Chapter 10
Beyond Metabolomics: A Review of Multi-Omics-Based Approaches

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1 Introduction

'Omics'-based techniques comprise a suite of tools and approaches, each with their own specific protocols and frameworks for setting minimum data and reporting standards (Field et al. 2008; Morrison et al. 2006; Sansone et al. 2007; Sumner et al. 2007; Orchard and Kerrien 2010). This suite of techniques primarily comprises metagenomics, transcriptomics, proteomics and metabolomics. There are also a number of other specialized 'omic'-based approaches that are included under the broader 'omics' banner, such as lipidomics, fluxomics (metabolic flux analysis), toxicogenomics, nutrigenomics and foodomics. However, these additional 'omics' approaches are not considered within the context of this chapter, as they are subcategories of the aforementioned suite of techniques. In addition, for completeness, it should be noted that within the context of this chapter, (meta)genomics has been defined as the analysis of genetic material recovered from an organism or environmental samples (Handelsman 2004); (meta)transcriptomics is the analysis of RNA molecules, including messenger RNA (mRNA), Ribosomal RNA (rRNA), transfer RNA (tRNA) and other non-coding RNA produced by an organism or a population of organisms (Pascault et al. 2015); (meta)proteomics is the analysis of proteins produced by an organism or population of organisms, and their function (Douterelo et al. 2014); and lastly, metabolomics is the analysis of the small chemical compounds produced and consumed by an organism or a population of organisms (Beale et al. 2016a).

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The application of these 'omics' techniques in isolation has been demonstrated to be beneficial in the understanding and characterization of numerous biological systems within the environment, engineered and industrial systems and treatment processes, in addition to providing insight into human health and clinical investigations (Cohen et al. 2015). It is when these 'omics'-based techniques are applied in combination, however, that their real power can be utilized. These techniques enable researchers to identify and characterize the entire microbial community present at greater depth (i.e. metagenomics) and, in combination with the other techniques studied in parallel, further enable researchers to identify what that community is doing, in terms of gene expression (i.e. transcriptomics), protein production (i.e. proteomics) and the community metabolism (i.e. metabolomics) (Turnbaugh and Gordon 2008). Figure 1 illustrates the chronological order (i.e. the magnitude of information that can be obtained) of these principal 'omics' based techniques, which inform researchers on the microbial potential, functionality, and activity starting at the metagenome through to the metabolome. This multiple 'omics'-based approach has been coined "*multi-omics*".

The objective of this chapter is to highlight examples in the literature that go beyond metabolomics only studies, giving rise to a greater depth of systems biology research that is multi-omics. While multi-omics research is not new, it is a growing area of research that has increased in popularity amongst the scientific community in recent years. Furthermore, the underlying aim of this review is not to provide a detailed chronology of multi-omics or a detailed guide on how to integrate multi-omics datasets; this has been the focus of recent reviews published

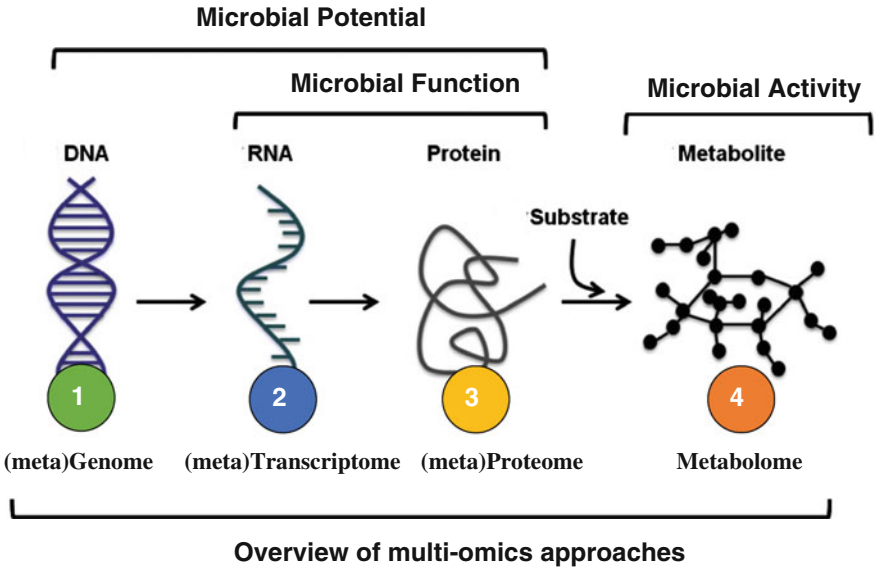

Fig. 1 Chronical order of 'omics' based techniques commonly used in multi-omics studies. Adapted from Abram (2015)

(Barh et al. 2013; Blanchet and Smolinska 2016; Fondi and Liò 2015; Kohl et al. 2014; Schneider and Orchard 2011; Zhang et al. 2010). Instead, the aim of this chapter is to provide an overview of the different approaches used in multi-omics-based research and the tools used to integrate multi-omics data, using examples from the literature from a range of environmental, industrial and biomedical applications to highlight the value of extending beyond metabolomics only research.

