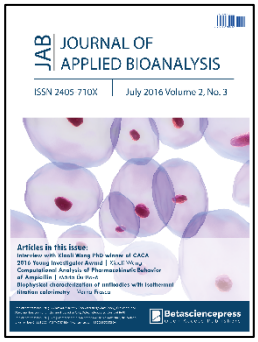

Multi-Omics for biomedical applications

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ABSTRACT

Multi-omics is a rising filed in –omics science. Despite progress in the multiple single –omics platform, the holistic look at the complex nature of the human cell, disease, and other biochemical pathways remain undiscovered. The multi-omics is considered the most integrated system currently available to obtain and measure the biochemical data-driven information for biomedical problems. The current review will look at the factors that play important roles in the rise of the multi-omics field and its application in biomedical studies.

In this review article we present some of the techniques and methods used to determine the short-term and long-term release of these monomers from modern dental materials and prove that analytical chemistry and especially bioanalysis can be a powerful tool in dentistry.

Keywords: omics; multi-omics: data integration; biomedical applications

1. Introduction:

Sometimes a few similar good things, when combined, can create a great outcome! The integrated omics or multi-omics has done this - by opening up a holistic look at the biological system by combining multiple omics systems [1]. The “Omes” table at Yale University records the first study with the “omics” keyword - published in 1938 in Pubmed [2]. The expansion of the field was so rocketed and within a short period of time, the field now has a large number of branches includes genomics, proteomics, transcriptomics, metabolomics and so on. The non-biological expansion of omics fields are also wide- foodomics, volatolomics, phytochemomics and many more. A search on Scopus with “omics” keyword during 2015-2019 has illustrated the trend of –omics, based on 9342 documents-clearly showing the rise of this field. The main field of studies was dedicated toward the biochemical and biomedical sciences whereas those studies were funded by the major world research organizations. During the last five years, almost 40% increase in the omics work was recorded. Among those, 20% of the studies were concentrated on the multi-omics approach, which is an indication of the expanding multi-omics field (Fig. 1).

2. Driving forces of multi-omics fields:

The primary reason for the expanding multi-omics fields during the last 10 years was the development of high-throughput and high-resolution technology for biological problem-solving [3]. One of the examples is expression array, a method to identify candidate marker genes of disease - could generate an overwhelming amount of data of hundreds of thousands of genes in a single run [4]. Another important innovation was the development of high-resolution mass spectroscopy. The HR-MS has emerged with extensive identification power that it has become an essential part of environmental, biochemical and chemical sciences [5]. Fig 2 presented a schematic to show the applications of the high-throughput and high resolution methods in omics fields.

The development of data science is the most critical and meaningful boost to the multi-omics field. To find the possible meaningful conclusion of the large data set produced in multi-omics, the data science including machine learning and artificial intelligence have been frequently used from their development [6]. The readers are referred to well written articles for more detailed reviews on multi-omics data integration and analysis [6-11]. A few main challenges of data integration method are still remain unsolved; limited biological knowledge guided integration and the heterogeneity of the data from different omics sources are considered the root of this problem.

3. Application of Multi-omics in biomedical research:

The table 1 listed the application of multi-omics in the different biomedical field. A brief introduction of the multi-omics application to cancer research, kidney disease,

infectious disease, cardiac disease and few other biomedical fields have been discussed in the following section.

a. *Cancer research*

The multi-omics study investigates the cancer causative tumor associated with genetic background. An integrative genomic study showed the evidence of the strong association between genetic status and multi-omics data for PCCs/PGLs type tumors (Pheochromocytomas and paragangliomas) [12]. Karnovsky et al., have used the multi-omics approach to classify the tumor subtypes which linked the metabolomics and gene expression data [13]. A multi-omics study combining transcriptomics, metabolomics and proteomics profiles of retinoblastoma cancer cell line has reported that 18 miRNAs possibly implicated with retinal cancer [14]. The breast cancer-causing gene association has been tracked down using an integrative whole-genome copy number and expression data [15].

