Division of Preclinical Innovation, National Center for Advancing Translational Sciences, Rockville, MD, USA
[6] Department of Computer Science, Tufts University, Medford, MA, USA
[7] Department of Chemical and Biological Engineering, Tufts University, Medford, MA, USA
[8] Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland

Corresponding authors: Ebbels, Timothy MD. (t.ebbels@imperial.ac.uk); Mathé, Ewy A. (ewy.mathe@nih.gov)

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Introduction

As the field of metabolomics continues to grow, computational methods that enable analysis and interpretation of these complex data are of paramount importance. This area, now known as computational metabolomics, is a highly interdisciplinary science lying at the intersection of computer science, bioinformatics, chemistry, medicine, and biology. It focuses on applying computational, statistical, and machine learning methods to analyze and interpret metabolomic data and its integration with other datasets, such as other omics or clinical data. Computational metabolomics is swiftly evolving, making reviews of the field quickly out of date. Nonetheless, there have been several excellent reviews of tools and resources in the last two years [1–3], serving as important guides to both experienced scientists and trainees. Program and community efforts also exist that consolidate information on the availability and usage of data and tools [4,5] and systematically identify challenges in the use of metabolomics data in multi-omics research [6]. Our intent here is i) to provide a current, concise overview of the latest advances in mass spectrometry-based computational metabolomics and ii) to reflect on current challenges and proposed solutions (Figure 1). This review stems from the most recent seminar in the Dagstuhl Computational Metabolomics series, held in Schloss Dagstuhl, Germany in May 2022, entitled "Computational Metabolomics: From Spectra to Knowledge".

Data acquisition and processing techniques

Recent developments in LC-MS metabolomic data processing include the latest releases of MZmine 3 [7], MS-DIAL 5 [8], and XCMS [9], which provide raw data