2 The Multi-Omic Data Analysis Challenge

Multi-omics based techniques are inherently data-rich studies. For example, the human genome comprises ca. 20,000–25,000 protein coding genes (Pertea and Salzberg 2010) and the human metabolome is estimated to comprise over 40,000 metabolites (Forsythe and Wishart 2009). As such, the challenge in all 'omic-based investigations', which is only compounded further when applying a multi-omics approach, is the handling of these large and complex datasets (Kohl et al. 2014; Röling et al. 2010). Röling et al. (2010) characterized the data processing and quantitative comprehension of multi-omic information as a bottleneck in the overall workflow, requiring input and interpretation of 'systems biologists' and microbiologists. In addition, the authors of this review propose that it needs further input from the bioanalytical chemist/biochemist/biostatistician to first evaluate the quality and validity of the study (experimental) design, as well as the quality of the data acquired from the instrument, before even attempting to integrate and synthesize findings (indeed the old adage of poor data in equals poor data out applies). In any case, assuming the data obtained are of high quality and are valid [following each 'omics' specific protocol and frameworks for minimum data and reporting standards as highlighted by the various societies (Field et al. 2008; Sansone et al. 2007; Sumner et al. 2007)], there are a number of approaches to analyzing and interpreting multi-omics data, namely: post-data analysis integration and integrated data analysis techniques.

In a post-data analysis approach, datasets are analyzed in isolation of each other and key features are *networked* in a post analysis exercise through the synthesis of significant features at joint nodes in the overall model metabolic pathway. This approach has been used in previous studies that focused on characterizing and assessing biological wastewater treatment systems (Beale et al. 2016b), the microbial resistance of marine sediments after an oil spill (Kimes et al. 2013) and characterizing permafrost (Hultman et al. 2015). In contrast, an integrated multi-omics approach employs specialized tools to merge datasets prior to undertaking any data analysis and interpretation (Kuo et al. 2013), thus enabling similarities of each omic approach to be statistically derived, as opposed to relying on human interpretation. The principal differences between the post-data analysis and integrated analysis approaches are graphically presented in Fig. 2.

In addition to post-data analysis integration and integrated data analysis techniques, a third model-based integration approach has been identified. However, a

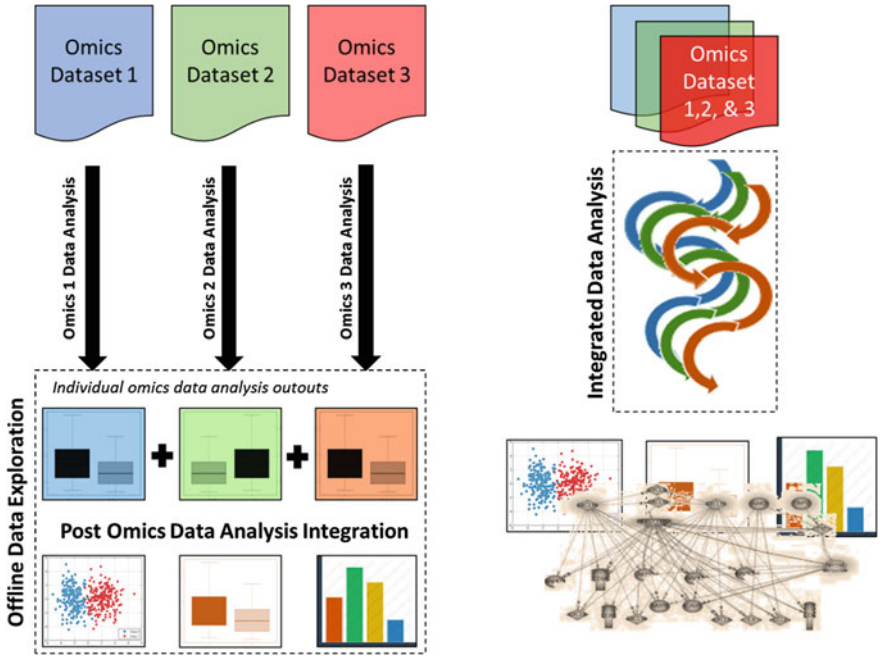

Fig. 2 Principal differences between the post-data analysis and integrated analysis approaches

model-based approach is considered unobtainable, in a practical sense, as stated by Kamburov et al. (2011). Model-based integration methods rely on a well-defined understanding of the system being investigated in order to compare new experimental findings against modelled predictions. That's not to say that a complete multi-omics model-based integration approach is not obtainable as suggested. There are already examples in the literature of its use. For example, Noecker et al. (2016) used a model-based approach to integrate taxonomic and metabolomics data to predict the effects of community ecology on metabolite concentrations and evaluated these predictions with measured metabolomic profiles from the vaginal microbiome. It was concluded that predicted species composition correlated with identified putative metabolic mechanisms underlying these predictions (Noecker et al. 2016). However, it is noteworthy to mention that a model-based integration approach was achieved primarily because of the vaginal microbiome investigated had already been well defined and studied beforehand, utilizing previously published data and publically available datasets (Erickson et al. 2012; Srinivasan et al. 2015; Theriot et al. 2014; Jansson et al. 2009; Jozefczuk et al. 2010). As such, the real challenge for model-based integration approaches is not that they are principally unobtainable, but that not all the systems studied are yet fully characterized as per the example presented by Noecker et al. (2016). Therefore, until a systems biology approach is taken for all studied systems (i.e. a multi-omics approach in

order to obtain baseline data), a model-based integration approach is limited to only those systems that are already well defined.

