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Research review paper

Using machine learning approaches for multi-omics data analysis: A review

Parminder S. Reel [a,1], Smarti Reel [a,1], Ewan Pearson [a], Emanuele Trucco [b], Emily Jefferson [a,*]

[a] Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, United Kingdom
[b] VAMPIRE project, Computing, School of Science and Engineering, University of Dundee, Dundee, United Kingdom

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ABSTRACT

With the development of modern high-throughput omic measurement platforms, it has become essential for biomedical studies to undertake an *integrative* (combined) approach to fully utilise these data to gain insights into biological systems. Data from various omics sources such as genetics, proteomics, and metabolomics can be integrated to unravel the intricate working of systems biology using machine learning-based predictive algorithms. Machine learning methods offer novel techniques to integrate and analyse the various omics data enabling the discovery of new biomarkers. These biomarkers have the potential to help in accurate disease prediction, patient stratification and delivery of precision medicine. This review paper explores different integrative machine learning methods which have been used to provide an in-depth understanding of biological systems during normal physiological functioning and in the presence of a disease. It provides insight and recommendations for interdisciplinary professionals who envisage employing machine learning skills in multi-omics studies.

1. Introduction

Digital information is growing rapidly, in terms of five V's (volume, velocity, veracity, variety and value), and hence this is hailed as the *big data* era (BCS, 2014; Bellazzi, 2014; Lee and Yoon, 2017). Health-based big data including linked information for patients, such as their clinical data (for example gender, age, pathological and physiological history) and omics data (such as genetics, proteomics and metabolomics) has now become more widely available (Canuel et al., 2015; Singhal et al., 2016). Recently, such data has been used for precision (also called personalised or stratified) medicine to provide customised healthcare, i.e. providing a bespoke treatment for individuals (Gibson et al., 2015; Kalaitzopoulos, 2016; Malod-Dognin et al., 2017). There has been unprecedented growth in the development of precision medicine supported by ML (machine learning) approaches (Delavan et al., 2017; Peterson et al., 2013; Zou et al., 2017) and data mining tools (Chawla and Davis, 2013; Cheng et al., 2015; Margolies et al., 2016). These techniques have also helped to discover novel omics biological markers which can identify the molecular cause of a disease.

A biomarker is a substance, structure, or process that can be measured in the human body or its products and can provide surrogate information about the presence of a disease/condition (Strimbu and

Abbreviations: ATHENA, Analysis Tool for Heritable and Environmental Network Associations; BCC, Bayesian consensus clustering; BN, Bayesian Network; CS, Concatenation-based Supervised Learning; CU, Concatenation-based Unsupervised Learning; DNA, Deoxyribo-Nucleic Acid; FCA, Formal Concept Analysis; FDA, Food and Drug Administration; fMKL-DR, fast multiple kernel learning for dimensionality reduction; FSMKL, Multiple Kernel Learning with Feature Selection; HI-DFNForest, Hierarchical integration deep flexible neural forest; JBF, Joint Bayes Factor; JIVE, Joint and Individual Variation Explained; KNN, k-nearest neighbors; LASSO, Least Absolute Shrinkage and Selection Operator; LDA, Linear Discriminant Analysis; lncRNAs, long non-coding RNAs; MDI, Multiple Dataset Integration; MDS, Multi-Dimensional Scaling; Meta-SVM, Meta-analytic SVM; miRNA, microRNA; ML, Machine Learning; MOFA, Multi-Omics Factor Analysis; MOLI, Multi-omics late integration; MORONET, Multi-Omics gRaph cOnvolutional NETworks; MOSAE, Multi-omics Supervised Autoencoder; mRNA, messenger Ribo-Nucleic Acid; MS, Model-based Supervised Learning; MU, Model-based Unsupervised Learning; NEMO, NEighborhood based Multi-Omics clustering; NMF, Non-negative Matrix Factorisation; PCA, Principal Component Analysis; PINS, Perturbation clustering for data integration and disease subtyping; PSDF, Patient-Specific Data Fusion; RF, Random Forest; rMKL-LPP, regularised multiple kernel learning for Locality Preserving Projections; RVM, Relevance Vector Machine; SDP-SVM, Semi-Definite Programming SVM; SmSPK, smoothed shortest path graph kernel; SNF, Similarity Network Fusion; SSL, Semi-supervised learning; SVM, Support Vector Machine; SVR, Support vector regression; TS, Transformation-based Supervised Learning; TU, Transformation-based Unsupervised Learning.

* Corresponding author at: Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK.
E-mail address: e.r.jefferson@dundee.ac.uk (E. Jefferson).

[1] These authors contributed equally to this study (shared first authorship).

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Table 1
The omics technologies which help us draw a complete picture of cell biology and related function.

S. No	Omic name	Term coined in	Data extracted	Commonly used High-throughput technologies	Common Reference databases	Recent reviews
1	Genomics	1986 (Kuska, 1998)	Single nucleotide polymorphisms, Rare variants and Copy number variations.	DNA-Sequencing (Sanger (Sanger et al., 1977), Whole-genome (Huang et al., 2017a), Whole-exome (Weisz Hubshman et al., 2018), Single-Cell DNA (Zhang et al., 2019a) and targeted sequencing (Bewicke-Copley et al., 2019)), Microarray (Bumgarner, 2013).	DDBJ (Tateno et al., 2002), GenBank (Benson et al., 2011), ENA (Leinonen et al., 2011)	(Reuter et al., 2015)
2	Transcriptomics	1999 ("Proteomics, transcriptomics,", 1999)	Messenger, Micro and Long non-coding RNA expression.	RNA-Sequencing (Sanger (Alidjinou et al., 2017), Single-Cell RNA (Hwang et al., 2018) and targeted sequencing (Mercer et al., 2012)), Microarray (Zhao et al., 2014).	miRBase (Kozomara et al., 2019), Rfam (Kalvari et al., 2018)	(Lowe et al., 2017)
3	Proteomics	1994 (Wilkins and Appel, 2007)	Protein expression	Reverse Phase Protein Array (Boellner and Becker, 2015), Liquid Chromatography - Mass Spectrometry (Karpievitch et al., 2010) and Mass Spectrometry (Timp and Timp, 2020)	HPA (Uhlen et al., 2010), PDB (Burley et al., 2019), Pfam (Finn et al., 2010), UniProt (The UniProt Consortium, 2019)	(Aslam et al., 2017)
4	Metabolomics	2001 (Lindon et al., 2011)	Metabolite expression	Mass Spectrometry (Glaves et al., 2014), Liquid Chromatography - Mass Spectrometry (Zhou et al., 2012), Gas Chromatography - Mass Spectrometry (Fiehn, 2016).	HMDB (Wishart et al., 2018), KEGG (Kanehisa and Goto, 2000)	(Zampieri et al., 2017)
5	Lipidomics	2003 (Wang et al., 2016)	Lipids	Liquid Chromatography - Mass Spectrometry (Li et al., 2020), High-performance Liquid Chromatography - Mass Spectrometry (Knittelfelder et al., 2014) and Direct-Infusion/ Shotgun - Mass Spectrometry (Köfeler et al., 2012).	LMSD (Sud et al., 2007), LipiDAT (Caffrey and Hogan, 1992), LipidBank (Watanabe et al., 2000), LipidHome (Foster et al., 2013), LipidPedia (Kuo and Tseng, 2018),	(Yang and Han, 2016)
6	Glycomics	1990 (Vasta and Ahmed, 2008)	Glycomes	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight - Mass Spectrometry (Zhang et al., 2019b).	GlyTouCan (Tiemeyer et al., 2017), UniCarb-DB (Campbell et al., 2014)	(Rojas-Macias et al., 2019)
7	Metagenomics	1998 (Handelsman et al., 1998)	Genetic data from environmental (soil, water) samples.	Target Gene Sequencing, Shotgun Metagenome Sequencing, Metatranscriptome Sequencing (Zhou et al., 2015)	MG-RAST (Meyer et al., 2008), SRA (Kodama et al., 2012), MGnify (Mitchell et al., 2020)	(Pérez-Cobas et al., 2020)

Tavel, 2010). Molecular biomarkers are discovered by analysing the cascade of information provided by different omics (Debnath et al., 2010). For example, the high-sensitivity C-Reactive protein test provides an accurate and quantitative risk assessment for cardiovascular disease (Pfützner and Forst, 2006; Shrivastava et al., 2015). Biomarkers play a significant role in planning preventive measures and decisions for patients (Nielsen, 2017) and can be classified as either *diagnostic*, *prognostic* or *predictive* (Le et al., 2016; Shaw et al., 2015). *Diagnostic biomarkers* are used for determining the presence of disease in a patient, while *prognostic biomarkers* provide information on the overall outcome with or without the standard treatment (Carlomagno et al., 2017). *Predictive biomarkers* are used to identify who is at risk of an outcome (Nalejska et al., 2014). All of these biomarkers can also be used to identify which treatment will be most suitable for a given patient. For example, the ADNI (Alzheimer's Disease Neuroimaging Initiative) study used a combination of neuroimaging, biochemical and genetic biomarkers to discriminate early Alzheimer's patients from healthy volunteers with an accuracy of 98% (Gupta et al., 2019). Similarly, different forms of Parkinson's syndromes have been investigated by developing an automated tool that fuses multi-site diffusion-weighted MRI imaging biomarkers and disease rating score (MDS-UPDRS III) (Archer et al., 2019). Biomarkers can help identify high-risk individuals before their physiological symptoms are evident. Moreover, they also help in measuring disease progression (Mandel et al., 2010).