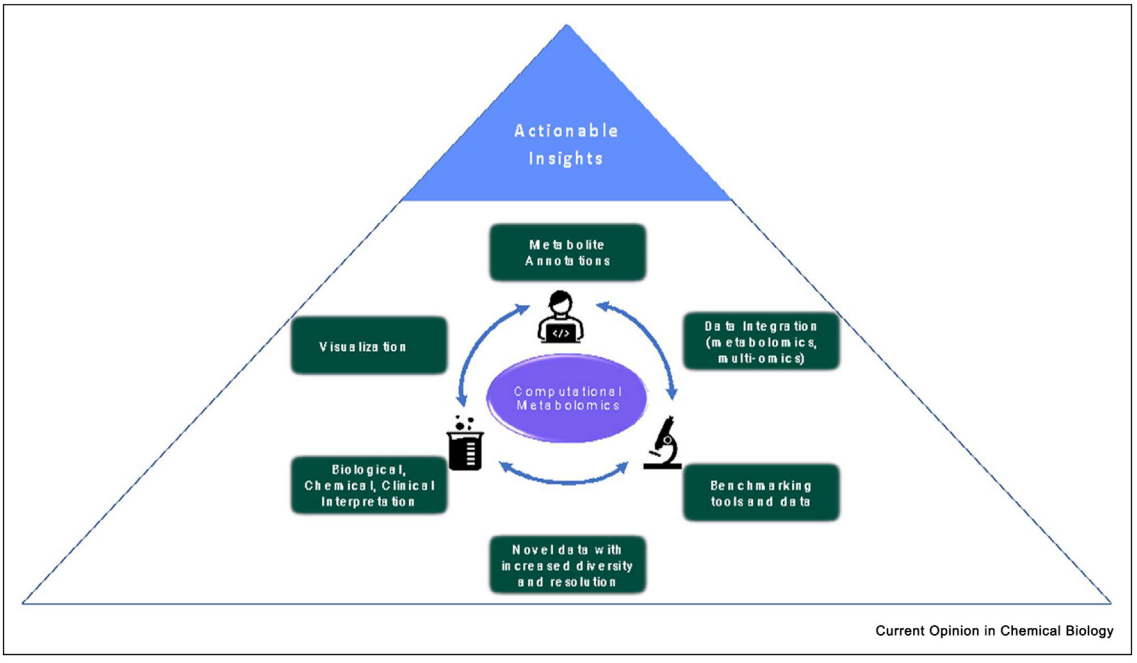
Abbreviations

API application programming interface
CANOPUS clear assignment and ontology prediction using mass spectrometry
CASMI Critical Assessment of Small Molecule Identification
CFM-ID competitive fragmentation modeling identification
COMETS Consortium for Metabolomics Studies
DDA data dependent acquisition
DIA data independent acquisition
EMM extended metabolic model
GNPS Global Natural Product Social Molecular Networking
HMDB Human Metabolome Database
KEGG Kyoto Encyclopedia of Genes and Genomes
LASSO least absolute shrinkage and selection operator
LC liquid chromatography
MassQL mass spectrometry query language
mQACC Metabolomics Quality Assurance and Quality Control Consortium
MS mass spectrometry
MS/MS tandem mass spectrometry
NLP natural language processing
NMDR National Metabolomics Data Repository
PCA principal components analysis
PUMA Probabilistic modeling for Untargeted Metabolomics Analysis
RaMP DB: relational database of metabolic pathways
SODA Software Data Exchange (part of the Metabolomics Association of North America)
t-SNE t-distributed stochastic neighbor embedding
TMAP tree manifold approximation and projection
UMAP uniform manifold approximation and projection

exploration and processing capabilities using state-of-the art approaches. In addition there have been new methods addressing problems such as scalability [10] and even peak detection-free processing [11]. Both the R and Python environments have seen considerable development for versatile MS and MS/MS data processing, with major efforts to modernize legacy code as well as adding new functionality [12–15].

Tandem mass spectrometry (MS/MS) supports confident annotation of metabolites and can, through improved selectivity and sensitivity, enhance quantitation accuracy. Data independent acquisition MS/MS (DIA) has emerged as an enticing alternative to traditional data dependent (DDA) methods. One clear advantage of DIA is the potential to provide complete MS/MS coverage, an area where DDA has generally

Figure 1



A conceptual overview of computational metabolomics.

struggled due to duty cycle limitations. DIA has recently been used to support stable isotope resolved metabolomics and to provide constant sampling of variably labeled precursors, with fragment ion spectra enabling position specific labeling assignments [16].

Fully untargeted precursor-product assignment using DIA increases coverage and MS duty cycle at the expense of decreasing (or even eliminating) precursor mass selectivity. As a result of the decreased selectivity, DIA spectra are more highly convoluted than DDA spectra. DIA is implemented on instruments with diverse architecture, where precursor selection can be performed by quadrupoles or ion mobility cells (or both), with discrete or overlapping precursor windows that can be wide or narrow. However, testing all fragmentation strategies that encompass the diversity and complexity of MS/MS spectra is impractical. A recent in silico framework addresses this issue by evaluating data acquisition strategies on their coverage and mass spectral quality, thus reducing machine time [17,18]. A particularly powerful approach to analyzing mass fragmentation spectra, including those from DIA, is molecular networking [19], enabled within the Global Natural Product Social Molecular Networking (GNPS) resource. This technique embeds spectra according to similarity within a large network of public data, enabling grouping of structurally related molecules and greatly aiding metabolite annotation. Additionally, both spectrum- [20] and chromatogram-centric [21] approaches are under active development in proteomics data processing, which can serve as inspiration for continued development of metabolomics DIA data processing for both qualitative and quantitative aims.

Several software tools have been released recently that enable guided interpretation of DIA metabolomics data. DIAMetAlyzer utilizes a DDA-guided approach to reap the quantitative benefits of DIA, while supporting confident annotation, flexibility in DDA library generation, and estimating annotation false discovery rates [22]. Another approach, DecoID, uses a LASSO regression model to estimate the proportions of the DDA MS/MS spectra that contribute to the DIA spectrum, thereby deconvolving chimeric DIA spectra [23]. MetaboAnnotatoR also addresses deconvolution by using peak shape correlation in DIA spectra, as well as exploiting highly configurable spectral libraries [24]. Despite this progress, there remains opportunity to more fully exploit DIA-based MS/MS to improve quantitative and qualitative metabolomics data.

Adductomics

Adductomics is an approach to studying the chemical modification of biological macromolecules by environmental exposures. A key premise of this approach is that highly abundant biological macromolecules, such as proteins or DNA, can serve as probes that reflect long-term trends in potentially short-lived or low concentration small molecules. As an example, 2-Amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP), a small molecule formed in cooked meat, is a potential carcinogen and can covalently modify DNA. PhIP, lipid peroxidation, and other DNA adduct types were profiled and associated with the prostate cancer Gleason score [25]. Dedicated methods for detecting and annotating DNA adducts, guided by user supplied accurate mass fragment ions and neutral losses, have been incorporated into MZmine to facilitate wider adoption of adductomics [26]. The resulting adducts can serve as potential biomarkers, for example, serum albumin Cys34 as a probe for monitoring air pollution [27] or albumin adducts as probes for prenatal exposure to airborne pollution [28]. Together, these analytical and computational approaches facilitate discovery of exposure markers that are otherwise inaccessible to traditional metabolomics.