Regardless of the multi-omics approach being applied, there are numerous tools and approaches that assist researchers to integrate omics-based datasets. As illustrated in Table 1, there are tools that have been developed that are context specific (i.e. targeted towards the integration of omics data from specific animal models, medical and clinical studies and selected plant species). There are also tools that are unspecified in terms of the studied system but provide users a set of statistical tools for data normalization and transformation, and a range of chemometric models for interpreting data once integrated.

3 Application of Multi-Omics

There are many examples in the literature of multi-omic studies, with various levels of integration. Some studies comprise simple levels of integrations (i.e. combing two different -omics datasets) through to more comprehensive and computationally demanding studies (i.e. integration of multiple omics datasets). Typically, a two-omics integration study combines either metagenomics or transcriptomics data with proteomics (Sunagar et al. 2016; Wildburger et al. 2015) or metabolomics datasets (Tokimatsu et al. 2005b; Garcia-Alcalde et al. 2011; Kamburov et al. 2011) or combines proteomics and metabolomics datasets (Xu et al. 2015). These studies demonstrate how predicted functional metabolism (metagenomics) or gene expression (transcriptomics) relate to actual protein and metabolite expression and, by extension, provide a means to self-validate findings through cross-referencing experimental findings (Fondi and Liò 2015). The following section provides some examples of multi-omics studies applied to various fields of research, all of which provided an extension beyond a metabolomics only study (or other singular omics-based approaches) and enabled further depth of analysis that would otherwise not be achieved.

3.1 Environmental Contaminants

Marine subsurface environments comprise an abundant and diverse microbial community (El-Serehy et al. 2016; Yanagawa et al. 2014). These communities have the ability to bio-transform and mineralize numerous contaminants (Kimes et al. 2013). The application of omics-based research has been used in the past to characterize and understand sediment and marine environment dynamics. Chariton et al. (2014) used metagenomics to investigate benthic invertebrate diversity in exposed sediments with elevated concentrations of triclosan (antibacterial and antifungal agent). However, a single omics-based approach only provides limited information. As is this case, a metagenomics approach will only provide

Table 1 Summary of multi-omic tools

Software tool	Omics integrated	Domain	Functionality	License	References
3Omics	– Transcriptomics – Proteomics – Metabolomics	Medical (human)	– Correlation network analysis – Co-expression analysis – Phenotype generation – KEGG/HumanCyc pathway enrichment – GO enrichment	Open	Kuo et al. (2013)
Biofomics	– Transcriptomics – Proteomics – Metabolomics	Biofilms	– Experiment library – Data depository	Open	Lourenço et al. (2012)
Escher	– Genomics – Proteomics – Metabolomics	Unspecified	– Web application for visualizing data on biological pathways – Rapidly design new pathway maps based on user data and genome-scale models – Visualize data related to genes or proteins on the associated reactions and pathways – Identify trends in common genomic data types	Open	King et al. (2015)
GIM3E (gene inactivation moderated by metabolism, metabolomics and expression)	– Transcriptomics – Metabolomics	Unspecified	– Establishes metabolite use requirements with metabolomics data – Model-paired transcriptomics data to find experimentally supported solutions – Calculates the turnover (production/consumption) flux of metabolites	Open (Python and requires a COBRApy 0.2.x.)	Machado and Herrgård (2014)
IMPaLA (integrated molecular pathway level analysis)	– Transcriptomics or proteomics – Metabolomics	Medical and clinical	– Enrichment analysis – Pathway analysis	Academic only	Kamburov et al. (2011)
Ingenuity pathway analysis	– Metagenomics – Transcriptomics – Proteomics – Metabolomics	Medical (human) and clinical	– Metabolic pathway analysis – Network visualization – Data integration – Upstream regulator analysis – Mechanistic networks – Causal network analysis – Downstream effects analysis	Commercial	Krämer et al. (2013)

(continued)

Table 1 (continued)

Software tool	Omics integrated	Domain	Functionality	License	References
INMEX (integrative meta-analysis of expression data)	– Transcriptomics – Metabolomics	Medical and clinical	– Meta and integrative analysis of data – Pathway analysis	Open	Xia et al. (2013)
IOMA (integrative omics-metabolic analysis)	– Proteomics – Metabolomics	Unspecified	– Integrates proteomic and metabolomic data to predict flux distributions	Open	Yizhak et al. (2010)
KaPPA-view	– Transcriptomics – Metabolomics	Plants	– Integrates transcriptomics and metabolomic data to map pathways	Open	Tokimatsu et al. (2005a)
MADMAX (management and analysis database for multiple ~ omics experiments)	– Metagenomics – Transcriptomics – Metabolomics	Plants, medical and clinical	– Integrates omics data – Statistical analysis and pathway mapping	Open	Lin et al. (2011)
MapMan	– Metagenomics – Transcriptomics – Metabolomics	Plants (developed for use with Arabidopsis. Includes more species)	– Compare data across these two species – KEGG classification – Classification into KOG clusters – Mapping expression responses	Open	Thimm et al. (2004), Usadel et al. (2005)
MarVis-Pathway (marker visualization pathway)	– Metagenomics – Transcriptomics – Metabolomics	Unspecified	– Toolbox for interactive ranking, filtering, combination, clustering, visualization and functional analysis of data sets containing intensity-based profile vectors	Academic only	Kaever et al. (2015)
MassTrix	– Transcriptomics – Metabolomics	Unspecified	– Integration of data – Generation of colored pathway maps KEGG data analysis	Open	Wagele et al. (2012)
MetScape 2	– Transcriptomics – Metabolomics	Medical and clinical	– Integrates data from KEGG and EHMN databases	Open	Karnovsky et al. (2012)
mixOmics (R package)	– Metagenomics – Transcriptomics – Proteomics – Metabolomics	Unspecified	– Integration of data – Chemometric analysis (similarity/difference)	Open	Günther et al. (2014)
Cytoscape with MODAM and Cytoscape with OmicsAnalyzer	– Transcriptomics – Proteomics – Metabolomics – Fluxomics	Unspecified	– Multi-Omic Data Miner and OmicsAnalyzer were designed as an accessible and handy Cytoscape plugin that facilitates omics analysis – Compile all biologically-relevant information regarding the model system through web link association – Map the network components with multi-omics data – Model omics data	Open	Enjalbert et al. (2011), Xia et al. (2010)