In the context of precision medicine, ML has been used to develop diagnostic, prognostic and predictive tools from single omics data (Dias-Audibert et al., 2020; Mamoshina et al., 2018; Sonsare and Gunavathi, 2019). However, ML may have deteriorated performance for certain single omics such as gene data due to inherent characteristics (Kim et al., 2020). ML methods are now also being applied to multi-omics data (Bersanelli et al., 2016), to investigate and interpret the relationships between data and phenotypes (Kim and Tagkopoulos, 2018). Although ML analysis of multi-omics is still in its embryonic stage, it has already been explored for a wide range of applications, as reported in recent reviews on brain diseases (Garali et al., 2018; Young et al., 2013), diabetes (Kavakiotis et al., 2017), cancers (Borad and LoRusso, 2017; Chaudhary et al., 2017; Wong et al., 2016) cardiovascular disease (Weng et al., 2017), medical imaging (Erickson et al., 2017), single-cell analysis in humans (Cao et al., 2020; Ma et al., 2020a) and plant science studies (Acharjee et al., 2011). Currently, many of the multi-omic reviews are focused on individual sub-topics. For example, designing studies (Haas et al., 2017; Hasin et al., 2017), setting up workflows (Kohl et al., 2014), choosing software tools (Misra et al., 2019) and evaluating overfitted performance (McCabe et al., 2020).

In contrast, this review aims at a broader focus, presenting an interdisciplinary perspective to new readers in this domain by providing a background on multi-omics and ML. It takes forward the integration terminologies introduced by Ritchie (Ritchie et al., 2015) and summarises the recent integrative state-of-the-art approaches. We aim to cover various integration methods concisely and include a recommendation flowchart enabling interdisciplinary scientists to have a quick head start in this domain (Bersanelli et al., 2016; Nguyen and Wang, 2020).

Scope of this review: This review investigates the two primary learning strategies in ML, i.e. supervised and unsupervised, which are commonly used within the context of multi-omics integration. This review considers *multi-omics integration* as a process of combining different single omics. Although various ML specialisations such as reinforcement (Coronato et al., 2020), hybrid (Zhou et al., 2019), multi-view (Zhao et al., 2017) and self-supervised learning (Chen et al., 2019) are now emerging in generic healthcare applications, they have not yet gained enough momentum in multi-omics analysis, hence they remain beyond the scope of this review.

Table 2
The different ML learning approaches reviewed for multi-omics integration.

Learning approach	Goal	Description
Supervised	Predict new data	Supervised learning involves fitting a model with labelled training data and then use it for prediction. It can be classed either as a regression (predicted variable is numeric) or classification (predicted variable is categorical) problems (Jiang et al., 2020). The three steps in supervised learning are: (1) fitting a model from the sample input observations (2) evaluating the model and then extensively tuning the hyper-parameters of the model (3) setting up the model for the production stage and using it for prediction (Foster et al., 2014).
Unsupervised	Identify clusters	Unsupervised learning is used to find the underlying patterns in unlabelled data using input feature variables without the target/output variable (Badillo et al., 2020). It can be used for clustering (Xu and Tian, 2015), anomaly detection (Thudumu et al., 2020) and dimensionality reduction (Xu et al., 2019a).

This paper is organised as follows. Section 2 provides a short background related to multi-omics and ML. Section 3 describes how ML is employed for multi-omics analysis and what are the various real-world challenges of it. In Section 4, details of different multi-omics integration approaches are presented. Section 5, published multi-omics studies using ML methods are discussed. Section 6 describes a recommendation flowchart for choosing an appropriate method for multi-omics integration. Conclusions are provided in Section 7.

2. Background

2.1. Multi-omics

In living beings, genetic information in the cells flows from DNA (deoxyribo-nucleic acid) to the mRNA (messenger ribo-nucleic acid) to protein and is dictated by the central dogma of molecular biology (Lodish et al., 2000). This flow of information is often considered analogous to a computer system which has facilitated the understanding of biological information processing (Wang and Gribskov, 2005; D'Onofrio and An, 2010).

The study of DNA, mRNA and proteins is broadly denoted as genomics, transcriptomics, and proteomics respectively. The genetic blueprint of a cell is explored using genomics, which looks at the DNA of individuals and helps us to investigate the presence or absence of certain genes (Gibson, 2015; Vogel and Motulsky, 1997). Transcriptomics studies the transcribed genetic material and examines the genes which are actively expressed and provides information about what is happening at the cellular level (Milward et al., 2016). Proteomics helps in characterising the information flow happening within the cell and the organism in the form of protein pathways and their networks (Wu et al., 2014).

Although metabolomics, lipidomics, and glycomics do not form part of the central dogma analysis (Cobb, 2017), they still provide an invaluable amount of information regarding the metabolites, lipids and glycans (synthesised by the proteome via biosynthetic pathways) (Barh et al., 2011). These substances are the intermediate products of a cell's information flow and therefore are considered to be excellent indicators of the cell's activity. Similar to single-genome studies, metagenomics is used to sequence genetic information from environmental samples without the requirement of isolating individual species (Hugenholtz and Tyson, 2008).

All measured omics data can be used as a biomarker which helps us to understand and analyse the underlying characteristics and complexities of biological systems (Alberts et al., 2008). Table 1 shows some of the important omics used to study biological systems (Handelsman et al., 1998; Kuska, 1998; Lindon et al., 2011; "Proteomics, transcriptomics,", 1999; Vasta and Ahmed, 2008; Wang et al., 2016; Wilkins and Appel, 2007). All of them are part of the same pipeline of biological information, whose output depends on the different inputs and regulation. As shown in Table 1, each of these omics can be measured using specialised high-throughput technologies (for example microarray (Bumgarner, 2013) and mass spectrometry (Glaves et al., 2014) for genomics and

Table 3
The standard ML terminology and related terms.

Term	Definition
Accuracy	It is a ratio of correctly predicted outcomes of a given class to the total outcomes. Accuracy is a measure of the performance of an ML model. It ranges from 0% to 100%.
Classification	It is a supervised learning method that provides predicted output as a discrete class. Classification can be binary, multi-class or multi-label.
Clustering	It is an unsupervised learning method that can group data based on the attributes of the input features.
Cross-Validation	It is a technique that allocates a given set of samples from the dataset which are not used for model training but set aside for testing (to evaluate model performance). K-fold and Leave one out are commonly used cross-validation methods.
Curse of dimensionality	It refers to a set of problems that arise when using datasets with high dimensionality. In the context of ML, it can impact the predictive performance of an ML model (Duda et al., 2001).
Dataset	It is a collection of structured data which comprises input feature variables and sometimes a corresponding target/output variable.
Ensemble Learning	It is a paradigm where different models are trained for solving the same problem and then combined to get better performance. Bagging, boosting and stacking are commonly used in ensemble learning methods.
Explainability	Supervised learning models can be classed as 'white' or 'black-box' based on their explanation (or lack thereof) of how a decision is reached. This is a growing and important domain of research in deep learning.
Feature Selection	It is a process for selecting the most discriminating features without impacting the classification performance.
Hyper-parameter	It is an empirically tuned internal parameter of an ML model.
Imputation	It is a process of replacing missing values in a dataset with a corresponding statistical estimate. Imputation can be done using mean, median values or employing methods such as KNN (Crookston and Finley, 2008) or MICE (Azur et al., 2011)
Outlier	It is an extremely low or high value of a feature in a dataset (based on the range and distribution). The performance of ML algorithms is sensitive to outliers, hence their detection and exclusion are crucial (Domingues et al., 2018).
Performance Metric	It is a method to evaluate and compare the performance of ML models. For example, precision, recall/sensitivity, specificity, F1 score, Kappa and mean absolute error.
Regression	It is a supervised learning method that provides predicted output as a continuous value.
Training	It is a first step in the learning process that uses a training dataset to fit the parameters of a supervised ML model.
Testing	It is a second step in the learning process which uses a testing dataset (independent of the training dataset) to assess the predictive performance of a trained supervised ML model.
Bias-variance trade-off	In order to achieve optimal prediction performance, a supervised model should ideally have low bias and low variance. A model is over or underfitted when a trade-off is not achieved.

Table 4
The commonly used ML algorithms and their attributes. The rank [1 – Low, 2 – Medium, 3 – High, 4 – Very High] denoted to attributes is pragmatically assigned based on available literature (Amancio et al., 2014; Barredo Arrieta et al., 2020; de Andrade et al., 2020; Lorena et al., 2011; Rashidi et al., 2019; Sakr et al., 2017).