Structural annotation of metabolites

In untargeted metabolomics studies, which aim to capture the broadest range of metabolites in a biospecimen, only a subset of observed signals (often called features) are structurally annotated. The matching of experimental MS/MS spectra to mass spectral libraries is generally recognized as the first step in the structural annotation process of MS/MS spectra that do not match to in-house standards [29]. It is important to note that many false positives are typically returned and that manual validation of key metabolite identities remains important. Since the annotation coverage of library matching remains low, recent annotation advances make use of machine and deep learning models, giving rise to conceptual frameworks that either map molecules to spectra, thus mimicking the physical processes such as fragmentation, or spectra to molecules, which is an inverse problem. Machine learning methods may represent molecular structures using fingerprints — vectors that capture the presence or absence of various structural properties. However, graph neural networks have emerged as strong competitors to fingerprint-based methods for representing molecules [30–32]. An exciting new development is the use of transformers and recursive neural networks that can generate molecular structures directly from spectra [33,34]. Learned spectral representations using unsupervised machine learning can enhance downstream annotation [32,35].

As structural annotation often remains ambiguous, partial annotation techniques have also gained prominence. For example, CANOPUS [36] uses deep learning to predict ClassyFire taxonomies from MS/MS spectra through an intermediate molecular fingerprint step. Another recent development is NPClassifier [37], which uses a deep neural network to predict the structural class of natural products. Molecular networking methods continue to develop, especially those within the GNPS platform, allowing propagation of structural information [38] and

can be combined with chromatographic peak shape correlations to recognize metabolite features [39]. MS2DeepScore, which trains a deep learning model on two spectra to predict their molecular similarity, shows promise in downstream annotation tasks such as library matching and analogue searches [40].

Interrogation of MS data is becoming easier with the introduction of MassQL, which enables queries based on precursor isotopic patterns, MS/MS spectra, drift time, and other parameters [41]. We note here that, whilst powerful, MS/MS spectra cannot discriminate between all molecules. For example, stereoisomers may have almost the same fragmentation spectrum. Here, complementary information is required, such as retention time information, although this is typically platform-dependent. Despite this, recent work that includes information from both MS/MS spectra as well as the platform-independent retention time order shows promise in further improvement of annotation performance [42]. A crucial remaining question is how machine learning methods can leverage the wealth of unpaired molecular and spectral data to better learn molecular and spectral representations and serve downstream annotation and classification tasks. It will be exciting to see how repository-scale analyses will assist in metabolite origin, structure, function, and novelty prediction [43,44].

Visualization

Visualization is an important component throughout the data analytical workflow, from quality control assessment to interpretation. To interpret metabolomics data, it is important to visualize it, perhaps in combination with other omics data, and in conjunction with additional information such as biological processes (e.g. diseases) and/or pathways. Many visualizations give insight into how metabolites relate to each other, for example through structural or spectral similarity or enzymatic reactions connections. Often the data are said to be visualized in a (bio)chemical space. However, this concept is context-dependent [45], as it could include for example, all known biomolecules (metabolites, genes, proteins, etc.), or those identified in one experiment, in a number of samples, or in a specific sample type.

A wide range of dimension reduction techniques have been applied to embed biomolecules [46,47], such as PCA, t-SNE, UMAP, and TMAP [47]. Figure 2 shows how TMAP highlights the chemical relationships between structures in GNPS mass spectral libraries [48], and how Treemap visualizes frequently occurring ClassyFire compound classes. Combining different visualization methods can provide insight into various aspects of the metabolomics pipeline, including assessment of biases in training data used for machine learning models.

Network-based visualizations are increasingly applied to connect structures or analytical features [49]. At a basic level, networks comprise nodes, which could represent metabolites, other biomolecules, or various annotations, and edges, which represent relationships between nodes. Examples of edge types include mass spectral similarity (quantified by e.g., cosine score), structure similarity (e.g., Tanimoto similarity), abundance correlation, or chemical relatedness [50]. Recent advances in scalable network visualization techniques simplify the complexity of networks and help identify areas for further study [51].

