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Systems biology approaches to study lipidomes in health and disease

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ABSTRACT

Lipids have many important biological roles, such as energy storage sources, structural components of plasma membranes and as intermediates in metabolic and signaling pathways. Lipid metabolism is under tight homeostatic control, exhibiting spatial and dynamic complexity at multiple levels. Consequently, lipid-related disturbances play important roles in the pathogenesis of most of the common diseases. Lipidomics, defined as the study of lipidomes in biological systems, has emerged as a rapidly-growing field. Due to the chemical and functional diversity of lipids, the application of a systems biology approach is essential if one is to address lipid functionality at different physiological levels. In parallel with analytical advances to measure lipids in biological matrices, the field of computational lipidomics has been rapidly advancing, enabling modeling of lipidomes in their pathway, spatial and dynamic contexts. This review focuses on recent progress in systems biology approaches to study lipids in health and disease, with specific emphasis on methodological advances and biomedical applications.

1. Introduction

When studying 'omics' data at multiple levels, one must individually consider the complexity of each layer, and the possibility of interactions between them [1]. The expression of a given protein is not determined only by the level of its corresponding mRNA, but by the activity of the translational apparatus, protein kinases, phosphatases and proteases [2]. Metabolite levels are dependent on the catalytic activity of different enzymes, which make up the proteome [3,4]. Therefore, for a deeper understanding of biological systems, and to identify relationships between different biological processes, the emphasis in 'multi-omics' studies has been increasingly on data integration as well as on modeling biological systems and processes, which is broadly referred to as systems biology. The application of systems biology approaches in life sciences typically involves the acquisition, integration and modeling of complex data sets from multiple experimental sources. In clinical settings, such an approach, often consequently referred to as systems medicine [5], involves the identification of molecular profiles and pathways associated with progression of disease, hence, an in-depth understanding of pathologies is expected to facilitate the development of personalized therapies and treatments [6,7].

Lipidomics is a rapidly-growing subfield of metabolomics which brings together lipid biology, biochemistry, analytical chemistry, bioinformatics, as well as physiology and (in medical applications) medicine. Lipids are essential constituents of biological systems, being associated with crucial functions such as being constituents of cellular membranes and lipid particles (*e.g.*, lipoproteins, exosomes), and being involved in cellular signaling, transport, protein trafficking, growth, differentiation and energy storage [8–10]. The entire collection of chemically-distinct lipid species in biological system has been referred to as the lipidome [11].

Because of their hydrophobic nature, lipids are typically analyzed separately (*i.e.*, requiring different analytical methods) from most polar metabolites (*e.g.*, amino acids, citric acid cycle intermediates) [10,12]. Even within the area of lipidomics, this analysis is challenging, since lipids are highly structurally and chemically diverse. Currently, many different analytical techniques are being applied to investigate molecular lipids in cells, biofluids, and tissues [10,12,13].

Current lipidomics investigations can be broadly classified into four main areas: (1) development of analytical methods for identifying and

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quantifying lipids, (2) bioinformatics approaches for the processing and annotation of lipidomics data, (3) pathway and biomarker analysis, which, in a biomedical context, elucidates lipid-related metabolic changes in health and disease, and (4) computational lipidomics, which involves modeling lipidomes on different spatial and temporal scales [14].

Herein, we review recent progress in systems biology approaches to study lipids in health and disease, with specific emphasis on methodological advances and specific biomedical applications. Based on our understanding of the chemical diversity of lipids, recent analytical advances in lipidomics are discussed, including the specific areas of quality control, identification and quantification. Next, bioinformatics and computational approaches to study lipidomes are discussed, including statistical methods, pathway analysis, with specific focus given to genome-scale metabolic modeling, and dynamic modeling of lipidomes. Finally, we also review recent clinical lipidomics applications, with specific focus on obesity, diabetes, psychotic disorders and neurodegenerative diseases.

2. Lipid metabolism – a need for a systems approach

Lipids form a group which encompasses a large number of chemically and functionally diverse molecules [15] and are typically classified based on their structure [16]. The LIPID MAPS Consortium developed a comprehensive classification system and nomenclature for lipids, the LIPID MAPS Lipid Classification System (LMLCS)(https://www.lipidmaps.org/) [17], which was recently updated [18], relying on well-defined chemical and biochemical principles and using a chemical entity designed to be extensible, flexible, and scalable. Currently, more than 44,800 lipid structures are listed in the LIPID MAPS database.

The remarkable chemical and functional diversity of lipids is also a major consideration when applying systems biology approaches to study lipids, from analytical methods to measure lipids, to sophisticated computational approaches to model lipid metabolism. Below we briefly summarize some of the key functions of lipids in biological systems.

2.1. Membrane function

The molecular composition of cellular membranes determines their structural organization, properties and function, *e.g.*, in the encapsulation of cells and the compartmentalization of their internal contents. Once assembled, a cell's membrane configuration remains dynamic and responds to changes in the lipid environment [19]. Lipids are essential for membranes as they form the structural base of the lipid bilayers, and its diversity can modulate membrane properties and vesicle movement between organelles in eukaryotic cells [20]. The length and saturation of fatty acyl chains regulate the fluidity and thickness of membranes. These features regulate the entry and exit of other molecules and ions as part of the cell's metabolism. The hydrophilic headgroups of these lipids are electrically charged, modulating membrane diffusion potentials between the external and internal membrane surfaces, resulting in selective permeability. Through lateral interactions, lipids can leave membranes as second messengers, diffuse to other intracellular compartments and trigger cellular responses [19,21,22].

The membranes of a eukaryotic cell can contain over one thousand different lipid species with three mayor categories of lipids: glycerophospholipids (*e.g.*, phosphatidylcholines, phosphatidylserines), sphingolipids (*e.g.*, ceramides, sphingomyelins, glycosphingolipids) and sterols (with cholesterol as the major sterol). Among those, the most abundant are glycerophospholipids, representing over 70% of the total lipids in the membranes [20,23]. When analyzing and interpreting lipidomics data, one must critically consider that the observed lipid concentrations are bulk results from different systems including subcellular compartments, extracellular space, and lipid-containing particles and vesicles [6].

2.2. Cellular signaling

Lipids can act as the primary messengers of cell surface receptors, such as sphingosine-1-phosphate (S1P), allowing cells to respond to their local environments [24]. However, signaling lipids can also be activated by membrane or intracellular enzymes, following metabolic reaction *via* their respective receptor. The cleaved fragments of lipid molecules then act as intracellular signals, or 'second messengers', generating an intracellular response [20]. One of the important precursors for second messengers is phosphatidylinositol 4,5-bisphosphate, $PI(4,5)P_2$, which, after being stimulated by other chemical signals such as hormones, produces reactive lipids such as diacylglycerol (DG) and arachidonic acid (AA), which act as precursors of several biochemical pathways [25].

Another way of generating lipid messengers is *via* the metabolism of fatty acyl tails. Through this mechanism, some reaction products can act on the membrane, as in the case of lysolipids (*e.g.*, lysophosphatidylcholines), which are important inducers of membrane flexibility, modulating their curvature by providing elasticity to the membrane [26,27]. After these reactions are catalyzed at the membrane surface, the second messengers can then be transported into the extracellular space or cytosol, as is the case of AA, a bioactive lipid that is a precursor of eicosanoids, important lipid mediators involved in inflammation [28,29].

2.3. Systemic lipid metabolism

The diet and lipolysis of adipose tissue are the two main sources of fatty acids in the body. FAs can be oxidized to act as precursors to key metabolites, participate in the synthesis of intracellular signaling or membrane components. In humans, this uptake occurs *via* hepatocytes using passive diffusion of FA from plasma or, mainly for long chain fatty acid (LCFA), *via* fatty acid transport proteins (FATPs) such as FATP5, a liver-specific protein [30,31]. Other membrane transporters of FAs include fatty acid translocase (FAT)/CD36 [32] and perilipin-2 [33].

In the intestinal lumen, TGs from the diet are emulsified by bile acids and form free FAs as the hydrolysis products of pancreatic lipases. The micellar product formed with phosphatidylcholine can accept cholesterol to form secondary micelles. These lipids can be resynthesized into TGs by enterocytes or they can be secreted into the lymphatic system in chylomicrons to be taken up by peripheral tissues, principally skeletal muscle, heart, and adipose tissue. The remnants of said chylomicrons are delivered to the liver and metabolized into FAs [34].

Synthesis of FAs and TGs can also occur by *de novo* lipogenesis (DNL) [35], regulated by transcriptional factors that are stimulated with glucose excess. This process involves liver X receptor α (LXRα), which induces cholesterol absorption, transport, efflux, excretion and conversion to bile acids (BAs) [9]. LXRα is activated by carbohydrate response element binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP1c) [36].

TGs can be stored in cytoplasmic lipid droplets (LDs) or secreted into the bloodstream using a lipoprotein transport system such as very low-density lipoprotein (VLDL) particles. This process facilitates the distribution of TGs, cholesterol and phospholipids into different compartments of the organism, such as skeletal muscle for energy consumption or to adipose tissue for storage. On the other hand, low-density lipoprotein (LDL) also contributes to maintaining cell membrane integrity and delivering cholesterol to peripheral tissues for a multistep process for biosynthesis of steroid hormones. Excess cholesterol from extrahepatic cells is transported by high- density lipoprotein (HDL) to the liver, where it can be recycled or catabolized to bile acids [37].