Identifying the survival rate of cancer – the relative time, patients would live after diagnose compare with health individuals, would improve the patients' care and treatment. Multi-omics approaches using RNA sequencing (RNA-Seq) and miRNA sequencing (miRNA-Seq) from The Cancer Genome Atlas (TCGA) could predict the survival rate of the liver cancer with a deep learning-based model [16]. A Bayesian model for discovering prognostic cancer subtypes by integrating gene expression and copy number variation data has been reported by Yuan et al. [17]. Using a multi-platform genomic data, a new model has been reported to highly correlate with survival time in ovarian cancer patients [18].

b. Chronic kidney disease

Integrative omics on the epithelial cells helps the diagnosis of progressive renal, interstitial fibrosis and inflammation. A gene expression data from Gene Expression Omnibus (GEO) [19] and proteome data from Human Protein Atlas (HPA) [20] have been used for a genotype-phenotype relationship in the human kidney [21]. The result has indicated a total of 267 potential metabolic biomarkers for kidney-related diseases using a multi-omics model.

There are several omics experimental datasets available to formulate the hypothesis for Chronic Kidney Disease (CKD). Such as Urinary Pathway Knowledge Base (KUPKB) [22], Chronic Kidney Disease database (CKDdb) [23] and so on [24]. Brain Abundant Signal Protein 1 (BASP1) has been identified as to modulate the albumin induced cellular death of kidney cell in a multi-omics study [25]. Authors have used albumin-induced BASP1 expression data and KUPKB database to find the association with patients with type 2 diabetes. A multi-omics study combining proteomics and metabolomics has been reported to understand the vascular changes including the renal disease in diabetes mellitus arteriopathy [26]. The proteomics data have also been integrated with Gene Ontology (GO) for interactomics of metabolites and signaling pathway analysis.

c. Infectious disease

Host-pathogen interaction in infectious disease is an important aspect for the understanding disease biomarkers, prognosis, and treatment [27]. Multi-omics studies have been used in this field particularly tuberculosis (TB), autoimmune disease and HIV. Genomics and transcriptomics have been used to stimulate with *Escherichia coli*

(*E. coli*) LPS, influenza virus, or IFN-β expression on human dendritic cells. A set of 121 genes were found associated with those exposures in that study [28]. The human macrophages and *Staphylococcus aureus* interactions in terms of proteomics and kinomics have also studied. Authors have reported the major macrophage signaling pathways that are triggered by pathogens [29]. An interesting study used metagenomics, metatranscriptomics, or metabolomics application of multi-omics on the identification of probiotic candidates for the Chytridiomycosis and other emerging infectious diseases in wildlife [30].

A longitudinal multi-omics study has been conducted on more than 100 healthy and pre-diabetics volunteers for a duration of 4 years to track the changes on transcriptomes, metabolomes, cytokines, and proteomes, as well as changes in the microbiome [31]. The result has broadened the understanding of the association between prediabetes biological stages and the identification of inflammation markers in immune signaling. A number of large scale association studies based on omics platform to understand the pathophysiology of HIV have also been reported [32]. These studies help to understand the link between the complex HIV infection process and the interpretation of actionable therapeutic or diagnostic targets.

d. Cardiac disease

Cardiovascular diseases are the leading causes of morbidity and mortality worldwide [33]. Coronary heart disease has found associated with a group of 150 genomes in a large scale genomics study [34]. The expression of those genetic loci and the integration of multi-omics data transcriptome, epigenome, proteome, metabolome have been reported in the literature [35]. A multi-omics study integrating transcriptomics and

proteomics has been conducted to evaluate their synergistic effect on the in-vitro cardiac hypertrophy model in mice [36]. That study identified 70 candidate disease signatures in the steady-state transcript and protein abundance.