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Table 1 (continued)

Software tool	Omics integrated	Domain	Functionality	License	References
PaintOmics	– Transcriptomics – Metabolomics	100 top species of different biological kingdoms	– Integration and visualization of transcriptomics and metabolomics data	Open	Garcia-Alcalde et al. (2011)
PathVisio 3	– Transcriptomics – Proteomics – Metabolomics	Unspecified	– Integration of omics data – Visualize omics data based on common data nodes and interactions in the pathway	Open (Apache)	Kutmon et al. (2015)
ProMeTra	– Transcriptomics – Metabolomics	Medical and Clinical	– Interactive visualizations of metabolite concentrations together with transcript measurements mapped on the pathways and GenomeMaps	Open	Neuweger et al. (2009)
SIMCA	– Metagenomics – Transcriptomics – Proteomics – Metabolomics	Unspecified	– Integration of data – Chemometric analysis (similarity/difference)	Commercial	Wheelock and Wheelock (2013)
VANTED (visualization and analysis of networks with related experimental data)	– Metagenomics – Transcriptomics – Proteomics – Metabolomics	Unspecified	– Comparison of multiple omics data sets – Visualization of metabolic maps – Correlation networks analysis	Open	Junker et al. (2006)
VitisNet	– Metagenomics – Transcriptomics – Proteomics – Metabolomics	Grapes	– Integration of data – Visualization of connectivity	Open	Grimplet et al. (2009)

information of the microbial diversity present (and by extension, a theoretical analysis of their functionality). Investigating beyond metagenomics would provide a greater depth to the analysis by measuring the actual function of the studied population using proteomics or metabolomics. Hook et al. (2014) investigated contaminated sediments using a similar approach, however, they used transcriptomics and metabolomics in order to better understand the modes of toxic action within contaminated ecosystems. The inclusion of metabolomics in such a study enabled the assessment of changes in the biochemical profiles of microbial communities living in contaminated sites (Jones et al. 2014; Llewellyn et al. 2015). In the study by Hook et al. (2014), the function of transcripts with altered abundance in *Melita plumulosa* (an epibenthic amphipod) following whole-sediment exposure to a series of common environmental contaminants was investigated. Contaminants included in the study comprised porewater ammonia, bifenthrin and fipronil (pesticides), diesel and crude oil (petroleum products) and metals (Cu, Ni and Zn). Subsequent data integration and hierarchical cluster analysis demonstrated grouped transcriptome and metabolome expression profiles by contaminant class. Many of the transcriptional changes observed were consistent with patterns previously described in other crustaceans (Osborn and Hook 2013).

Furthermore, following the Deepwater Horizon (DWH) oil spill in the Gulf of Mexico, researchers used metagenomic analysis and metabolomic profiling of deep-sea sediment samples (Kimes et al. 2013). Post-data analysis integration of the two datasets identified the presence of aerobic microbial communities and their associated functional genes among all the samples collected, whereas, a greater number of Deltaproteobacteria and anaerobic functional genes were found in the sediments closest to the point of oil contamination. Metabolic profiling revealed a greater number of putative metabolites in sediments surrounding the contamination site relative to background sites. These putative metabolites were identified as a series of benzylsuccinates (with carbon chain lengths from 5 to 10), suggesting that increased exposure to hydrocarbons enriched the Deltaproteobacteria, which are known to be capable of anaerobic hydrocarbon metabolism. Lastly, through a combined multi-omics approach, it was surmised that the sediment samples collected at the site of contamination comprised an active indigenous microbial community capable of metabolising aromatic hydrocarbons in deep-sea sediments of the Gulf of Mexico (Kimes et al. 2013).

Hultman et al. (2015) undertook a similar study investigating the microbial metabolism of permafrost. They used several ‘omics approaches, combined with post-data analysis in order to determine the phylogenetic composition of microbial communities of intact permafrost, the seasonally thawed active layer and thermokarst bog (surfaces of marshy hollows). The multi-omics strategy revealed good correlation of process rates for methanogenesis (the dominant process), in addition to providing insights into novel survival strategies for potentially active microbes in permafrost (Hultman et al. 2015).