Given the major lipids in the blood such as TGs, phospholipids, cholesterol (including cholesterol esters), and FAs [38] are part of complex inter-organ circulation and are compartmentalized into lipid particles, interpretation of bulk lipidomics data from serum or plasma samples is highly challenging, necessitating caution. Individual

lipoprotein fractions have different lipidomic profiles, with VLDL most enriched with TGs, and HDL with phospholipids [39]. Similar changes in specific plasma lipids may thus reflect different underlying phenomena, depending on context. While, ideally, lipidomes would be determined in parallel across different lipoprotein fractions from the same blood samples, providing an important insight into the lipoprotein metabolism [40], this is, in practice, not feasible in most clinical studies, for reasons of both time and cost. Solving an 'inverse problem', where lipoprotein composition is estimated from bulk plasma lipidomic profiles [41], remains a largely unexploited area of computational lipidomics.

3. Measuring the lipidome

3.1. Analytical methods for lipidomics

Lipidomics analysis has become an area of major interest in analytical chemistry due to the physicochemical diversity of the lipidome, in addition to their biological importance. Furthermore, in biological samples, there is a great dynamic range of lipid concentrations, from pM to μM [42]. In this part of the review, we summarize and review methods for lipid analysis. For more detailed reviews of lipid analytics, see *e.g.* [12,43], with key steps summarized in Fig. 1.

3.1.1. Lipid extraction

Lipid extraction procedures are needed in order to efficiently isolate and recover lipids and reduce signal interference from the complex biological matrix from which they are extracted. The most common extraction methods used in lipidomics are based on liquid extraction. The first such method was developed by Folch et al. [44], and is still the most used method for lipid extraction. The other methods commonly used are the modified Folch method by Bligh and Dyer [45], the methyl tert-butyl ether (MTBE)/methanol/water developed by Matyash et al. [46] [47]. This extraction solved some of the difficulties present in the chloroform-based methods [46] and the recovery of different classes of lipids was similar or superior to the Folch method. Other extraction methods applied involve butanol/methanol mixture (3:1), and heptane/ethyl acetate extraction (BUME method) [48]. Another one-phase extraction method, using a mixture of methanol, MTBE and chloroform [49] has also been shown to give good coverage of the lipidome with a simple extraction system [50]. It should be noted that one-phase extraction results in an increased number of nonlipid compounds in the extract compared to two-phase systems. This may cause instrument contamination and increase ion suppression. That said, one-step protocols are simpler and more robust, and they have been shown to give higher extraction efficiencies for polar lipids (*e.g.,* lysophospholipids) than, *e.g.*, the MTBE or Folch methods.

There have been several proposals for improving lipid extraction. The use of inorganic ions such as potassium chloride in the separation step, aims to promote a salting- out effect, increase lipid exchange between the aqueous and organic phase in LLE [51]. For the analysis of less abundant classes of lipids, LLE can be combined with the use of SPE cartridges or plates, where the organic stationary phase (*i.e.*, C8 and C18) retains lipids with similar properties, thus improving extraction of eicosanoids and steroid hormones [52,53].

3.1.2. Analytical techniques

Lipidomics approaches can be divided into global lipidomics analyses, covering the main classes of lipids, and targeted (quantitative)

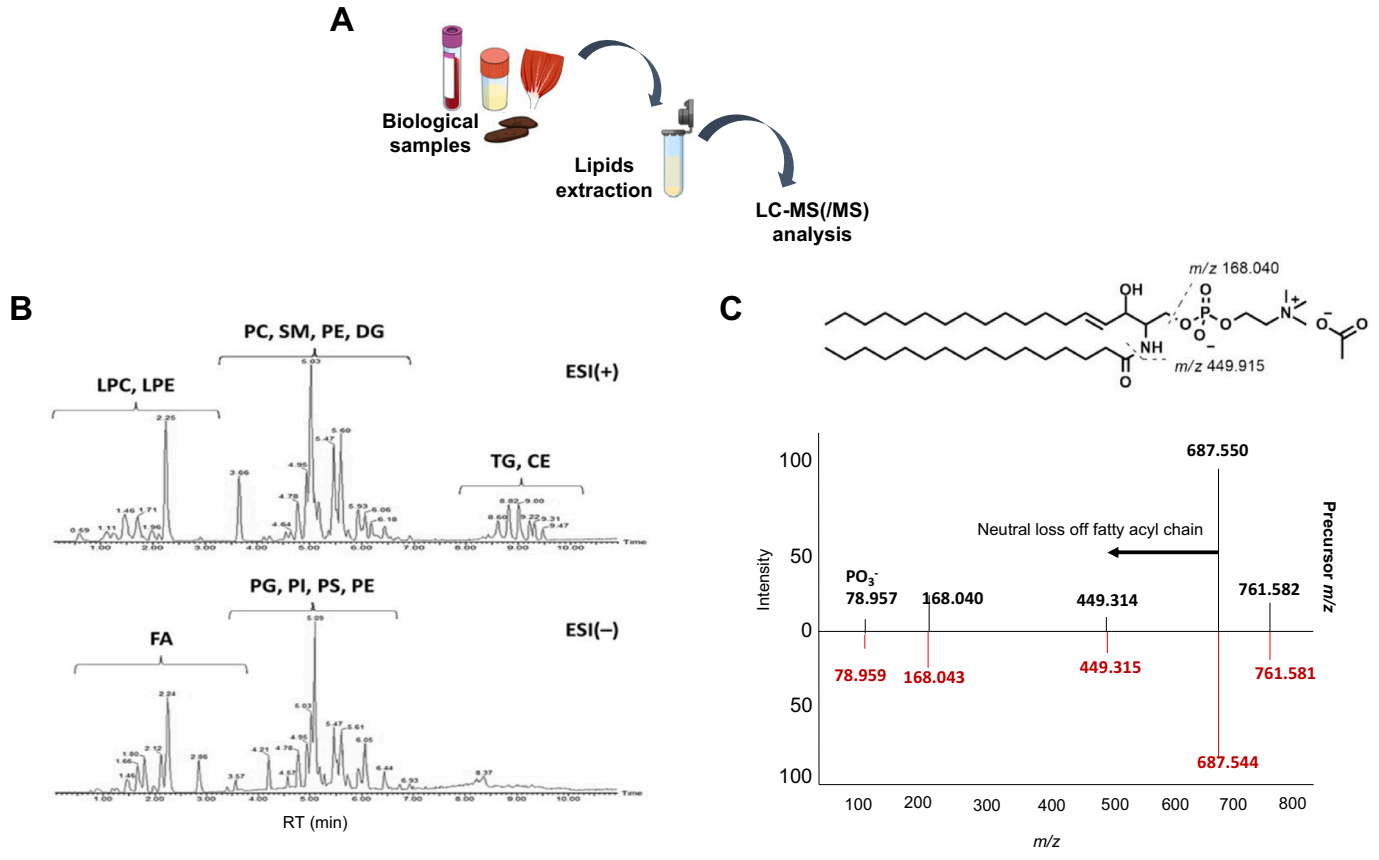

Fig. 1. Analytical workflow for lipidomics. (A) Overview of sample preparation, analysis by LC-MS and lipidomics data pre-processing. (B) LC-ESI(+/−)-QTOFMS chromatograms of lipids plasma profile using RP-C18 column, showing the most representative lipids classes per ESI mode. (C) Representative annotation of sphingomyelin SM(18:1;2O/16:0) (*m/z* 761.581) by matching experimental mass spectra against the mass spectral libraries of LipidBlast. Figure adapted from [76] and [232], with permission under CC BY license.

analyses of specific lipids classes, typically focusing on those which are found at low concentrations in biological matrices [12]. Majority of the methods are based on mass spectrometry (MS), and, in specific applications, nuclear magnetic resonance (NMR). The latter is limited to the determination of the most abundant lipids. In addition, lipid signals tend to be overlapping in NMR spectra, making the interpretation of lipid data at the molecular level highly challenging. New 2-dimensional NMR workflows have recently been designed to detect and quantify lipids [54], however, these are not yet widely utilized in the field of clinical lipidomics. MS, on the other hand, has the advantage of being highly sensitive, with possibility to detect and with use of suitable standards, quantify a large number of molecular lipids in a single experiment. Therefore, this is the most commonly utilized tool for characterizing lipids in biological samples.

Most global lipidomic methods currently utilize high-resolution MS instruments, such as Orbitrap, Fourier-transform ion cyclotrom resonance mass spectrometry (FT-ICR-MS), or quadrupole time-of-flight mass spectrometry (QTOF-MS) instruments, mostly relying on electrospray ionization (ESI), while triple quadrupole MS systems are applied mainly in targeted analysis of lipids.