A genomic and transcriptomic study identified 3 master regulatory genes for Coronary Artery Disease (CAD) patients in a population of Europe; Stockholm Atherosclerosis Gene Expression (STAGE) study [37]. Another study by Feng et al. has utilized metabolomics and metagenomics to study the association of gut microbiota with the CAD risk. This study has found that GlcNAc-6-P, mannitol, and 15 plasma cholines were associated with the higher risk of CAD and showed a correlation of the *Clostridium sp.* and *Streptococcus sp.* in the intestine [38].

Diagnosis for myocardial dysfunction and heart failure is an important indicator for the care and treatment control. A multi-omics study in myocardial tissue and blood has identified epigenetic regions and novel biomarkers for diagnosis of heart failure. The result has reported a set of 517 epigenetic loci and a CpGs makers of the heart failure diagnosis [39]. Multi-omics study on CAD not only helps to understand the mechanism of genetic connection but also helps to identify the key drivers and pathways that contribute to the risk [35]. For examples, an integrated network has been developed using genome-wide association studies and identified a set of 30 related to CAD [40].

e. Others

The rise of the omics technologies over the last few years have lead a better understanding of the mechanism of diet in metabolic regulation and overall health [41]. As a result, a number of literature integrating the multiple omics in nutritional research has been reported. Orotic acid-induced fatty liver disease has been investigated using

transcriptional and metabolic levels [42]. The study finding has indicated a few metabolic pathways that demonstrate the association of orotic acid with fatty liver disease. Another example of the multi-omics study by metabolomics, proteomics, and trascriptomics is the evaluation of the effect of valproci acid in the liver. The result has indicated a perturbation in glycogenolysis pathway by two proteins, glycogen phosphorylase and amylo-1,6-glucosidase different from the control [43]. Another nutritional multi-omics study has explored the relation of arachidonate-enriched diet over eicosapentaenoic (EPA)/docosahexaenoic (DHA) diet, to find any differential response on hepatic lipid metabolism [44].

Molecular changes during the aging process have an important significance in the preservation and treatment of aging person. The multi-omics study that links genomics, metabolomics, metagenomics, and transcriptomics have been used to understand the human again process [45]. The study has showed the importance of the relationship between epigenetic factors such as histone modification and DNA methylation in aging [46]. A lipidomics study has suggested a strong association with lipid profile with the longevity [47]. On the other hand, an *in-vitro* study with rat brain has illustrated the dynamics of changes in the dark matter of the genome [48]. A combine genomic and transcriptomic study has revealed a set of 56 genes that are overexpressed with aging and 17 genes that are under-expressed with age [49].

4. Tools and methods used in the Multi-omics:

Understanding complex biological problems remain a quest for many omics research. With the technological advances, we could now have a huge amount of data from a different level of probes for a better and comprehensive look of a disease. Although the

integration of these heterogeneous data remains a major challenge in multi-omics field, an immense effort by the data scientist and developer has been given. There are a number of different data integration methods and tools have been developed and applied to the multi-omics dataset (Table 2). These tools are able to integrate genome, transcriptome, and proteome and many more [50, 51].

The web-based method for multi-omics data integration and visualization is a recent and modern approach to tackle data integration tools. This process allows users to create a job and submit the data to understand the interconnection between the multi-layer omics dataset. PaintOmics 3 could be an example [52]. This web tool uses the KEGG database to show the integration of the biological pathway. Another good example is the LinkedOmics, which has a billion data points combining mass spectrometry (MS)-based global proteomic and cancer genomic datasets. Users can explore the link between these datasets and generate hypotheses for experimental validation [53]. Tables 2 listed a few other examples of these types of tools developed for the multi-omics integration.

The mathematical integration of the different sources of data with the different noise levels, different variables, non –comparable data types and many other data issues are also challenging in the multi-omics studies. A number of methods have been developed in this regard and mainly divided into two methods; 1) unsupervised data integrating, a method that does not assign the response variables before analysis and 2) supervised data integration, which assigns the response variables before the analysis [6] (Fig 3).