Family	Models	Comparative Accuracy	Overfitting Risk	Samples needed	Explainability	Hyper-parameter Tuning	Complexity	Implementation Time	Computation Cost
Probability-based (Bayesian)	Bayesian Network	2	2	2	2	3	3	2	3
	Naive Bayes	2	2	2	2	2	3	2	3
Information based (Tree)	Decision Tree	2	3	2	3	2	2	1	2
	Random Forest	3	2	1	3	3	2	1	2
	Gradient Boosting	3	3	2	1	4	4	2	3
Error based (Linear)	Linear Regression	1	3	2	3	1	2	1	2
	Logistic Regression	1	3	2	3	1	2	1	2
	Partial Linear Regression	2	1	3	3	2	2	1	2
Similarity-based (Instance)	K nearest neighbour	2	3	2	2	2	3	1	1
	Self-Organising Maps	2	3	2	2	3	3	1	1
Support Vectors	Linear SVM	3	3	3	1	3	2	2	2
	Non-linear (Kernel) SVM	3	3	3	1	3	3	3	3
Neural Network-based	Artificial Neural Network	3	3	2	1	3	3	3	3
	Deep Learning (Neural Network)	4	1	4	1	4	4	4	4

metabolomics respectively). The table also includes a list of recent reviews on each of these omics. High-throughput generated omics data (Lightbody et al., 2019) has played a pivotal role in developing precision medicine biomarkers for diseases such as Alzheimer's (Hampel et al., 2017; Hampel et al., 2016; Kovacs, 2016), diabetes (Capobianco, 2017; McCarthy, 2017; Mutie et al., 2017), cancer (Borad and LoRusso, 2017; Senft et al., 2017), hypertension (Barnes et al., 2016; Dominiczak et al., 2017), cardiovascular (Costantino et al., 2017) and chronic respiratory diseases (Agache and Rogozea, 2017; Hanania and Diamant, 2017). Recently, these omics have also been integrated for COVID-19 studies (Barh et al., 2020; Overmyer et al., 2020; Zhou et al., 2020). Many other specialised omics have also emerged such as pharmacogenomics (Wang, 2010), methylomics (Liu et al., 2013), interactomics (Luck et al., 2017) and radiomics (Lambin et al., 2017; Wong et al., 2016).

Overall, these omics provide a complete picture of cell biology and related cellular function (Cox, 2009). This provided the impetus for the development of various software mechanisms which can offer a prediction of a particular phenotype while using the available next-generation multi-omics data (Ritchie et al., 2015). Furthermore, they can be utilised to develop materials and devices which be used for diagnostic and preventive purpose at the molecular level while targeting molecules with greater accuracy (Giovanni Martinelli et al., 2015).

2.2. Machine learning

Classical statistical modelling has always been the *de facto* standard choice for health data analysis and its interpretation. In recent years, with the increasing availability of affordable computing power and high-throughput omics data and the success of artificial intelligence technology in various fields, the use of ML has become popular in health sciences (Lee and Yoon, 2017; Clifton et al., 2015; Hung, 2019; Barnett-Itzhaki et al., 2020; Kirchebner et al., 2020). ML can be used to mine information hidden in the experimental data. In contrast, a conventional statistics-based model is usually developed using statistical assumptions and draws an inference about a population from a given dataset (Bzdok, 2017).

The objective of ML methods is to acquire knowledge from historic or present-day data and utilise that understanding to make forecasts or choices for unidentified forthcoming data measures (Gammerman, 2010; Obermeyer and Emanuel, 2016). To assist beginners in the ML domain, a glossary of learning approaches covered in this review (Table 2), standard ML terminology (Table 3) and commonly used ML algorithms (Table 4) are provided. The basic foundations of ML and its uses have been extensively covered in the literature (Bishop, 2006).

ML is employed in a wide range of scenarios, where designing and programming explicit algorithms with optimal results is challenging, such as email filtering (Dada et al., 2019), hand-written optical character recognition (Memon et al., 2020), and computer vision (O'Mahony et al., 2020). Also, it has been deployed for self-driving cars (Badue et al., 2021), cyber-security (Handa et al., 2019), automated assistants such as 'Siri', websites that recommend items based on the purchasing decisions of other people and novel solutions to some of the challenging problems of the real world (Watt et al., 2020).

Deep learning has emerged in recent years as the leading class of ML algorithms. It uses neural networks composed of hidden layers performing different operations to find complex representations of data. It has pushed the performance of classifiers beyond that of traditional ML algorithms, especially in scenarios involving large-scale datasets with high dimensionality. On the other hand, it is very computationally intensive, requiring high-throughput or high-performance hardware, and lacks explainability (transparency) in feature selection (*black-box* approach), in the sense that it is difficult to extract from the network the features that the network has found as mainly responsible for the task, e.g. classification (LeCun et al., 2015). However, in the context of multi-omic integration, deep learning offers an exciting opportunity.

Fig. 1 shows the number of publications indexed on the *Web of Science* website (Clarivate Analytics, 2020) with different key topics. This information was collected from the Web of Science by entering a

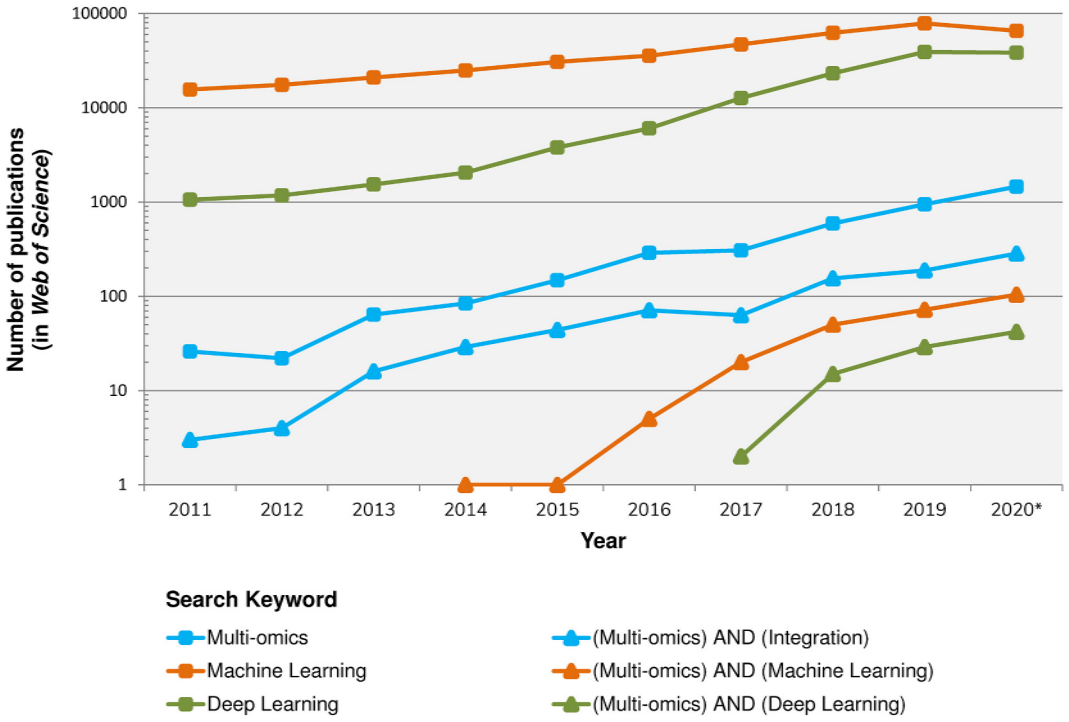

Fig. 1. Number of publications published per year on different search keywords. *For the year 2020, the annual count was extrapolated using the count of publications until October 2020.

different keyword and searching across all databases[2]. Although the use of ML in medical science can be dated back to the 1970s (Davenport and Kalakota, 2019), more rapid growth is evident in the past 10 years. Moreover, publications based on 'multi-omics integration' and 'multi-omics and machine learning' have started to emerge in the last 5 years and have gained popularity in the precision and computational medicine domain. Although deep learning is widely popular in other related domains (such as medical imaging (Erickson et al., 2017) and clinical natural language processing (Wu et al., 2020)), the interest has been more limited for multi-omics analysis (Tan et al., 2020b). This is because multi-omics studies are challenging to deploy as they require specialised high-throughput omic infrastructure (as highlighted earlier in section 2). This fact is reinforced by the evidence that most of the current literature employs deep learning on large-scale multi-omics datasets from open sources such as TCGA[3], CCLE[4] and GDSC[5] for cancer prognosis (Poirion et al., 2018; Seal et al., 2020; Tong et al., 2020; Lee et al., 2020; Zhu et al., 2020) and anti-cancer drug response (Sharifi-Noghabi et al., 2019; Li et al., 2019; Deng et al., 2020).

3. Challenges in multi-omics analysis using machine learning

The use of ML to analyse high-throughput generated multi-omic data poses key unique challenges. They can be summarised as follows.

3.1. Heterogeneity, sparsity and outliers

Multi-omic data from different high-throughput sources are usually heterogeneous (Bersanelli et al., 2016). For example, transcriptomics and proteomics use different normalisation and scaling techniques before omics analysis. This leads to different dynamic ranges and data distribution. Also, some omics are more prone to generating sparse data (e.g. in the case of metabolomics, some values might be below the limit of detection and hence assigned null value (Antonelli et al., 2019)) than others. Therefore, imputation (Liew et al., 2011) and outlier detection (Vivian et al., 2020) should be considered for each omic separately, before planning their integration.