Both direct MS infusion, or 'shotgun lipidomics' [55] as well as methods utilizing chromatographic separation are applied in lipidomics [12,43]. Shotgun lipidomics does not include chromatographic separation and thus prevents shifting matrix effects, which commonly occur during lipid separation in chromatographic columns. Also, method optimization and validation is generally simpler than for those methods involving additional chromatographic separation. However, shotgun lipidomics also has some challenges, such as ion suppression accompanied by decreased sensitivity, maintenance of a steady flow of analytes, and keeping the MS instrument clean. Ion suppression, which varies from sample to sample due to variation in matrix composition, is an inherent challenge of direct infusion MS approaches, which can only be resolved with additional separation [12,56].

One of the key issues in MS analysis of lipids is the high number of isobaric compounds, or compounds with very similar masses. Increasing the resolution of the MS instrument can only partially resolve this issue. In shotgun lipidomics, analysis is performed by MS/MS, typically by using fast scanning, high-resolution MS such as a QTOF or Orbitrap [57]. Since the MS instrument must be set up to scan a wide range of collision energies and fragments, this can lead to a drop in sensitivity due the time needed to perform these scans. Therefore, maintaining a constant flow is critical to the success of any shotgun lipidomics experiment. Any baseline deviation can cause issues with lipid quantification.

Liquid chromatography (LC) combined with MS is currently the most widely used method in lipidomics analysis. Basically, two approaches have been utilized, namely (1) lipid-class separation by normal-phase (NP) chromatography and Hydrophilic Interaction Liquid Chromatography (HILIC), or (2) separation of individual lipids by reversed-phase LC (RPLC) [6,58]. The main difference in the two approaches is that, in RPLC-MS, isomeric lipid species can be separated and thus, detailed structural elucidation is possible. However, more internal standards per lipid class are required because the species are spread across a wide retention time window. Recent, systematic comparison between HILIC and RPLC MS targeted quantification of 191 lipids showed that in terms of accuracy of quantification, both workflows were comparable for most of the studied lipid species, including lysophosphatidylcholines (LPCs), lysophosphatidylethanolamines (LPEs), phosphatidylcholines (PCs), phosphatidylethanolamines (PEs), and sphingomyelins (SMs), with the exception of highly unsaturated phosphatidylcholines (PCs), where some deviation was detected for HILIC [59].

New developments in this field include use of novel column types, such as charged surface hybrid (CSH)-C18, which has shown superior performance (+34% lipids identified over traditional RP techniques) [60] [58]. Also nano-liquid chromatography (nLC)–nanoelectrospray (NSI) has been applied to the lipidomics, however the methodology is not yet mature for routine, large-scale lipidomic analysis, although it is considered a promising tool for global lipidomics. This platform has been achieving an intensity gain between 2 and 3 orders of magnitude, resulting in better detection limits for individual lipid classes, resulting also in more than a 3-fold gain in lipid identification [61].

LC-MS based separation can be combined with ion-mobility (LC-IM-MS), with novel developments including methods that enable rapid profiling of lipids in biological fluids [62] as well as the use of parallel accumulation serial fragmentation that synchronizes trapped ion mobility spectrometry with MS/MS precursor selection for sensitive lipidomics analyses [63]. These approaches demonstrate the possibility of an additional separation dimension for enhanced lipid analysis, however, there are currently still challenges in the data processing of large-scale data using this methodology.

In addition to shotgun MS and LC-MS methods, other chromatographic methods have been used for lipid analyses. Application of gas chromatography (GC) is limited to the analysis of sufficiently volatile lipids and is generally applied in the analysis of free fatty acids or, with saponification, the total fatty acid content of samples, as well as in the analysis of (oxy)sterols. Recently, Chiu et al. [64] summarized different analytical approaches for investigating fatty acids in biological systems. Acidic and basic derivatization strategies and the comparison of different ionic liquid GC columns for the separation of geometric and positional fatty acid isomers, were summarized. However, in order to truly resolve the different isomers, long analytical methods are needed. Coupled with derivatization this can lead to analytical instability, thus analyzing large numbers of samples can be challenging.

Methods based on supercritical or subcritical fluid chromatography (SFC) have also been developed for lipidomics, as reviewed recently [65]. SFC combines some of the advantages of LC and GC. SFC has been applied in targeted methods for fatty acid analysis [66], global lipidomics [67,68], and in preparative fractionation [69]. Also, two dimensional systems, including different LC-LC and SFC-LC combinations has been developed [70]. However, both SFC-MS and the two-dimensional systems still face many challenges before they become routinely used techniques to rival LC-MS.

3.1.3. Lipidomics data pre-processing

Before data-analysis and interpretation (Section 4), the lipidomics data first need to be transformed from raw binary instrumental data to tabular format, which can then be further analyzed by statistical and pathway analysis approaches. In untargeted lipidomics approaches (or in hybrid approaches combining targeted and untargeted profiling), the data preprocessing typically includes peak picking, integration, alignment, identification as well as several data filtration steps. In addition to software from the instrument vendors, popular open-source software packages for metabolomics, *e.g.*, XCMS [71,72], MZmine [73,74] and MS-DIAL [75,76], have been widely applied for data processing in lipidomic studies. LIPID MAPS developed a LipidFinder tool as an add-on to XCMS, facilitating peak filtering and lipid identification [77]. In a systematic evaluation of five popular software packages for metabolomics data processing, MZmine outperformed other tested software in terms of quantification accuracy, while having the greatest number of true discriminating markers together with the fewest false markers [78]. Additionally, data processing solutions have also been developed specifically for lipidomics applications [79,80].

3.2. Identification of lipids

Reliable identification of complex lipids is generally straightforward at the class and bulk composition levels (total acyl carbon number and double bond count), due to characteristic structural groups and corresponding MS/MS (or MS^n in general) spectra. In specific acquisition mode, based on MS fragment spectra, one can also acquire information about acyl chain composition in complex lipids. Use of resources such as LIPID MAPS [81] facilitate the identification of lipids. Recently, the LipidLinxX data transfer hub was introduced, which facilitates the

integration of lipidomics datasets, including linking various lipid annotations [82].

Precise structural characterization of lipids, including, *e.g.*, positions of double bonds in acyl chains is required in modeling of lipid biochemical pathways at the molecular levels, such as by genome-scale metabolic modeling (Section 4.2). We have reviewed recent analytical advances in identification of double bond positions in lipids [12]. The current trend is to develop approaches for the determination of double bond positions amenable to routine lipidomics analysis [83]. Ddue to the high bond dissociation energies associated with cleaving a C=C bond, special techniques are needed for reliable identification of their location, including ozone induced dissociation [84], radical directed dissociation [85], hydrogen attachment/abstraction dissociation [86] and charge remote fragmentation [87]. Another option is to utilize specific chemical derivatization methods for C=C bonds such as ozonolysis [88], Paternò-Büchi (PB) reactions [89,90] and epoxidation reactions [91]. More recently, methods such as combining charge-switch derivatization with ozone-induced dissociation (OzID), photodissociation and PB reactions, as well as using alternative PB reaction reagents have been developed to sensitively pinpoint C=C location(s) [83,92–94]. Additionally, ion mobility mass spectrometry (IMMS) has recently emerged as an important tool for lipid isomer identification including C=C location and sn-position isomers [95]. OzID, ozonolysis and ultraviolet photodissociation (UVPD) have also been used to determine both sn-positions and C=C locations simultaneously [88,96,97].

3.3. Lipid quantification and data harmonization

Accurate quantification requires a method to control the variability of sample preparation as well as in analysis, including chromatographic and mass spectrometric steps, and, in the latter, ionization efficiency and systematic drift in the mass spectrometer. Typically, the main source of variation in lipidomics comes from the mass spectrometric part, which is challenging to control due to the competitive nature of the electrospray (ESI) process as well as the isotopic distribution and mass dependence of the fragmentation patterns.

In lipidomics, where the goal is to comprehensively measure the lipidome, hundreds or more compounds are measured, and it is not possible to have ISTDs for each compound. Ideally, a stable isotope-labelled internal standard, at least one per lipid class, is the preferred option for accurate quantification, preferably, combined with external calibration curves. In the selection of calibration standards, it is important to consider the factors which influence the analytical response, which is dependent on the lipid headgroup, the types of chemical bonds (*e.g.*, ether *vs.* ester), the number of double bonds as well as length of the fatty acyl chains [98,99]. The optimal number of ISTDs may also vary depending on the method applied. In lipidomics, it is typically not possible to have a matrix-spiked calibration, except for specific lipid groups for which blank matrix can be prepared (*e.g.*, bile acids using charcoal removal), and thus, it is important to characterize the impact of the matrix on quantitation. Here, the use of reference materials with certified concentrations or reference values, such as NIST certified materials, are recommended. When reporting the data, the type of normalization and quantitation should be specified. The quantitation can be classified into four classes [100]:

- Level 1: matching ISTD together with external calibration.
- Level 2: lipid-class-specific ISTD, with or without external calibration.
- Level 3: non-matching ISTD (*i.e.*, another lipid class than analyte) with or without external calibration.
- Relative quantification (%): normalization to total amount of a lipid class or all measured lipids.

Of these, the quantitation is accurate in level 1, while in levels 2 and 3, the accuracy is dependent on the selection of lipid standards, the methods and matrix effects, the latter depending also on the type of the sample.