It is important to recognize that visualization techniques can be biased and may erroneously display artifacts or redundant information [52]. The use of robust statistical and heuristic techniques is critical to ensure appropriate interpretation and reproducibility of findings.

Data interpretation

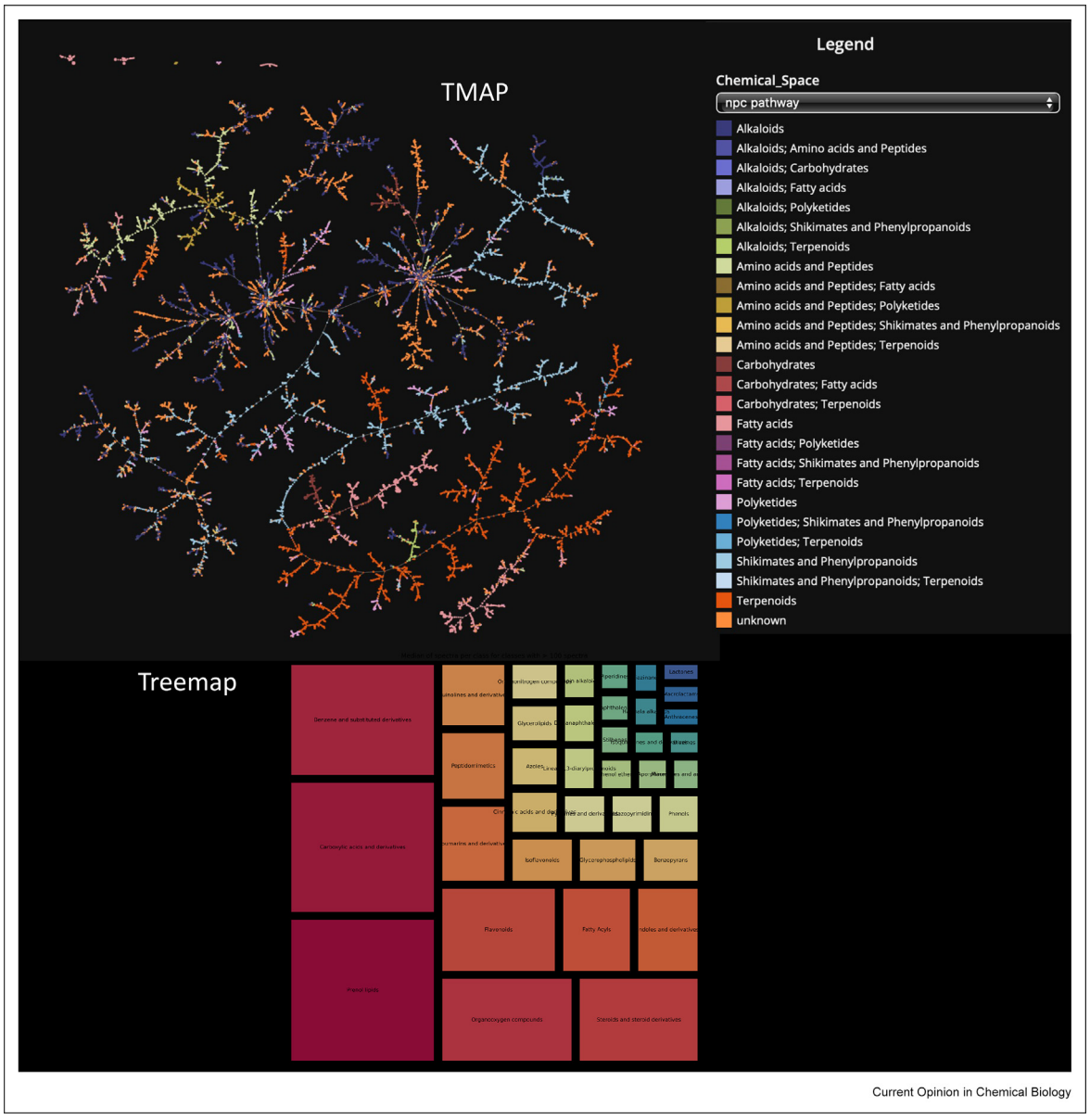
Databases and knowledge resources

Databases and knowledge graphs form critical components of any computational workflow, allowing users to compare experimental data to existing knowledge. For example, LOTUS reports structures of most plant natural products along with their taxonomy [53]. Similarly, the NP Atlas provides curated information on microbial metabolites with taxa descriptions [54]. Another large curation effort generated annotations and bioactivities of exposome-relevant molecules in PubChemLite [55]. HMDB 5.0 provides an increasing amount of biochemical, analytical, and pathway information on the human metabolome, with currently >200 K metabolite entries [56].