3.2. Class imbalance and overfitting

In disease classification, certain disease classes are rarer than others which can cause a class imbalance in the multi-omics dataset (Haas et al., 2017). For example, primary hypertension is the most common form of hypertension with 95% prevalence while endocrine hypertension occurs in only 5% (Rimoldi et al., 2014). The ML model trained using an imbalanced dataset may be overfitted i.e. high accuracy for training data but underperformance for unseen test data. Therefore, to classify these two types of hypertension one of the following approaches can be used: 1) Collect more data if possible, or 2) consider using weighted or normalised metrics to measure the ML performance (such as F1-Score or Kappa (Jeni et al., 2013)), or 3) consider over or under-sampling the under or over-represented class respectively, or 4) consider synthetic sample generation (such as SMOTE (Chawla et al., 2002) or ADASYN (Haibo He et al., 2008)) for the under-represented class. Similarly, techniques such as regularisation, bagging, hyper-parameter tuning and cross-validation can be used to balance bias-variance trade-off (Lee, 2010). Any of the above approaches can be used, depending on data and problem, to overcome the class imbalance and overfitting problems.

3.3. More features than data ($p >> n$)

Most multi-omics datasets suffer from the classical '*curse of dimensionality*' problem, i.e. having much fewer observation samples (n) than

[2] All Web of Science databases included: Web of Science Core Collection, BIOSIS Citation Index, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, MEDLINE®, Russian Science Citation Index, SciELO Citation Index and Zoological Record.

[3] TCGA: The Cancer Genome Atlas

[4] CCLE: Cancer Cell Line Encyclopaedia

[5] GDSC: Genomics of Drug Sensitivity in Cancer

multi-omics features (p) (Misra et al., 2019). The resulting high-dimensional space often contains correlated features which are redundant and can mislead the algorithm training (James et al., 2017). The dimensional space of the data can be reduced by employing dimensionality reduction techniques such as *feature extraction* and *feature selection*. Feature extraction refers here to techniques computing a subset of representative features which summarise the original dataset and its dimensions[6]. These features are *functions of the original ones*, for instance, PCA (principal component analysis) (Jolliffe, 2002), LDA (linear discriminant analysis) (Martinez and Kak, 2001) and MDS (multidimensional scaling) (Young and Hamer, 1987). On the other hand, feature selection finds a subset of the *original* features that maximise the accuracy of a predictive model (Guyon and Elisseeff, 2003). It can be based on prior knowledge i.e. evident from known literature or based on a database such as a Biofilter (Bush et al., 2009). Formally, feature selection methods can be classed as *filter* (Information gain (Roobaert et al., 2006), ReliefF (Beretta and Santaniello, 2011), Chi-square statistics (Lee et al., 2011)), *wrapper* (Recursive feature elimination (Guyon et al., 2002), Sequential feature selection (Pudil et al., 1994)) and *embedded* (such as LASSO (Least Absolute Shrinkage and Selection Operator) (Zou, 2006)) techniques. Xu et al.(Xu et al., 2019b) and Stańczyk (Stańczyk and Jain, 2015) provide an excellent resource for understanding and exploring the use of different dimensionality reduction techniques in the generic ML domain. Meng (Meng et al., 2016b) offers a review of these methods from the perspective of multi-omics data analysis.

3.4. Computation and storage cost

The use of ML for multi-omics analysis comes with computational and data storage cost (Herrmann et al., 2020). Most ML algorithms require high computation power and large volumes of storage capacity to save the logs, results and analysis. In recent years, ML models can be deployed on dedicated graphics processing units (Schmidhuber, 2015) and cloud computing platforms (Armbrust et al., 2010) such as Amazon EC2 ("Amazon EC2,", 2021), Microsoft Azure ("Cloud Computing Services | Microsoft Azure,", 2021a) and Google Cloud Platform ("Cloud Computing Services,", 2021b). The related costs should be considered well in advance before planning an ML-based multi-omics workflow.

3.5. What algorithm works best for what conditions?

The commonly used ML algorithms have different attributes (Table 4) and therefore it is crucial to choose an appropriate algorithm for the multi-omics analysis. In the literature, many reviews cover the key strengths and weaknesses of different ML algorithms using single omics (Amancio et al., 2014; López Pineda et al., 2015; Sakr et al., 2017; Uddin et al., 2019) and multi-omics (Ma et al., 2016; Francescatto et al., 2018; Xu et al., 2019a; Sathyanarayanan et al., 2020) datasets. Most of them use a systematic workflow that involves simultaneous performance evaluation of different algorithms using a common dataset. Since each multi-omics dataset is unique, using a similar workflow could allow the selection of the best-suited algorithm. Later, in Section 6 a recommendation flowchart is proposed which can help the inter-disciplinary user to choose from available methods.

Recently, various artificial intelligence-driven automated ML platforms and tools (Feurer et al., 2015; Olson et al., 2018; Waring et al., 2020) have also emerged which can be utilised to exhaustively search for the best ML model and corresponding parameter tuning, however, they are computationally expensive.

[6] We note that "feature extraction" has a different meaning in image processing and computer vision.

3.6. Translating ML: bench to bedside

Various ML-based multi-omics publications have emerged in the past 5 years (see Fig. 1) and some use performance metrics such as decision curve (Vickers and Elkin, 2006) and calibration (Dankers et al., 2019) analytics to evaluate their diagnostic utility. Still, only very few have been translated into clinical practice, for example, *Idx* (diabetic retinopathy detection), *FerriSmart* (measure liver iron concentration) and *SubtleMR* (image processing software for radiology) (Benjamens et al., 2020; Hamamoto et al., 2020).

One of the key issues which hinder the clinical deployment of ML methods is *transparency* and *explainability* (*Black* box medicine and transparency, 2020). A transparent and explainable ML algorithm seems essential to building trust for clinical decision making (Gunning et al., 2019). Recently, the U.S. Food and Drug Administration (FDA) has issued the "*Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device* Action Plan" to ensure deployment of ML-based products is safe for patients to better assist the health care providers (Health, 2021). A recent in-depth analysis by Muehlematter showed most of the FDA approved and "*Conformité Européenne*" marked ML products are in the field of radiology. It also highlighted the key differences between U.S. and European policy implications around the approval of AI/ML-based devices (Muehlematter et al., 2021).

All the above challenges directly impact the use of ML for multi-omics analysis. However, there are few other challenges related to multi-omics studies which are not ML related such as study design (Haas et al., 2017), multi-site sample collection & management (Pinu et al., 2019), multi-site data sharing and governance (Saulnier et al., 2019), visualisation (Mougin et al., 2018), ethical standards (Lévesque et al., 2018), and finally making the research reproducible (Conesa and Beck, 2019) and translational (Schumacher et al., 2014). A broader checklist of criteria is investigated by McShane while focussing on various aspects ranging from specimen requirements, predictive model development to clinical trial designing and related regulatory approvals (McShane et al., 2013b; McShane et al., 2013a).

4. Data integration methods for multi-omics

In recent years, various new data integration methods have been introduced from the modern developments in mathematical, statistical and computational sciences. For the benefit of the readers, Table 5 includes a summary of a few reviews which cover the breadth of multi-omics integration for generic as well as specialised domains such as oncology (Buescher and Driggers, 2016; Nicora et al., 2020) and toxicology (Canzler et al., 2020). Most of these reviews have strived to introduce different categorical terminologies (for example: "early', 'late' and 'intermediate' in (Gligorijević and Pržulj, 2015) or 'bottom-up' and 'top-down' in (Yu and Zeng, 2018)) which enable them to group the integration methods based on different factors/parameters.

As mentioned earlier, this section adopts the categorical terminologies from Ritchie (Ritchie et al., 2015) and builds upon it to summarise a complete spectrum of recent integration methods. It concisely covers them giving a clear perspective to a new interdisciplinary user. The various integration methods are classed as either 'concatenation-', 'model-' or 'transformation'-based and described below in detail.