The wide variety of methods in current lipidomic workflows makes it highly challenged to compare reported data between studies [101,102]. Therefore, data harmonization using, *e.g.*, certified reference standards, is important, and several guidelines are under development. A recent interlaboratory lipidomics study involving 31 different laboratories was done by analyzing NIST SRM-1950 reference plasma, with each laboratory using its own lipidomics workflow [101]. The main goal of the interlaboratory study was to provide consensus values to help harmonize lipidomics, and to identify specific areas for improvement. A high degree of variation in reported results highlights the need for improved workflows for quantification. Another ring study, comprised of 14 laboratories and using the same analytical method showed interlaboratory variance for the NIST SRM-1950 below 25% for lipids measured (glycerolipids, glycerophospholipids, cholesteryl esters, sphingolipids) [102].

Recently, a comprehensive comparison of commonly used lipidomic methods, including both chromatographic and direct infusion (DI) sample introduction approaches, coupled to high-resolution MS, was applied for the analysis of two pooled plasma samples [103]. The different methods (RP, HILIC, DI) provided different lipid class and species coverage in plasma, and some classes were not detectable with specific methods, such as ceramides with DI or DG or CEs with HILIC. The highest number was detected with RPLC. Only 75 lipids that could be quantified with all three methods and which had consensus values given by NIST were used. Originally, the final calculated concentrations substantially differed between the methods, but after using the NIST SRM 1950 for normalization, the results showed good agreement. This shows that it is possible to obtain comparable values with different protocols, when standard reference values are used or reported together with the data. There are also simple tools available to compare observed lipid levels to NIST SRM-1950 [104]. However, the accurate quantitation of lipid concentrations still remains a challenge.

4. Modeling of lipid metabolism

Due to the structural diversity and many functional roles of lipids, including as being part of 'lipid ensembles' such as membranes, modeling lipid metabolism requires the application of different computational approaches compared to those typically done for studies of metabolites in general [6,79]. Below we review three specific core areas as related to modeling lipidomes: statistical modeling of lipidomes, genome-scale modeling of lipid metabolism, and modeling of lipid ensembles based on lipidomics data (Fig. 2).

4.1. Multivariate approaches to study lipids

4.1.1. Data preprocessing

Lipidomics data requires pre-processing before it can be used to make biologically meaningful inferences. The pre-processing methods used are best tailored to the downstream questions of interest, insofar as the various transformations and scaling methods lend themselves best to specific investigation types [105]. A common investigation type concerns the relationships between the levels of lipids between different samples/sample groups, and this kind of investigation is recommended to be performed with data pre-processed by log-transformation followed by autoscaling (unit variance scaling). Various other methods apply well to other types of investigation, as reviewed in [105]. Typically, the resulting lipidomics data identifies and/or quantifies several hundred lipid species [106], generally this results in a dataset with many more variables than there are samples.

4.1.2. Univariate models

Univariate and multivariate methods are routine data processing approaches for extracting biologically relevant information from such

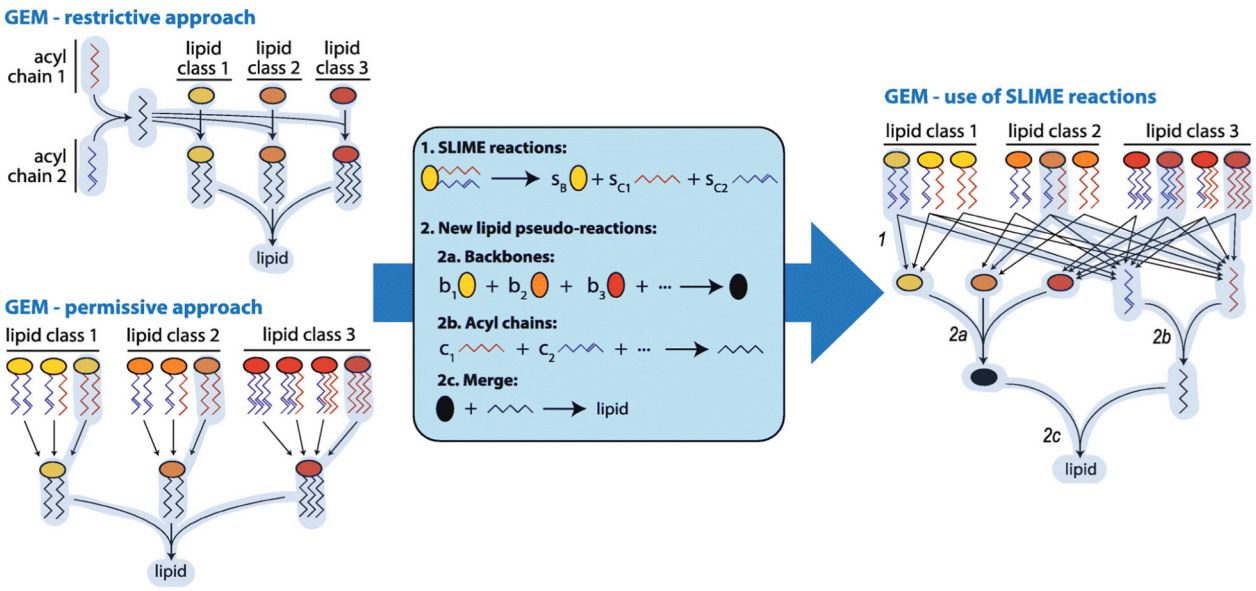

Fig. 2. Genome-scale metabolic modeling (GSMM) of lipid metabolism by constraining genome-scale metabolic models (GEMs) on the lipid classes and the acyl chain distribution. *Split Lipids Into Measurable Entities* (*SLIME*), was introduced to formalize and correctly represent lipid requirements in a GEM by using available experimental data. SLIME reactions (*SLIMEr*) can stratify and convert the lipid reactions of a GEM into a hypothetical model of three lipid classes and two types of acyl chain. By taking into account, both the lipid classes and the acyl chain distribution, GEMs enhanced with *SLIMEr* can accurately predict the lipid biomass over the restrictive and/or permissive approaches. Figure adapted from [135] with permission under CC BY 4.0 license.

complex lipidomics data [107]. Univariate approaches involve the comparison of an individual lipid signal between study groups (*e.g.* case *vs.* control) [108]. Both parametric and non-parametric univariate approaches, including *t*-tests (paired or unpaired), Wilcoxon rank-sum tests, Kruskal–Wallis tests, analyses of variance (ANOVA), Tukey's honest significant differences (Tukey's HSD), linear mixed models (LMM) are used in lipidomics studies, dependent on study design. For instance, LMM and ANOVA are useful methods for identifying within- and between-subject variations in a dataset. Systemic lipids are dynamic and, additionally, are affected by several factors including age, sex, diet, body mass index (BMI), and ethnicity [12]. Accounting and/or controlling for such confounding effects may contribute to better evaluation of lipidomic markers of health and disease. However, univariate approaches can only provide useful information if the biological effect of interest occurs at the level of individual, separate lipids, and does not arise as the result of the interplay of multiple lipids/outside factors.

4.1.3. Multivariate models

In a biological system, functional information relevant to a phenomenon of interest (*e.g.* a disease state) may be the result of subtle and/or heterogeneous signatures found as co-varying lipids and/or demographic variables. Untargeted lipidomics, in combination with multivariate analyses, provides a holistic approach to extract such deeper structures from lipidomic data [107,109].

A variety of multivariate data analysis methods have been applied to study the lipidome in health and disease. Here, a general first step following the aforementioned pre-processing of lipidomics data is dimensionality reduction. Reducing the (usually large, with n in the hundreds) of lipids to representative values facilitates the observation of discernible, informative patterns across study groups (*e.g.*, disease state *vs.* healthy).

Dimensionality reduction methods such as principal component analysis (PCA) and partial least square discriminant analysis (PLS-DA) are classical multivariate methods used in lipidomics [107]. PCA transforms the full dataset into principal components - orthogonal, linearly-weighted sums of the original variables [110]. This aim to capture the overall view of the variables with greatest variance in the data as the first principal component, followed by the next set with greatest (but orthogonal) variance in the next principal component, and so on. Due to its unsupervised nature, PCA, as applied to lipidomics, can also serve as an initial data quality control method for the identification of outliers, atypical clustering (*e.g.* batch effect), and trends/drift (*e.g.* degradation of sample over time/technical variation) in the dataset [111,112]. Besides that, PCA can be a useful tool to identify confounding factors in lipidomics studies. For example, it may reveal an age-related clustering effect in a longitudinal study design [113], where samples visibly group by their age far more so than they group by an outcome of interest. PCA assumes and searches for linear relationships to be found in the data.

However, the structures of relationships within lipidomic datasets include non-linear structures. Therefore, PCA is unlikely to reveal all lipidomic phenomena of interest unless the within-group variation (the treatment effect) in the dataset is larger than between-group variation (confounding effect). Thus, PCA remains a powerful dimensionality reduction approach as well as gross-observational tool rather than an explicit method to model/elucidate potential lipidomic markers differentiating between states/groups of interest. Another unsupervised multivariate method used for dimension reduction in the lipidomics is the clustering approach. For instance, Gaussian model-based clustering methods such as the *mclust* implementation in R [114] can reveal clusters related to functional lipid classes and, as part of a larger analysis pipeline, has shown promising applicability in lipid biomarker evaluation [115].