The advancement of omics-based techniques and their integration have contributed towards marine biologists and molecular biologists pushing the boundaries of our understanding of marine molecular biology (Thakur et al. 2008). This is best evident in a global holistic approach to the study of marine ecosystems presented by Karsenti et al. (2011). In this study, the application of multi-omics was extended by including additional meta-data, linking biogeography with ecology, genetics and morphology datasets to provide a global perspective to marine systems.

3.2 Food and Nutrition

Metagenomics-based characterization of microbial communities provides a very promising and powerful approach to food safety testing, with research to date undertaken focusing on foodborne pathogen biology (Stasiewicz et al. 2015). However, transcriptomics, proteomics and metabolomics approaches have also been demonstrated to have the potential for food safety applications (Valdés et al. 2013; Jadhav et al. 2014, 2015; Beale et al. 2014b). To date, transcriptomics, proteomics and metabolomics have become the three most commonly used techniques in food and nutrition-based 'omics' research (Kato et al. 2011).

Takahashi et al. (2014) combined gene expression profiles using DNA microarrays with proteomic and metabolomics data in order to assess the anti-obesity effects of coffee in mice. The underlying premise was that coffee consumption may reduce the risks of developing obesity and diabetes. As such, gene expression, protein and metabolite profiles in the livers of C57BL/6J mice fed a high-fat diet containing three types of coffee (caffeinated, decaffeinated and green unroasted coffee) were investigated. The data were integrated using an in-house software tool and visualized in KEGG pathways (summarized in Fig. 3). Takahashi et al. (2014) concluded that the alterations within and around the urea cycle were found to be highly consistent between transcripts and metabolites, suggesting that expression of the genes related to the urea cycle were downregulated by a high-fat diet and up-regulated by coffee consumption. These findings were also consistent when integrated post-data analysis of each omics dataset.

For nutrition-based research, to further advance the application of multi-omics research and disseminate current findings more broadly for other researchers to use, a database of nutrition-focused omics (genomics and DNA microarray data) has been created (Nutrigenomics Database) (Saito et al. 2005). Similar approaches have been applied to other areas of research. For example, VitisNet was created in order analyze omics-based data relating to common wine grapes enabling the integration of large datasets, streamlining biological functional processing and improving the understanding of dynamic processes in systems biology experiments (Grimplet et al. 2009). PaintOmics has similar functionality but is targeted towards a defined list of plants (Garcia-Alcalde et al. 2011).

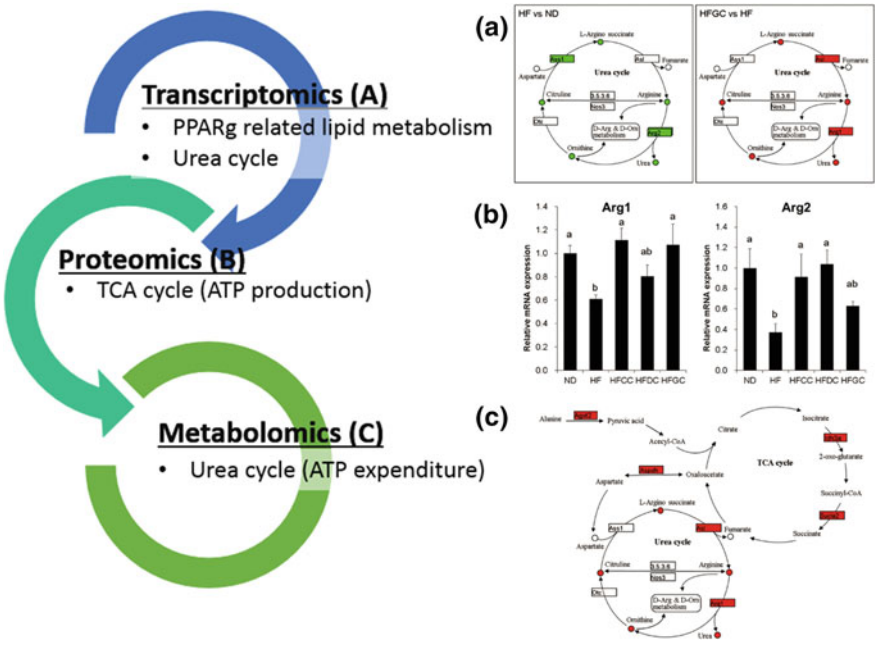

Fig. 3 Integrated analysis of transcriptomics, metabolomics and proteomics of liver tissue samples collected from mice fed a high-fat diet containing high levels of coffee. Adapted from Takahashi et al. (2014)

3.3 *Water and Wastewater Systems*

The application of metagenomics to characterize microbial populations in wastewater treatments systems (Talbot et al. 2008; Vanwonterghem et al. 2014; Pap et al. 2015; Kovács et al. 2015; Ma et al. 2014; Albertsen et al. 2012) and pipes (Vincke et al. 2001; Santo Domingo et al. 2011; Neria-González et al. 2006) is not new. However, to the authors' knowledge, the application of multi-omics approaches is limited. Gomez-Alvarez et al. (2012) analyzed the whole-metagenome to determine the microbial composition and functional genes associated with biomass harvested from sections of a corroded wastewater pipe. Taxonomic and functional analysis demonstrated that approximately 90 % of the total diversity was associated with the phyla *Actinobacteria*, *Bacteroidetes*, *Firmicutes* and *Proteobacteria*. Furthermore, the biofilm was found to have an abundance of sulphur-oxidizing bacteria and sulphate-reducing bacteria. Combined with transcriptomics, Gomez-Alvarez et al. (2012) also demonstrated an enrichment of genes associated with heavy metal resistance, virulence (protein secretion systems) and stress response in the biofilm analyzed.