Machine learning, Artificial intelligence, Bayesian method, Network-based analysis, Kernel method, and many more mathematical methods and their mathematical

background have been reported in literature [6, 7]. The second consideration is the platform or software used for the data analysis. Some of these tools are based on web server, some on C++, R, Matlab, Python and many more. This field of multi-omics method and tools are in the developmental stage and many new methods are appearing in the literature.

5. Future Perspectives:

A growing number of multi-omics studies have been reported in the last couple of years, incorporating many different omics platforms, new technology, tools and methods for data integration. The multi-omics process provided unprecedented utility and benefits that could not be provided by any single omics approach. This is now considered the most comprehensive and holistic approach for analyzing the samples and understanding between multiple biological phenomena by visualization, linking multiple biological pathways, finding association between genotypes and phenotypes and many more. The omics platform has opened a new era in biomedical science and the combination of the multi-omics is considering the future in this field.

As the multi-omics platform is getting more mature in terms of the tools and resources, it will facilitate the development of newer fields. Multi-omics will help to understand the link between the molecular and clinical characteristics of the disease, the discovery of biomarkers by pathway analysis and observed the association from a large scale mechanistic study. The ongoing effort on the multi-omics and leveraging integrative strategies would further improve the application of this filed on the biomedical problems solving.

6. Conclusion:

This mini-review provides a concise overview of the multi-omics platform. The motivation of the multi-omics and its applications in biomedical problem solving have been discussed here. The omics platform integration tools and the methods that require special data science background have also been illustrated. The multi-omics is so far the most holistic analysis tool and would be the future of the omics fields.