Next, PLS-DA is another multivariate method widely used for lipid biomarker exploration [107]. Somewhat similar to the underpinning idea of PCA (that is, projection to orthogonal space), PLS-DA is a supervised classification model which aims to elucidate lipidomic signatures or discriminating signatures between the two or more study groups (*e.g.* treated *vs* placebo). Given that supervised models require *a priori* knowledge about the sample groups rigorous cross-validation is required to avoid biased results. Szymańska et al. provide details about the statistical approaches that could be used to validate outcomes of PLS-DA [116]. These apply to more than just the use of PLS-DA, however. PLS-DA has rapidly gained popularity in the lipidomics community to identify biologically-important variables (*i.e.,* discriminant lipids) from those that are unrelated to the phenomenon of interest [113]. However,

it should be noted that PLS-DA models remain prone to overfitting as it can highlight variables (in orthogonal space) that may not be related to the defined group [117]. Orthogonal PLS-DA (OPLS-DA) and multi-level PLS-DA (ML-PLS-DA) are extensions of PLS-DA, designed to produce less class-biased classification results by dealing with the within- and between- subject variation [118], but these multilevel models require suitable data structures. In addition, other discriminant analysis methods such as linear regression models have been applied to lipidomics data for biomarker evaluation [115,119]. For regression classification, a researcher identifies important variables either using univariate analysis or targeted analysis prior to statistical modeling. Besides classification, ANOVA Simultaneous Component Analysis (ASCA) has been applied to improve the inference of covariate effects (*e.g.*, sex, age, BMI) in lipidomics settings [113]. Such approaches are more reliable in lipid biomarker evaluation as these models extract the information of interest while accounting for covariance in the data structure. However, the limiting factor here remains the availability of data generated with appropriate experimental design amenable to these methods, which many times is difficult to implement in human study settings.

4.1.4. Machine learning methods

Machine learning techniques can also be applied to lipidomics such as classification using random forest (RF) [120,121] and deep artificial neural networks (ANN) [121], both of which have been used for stratification of phenotypes based on lipid profiles and to extract biologically-meaningful information [122].

The various machine learning approaches lend themselves to different goals in biomedical science. Methods such as random forests lend themselves to identification of biomarkers for clinical use, for two major reasons. Firstly, random forests are highly amenable to the extraction of the relative importances of predictors, through measures such as Gini impurity. There is debate as to the best way to use such measures, particularly when considering data with high collinearity among the predictors (correlated variables), although these considerations do not hinder the use of the method to provide useful lists of important variables (*i.e.*, potential biomarkers). Secondly, given that random forests are ensemble methods involving decision trees, thresholds can be extracted from the best-performing random forest models and used to form the basis of clinical tests.

More complex machine learning methods such as deep ANNs (*i.e.* deep learning) are showing great promise across a plethora of fields, not least biomedical science, including metabolomics [123]. These have the potential to elucidate potentially more complex patterns in lipidomic data, but there is, as yet, considerable difficulty in calculating the relative importances of the predictors given to the model, and great difficulty (again, at present) regarding the interpretation of the final, best model. Indeed, more than one neural network approach may provide equivalent predictive ability, but may generate an internal architecture (therefore model) entirely different to the first. This raises the question of deciphering the "black box" nature of deep neural networks to provide useful information to human interpreters, although work is already underway to extract feature importances and improve interpretability of neural networks, using so-called explainable neural networks (xNNs) and, further, adaptive explainable neural networks (axNNs) [124].

One way in which neural networks can already be of great assistance in biomedical fields such as lipidomics is the advent of the autoencoder. Briefly, autoencoders do not seek to turn predictions into classifications or even regressions, as are the two best known machine learning tasks. These are smaller neural networks (fewer hidden layers), whose only task is to recapitulate the input data. The key here is that the hidden layer(s), at least in one layer, have considerably fewer nodes than the input layer. The output layer has the same number of nodes as the input layer. The idea of the autoencoder is that it attempts to reconstruct the original data as closely as possible. Given the forced information loss that is inherent in the hidden layer with only a limited number of nodes, the autoencoder is run iteratively until the output most closely matches the input. Various forms of encoder exist (*e.g.* the popular "denoising" autoencoder which adds noise to the input data to prevent over-fitting and provide generalization capability of the model) but a detailed discussion of these is beyond the scope of this review. The deceptively simple idea of the autoencoder nonetheless has great promise in building simplified-yet-useful models of lipidomics data by dimensionality reduction/clustering (clustering to the smallest number of nodes in the central hidden layer(s) which can still approximately reconstruct the original data. In a world, and particularly a field, inundated with (one could aptly say "cursed", given the term "the curse of dimensionality) datasets of fewer sample sizes, but great numbers of features, the ability to perform dimensionality reduction using these advanced methods has the potential to tease out the most important patterns in lipidomic data. Further, when combined across multi-omics fields, reducing the number of features, but demonstrably maintaining the structure and, crucially, relationships of the input data, a new landscape of potential lipidomic and multi-omic experiments becomes possible, where previously, unwieldy and wholly-incompatible datasets would be the terminal frustration point.

At present the application of machine learning-based approaches to lipidomics remains currently somewhat limited, potentially due to their relative novelty and the aforementioned issues regarding interpretability. Yet, given the rapid rise of machine learning and its promise across a plethora of fields in biology, including the nascent field of metabolomics and specifically lipidomics, acceptability will doubtless increase. This requires a conscious, constructive and earnest drive by those in the field. Rigorous work, both theoretical and translational needs to be completed regarding the interpretability of the models generated by such methods and nascent efforts must be handled appropriately so as to not sell short the potential of such powerful approaches which will, doubtless, revolutionize the field in time.

4.2. Genome-scale metabolic modeling

With advances in genome-scale metabolic reconstructions, genome-scale metabolic modeling (GSMM) is increasingly being used to study lipid metabolism, as reviewed by Nielsen [125], Thiele [126], and ourselves [127].

Lipid metabolism in a eukaryotic cells involve the regulation of complex metabolic pathways spanning different cellular compartments [125]. These pathways involve a large number of enzyme-catalyzed reactions modulated by transcriptional, translational and metabolic processes [125,128]. It is therefore challenging to dissect the regulatory modules of lipid metabolism and to understand how different lipid species interact with each other in response to environmental conditions (*e.g.*, changes in diet and gut microbial composition).

Mathematical modeling plays a central role in systems biology [126,129]. It has been used to model and study complex biological systems, and to infer causal relationships in experimental data. Genome-scale metabolic modeling (GSMM) is a constraint-based modeling approach that integrates biochemical and genetic information within a computational framework. Genome-scale metabolic models (GEMs) are comprehensive mathematical representations of biochemical pathways of a given cell and can be used to decipher the metabolic genotype-phenotype relationship of an organism [130,131].

Metabolic models of yeast have been extensively used to study lipid metabolism. A GEM of *Saccharomyces cerevisiae* (*iIN800*) has been used to evaluate the regulatory importance of lipid precursors [132]. This model was used to predict cellular growth as well as evaluate the essentiality of a metabolic reaction by 'single' gene deletion. It also showed an improvement in the predictions of both the fluxes and growth rates of *S. cerevisiae* by incorporating lipid species into the biomass/growth equation. The model's predictions were validated by ^{13}C-labeling experiments [132]. By integrating mRNA expression, metabolomics,

lipidomics, and ^{13}C- reaction flux data into the GEM framework, Jewett et al., modeled the regulation of lipid pathways in *S. cerevisiae* under eight different conditions [133]. This integrative approach identified sterols as the regulators of lipid metabolism. Moreover, *redLips*, a comprehensive metabolic model, was developed to capture lipid metabolism in *S. cerevisiae* by unifying known lipid reactions/pathways [134]. *redLips* strategically reduced redundant pathways around the lipid subsystems. To this end, the *Split Lipids Into Measurable Entities reactions* (*SLIMEr*) [135] tool was developed to determine the biomass requirements of lipids (over 20 different classes) in GEM. SLIMEr divided lipids into their respective classes and estimates acyl chain carbon distributions, thereby imposing appropriate flux constraints onto the lipid reactions by both lipid classes and their acyl chain distribution, rather than by lipid class alone. This approach has been demonstrated over multiple experimental conditions. In addition, a GEM (*iYL_2.0*) of *Yarrowia lipolytica*, an oleaginous yeast, which is capable of accumulating of neutral lipids, was developed to identify and optimize the metabolic pathways for the biosynthesis of TGs [136].