4.1. Concatenation-based integration methods

Concatenation-based integration methods consider developing a model using a joint data matrix which is formed by combining multiple omics datasets. Fig. 2 shows the stages of concatenation-based integration. *Stage 1* includes the raw data from three individual omics (e.g. genomics, proteomics, and metabolomics) along with the corresponding phenotypic information. Commonly, concatenation-based integration does not require any pre-processing and hence does not have a *Stage 2*. In *Stage 3*, the data from the individual omics is concatenated to form a single large

Table 5
Summary table of few reviews in multi-omics integration

Year of review	Review reference	Terminology introduced for classifying various integration methods	Omics reviewed									Application domain covered
			Genomics	Transcriptomics	Metabolomics	Proteomics	Epigenomics	Interactomics	Metagenomics	Lipidomics	Phosphoproteomics	
2009	(Van Deun et al., 2009)	Matrix decomposition			✓							Micro-organism (Escherichia coli)
2009	(Ebbels and Cavill, 2009)	'Conceptual', 'statistical' & 'model'			✓	✓						Generic
2012	(Lussier and Li, 2012)	'Cross-scale' & 'multi-scale'	✓	✓								Prediction of clinical outcomes.
2015	(Ritchie et al., 2015)	'Concatenation', 'transformation' & 'model'	✓	✓								Generic
2015	(Gligorijević and Pržulj, 2015)	'Early', 'late' & 'intermediate'	✓	✓								Generic
2016	(Bersanelli et al., 2016)	'Sequential', 'simultaneous', 'network-based versus network-free' & 'Bayesian vs non-Bayesian'	✓	✓		✓						Generic
2016	(Gligorijević et al., 2016)	-	✓	✓			✓					Disease subtyping, biomarkers discovery & drug repurposing.
2016	(Buescher and Driggers, 2016)	-	✓	✓	✓	✓						Cancer biology
2017	(Lin and Lane, 2017)	-	✓	✓	✓	✓						Investigated (Ritchie et al., 2015) from ML perspective
2017	(Huang et al., 2017b)	-	✓	✓		✓						Patient survival prediction
2017	(Hasin et al., 2017)	'Genome', 'phenotype' & 'environment-' first approach	✓	✓	✓	✓	✓					Generic
2018	(Yu and Zeng, 2018)	'Bottom-up' & 'top-down' mode	✓	✓	✓	✓						Generic
2018	(Kim and Tagkopoulos, 2018)	'Data-to-data', 'data-to-knowledge' & 'knowledge-to-knowledge'	✓	✓	✓	✓	✓	✓				Generic
2018	(Rappoport and Shamir, 2018)	-	✓	✓		✓						Cancer benchmarking
2019	(Tini et al., 2019)	-		✓	✓	✓	✓					Multiple (Mitochondrial metabolism, Platelet reactivity & Breast cancer)
2019	(Mirza et al., 2019)	-	✓	✓	✓	✓	✓					Generic (more focussed on ML)
2019	(López de Maturana et al., 2019)	OnO (omics & non-omics)	✓	✓	✓	✓	✓		✓			Generic
2019	(Wu et al., 2019)		✓	✓	✓	✓						Generic

(*continued on next page*)

Table 5 (*continued*)

Year of review	Review reference	Terminology introduced for classifying various integration methods	Omics reviewed									Application domain covered
			Genomics	Transcriptomics	Metabolomics	Proteomics	Epigenomics	Interactomics	Metagenomics	Lipidomics	Phosphoproteomics	
		'Vertical', 'horizontal', 'parallel' & 'hierarchical'										
2020	(Canzler et al., 2020)	-	✓	✓	✓	✓	✓				✓	Toxicological research
2020	(Eicher et al., 2020)	-	✓	✓	✓	✓						Generic (more focussed on ML)
2020	(Nicora et al., 2020)	-	✓	✓	✓	✓						Oncology
2020	(Jamil et al., 2020)	'Element', 'pathway' and 'mathematical' based approach		✓	✓	✓						Plant systems biology.
2020	(Nguyen and Wang, 2020)	'Single-view' & 'multi-view'	✓	✓	✓	✓			✓	✓		Generic

matrix of multi-omics data. Finally, in *Stage 4* the joint matrix is used for supervised or unsupervised analysis. The main advantage of using concatenation-based methods is the simplicity of employing ML for analysing continuous or categorical data, once the concatenation of all individual omics is completed. These methods use all the concatenated features equally and can select the most discriminating features for a given phenotype.

The different concatenation-based integration methods can be further classed as:

4.1.1. Supervised learning concatenation-based methods

Different concatenation-based supervised learning methods have been used for phenotypic prediction. In scenarios where the number of features in the joint matrix are higher, different feature selection methods described in Section 3 can be employed during concatenation (Sorzano et al., 2014).

The concatenated multi-omics data (in the form of a joint matrix) is provided as input to different classical ML methods such as DT (decision tree) (Quinlan, 1993), NB (naive Bayes) (Domingos and Pazzani, 1997), ANN (artificial neural networks) (Bishop, 1995), SVM (support vector machine) (Vapnik, 1995), KNN (k-nearest neighbors) (Altman, 1992), RF (random forest) (Breiman, 2001) and K-Star (Cleary and Trigg, 1995) in the literature (Kim and Tagkopoulos, 2018; Lin and Lane, 2017; Auslander et al., 2016; Acharjee et al., 2016; Zhang et al., 2018; Ding et al., 2018; Wang et al., 2020). For example, a joint matrix of multi-omics features (which included gene expression, copy number variation and mutation) was used with classical RF and SVM to predict anti-cancer drug response (Stetson et al., 2014).

Similarly, multivariate LASSO models (Zou, 2006; Nicolai and Peter, 2010; Mankoo et al., 2011) have been investigated. Also, Boosted trees (Elith et al., 2008) and SVR (support vector regression) (Awad and Khanna, 2015) have been investigated for finding the longitudinal predictors of glycaemic health (Prelot et al., 2018).

Other than classical ML algorithms, deep neural networks (Tang et al., 2019) have also been widely used to analyse concatenated multi-omics data. They have been studied to identify robust survival subgroups of liver cancer using RNA, miRNA and methylation data (Chaudhary et al., 2017).

4.1.2. Unsupervised learning concatenation-based methods

Various concatenation-based unsupervised methods have been used for clustering and association analysis. Different matrix factorisation-based methods have evolved in recent years. Joint NMF (non-negative matrix factorisation) (Zhang et al., 2012) was proposed to integrate multi-omics data with non-negative values. It involved decomposing the joint matrix into loadings and factors, bringing the different omics into a common basis matrix. Joint NMF is computationally slow and needs large memory allocation.

Similarly, Shen (Shen et al., 2009) proposed iCluster framework which used principles similar to NMF but allows integration of datasets having negative values. They showed the functioning of the framework by using copy number, mRNA expression and methylation data to conduct a cancer subtype discovery in glioblastoma. This framework was also employed for a landmark study that used genomic and transcriptomic data from 2,000 breast tumours and discovered novel subgroups amongst them (Curtis et al., 2012).

Later, the iCluster+ framework by Mo (Mo et al., 2013), offered a significant enhancement over iCluster framework. The iCluster+ framework can discover patterns and combine a range of omics having binary, categorical and continuous values and was demonstrated by combining genomic data from the colorectal cancer datasets.

Another adaptation of NMF was evaluated as JIVE (Joint and Individual Variation Explained) which captures joint variation across integrating data types and structural variation of each data type along with the residual noise (Lock et al., 2013). It was used to investigate gene expression and miRNA data on brain tumour samples. The sparsity

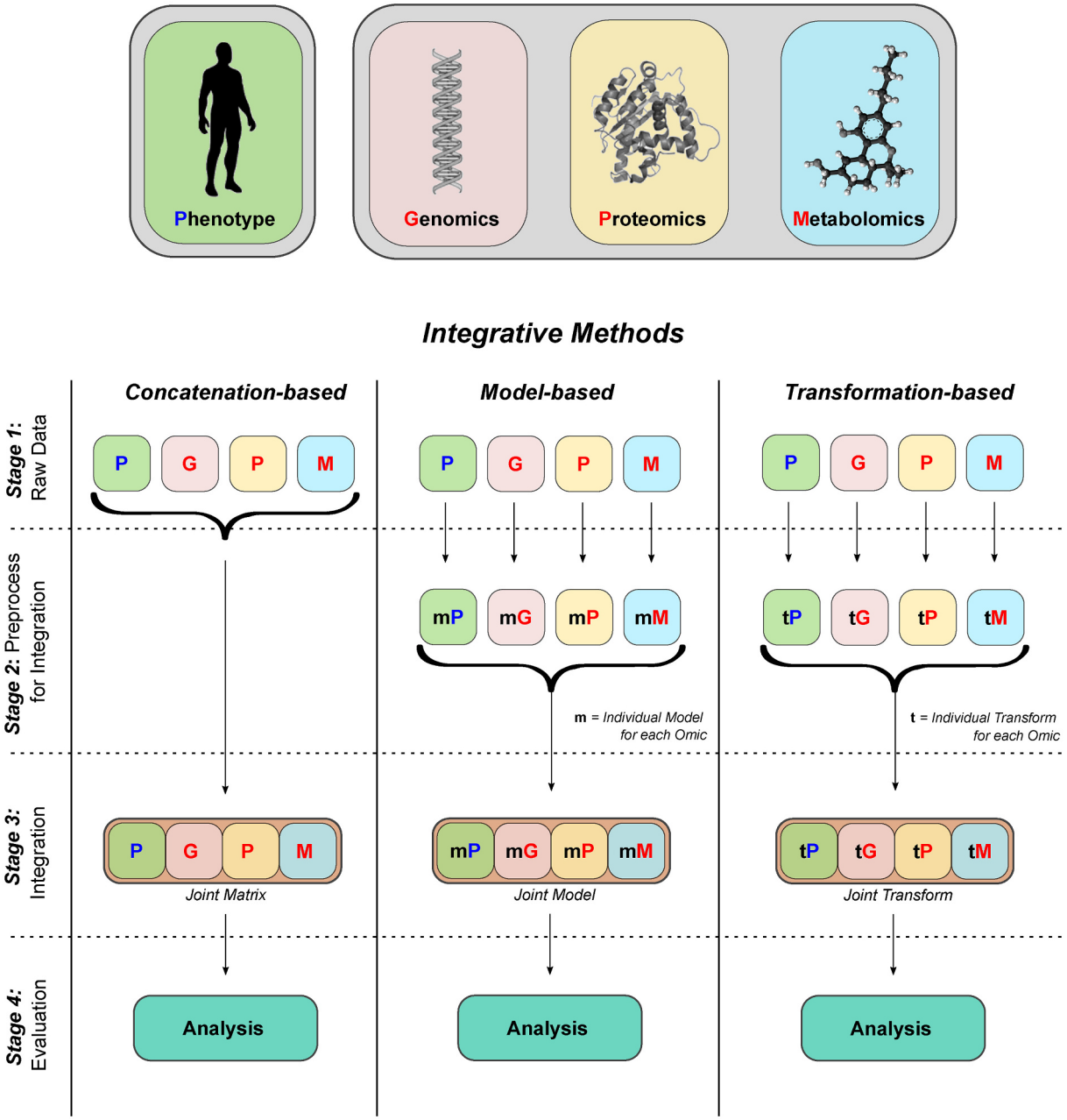

Fig. 2. Workflow pipelines for different types of integration methods for multi-omics analysis.