A noticeable recent trend is the use of natural language processing (NLP) to annotate metabolomic data by mining the literature. NJC19, for example, maps metabolites to microbes that produce or consume them [57], while FORUM [58] maps metabolites to diseases, enabling users to associate metabolites with disease risk. Deep learning algorithms are also becoming more prominent in this area [59]. Based on these developments, we anticipate an increase in this use of NLP in computational metabolomics.

Integrative platforms, such as MetaboAnalyst [60] streamline data analysis and interpretation using biochemical and clinical annotations through a web-based environment and are of great help to labs with little computational support. Importantly, there are multiple source databases that provide annotations for interpretation of metabolomic and multi-omic data. Recently updated resources include KEGG [61], HMDB [56], Reactome [62], WikiPathways [63] and LIPIDMAPS [64]. To expand the breadth of useful and up-to-date annotations, RaMP-DB [65] aggregates

Figure 2



Visualization of biochemical space. Top - TMAP visualization of ~24 K unique GNPS mass spectral library molecules colored by the NPClassifier pathway level. Various branches of specialized metabolism become visible. Bottom - Treemap visualization of a subset (with >100 spectra in the library) of unique GNPS mass spectral molecules tiled by ClassyFire chemical compound classes.

biological and chemical annotations on human metabolites and proteins/genes from multiple sources. Users can interact with RaMP-DB to perform batch queries and enrichment analyses through a web application, APIs, and an R package.

We note two major opportunities for maximizing the utility of these knowledge sources. First, there are varying degrees of structural resolution represented in metabolite annotations, such that mapping of analytes across data resources or annotation types (e.g., ontologies, diseases) is not always one-to-one. RefMet [66] aims to address this issue by mapping metabolite names and IDs to a common lowest denominator structure. Second, large-scale efforts, such as the Metabolomics Standards Initiative [67] and the Lipidomics Standards Initiative [68], are making strides to create ontologies for standardized reporting of metabolomics data. However, there is currently no widely used and mature ontology for the metabolomics community, which leads to the need for extensive manual curation to match database IDs across resources.

Pathway and chemical class analysis

It is widely acknowledged that molecular biology is well described as a network of interacting molecules, where molecules in one neighborhood belong to a 'pathway'. Such pathways may correspond to biological functions (e.g., glycolysis), chemical classes (e.g., triglycerides) or other meaningful categories. Metabolomic data can be interpreted by finding which pathways are enriched for differentially abundant metabolites [69]. Many methods, such as over-representation analysis, have been developed for transcriptomic data, and a cautious approach should be taken when applying them to metabolomics. The major difficulties relate to the low coverage and inexact structural identification present in most metabolomics datasets [70]. Metabolites can also be interpreted in light of their enriched chemical classes, as supported by ChemRICH and RaMP-DB, which, to some extent, is less affected by these drawbacks primarily because all metabolites can be mapped to a chemical class [71]. A promising alternative to traditional pathway methods is Pathway-Activity Likelihood Analysis (PUMA), a machine learning model that infers the likelihood of pathway activities and the activity of metabolites within pathways [72]. Another new development is the application of single sample pathway approaches, which allow transformation of metabolomic data into a 'pathway space' [73], facilitating a wide array of downstream analyses.

Data integration

There are many reasons to integrate data, and clarifying the intended purpose will dictate which computational methods are appropriate. For example, the focus could be to improve predictions or to find new connections between data sources. Integrative models should not only be able to match and harmonize data from different sources, but they should develop a unified view of a biological system, allowing the different sources to contribute according to the information present [74–76].

Integration within metabolomics

Metabolomics experiments often generate multiple data blocks, for example when more than one assay (e.g., ionization mode or chromatographic method) is used on the same samples. Within-metabolomics integration can yield chemical information, such as connecting signals from the same metabolite in different assays, which might help with annotating unknown metabolites and interpretation [51]. Further, biological insights can be made by integrating metabolomics data recorded on different sample types from the same individual [77]. A further dimension to within-metabolomics integration is the combination of multiple sample sets measured with the same assay, for example when several human cohorts are combined in large epidemiological studies. For untargeted metabolomics, matching metabolites, including unannotated features, between datasets is required [78], as is efficiently running error-free models for multi-cohort meta-analyses, as supported by the COMETS Analytics software [79].