GSMM of lipid metabolism is, however, not limited to yeast cells. A GEM of human adipocytes (*iAdipocytes1809*) [137] enabled mechanistic insight into the metabolism of adipose tissue. The *iAdipocytes1809* model reconstruction was extended to include individual FAs and sterol esters. Integration of transcriptomic and metabolite flux data with *iAdipocytes1809* have identified increased metabolic activity concerning gangliosides (GM2), and a decrease in the mitochondrial activities of obese subjects when compared to lean subjects [137]. Recently, GSMM of human peripheral blood mononuclear cells (PBMCs) identified altered ceramide pathways, known to play a vital role in immune regulation, as specifically associated with progression to type 1 diabetes [138]. Furthermore, a GEM of human hepatocytes (*iHepatocytes2322*) was extended from previous liver models to include pathways of lipid metabolism [139]. *iHepatocytes2322* was used to evaluate metabolic differences between patients having non-alcoholic steatohepatitis (NASH), with or without fibrosis. When integrated with liver transcriptomics data, *iHepatocytes2322* identified serine deficiency in patients with NASH. In a similar study, by integrating GSMM together with transcriptomic data obtained from human liver biopsies, and fluxomics data, we showed that increased liver fat associated with reduced metabolic adaptability and this, in turn, may lead to co-morbidities of non-alcoholic fatty liver disease (NAFLD) [127].

Recently, advancements in high-resolution mass-spectrometry have enabled researchers to identify several lipid species. However, mapping experimentally-measured lipids onto genome-scale metabolic networks is challenging due to differences in identifiers and/or annotations. Several efforts have been undertaken to resolve this issue. One such effort includes a matching method based on *ChEBI* ontology [140], linking a generic class of lipids (*e.g.*, PC, SM) present in the metabolic network with the molecular species (*e.g.*, PC(45:0), PC(45:0) and SM (36:1), SM(36:2)), at the identification level provided in the experimental dataset. The mapping method evaluates the distances among the molecules represented in the *ChEBI* ontology [140]. One other future possibility is to associate ontology-based mapping with chemical representations. This requires continuous effort from the metabolomics and GSMM community to annotate both lipids and GEMs with ontology (*e.g.*, *ChEBI*) and chemical *(InChIKeys, SMILES)* identifiers. Furthermore, assigning lipids to their corresponding pathways, and characterization of novel metabolic pathway(s) are instrumental in increasing coverage of lipid metabolism as represented by GEMs.

4.3. Modeling of lipidomes at the level of ensembles – membranes, lipoproteins

As lipids are ensembles such as cellular membranes and particles (*e.g.*, lipoproteins, exosomes), it follows that changes in lipid composition may also alter cellular physiology *via* consequent changes in the function of these lipid ensembles. In order to understand how the composition of the lipidome impacts the core biophysical and structural properties of lipid membranes, such as fluidity and lateral pressure, lipids must be considered and modeled as parts of ensembles.

Molecular dynamic simulations, including multi-scale modeling, have been extensively used to study lipids and lipid-protein interactions in membranes, with the current trend being transition from simulations of simpler membrane models to biologically more realistic, multicomponent systems, as reviewed in detail recently [141–143]. Nevertheless, applications including integration of lipidomics with such multi-scale modeling have so-far been scarce, although this is a rapidly emerging area of computational lipidomics. Initial efforts to integrate lipidomics with molecular dynamic simulations of lipids included atomistic modeling of adipose lipid membranes in adipose tissue in monozygous twins discordant for obesity [144], and of HDL particles in individuals with high and low HDL-cholesterol (HDL—C) [145]. Yetukuri et al. studied the lipidomic profiles of individuals with high or low HDL—C, and found that those with low HDL—C had increased levels of TGs and decreased levels of both LPCs and SMs in HDL particles. Based on this information, HDL particles in high and low HDL—C subjects were reconstituted *in silico* by molecular dynamics simulations. These simulations confirmed the measured change in particle size, as well as identified altered spatial distribution of lipids due to changing lipid composition of HDL particles, including a higher amount of TGs at the surface of HDL particles in low HDL—C subjects [145].

In a twin study by Pietiläinen et al., lipidomic analysis of adipose tissue revealed phospholipid remodeling in obese co-twins, characterized by including increased levels of AA-containing ethanolamine plasmalogens and decreased levels of saturated fatty acid-PCs containing. Information gathered from lipidomics was used to build simplified model lipid bilayers for obese and lean co-twins, which revealed that lipid remodeling maintained the biophysical properties of lipid membranes [144]. These results, together with other data in the study, led to the conclusion that the observed lipid remodeling is likely an adaptive response aimed at the maintenance of lipid membrane homeostasis, while, as a consequence, this may lead to increased vulnerability to inflammation. Due to the computational complexity of atomistic molecular dynamics simulations, tradeoffs had to be made when incorporating information at the level of lipidomics data – with similar simplifications still needed today: (1) only few abundant representative lipids were incorporated into the models (containing a total of 128 lipid species and 3500 water molecules), (2) simulations were performed over a short time scale of 100 ns, and (3) lipid bilayers were considered as symmetric and homogeneous. More recently, Róg et al. studied the coupling of two leaflets in a lipid bilayer [146]. Informed by lipid composition from an earlier lipidomics study of exosomes released by PC-3 prostate cancer cells [147], various asymmetric lipid membrane models were studied using atomistic molecular dynamics simulations. The study found that amide-linked long acyl chain (24 carbons) of SM molecules in the outer layer extended deeply into the opposing, inner membrane layer, where it interacted with lipid chains in cholesterol-dependent manner [146]. Such interdigitation of long-chain SMs may help explain how the two leaflets in a lipid bilayer modulate each other's biophysical properties.

In simulations of membranes, generation of a lipid bilayer is a critical step for setting up the system. This is particularly true for complex membranes, comprising multiple components and aimed at more accurate simulation. In order to address this challenge, a computational tool *insane* (INSert membrANE) was developed, which uses preset, coarse-grain molecular lipid templates to build the membrane [148]. The resulting membrane models can be equilibrated, after which a relaxed atomistic model can be obtained by reverse transformation. For multicomponent membranes, such as those derived from lipidomics data, this provides an efficient means for generating equilibrated atomistic models – a starting point for atomistic molecular dynamics simulations. By using *insane*, and informed by several lipidomics datasets, Ingólfsson et al. compared the 'average' mammalian plasma

membrane with the 'brain' plasma membrane [149] (Fig. 3). In the brain model, higher cholesterol concentration was balanced by higher concentration of unsaturated acyl chains, leading to similar average bilayer properties as compared to 'average' mammalian plasma membrane. Both mixtures also exhibit a range of dynamic lipid lateral inhomogeneities. In the Brain model these were mostly small and transient, while the 'average' mammalian plasma membrane also contained larger and more persistent domains at the simulation time scale [149].

The field of computational lipidomics, aiming to study the spatial and temporal properties of realistic (informed by lipidomics) lipid-containing membranes and particles, is in its infancy, yet is already showing great promise. Several studies to-date have offered interpretations of complex phenomena, based on lipidomics data, which could not otherwise be provided based on statistical or pathway-centric approaches.

5. Biomedical applications of lipidomics

As lipids possess a variety of biological functions, it is not surprising that they play crucial roles in the pathophysiology of many diseases [6,12]. Lipidomics, when applied to biological matrices such as serum and tissue, can capture snapshots of systemic metabolic state, therefore the lipidome has the potential to (i) identify disease risk early, (ii) improve understanding of disease pathophysiology, and (iii) open avenues to better strategies for disease prevention, treatment, and management [150]. Consequently, over the past decade, lipidomics has received increasing attention in the context of clinical application to various disease conditions [6,150]. While a comprehensive review of the clinical applications of lipidomics is beyond the scope of this review, below we discuss recent lipidomics applications, and highlight the key lipid-related pathways involved, in three, specific, related medical areas where lipid-related disturbances play a key role in disease pathogenesis: metabolic disease, psychotic disorders (including metabolic co-morbidities), and neurodegenerative diseases.

5.1. Obesity, non-alcoholic fatty liver disease and type 2 diabetes

The plasma lipidome can directly capture the metabolic features associated with complex metabolic traits. For that reason, the study of metabolic disorders is an active area of research in lipidomics. Up to now, several studies have consistently reported altered levels of circulating lipids including LPCs, SMs, PCs and TGs in obese individuals [151–153]. Recently, Mousa et al. identified a relationship between lysophosphatidylinositol (LPI) and insulin secretory responses [154]. In