problem in JIVE was improved by JBF (Joint Bayes Factor) (Ray et al., 2014). JBF used joint factor analysis to evaluate the feature space and converted it into shared and datatype-specific components.

The MoCluster proposed by Meng (Meng et al., 2016a), used multi-block multivariate analysis for highlighting the patterns across different input omics data and then finds the joint clusters amongst them. MoCluster was validated by integrating proteomic and transcriptomic data and shows a noticeably higher clustering accuracy and lower computation cost in comparison to both Cluster and iCluster+.

Fridley (Fridley et al., 2012) has studied the genomic effects due to the gemcitabine drug using high-throughput data from mRNA expression and SNPs. They integrated these two datasets into one large input matrix and developed a Bayesian pathway analysis that uses a stochastic search variable selection. Their proposed that the Bayesian integrative model offers better performance in detecting the genomic effects in comparison to using conventional single-omics analysis. Similarly, Zhu (Zhu et al., 2012) has also explored BN (Bayesian network) to understand cell regulation in yeast using metabolomics and transcriptomics data.

Also, LRAcluster (Wu et al., 2015) was developed to integrate high-dimensional multi-omics data and find low-dimensional manifold to identify molecular subtypes of cancer.

Recently, iClusterBayes was introduced by Mo (Mo et al., 2018), which is a fully Bayesian latent variable model. It overcomes the limitations of iCluster+, in terms of statistical inference and computational speed. iClusterBayes includes a binary indicator prior for selection of variable and generalises for binary data and count data. Also, Argelaguet (Argelaguet et al., 2018) have developed MOFA (Multi-Omics Factor Analysis) which disentangles the heterogeneity shared across different omics to discover the principal source of variability. It can integrate partially overlapping datasets.

4.2. Model-based integration methods

Model-based integration methods create multiple intermediate models for the different omics data and then build a final model from various intermediate models (Fig. 2). *Stage 1* sets up the raw data from the three individual omics along with the corresponding phenotypic information. In *Stage 2*, individual models are developed for each of the omics which are later integrated into a joint model in *Stage 3*. Finally, in *Stage 4* the joint model is analysed. The major advantage of model-based integration methods is that they can be used for merging models based on different omic types, where each model is developed from a different patient group having the same disease information (He et al., 2016; Ritchie et al., 2015).

Model-based integration approaches facilitate the understanding of interactions amongst different omics for a certain phenotype (for example, survival in pancreatic cancer). The final multi-dimensional joint model in *Stage 4* can be built using an ML algorithm (such as neural networks) which uses the most relevant variables from each omics models (from *Stage 3*). This approach allows the analysis of the improvement in the predictive power for individual models and also finds the best discriminating features.

The different model-based integration methods can be further classed as follows.

4.2.1. Supervised learning model-based methods

Model-based supervised learning methods include a variety of frameworks for developing a model, such as majority-based voting (Drăghici and Potter, 2003), hierarchical classifiers (Bavafaye Haghighi et al., 2019) and ensemble-based approaches (such as XGBoost (Ma et al., 2020b) and KNN (Shen and Chou, 2006)).

Deep learning methods have also been adopted for model-based supervised learning (Poirion et al., 2020). MOLI (multi-omics late integration) (Sharifi-Noghabi et al., 2019) method used type-specific encoding sub-networks to learn features from somatic mutation, CNA and gene expression data independently and then later concatenated them for predicting the response to a given drug. Lee (Lee et al., 2020) has proposed a deep learning-based auto-encoding approach for integrating four omics to create a survival prediction model. Also, HI-DFNForest (hierarchical integration deep flexible neural forest) framework (Xu et al., 2019a) was developed which uses a stacked auto-encoder (Vincent et al., 2010) to learn high-level representations from three omic datasets. Later, these representations are integrated to predict cancer subtype classification. Similarly, Chaudhary (Chaudhary et al., 2017) has used autoencoders along with SVM for survival prediction in subgroups of hepatocellular carcinoma.

In the past years, ATHENA (Analysis Tool for Heritable and Environmental Network Associations) was developed for analysing multi-omics data (Chung and Kang, 2019; Holzinger et al., 2014). It uses grammatical evolution neural networks along with Biofilter (Bush et al., 2009) and Random Jungle (Schwarz et al., 2010) to investigate different categorical and quantitative variables and develop prediction models.

Recently, MOSAE (Multi-omics Supervised Autoencoder) (Tan et al., 2020a) was developed for pan-cancer analysis and compared with conventional ML methods such as SVM, DT, naïve Bayes, KNN, RF and AdaBoost. Similarly, Denoising autoencoder has been incorporated along with L1-penalized logistic regression for identifying ovarian cancer subtypes (Guo et al., 2020).

4.2.2. Unsupervised learning model-based methods

Various model-based unsupervised learning methods have been implemented in the past. PSDF (Patient-Specific Data Fusion) (Yuan et al., 2011) is a non-parametric Bayesian model for clustering prognostic cancer subtypes by combining gene expression and copy number variation data. It uses a two-step process and limits the integration to only two datatypes. Similarly, CONEXIC (Akavia et al., 2010) also uses a BN to integrate gene expression and copy number variation from tumour samples to identify driver mutations. On the other hand, clustering methods such as FCA (Formal Concept Analysis) consensus clustering (Hristoskova et al., 2014), MDI (Multiple Dataset Integration) (Kirk et al., 2012), PINS (Perturbation clustering for data integration and disease subtyping) (Nguyen et al., 2017), PINS+ (Nguyen et al., 2019) and BCC (Bayesian consensus clustering) (Lock and Dunson, 2013) are more flexible and allow late-stage integration of clusters.

Different network-based methods are also available for association analysis. Lemon-Tree (Bonnet et al., 2015) implemented ensemble methods for reconstructing module networks which used somatic copy number alterations and gene expression in brain tumour samples. Furthermore, SNF (Similarity Network Fusion) (Wang et al., 2014) constructs networks of samples for respective data type and then effectively fuse them into a joint network which denotes the complete range of original data. It combines mRNA expression, DNA methylation and microRNA (miRNA) expression data from cancer datasets.

4.3. Transformation-based integration methods

Transformation-based integration methods transform each of the omics datasets firstly into graphs or kernel matrices and then combines all of them into one before constructing a model.

Fig. 2 shows the various stages of transformation-based integration. *Stage 1* sets up the raw data from the three individual omics along with the corresponding phenotypic information. In *Stage 2*, the individual transformations (in the form of graph or kernel relationship) are developed for each of the omics which are later integrated into a joint transformation in *Stage 3*. Finally, in *Stage 4* it is analysed. The primary advantage of the transformation-based integration methods is that they can be used to combine a wide range of omics if unique information (such as patient ID) is available.

Graphs provide a formal means to transform and portray relationships between different omics samples where the nodes and edges of a graph represent the subjects and their relationships, respectively. Similarly, Kernel methods enable the transformation of data from its original space into a higher dimensional feature space. These methods then explore linear decision functions in the feature space which were non-linear in the original space.

The transformation-based integrative methods can be classed as follows.

4.3.1. Supervised learning transformation-based methods

In the past, various *transformation-based supervised learning methods* have been presented. Most of them are kernel and graph-based algorithms (Yan et al., 2017). The kernel-based integration approaches include SDP-SVM (Semi-Definite Programming SVM) (Lanckriet et al., 2004), FSMKL (Multiple Kernel Learning with Feature Selection) (Seoane et al., 2014), RVM (Relevance Vector Machine) (Bowd et al., 2005; Tipping, 2001) and Ada-boost RVM (Wu et al., 2010). Moreover, fMKL-DR (fast multiple kernel learning for dimensionality reduction) (Giang et al., 2020) has been used along with SVM for combining gene expression, miRNA expression, and DNA methylation data. Similarly, the graph-based integration approaches consist of graph-based SSL (semi-supervised learning[7]) (Tsuda et al., 2005; Culp and Michailidis, 2008; Kim et al., 2015; Yue et al., 2017; Bhardwaj and Van Steen, 2020), graph sharpening (Shin et al., 2010; Shin et al., 2007), composite network (Mostafavi and Morris, 2010) and BN (Rhodes et al., 2005).