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5. FIGURES AND TABLES

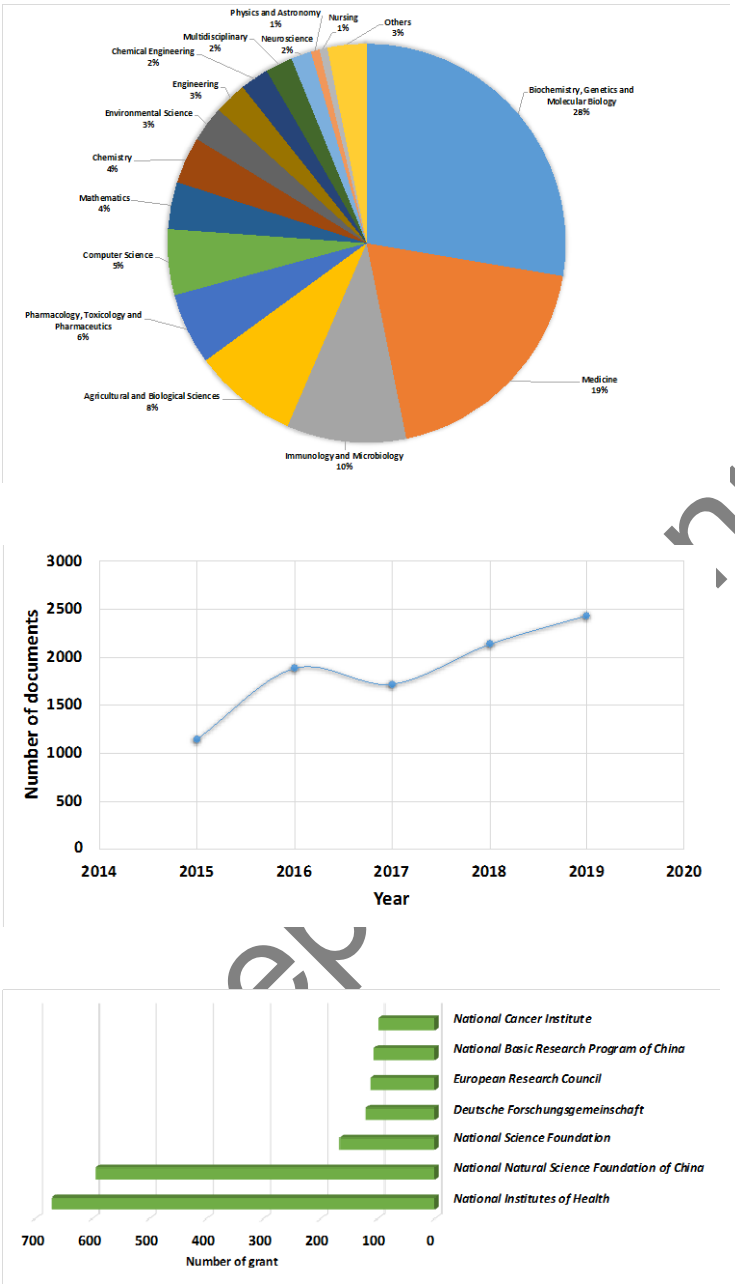

Fig 1: The "omics" keyword in Scopus© database from 2015-2019 showing the (a) fields of study (b) number of documents and (c) funding organization of –omics study.

In this mini review, we will look at the important factors of the multi-omics field and then will discuss the applications of multi-omics for the solving of biomedical problems.

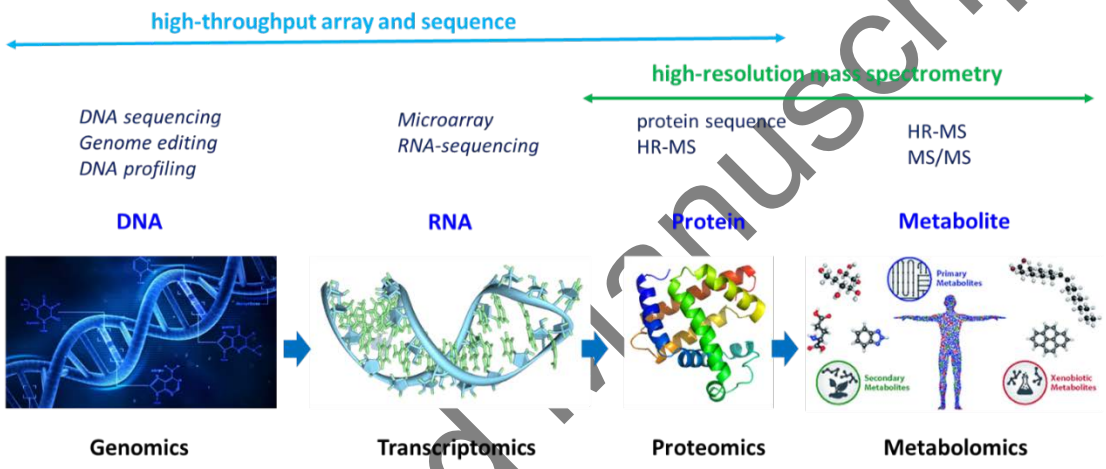

Fig.1. The schematic application of high-throughput and high-resolution–omics techniques for multi-omics studies.