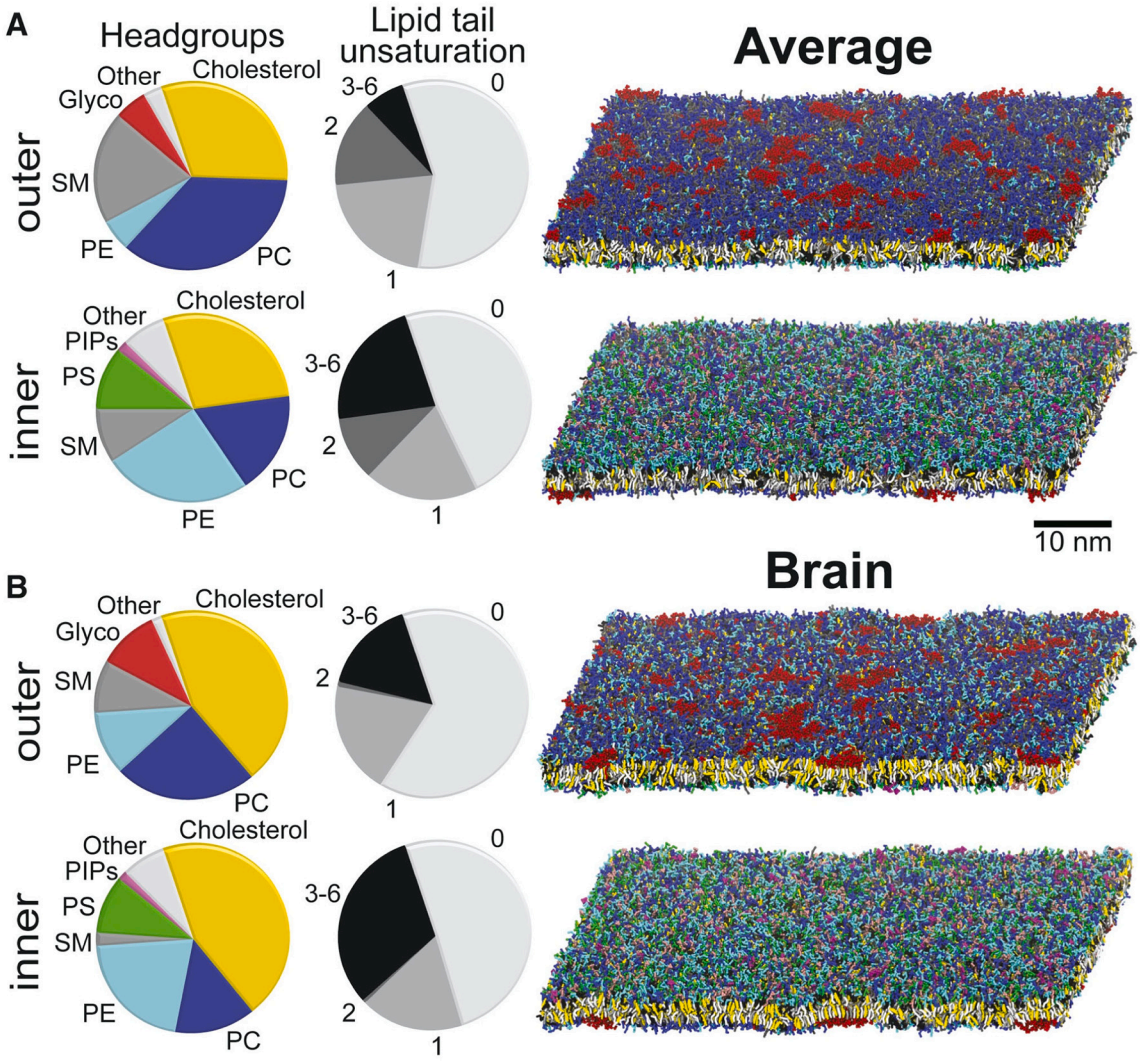

Fig. 3. Plasma membrane lipid distributions for the (A) "average" and (B) brain membranes [149]. Pie charts depicting the overall distribution of the main lipid headgroups and level of tail unsaturation in the outer/inner leaflet are shown on the left, with the average lipid compositions derived from published lipidomics datasets. Snapshots of the outer/inner leaflet of the simulations after 80 μs are shown are shown on the right, with the lipid group coloring the same as in the pie charts. Image reproduced from Ingólfsson et al., Fig. 1 from [149], without changes, with permission under CC BY-NC-ND 4.0 license.

the same study, inverse an association between dihydroceramides (dhCer) and insulin sensitivity was detected. These findings suggest that LPI and dhCer may be potential lipid biomarkers, able to identify individuals at high-risk for T2D [154]. However, the Mousa et al. study was limited to statistical associations and no predicative modeling was carried out. Intriguingly, in another study, Gerl et al. trained a machine learning model to predict obesity, usinglipid subspecies as predictors in the FINRISK population cohort with ($n = 1061$) participants, and validated their prediction in an independent study population (250 participants) from the Malmö Diet and Cancer Cardiovascular Cohort [155]. Here, the lipidome was regressed on various measures of obesity using Lasso modeling. The best model was achieved for body fat percentage ($R^2 = 0.73$), suggesting that the lipidome, in obesity, is what best reflects the amount of body fat. In another study, Gu et al. showed that clinical parameters are similarly powerful for estimating obesity and the risk of metabolic syndrome [156].

Several lines of evidence suggest that ceramides, in particular, are indicators of dysfunctional adiposity as well as contributor to risk of T2D [157,158]. Ceramides are bioactive lipids, which act as antagonists of insulin action and pro-inflammatory molecules [158,159]. Modulation of circulating ceramide levels ameliorates obesity-induced insulin resistance in model organisms [160] as well as in humans [161,162]. Insulin resistance and weight gain are also contributing factors to nonalcoholic fatty liver disease (NAFLD). Several studies suggest that obesity-dependent lipid signatures are strongly associated with NAFLD progression, with the most common signature of steatosis being increased circulating TGs of low carbon number and double bond count [163,164]. Luukkonen et al. also showed that 'metabolic' NAFLD, *i.e.* increased liver fat associated with insulin resistance, is specifically associated with increased ceramides in the liver [165]. Clinical lipidomics in NAFLD was recently comprehensively reviewed by Masoodi et al. [166].

In summary, studies so-far suggest that lipidomic analysis can enable better understanding of metabolic disease processes and earlier identification of disease risk, which could be useful in clinical settings for the early prediction of and subsequent intervention in various diseases.

5.2. Metabolic co-morbidities in psychotic disorders

Psychotic disorders form a heterogeneous group of severe mental disorders characterized by impaired reality testing or reality distortion, yet, in many cases these disorders are characterized also by cognitive, negative and affective symptom dimensions. Psychotic symptoms are typically observed as delusions, hallucinations, disorganized speech, and bizarre or catatonic behavior. Compared to the general population, schizophrenia patients also suffer increased rates of somatic comorbidities such as hypertension, diabetes and coronary heart disease, further complicating attempts at management of their disease [167].

Unhealthy lifestyles and pharmacological side effects have been suggested as major causes of excess morbidity and mortality in patients with psychotic disorders. Within these patients, those with negative or deficit symptoms are more prone to becoming overweight and have greater rates of metabolic syndrome. These patients with *deficit* schizophrenia (*i.e.*, negative symptoms) have less healthy and more sedentary lifestyles, which may, in turn, induce increased cardiovascular morbidity [168]. On the other hand, the use of antipsychotic drugs, especially second-generation ones, has been consistently associated with weight gain, insulin resistance and the development of metabolic syndrome [169–171], which seems to be more pronounced in younger people [172].

Lipid metabolism has been an area of increased interest in psychosis research, not only due to its obvious link to metabolic co-morbidities [173], but also due to its putative role in the pathophysiology of psychosis, as *e.g.* highlighted by the so-called 'phospholipid hypothesis' by David F. Horrobin – the proposed biochemical basis for the neurodevelopmental concept of schizophrenia [174,175]. Indeed, pre-clinical and human studies suggest altered polyunsaturated fatty acids (PUFAs), phospholipids, sphingolipids, including specifically sphingomyelin and ceramide, in psychotic patients' brains, as well as in the periphery/circulation [176–178]. Lipid disturbances were also recently observed in the period preceding the onset of psychosis [179,180]. Madrid-Gambin et al. performed integrative lipidomic and proteomic analysis of samples from 12-year old children, who had psychotic experiences at the age of 18 years and controls (ALSPAC cohort) [179]. Multiple LPCs and PCs were found increased in children who went on to have psychotic experiences later in life. Dickens et al. performed lipidomics in a cohort of individuals at clinical high risk for psychosis (the EU-GEI study), and found that the individuals who transitioned to psychosis within a 2-year follow-up period displayed decreased levels of ether phospholipids [180]. This finding may be of direct (patho)physiological relevance, as ether phospholipids (particularly plasmalogens, a major subgroup of ether phospholipids) are highly enriched in the brain [181], are supplied to the brain by the liver [182], have many structural and functional roles [183], and may act as endogenous antioxidants [184,185].

Accumulating evidence also suggests that lipid disturbances play a crucial role in the development of metabolic co-morbidities associated with psychotic disorders [173]. Lipidomic studies have shown that psychotic patients who rapidly gain weight during follow-up have elevated TGs with low double bond count and carbon number at baseline [186,187]. These TGs are known to be associated with NAFLD [163,165] and with increased risk of type 2 diabetes [188,189]. Lamichhane et al. also found that the same TG signature predictive of weight gain in psychotic individuals, also predicts weight gain in individuals at clinical high risk (CHR) for psychosis [187]. These findings may have implications for the treatment of psychotic individuals, as they may provide information regarding the need to prevent metabolic complications in specific individuals, *e.g.*, by a choice of alternative antipsychotic medication or by adjunct anti-obesity therapy.

There is emerging evidence suggesting that the endocannabinoid system (ECS) might be dysregulated in psychotic disorders [190–196]. The ECS is known to regulate several metabolic processes including food intake and thermogenesis [197]. Altered activation of the ECS causes an impairment in brown adipose tissue activity [198], which, in turn, may influence body weight, glucose and lipid metabolism [199]. There is a large body of literature suggesting that the development of NAFLD is promoted by peripheral activation of the ECS [200]. Recent evidence suggests that central cannabinoid receptor type 1 (CB1R) availability is altered in psychosis [201–203]. Greater reductions in CB1R levels were found associated with greater symptom severity and poorer cognitive functioning [203]. There is also evidence that endogenous cannabinoid ligands which act as CB1R agonists are elevated in the cerebrospinal fluid of medication-naïve psychotic patients [191,194,204–206]. A recent, integrative study of circulating endocannabinoids and central CB1R availability identified inverse associations between several circulating endocannabinoids and CB1R availability in the posterior cingulate cortex in healthy individuals, but not in patients with first-episode psychosis [207].