Overall, it is evident from the literature that kernel-based algorithms have superior performance to graph-based approaches, but they usually need more time for the training phase. In contrast, graph-based approaches can disclose the relations between samples while taking less computation time. Yan (Yan et al., 2017) provide an extensive

[7] For the sake of simplicity, the semi-supervised integration methods (graph-based) are grouped under supervised learning.

Table 6
The advantages and disadvantages of using different integrative methods.

Integrative Method	Advantages	Disadvantages
Concatenation-Based	• Easy and straightforward. • Enables the use of classical supervised and unsupervised methods.	• Ideally, requires all omics data for all patients. • Need proper normalisation before concatenation. • Does not consider the unique distribution of each omics. • Memory and computation-intensive when the concatenated matrix is large.
Model-Based	• Facilitates the understanding of interactions amongst different omics. • Omics data can be from a different set of patients with a similar phenotype. • Does not increase dimensional complexity.	• Not effective if omics data is extremely heterogeneous. • Could lead to an overfitted solution • Weak signals could be lost.
Transformation-Based	• Graph representation easy to understand and computationally less intensive. • Kernel methods provide superior performance. • Multi-omics data for the same patient can be used for their disease subgroup analysis.	• Kernel methods are computationally more intensive than graph methods. • Transformation can be sometimes challenging.

comparison between different graph- and kernel-based integration approaches in a supervised learning context using various standardised test datasets. It highlights the better classification performance of RVM, Ada-boost RVM and SDP-SVM in comparison to SSL, graph sharpening, composite network and BN.

Recently, MORONET (Multi-Omics gRaph cOnvolutional NETworks) (Wang et al., 2020) is introduced, which use graph convolutional networks taking benefit of the omics features and the associations among patients (as defined by the patient similarity networks) for better classification results.

4.3.2. *Unsupervised learning transformation-based methods*

Different *transformation-based unsupervised methods* have been introduced. Some of them are kernel- and graph-based methods. Lately, rMKL-LPP (regularised multiple kernel learning for Locality Preserving Projections) (Speicher and Pfeifer, 2015) was implemented for clustering analysis. It used an individual kernel for each omics along with a graph embedding framework to identify biologically meaningful subgroups for five different cancer types. Similarly, PAMOGK (Tepeli et al., 2019) is developed for integrating multi-omics data with pathways using graph kernel, SmSPK (smoothed shortest path graph kernel). It used somatic mutations, transcriptomics and proteomics data to find subgroups of kidney cancer.

Meta-SVM (Meta-analytic SVM) is proposed by Kim (Kim et al., 2017), which integrates multiple omics data and able to detect consensus genes associated with diseases across studies such as breast cancer and idiopathic pulmonary fibrosis. Recently, NEMO (NEighborhood based Multi-Omics clustering) (Rappoport and Shamir, 2019) is introduced which uses an inter-patient similarity matrix–based distance metric for evaluating the input omic datasets individually. These omics matrices are then combined into one matrix and then analysed using spectral-based clustering. It can work on partial data sets (no imputation needed), where measurements are only available for a subset of omics data.

Table 6 highlights the advantages and disadvantages of various integration methods. Table 7 summarises various multi-omics integration methods based on learning type.

5. Application of integrative methods in multi-omics studies

The availability of high-throughput omics provides a unique opportunity to explore the complex relationships between different omics and phenotypic targets instead of mono-omics evaluation. This section describes various multi-omics studies which deployed methods investigated in the previous section. Table 8 summarises different phenotypic target-based, multi-omics studies published and tabulates them across the span of 7 main omics namely, genomics, transcriptomics, metabolomics, proteomics, glycomics, lipidomics and epigenomics. Genomics is further divided into gene expression, DNA methylation, somatic point mutation and copy number alteration. Similarly, transcriptomics is further classed into lncRNAs (long non-coding RNAs) and microRNAs (mRNA and miRNA). The various multi-omics studies are broadly

Table 7
The summary of multi-omics integration methods based on learning type. For abbreviations please refer to *List of Abbreviations*.

		Multi-omics Integration Methods		
		Concatenation-based	Model-based	Transformation-based
Learning Type	Supervised	• Classical ML (DT (Quinlan, 1993), NB (Domingos and Pazzani, 1997), ANN (Bishop, 1995), SVM (Vapnik, 1995), KNN (Altman, 1992), K-Star (Cleary and Trigg, 1995) • LASSO (Zou, 2006; Nicolai and Peter, 2010; Mankoo et al., 2011) • BT (Elith et al., 2008) • SVR (Awad and Khanna, 2015) • DNN (Tang et al., 2019)	• Majority-based voting (Drăghici and Potter, 2003) • Hierarchical Classifiers (Bavafaye Haghighi et al., 2019) • Ensemble-based classifiers (XGBoost (Ma et al., 2020a) and KNN (Shen and Chou, 2006)) • MOLI (Sharifi-Noghabi et al., 2019) • HI-DFNForest (Xu et al., 2019a) • ATHENA (Chung and Kang, 2019; Holzinger et al., 2014)	• SDP-SVM (Lanckriet et al., 2004) • FSMKL (Seoane et al., 2014) • RVM (Bowd et al., 2005; Tipping, 2001) • Ada-boost RVM (Wu et al., 2010) • fMKL-DR (Giang et al., 2020) • SSL (Tsuda et al., 2005; Culp and Michailidis, 2008; Kim et al., 2015; Yue et al., 2017; Bhardwaj and Van Steen, 2020), • Graph sharpening (Shin et al., 2010, Shin et al., 2007) • Composite network (Mostafavi and Morris, 2010) • BN (Rhodes et al., 2005) • MORONET (Wang et al., 2020)
	Unsupervised	• Joint NMF (Zhang et al., 2012) • iCluster (Shen et al., 2009) • iCluster+ (Mo et al., 2013) • JIVE (Lock et al., 2013) • JBF (Ray et al., 2014) • BN (Fridley et al., 2012; Zhu et al., 2012) • MoCluster (Meng et al., 2016a) • iClusterBayes (Mo et al., 2018) • MOFA (Argelaguet et al., 2018)	• PSDF (Yuan et al., 2011) • FCA consensus clustering (Hristoskova et al., 2014) • MDI (Kirk et al., 2012) • BCC (Lock and Dunson, 2013) • Lemon-Tree (Bonnet et al., 2015) • SNF (Wang et al., 2014)	• rMKL-LPP (Speicher and Pfeifer, 2015) • PAMOGK (Tepeli et al., 2019) • Meta-SVM (Kim et al., 2017) • NEMO (Rappoport and Shamir, 2019)

Table 8
Multi-omics studies using different ML methods. For abbreviations please refer to *List of Abbreviations*.

	Genomics				Transcriptomics										
OMICS ▶ Target ▼	Gene expression	DNA methylation	Somatic point mutation	Copy number alteration	mRNA	miRNA	IncRNA	Metabolomics	Proteomics	Glycomics	Lipidomics	Epigenomics	Method Used	Method Type	Reference
Humans															
Age-related					✓			✓		✓		✓	Graphical RF	CU	(Zierer et al., 2016)
Acute myeloid leukaemia	✓	✓											LASSO	CS	(Taskesen et al., 2015)
Anti-cancer therapeutic response	✓			✓									RF & SVM	CS	(Stetson et al., 2014)
Biomedical data classification		✓			✓	✓							MORONET	TS	(Wang et al., 2020)
Brain cancer	✓	✓	✓	✓		✓							LASSO	CS	(Lu et al., 2016)
	✓					✓							JIVE	CU	(Lock et al., 2013)
	✓		✓	✓	✓								iClusterBayes	CU	(Mo et al., 2018)
	✓			✓									Lemon-Tree	MU	(Bonnet et al., 2015)
		✓			✓	✓							SNF	MU	(Wang et al., 2014)
Breast cancer	✓	✓											RF	CS	(List et al., 2014)
	✓	✓											LASSO	CS	(Lee et al., 2017)
	✓							✓					RF & SVM	CS	(Nam et al., 2009)
	✓	✓		✓									LASSO	CS	(Chen et al., 2017)
	✓							✓					SVM	CS	(Auslander et al., 2016)
	✓			✓									iCluster	CU	(Shen et al., 2009)
	✓			✓					✓				SVM, RF, SVM & Multi-Kernel Learning	CS & TS	(Ma et al., 2016)
	✓			✓									iCluster	CU	(Curtis et al., 2012)
		✓			✓	✓			✓				BCC	MU	(Lock and Dunson, 2013)
	✓			✓									FSMKL	TS	(Seoane et al., 2014)
		✓		✓	✓								Meta-SVM	TU	(Kim et al., 2017)
Cancer survival					✓			✓					SVM & RF	CS	(Kim et al., 2014)
Cancer prognosis	✓	✓		✓		✓							LASSO	CS	(Zhao et al., 2015)
	✓			✓									PSDF	MU	(Yuan et al., 2011)
	✓			✓									CONEXIC	MU	(Akavia et al., 2010)
Cancer drug response	✓		✓	✓									MOLI (DL)	MS	(Sharifi-Noghabi et al., 2019)