Mohan et al. (2014) analyzed hydraulic fracturing source water and wastewater produced during fracking using metagenomic and metabolomic techniques.

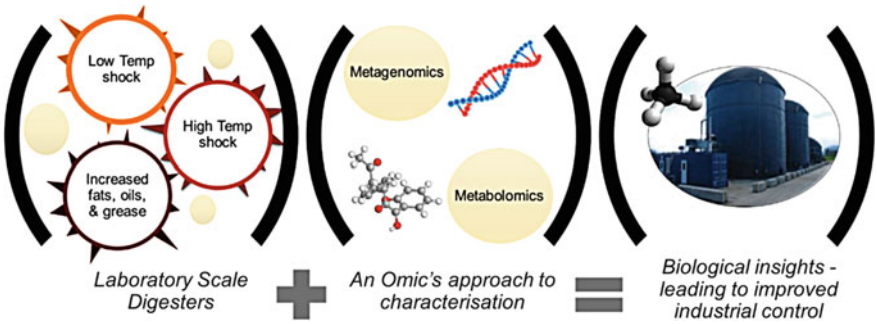

Fig. 4 Post-data analysis approach applied to a multi-omics study investigating operational shocks within laboratory scale digesters treating municipal waste. Adapted from Beale et al. (2016b)

The post-data analysis of the multi-omic datasets revealed a relative increase in genes responsible for carbohydrate metabolism, respiration, sporulation and dormancy, iron acquisition and metabolism, stress response and sulphur metabolism in the produced water samples from a diverse microbial community (Mohan et al. 2014). These results suggest that microbial communities in potable water have an increased genetic ability to handle stress, which has significant implications for infrastructure management, such as biofilm control and combating microbial influenced corrosion.

Another multi-omics study conducted by Beale et al. (2016b) investigated operational shocks in laboratory scale Anaerobic Digesters (AD) treating municipal wastewater (Fig. 4). The laboratory scale digesters were operated to simulate potential shocks to the AD process experienced at a 350 ML/day wastewater treatment plant. The shocks included high (42 °C) and low (32 °C) temperature (either side of the optimum temperature of 37 °C) and a 20 % loading of fats, oil and grease (20 % w:v). These variables were explored at two sludge retention times (12 and 20 days) and two organic loading rates (2.0 and 2.5 kg TS/m^3 day). Metagenomics and metabolomics approaches were then used to characterize the impact of operational shocks in regard to temperature and fats, oil and grease addition, as determined through monitoring of biogas production, the microbial profile and their metabolism. Results showed that AD performance was not greatly affected by temperature shocks. Post-data analysis of the metagenomics and metabolomics data indicated that methanogens and methane oxidizing bacteria were low in relative abundance, and that the ratio of oxidizing bacteria (methane, sulphide and sulphate), with respect to sulphite reducing bacteria had a noticeable influence on biogas production. Furthermore, increased biogas production correlated with an increase in short chain fatty acids, a product of the addition of 20 % fat, oil and grease.

As demonstrated by the works of Gomez-Alvarez et al. (2012), Mohan et al. (2014), Beale et al. (2016b), the application of omics-based techniques to characterize the microbial community and their function provides insight to the resilience

of crucial microbial populations within water sources, pipes and treatment process. In addition, it is anticipated that through multi-omics approaches, new insights into microbial populations in terms of diversity, resilience and activity when exposed to shocks and stresses (such as illegal discharges within sewer networks and operational shock during treatment) will be obtained. Furthermore, multi-omics may provide insight into driving higher biogas and methane production during treatment and collection systems for reuse.

3.4 Biofilms and Biofilms Known to Influence Corrosion

The safety and quality of potable water is often assumed and taken for granted by consumers in most developed countries. However, our understanding of potable water biofilms is limited, partly as they are difficult to access and traditional microbiology approaches fail to provide sufficient information on their composition and activity (Douterelo et al. 2014). To date, numerous researchers have applied omics-based techniques to characterize and assess aquatic biofilms, in a range of environments. For example, Shaw et al. (2014), Chao et al. (2013) assessed the community structure of potable water biofilms using metagenomics when exposed to different water treatment strategies. Metagenomics was also used to investigate intertidal marine biofilm communities (Zhang et al. 2013) and black fungal biofilms growth in domestic water fixtures (Heinrichs et al. 2013). Metabolomics has also been used to investigate biofilms found on the surface of copper pipes (Beale et al. 2010; Beale et al. 2012) and within potable water distribution networks (Beale et al. 2013). However, the application of multi-omics approaches has been limited. Leary et al. (2014) used a metagenomic and metaproteomic approach to analyze the composition and function of marine biofilms; others have investigated microbial communities in extreme environments using metagenomics and proteomics (Singer 2012; Schneider and Riedel 2010). Nevertheless, it has been identified that there is a need for a multi-omics approaches to assess biofilms. This has resulted in the recently proposed term "Biofomics" and web-based interface for biofilm data (Lourenço et al. 2012). Biofomics provides a framework, database depository and selection of statistical tools for researchers to follow, merge and examine data from different approaches such as metagenomics, transcriptomics, proteomics and key metabolites (metabolomics) (Nozhevnikova et al. 2015). The biofilm data results from experiments involving several types of bacterial genera such as *Salmonella* spp., *Escherichia coli* and *Candida* spp., and is supported by the minimum information about a biofilm experiment (MIABiE) initiative (Lourenço et al. 2012). To date, the majority of biofomics work has been related to the biomedical and clinical fields.