Given that the ECS plays a role in the pathophysiology of metabolic disease, including NAFLD, and in psychosis, it is plausible that the ECS might be the underlying link between psychosis and the development of metabolic co-morbidities. In order to examine this hypothesis, more studies are clearly needed, investigating the ECS simultaneously both centrally and in the periphery [208].

5.3. Neurodegenerative diseases

Neurodegenerative diseases can be characterized by the progressive loss of selectively vulnerable populations of neurons, and share many fundamental processes associated with progressive neuronal dysfunction [209], cognitive deficits [210], and memory impairments [211]. Among the neurodegenerative diseases, Parkinson's disease (PD) and Alzheimer's disease (AD) are among the most widely-known and

common neurodegenerative diseases, but they are by far not the only ones. Other neurodegenerative diseases include Huntington's disease (HD), amyotropic lateral sclerosis (ALS), multiple sclerosis (MS), frontotemporal dementia (FTD), among many others [209–211]. Lipidomics, and metabolomics in general, has been applied to study neurodegenerative diseases over the past two decades, particularly in AD (Fig. 4), with the literature extensively reviewed elsewhere [6,212–216]. Below, we highlight some of the most recent research in neurodegenerative diseases involving lipidomics.

AD is the most common form of progressive dementia, which is characterized by initial or primary alterations in amyloid metabolism which may lead to progressive cognitive deficits [209,210,212]. Plasma lipidomics from AD patients and healthy elderly controls showed strong associations between specific lipid levels and AD, suggestive of the dysregulation of phospholipid biosynthesis, turnover and acyl chain remodeling [217]. In another study, Kim et al. analyzed 28 lipid species in plasma and identified a strong correlation with brain degenerative changes and increased levels of HDL also associated with the degree of lesion and atrophy [218]. In a case-control study, Paglia et al. found phospholipid disturbances in brain tissue samples, observing alterations in key mitochondrial pathways that can be correlated with symptoms of dementia and AD pathology [219]. Kaya et al. performed a spatial lipidomics study, using matrix-assisted laser desorption ionization imaging MS (MALDI-IMS), of amyloid plaques in hippocampal and adjacent cortical regions in a murine model of AD (5xFAD mouse) [220]. The study identified accumulation of long-chain sphingosine base monosialogangliosides in the hippocampal and cortical amyloid plaques, suggesting that these gangliosides contribute to amyloid-associated AD pathogenesis.

Repetitive mild traumatic brain injury is a major risk factor for AD [221]. Given the recognized role of lipids in the early AD pathogenesis, Ojo et al. analyzed the cortex and hippocampal tissue phospholipid profiles in murine models of rmTBI (experimental closed head injury *vs.* sham) and AD (PSAPP mice *vs.* C57BL/6 mice as wild type controls) at multiple time points [222]. The study found specific increases in PCs, PEs (including ether PEs and PCs), LPEs and PI species post-injury in both brain regions in the rmTBI model (*vs.* control), while these lipids were unchanged (hippocampus) or decreased (cortex) in the AD model (*vs.* control). Overlapping, increasing trends were, however, observed for hippocampal SMs and LPCs in both models. In a follow-up study by the same team, Muza et al. observed a significant increase in SMs, phospholipids and fatty acids in the rmTBI model with APOE4 genetic background, but not in rmTBI APOE3 mice [223]. This preliminary study thus suggests APOE3- and APOE4-specific impacts follow on from injury in the murine model of rmTBI.

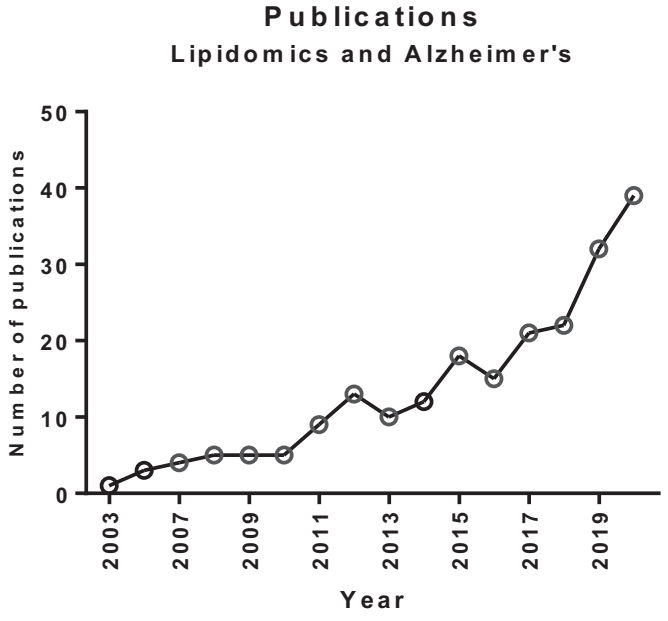

Fig. 4. Growing trend of lipidomics studies in Alzheimer's disease. Search term in Pubmed: Lipidomics & Alzheimer's (October 7, 2020).

PD is the second most common age-related neurodegenerative disease and is caused by neurodegeneration of dopaminergic neurons in *substantia nigra.* It is associated with dementia and impairment of the motor system, causing symptoms such as ataxia and tremor [212]. In a study of 170 PD patients and 120 controls, Zhang et al. found that plasma concentrations of TGs were decreased, while lipids of the ganglioside-NANA-3 lipid class were elevated in PD patients [224]. These findings are in line with earlier reports of reduced glucocerebrosidase activity in PD [225,226]. Hertel et al. performed a longitudinal metabolomics study in 30 PD patients and 30 controls, and used GSMM to integrate these data with gut microbiome data from another PD cohort and data from the general population [227]. The study found that taurine-conjugated bile acids associated with the severity of motor symptoms in PD, while low levels of sulfated taurolithocholate were associated with PD incidence in the general population. Furthermore, the study also found that dopaminergic medication had a marked impact on the lipidome, with changes (mainly a decreasing trend) in the major phospholipids, TGs and amine breakdown products of phospholipids (ethanolamine, serine). The study by Chan et al. also points toward alterations in the levels of TGs and monosialodihexosylganglioside (GM3), suggesting that increased GM3 levels may also be associated with PD [228]. Ji et al. performed integrative brain proteomics and metabolomics/lipidomics in a (C57BJ/L) murine model of 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47)-induced PD [229]. The study identified decreased LPC and LPE levels in the frontal cortex and midbrain, along with increased acylcarinitines, ceramides, DGs and SMs in both brain regions. Taken together with other omics data, the study suggests that BDE-47 induces pro-apoptotic molecular changes and oxidative stress.

Multiple sclerosis is a demyelinating neurodegenerative disorder of the central nervous system, which results in impairment of motor function, leading to paralysis [230,231]. Following the observation that exposure of neurons to cerebrospinal fluid from progressive multiple sclerosis patients induces mitochondrial elongation, Wentling et al. performed lipidomic analyses of cerebrospinal fluid samples from patients with (primary, secondary) progressive multiple sclerosis (SPMS, PPMS) and relapsing remitting multiple sclerosis (RRMS) [230]. The study showed that sterol esters and glycerophospholipids were decreased in PPMS patients, while LPCs were increased. Ceramide C24 was the most significantly-elevated lipid in progressive multiple sclerosis patients, in comparison with RRMS, which also associated with mitochondrial elongation. In another preliminary study, Vergara et al. performed lipidomic analysis (MALDI-TOF) of CD4+ T lymphopcytes from 8 RRMS patients and 5 healthy controls [231]. Two cardiolipin species were found significantly increased in the RRMS patients.

6. Conclusions

Lipid disturbances appear involved in a variety of common and debilitating diseases. While some of these disturbances may be disease-specific, mostly they are shared between different diseases, reflecting common underlying pathophysiological phenomena. Adoption of a systems biology approach is essential if one is to disentangle common and specific lipid-related features behind different disorders. Over the past few years, important advances have been made in computational systems biology, providing better tools (1) to study lipid metabolism at the genome scale, by improved coverage of lipid metabolism in genome-scale metabolic reconstructions, and (2) to simulate lipid dynamics at different spatial scales. By using these tools together with lipidomics (and other relevant omics) data, one may considerably expand the capacity to interpret lipidome data in the context of local or systemic

metabolic changes and in the context of structural/functional changes of lipid-containing membranes and particles.

In parallel with these computational systems biology developments, rapid advances have also been made in analytical and informatics tools to characterize the lipidomes in biological matrices. These advances, particularly those enabling more accurate lipid quantification and identification, will also facilitate comparability of lipidomics data across different studies, one of key issues currently being discussed within the lipidomics community [100–102].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure created in the Mind the Graph platform (www.mindthegraph.com).

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