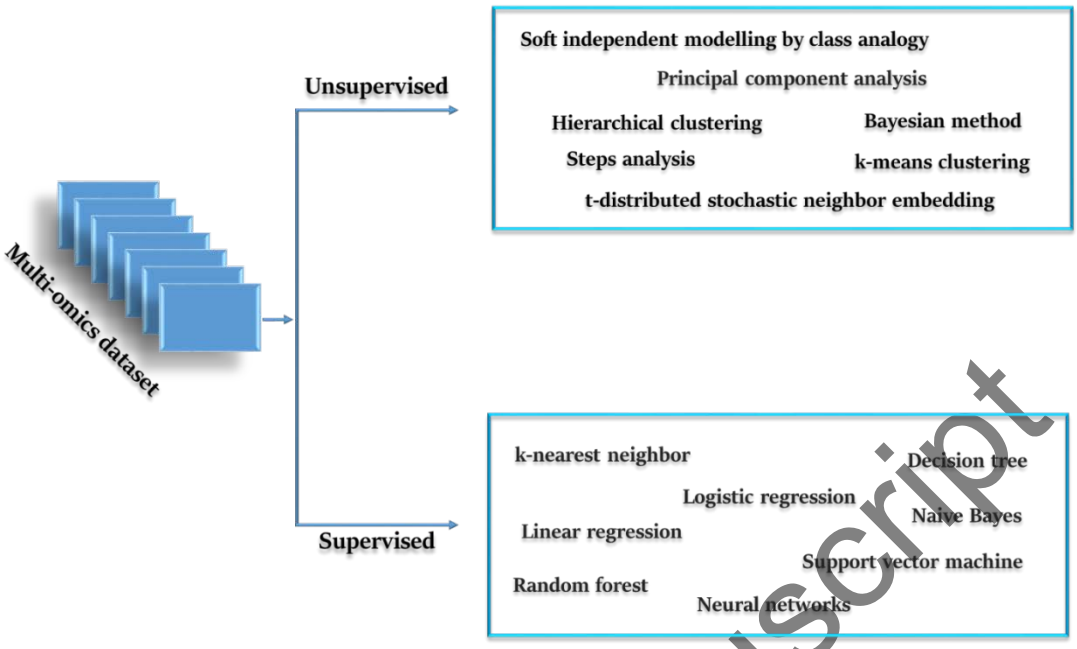

Fig.2. The mathematical basis of multi-omics data integration methods.

Table 1. Application of multi-omics in the biomedical fields.

Disease	Omics technologies	Objectives	Reference
Cancer	Genomics and metabolomics	To classify the tumor subtypes	13
Retinal Cancer	Transcriptomics, metabolomics and proteomics	To profile retinoblastoma cancer cell	14
Prognostics cancer	Genomics and transcriptomics	To discover prognostic cancer subtypes	17
Renal disorders	Proteomics and metabolomics	To correlate vascular changes in diabetics for renal disfunction	26
Infectious disease	Genomics and transcriptomics	To identify genes associated with *E. coli*, LPS, influenza virus, or IFN-β expression on human dendritic cells	28
Infectious disease	Proteomics and kinomics	To study the interaction between human macrophages and *Staphylococcus aureus*	29
Infectious disease	Metagenomics, metatranscriptomics, and metabolomics	To identify probiotic candidates for the Chytridiomycosis and other emerging infectious diseases in wildlife	30
Cardiac disease	Genomic and transcriptomic	To identify master regulatory genes for coronary artery disease	37
Cardiac disease	Metabolomics and metagenomics	To study the association of gut microbiota with the cardiac artery disease risk	38
Cardiac disease	Multi-omics	To identify epigenetic regions and novel biomarkers in myocardial tissue and blood for diagnosis of heart failure	39

Fatty liver disease	Transcriptomics and metabolomics	To investigate orotic acid-induced fatty liver disease.	42
Liver disease	Metabolomics, proteomics, and transcriptomics	To evaluate of the effect of valproci acid in the liver.	43
Aging process	Genomics, metabolomics, metagenomics, and transcriptomics	To understand the human again process by molecular changes.	45
Aging process	Genomic and transcriptomic	To identify genes that are overexpressed and under-expressed with aging.	49

Table 2: Tools used for multi-omics studies

Name	*Data platform*	*Omics techniques*	*Reference*
PaintOmics 3	Web based	transcriptomics, proteomics and metabolomics	[52]
web-rMKL	Web based, Java based	NA; multiple OMICS data types	[54]
LinkedOmics	Web based	genomic, epigenomic, transcriptomic, and proteomic	[53]
KeyPathwayMinerWeb	Web based	multiple OMICS data types	[55]
iPath3.0	Web based	metabolomics	[56]
GENEASE	Web based	genomics, reactomics and other cancer phenotypes	[57]
3Omics	Web based	transcriptomic, proteomic, metabolomic	[58]
MixOmics	R	transcriptomics, metabolomics, proteomics, metagenomics	[59]