An issue of particular concern to infrastructure asset managers is biofilms that cause biocorrosion/biodeterioration (also known as MIC). Due to their potential financial and economic impact to infrastructure, there has been a considerable amount of research published on the role of microorganisms in promoting

corrosion. The majority of this work has been undertaken to address the problem of MIC in offshore oil and gas pipelines, and concrete structures with some preliminary research on microbial/metal surface interactions in water pipes. As such, a number of extensive reviews have been compiled on MIC mechanisms over the past 20 years (Videla and Herrera 2009; Edyvean and Videla 1991; Videla 2003; Beech and Gaylarde 1999; Flemming 1994; Beech et al. 2014).

Corrosion is the result of a series of chemical, physical and (micro) biological processes leading to the deterioration of materials. The mechanisms of MIC and MIC inhibition are not completely understood, because they cannot be linked to a single biochemical reaction or specific microbial species or group (Kip and van Veen 2015). As such, MIC biofilm communities can be studied at both their compositional and functional levels through the use of multi-omics. A number of traditional techniques, such as clone libraries and genetic fingerprinting, along with more recent metagenomics and transcriptomics, are being used to characterize and understand MIC biofilms (Chakraborty et al. 2014).

Relatively few metabolomic-MIC studies have been reported. The role of corrosion products on MIC of carbon steel has been investigated by gas chromatography-mass spectrometry (GC-MS) (Liu et al. 2000), where S^{2-} and organic acids were found to destroy the protective layer and promote hydrogen permeation. Furthermore, GC-MS-based metabolomics has also been explored as a potential tool in monitoring MIC in copper pipes in water distribution systems (Beale et al. 2010, 2012). It was found that the biofilm metabolites of bacteria causing copper pipe MIC comprised a combination of organic acids, amino acids and lipids. These are common in biological metabolic processes, specifically those relating to soluble monomers and sulphite reducing substrates. In addition, the range of carboxylic acids released from the isolates (*Bosea*, *Methylobacterium*, *Paenibacillus*, *Sphingomonas* and *Variovorax*) suggests that the corrosion potential of these biofilms varies, which would account for localized pitting corrosion commonly observed in metallic pipes (Beale et al. 2014a). Kouremenos et al. (2014) investigated the metabolic profile of *Pseudomonas putida* in potable water exposed to high and low doses of soluble and insoluble iron using LC-TOFMS and identified metabolites that included nucleobases, nucleosides, dipeptides, amino acids, fatty acids, sugars and phospholipids as a response to exposure. While not directly related to MIC, the approach by Kouremenos et al. (2014) and the preliminary work of Beale et al. (2010, 2012) demonstrate the feasibility of GC and LC-based metabolomics techniques to assess microbial populations exposed to metals or isolated from biofilms known to cause MIC in potable water networks. In a study by Booth et al. (2011), the difference in response to metal stress between sessile and planktonic bacterial populations was characterized. The planktonic population had an oxidative stress response to copper ion exposure, whereas the same species within a biofilm environment responded by shifts in exo-polysaccharide-related metabolism. This finding suggests that microbial responses pertinent to corrosion are different between sessile and planktonic populations, and through more research using metabolomic-based techniques, linkages between the metabolite activity of both sessile and planktonic populations and their

release of extracellular metabolites from a biofilm can be achieved. While biofilms, in general, and their influence on corrosion, in particular, have been subject to extensive research, there has been limited experimental work performed on the in situ characterization of the organic compounds within biofilms (Beech et al. 2014; Graeber et al. 2014).

With DNA sequencing costs decreasing, omics-based techniques are enabling an increasing number of laboratories to taxonomically and functionally classify a wide range of the organisms that are present in biofilms, and the extension of proteomics and metabolomics techniques enables the assessment of biofilm microbiological communities more broadly (Douterelo et al. 2014). The study of functional genes involved in metabolic pathways is essential when attempting to link microbial diversity with specific ecological functions. In the context of biofilms, better knowledge of the role microorganisms play in MIC and MIC processes such as biofilm formation and corrosion is required and through the application of multi-omics research, such knowledge will be realized.

3.5 Medical and Clinical

Metabolomics studies have been used to investigate the gut microbial population structure associated with a wide range of human diseases (Alam et al. 2014; Garrett 2015; Gevers et al. 2014; Goldman et al. 2014; Ley et al. 2006; Smith et al. 2013). Expression profiling studies have contributed significantly to the understanding of underlying molecular mechanisms of several diseases. In the context of cancer research, this has resulted in the improved classification of tumour subtypes (Karnovsky et al. 2012). However, the lack of early diagnostic markers still remains a problem (Diamandis 2010). Proteomics and metabolomics have the potential to provide additional biological insight for solving this problem (Enjalbert et al. 2011).