Metabolomics-focused multi-omic data integration

Methods for combining metabolomics with other omics modalities enable discovery of multi-omic biomarkers, linking genes to metabolites for pathway prediction, or elucidating interactions between multiple omics layers. These wide-ranging aims and diverse data types lead to a range of challenges, from sourcing and matching datasets, to developing statistical and machine learning models that accommodate high degrees of heterogeneity.

Multi-omic datasets are typically available in omic-specific repositories, for metabolomics, including Metabolights, Metabobank, and the National Metabolomics Data Repository (NMDR, formerly Metabolomics Workbench), making it difficult to discover datasets amenable to integration. Further, inconsistent use of standard ontologies across resources make it time- and resource-intensive to identify publicly available multi-omic datasets [6,80]. Recently, the Paired Omics Data Platform addressed some of these challenges for natural products researchers by using a controlled vocabulary to make links between biomolecules and omics data from public repositories [81].

We also highlight a significant strand of recent work focused on modeling of metabolic flux to integrate data in a systems biology context [82]. For example, estimation of whether metabolic or transcriptional effects are dominant in controlling a given flux were made by applying a constraint based stoichiometric model that integrates metabolomic and gene expression data [83]. Neural network and deep learning approaches to integration are also gradually appearing in the literature, and recent applications have uncovered novel metabolite-microbe connections and biomarkers of cervicovaginal phenotypes [84]. However, interpretability of these highly complex models is of paramount importance if they are to yield actionable biological insights [85].

Augmenting these models can shed light on metabolite identities and uncover unknown metabolic pathways. Creating extended metabolic models (EMMs) [86], based on metabolic models consisting of known metabolites and enzymes for the sample under study and cataloging putative metabolic products in databases [87], is a promising approach for identifying putative cellular products. Underlying this idea is the ability to predict the promiscuity of enzymes on a large number of substrates [88] and the feasibility of the relevant biochemical reactions [89]. Using known metabolism to interpret metabolomics data is a promising direction that deserves further research.

Benchmarking tools and datasets

As computational metabolomics methods continue to develop along with analytical instrumentation, benchmarking datasets for testing new tools and methods are essential. The community has developed some key standards to facilitate the generation of benchmarking datasets. These include the NIST 1950 samples [90], COMETS reference samples [91], and efforts from mQACC and MetQual [92] that evaluate comparability of metabolite measurements across different labs. Further, NMDR and CASMI [93] provide datasets that can be used to develop algorithms. Yet, there are still challenges to finding appropriate benchmarking datasets, and data used for developing new algorithms are not consistently made available. Possible solutions for increasing the findability and utility of benchmarking data include tagging benchmarking datasets in repositories and clearly defining use cases. The SODA (SOftware and DAta exchange) interest group from the Metabolomics Association of North America provides a forum for exchanging information on current software, datasets, and data analysis results [94]. An important point is the potential bias training datasets may introduce into bioinformatics tools. Recent developments in the mass spectral prediction software CFM-ID 4.0 [95] showed how spectral prediction performance of specific chemical classes were improved based on available training data and fragmentation rules. Notably, a recent benchmarking study demonstrated clear performance differences of CFM-ID for various chemical classes [96]. Application of best practices for tool development and benchmarking is also key in ensuring appropriate usage, reliability, and long term maintenance of tools [15,97].

Conclusions

Computational metabolomics will continue to grow as metabolomics is increasingly applied across the scientific community and new instrumentation modalities are developed. In the last two years, there have been highly impactful advances in machine learning techniques for annotating metabolites, visualization, data interpretation and integration, as well as benchmarking software. Other areas of metabolomic technology such as single cell techniques and imaging mass spectrometry are rapidly expanding and will no doubt lead to new computational challenges. We also observe increasing awareness of best practice and standardization in how data and computational methods/tools are developed, reported and made available [15]. Overall, it is important to emphasize the value of continued communication and collaborations among scientists working on data analysis, knowledge sources, and tools, and most importantly among biologists, chemists, clinicians and informaticians. This interdisciplinary conversation will bring clarity in which methods and tools should be developed and, importantly, how they should be used correctly.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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