The multi-omics approach has been applied to identify markers related to retinoblastoma which is caused by the RB1 gene inactivation. The miRNA pathway analysis, coupled with miRNA microarray indicated a presence of 18 novel miRNAs responsible for the onset of this type of retinal cancer (Guha et al. 2015). In addition to cancer studies, multi-omics approach has been applied to other studies such as asthma-COPD overlap syndrome (Trentacoste et al.), autism disorders, sickle cell anemia and kidney disorders among many (Megan et al. 2016; Zeidan-Chulia et al. 2014; Goodman et al. 2016; Cisek et al. 2015). A very recent research conducting ACOS pattern among asthma patients recorded a trend of increased Immunoglobulin E (IgE) antibody. A differential gene expression of Toll-like receptor 10 (TLR10), an asthma related gene was observed. Also, a further study of single nucleotide polymorphisms (SNPs) indicated a role of another gene IL21R in ACOS. Based on pathway analysis, the pattern was also observed to affect the activities related to cytochrome P450 system (Megan et al. 2016).

A recent review by Higdon et al. (2015) indicated numerous domains (genes, RNA and proteins) related to autism spectrum disorders (ASD) such as fragile-X

mental retardation protein (FMRP) and chromatin modifying genes and postsynaptic and embryonic development proteins. Expression analysis models such as linear models for microarray analysis (LIMMA) and significance analysis of microarrays (SAM) have been used to identify differential expressions based on several databases and networks such as KEGG, HMDB, BioCyc, Panther among many others. The former modelling approach (LIMMA) was used to identify Alzheimer's related genes and signal transduction pathways such as NOTCH and Wnt in mitochondrial expressional system of ASD patients (Zeidan-Chulia et al. 2014).

Overall, it has been observed that multi-omics research has been at fairly advanced levels in cancer research, and has made inroads into other clinical researches. It is expected that a rapid growth in those studies will be observed in near future, with a further expansion in other related fields, thereby leading to 'personalized medicine' development.

3.6 Biofuels

In recent years, one of the prominent fields of multi-omics applications is algal origin biofuels. Although, the studies involving these applications have been generally referred to as 'metabolic engineering', they involve more than two approaches (mostly, genomics or transcriptomics and metabolomics). A recent study reported by Trentacoste et al. (2013) was conducted to improve the lipid accumulation in microalga *Thalassiosira pseudonana*. Transcriptomic analysis indicated the role of hydrolase Thaps3_264297. A knocking out of this gene by lipase enzyme overexpression by RNAi and antisense approach resulted in a 3-5 fold increased output of lipids.

Another approach of multi-omics in improving lipid accumulation is by nitrogen starving of algal cells. The responses based on triacylglycerol (TAG) synthesis by *Chlamydomonas reinhardtii* showed a switching on of gluconeogenic phase ($\leq$30 min), followed by a transition to glycolytic phase ($\geq$4 h). Additionally, a transduction to Carbon–Nitrogen responsive pathways occurred (due to alterations in cw15 proteome), causing increased carbon assimilation and nitrogen metabolism. This led to an increased TAG synthesis in two stages of 'before TAG synthesis (BTS)' and 'after TAG synthesis (ATS)' (Park et al. 2015). Similar approaches have been previously reported for alga mediated high density biofuels (biodiesel fuel) (Beer et al. 2009; Hossain et al. 2008), indicating an estimated 13 % in energy surplus (Dassey et al. 2014).

Similar results to that of algal research mentioned above have also been observed in other organisms regarding biofuel production capabilities of microbial cells. A recent example is that of metabolome and proteome analysis of the yeast *Yarrowia lipolytica*. Nitrogen depletion in this yeast induced an alteration in 133 phosphorylation sites, thereby enriching phosphorylating proteins, causing up-regulation of lipid synthesis (Pomraning et al. 2016).

4 Conclusion

Enhanced knowledge through the application of 'omics'-based techniques provides a holistic opportunity to measure biological systems and the impact of these systems under stress. Furthermore, through the application of multi-omics, researchers are able to obtain a greater depth of knowledge that otherwise would not be achieved through a single 'omics'-based study. Combining metagenomic and transcriptomic data with proteomics and metabolomic datasets will provide researchers and clinicians details on the microbial population present and their metabolic functions. In addition, multi-omics research provides a path for self-validating findings through a combined parallel 'omics' approach, and will ultimately result in the accelerated understanding of these complex populations and processes, driving better diagnostic techniques and drug therapies, environmental remediation strategies and the development of innovative synthetic/engineered biological products.

It is anticipated that the rise of multi-omics research will enable biological systems to be well characterized, enabling model-based assessments to be generated and future research undertaken with only a subset of the data needed for clinical and experimental research, resulting in cost-effective more affordable research (through data mining of available literature and datasets and reducing the amount of experimental data needed). Although it is currently considered to be a nascent field, various potential applications and data integration tools are either currently underway or are expected to appear on the scientific horizon in the near future. It is expected that the exponential development in overall 'omics' knowledge coupled with rapidly developing technology in this field, will assist in the exploration of various multi-omics applications and related scientific discoveries in the fields of environmental, industrial and clinical biology.

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