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Table 8 (*continued*)

	Genomics				Transcriptomics										
OMICS ► Target ▼	Gene expression	DNA methylation	Somatic point mutation	Copy number alteration	mRNA	miRNA	IncRNA	Metabolomics	Proteomics	Glycomics	Lipidomics	Epigenomics	Method Used	Method Type	Reference
Cardiac tissue ageing					✓	✓							RF	CS	(Dimitrakopoulos et al., 2014)
Colorectal cancer					✓	✓							Neural Fuzzy Network	CU	(Vineetha et al., 2013)
COVID-19 analysis								✓	✓		✓		PLS-DA	CS	(Thomas et al., 2020)
								✓	✓		✓		Extra Trees	CS	(Overmyer et al., 2020)
Chronic lymphocytic leukaemia		✓	✓		✓								MOFA	CU	(Argelaguet et al., 2018)
Gastric cancer	✓					✓							SVM & RF	CS	(Yan et al., 2012)
Kidney cancer		✓	✓	✓	✓	✓							iClusterBayes	CU	(Mo et al., 2018)
	✓		✓						✓				PAMOGK	TU	(Tepeli et al., 2019)
Liver cancer		✓			✓	✓							Auto-encoder, SVM	MS	(Chaudhary et al., 2017)
Lung cancer	✓			✓									iCluster	CU	(Shen et al., 2009)
		✓		✓	✓	✓							Auto-encoder	MS	(Lee et al., 2020)
Neuroblastoma	✓			✓									Auto-encoders, SVM & NB	CS	(Zhang et al., 2018)
Ovarian cancer					✓	✓							RF	CS	(Andël et al., 2015)
		✓			✓								RF	CS	(Paik et al., 2017)
	✓	✓		✓		✓							LASSO	CS	(Mankoo et al., 2011)
	✓	✓				✓							Joint NMF	CU	(Zhang et al., 2012)
	✓	✓		✓									JBF	CU	(Ray et al., 2014)
	✓	✓	✓	✓									BN	TS	(Zhang et al., 2014)
	✓	✓		✓		✓							Graph SSL	TS	(Kim et al., 2015)
Oral squamous cell carcinoma					✓	✓	✓						SVM	CS	(Li et al., 2017)
Pan-cancer analysis	✓		✓	✓									iCluster+	CU	(Mo et al., 2013)
					✓				✓				moCluster	CU	(Meng et al., 2016a)
	✓	✓	✓	✓									LRAcluster	CU	(Wu et al., 2015)
		✓			✓	✓							XGBoost	MS	(Ma et al., 2020a)
	✓	✓	✓										RF	MS	(Bavafaye Haghighi et al., 2019)
	✓	✓				✓							HI-DFN Forest (AE)	MS	(Xu et al., 2019a)
		✓			✓	✓			✓				MOSAE	MS	(Tan et al., 2020a)
	✓	✓		✓		✓							PINS	MU	(Nguyen et al., 2017)

(*continued on next page*)

Table 8 (*continued*)

	Genomics				Transcriptomics										
OMICS ▶ Target ▼	Gene expression	DNA methylation	Somatic point mutation	Copy number alteration	mRNA	miRNA	IncRNA	Metabolomics	Proteomics	Glycomics	Lipidomics	Epigenomics	Method Used	Method Type	Reference
	✓	✓			✓								fMKL-DR	TS	(Giang et al., 2020)
	✓	✓				✓							rMKL-LPP	TU	(Speicher and Pfeifer, 2015)
	✓	✓				✓							NEMO	TU	(Rappoport and Shamir, 2019)
Pancreatic cancer					✓	✓							SVM	MS	(Kwon et al., 2015)
Prostate cancer								✓	✓				RF	CS	(Fan et al., 2011)
Precision oncology	✓			✓									Auto-encoders, Elastic Net, SVM & Consensus Clustering	CS & MU	(Ding et al., 2018)
Thyroid function								✓	✓				RF	CS	(Pietzner et al., 2017)
Ulcerative colitis					✓			✓					LASSO	CS	(Bjerrum et al., 2014)
Plants															
Potato flesh colour	✓							✓	✓				RF	CS	(Acharjee et al., 2016)
	✓							✓					RF	MS	(Acharjee et al., 2011)
Animals & Micro-organisms															
Dog heart disease					✓			✓					RF	CS	(Li et al., 2015)
Yeast	✓							✓					BN	CU	(Zhu et al., 2012)

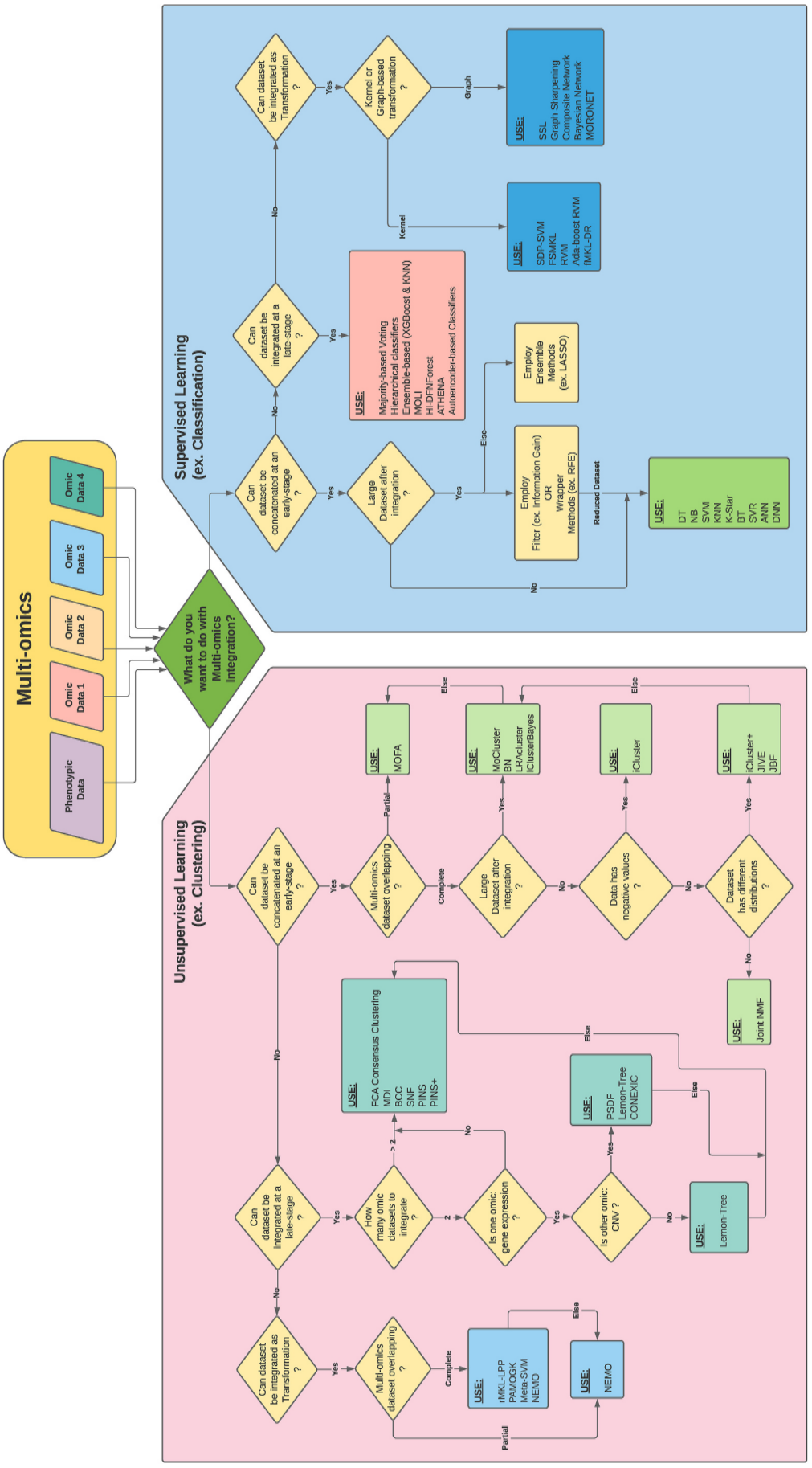

Fig. 3. Recommendation flowchart for choosing a method for multi-omics integration. For abbreviations please refer to *List of Abbreviations*.

grouped based on the target and the corresponding ML method used.

It is evident from Table 8 that most of the multi-omics studies focus on different forms of cancer. In particular, the presence of many multi-omics studies related to the breast (Chen et al., 2017; Lee et al., 2017; List et al., 2014; Ma et al., 2016; Nam et al., 2009) and ovarian (Andël et al., 2015; Mankoo et al., 2011; Paik et al., 2017; Zhang et al., 2014) cancer highlights the research thrust by the scientific community in these domains.

Many intra-omics studies have successfully explored the integration of gene expression and DNA methylation. LASSO methods have been used for this particular integration by Taskesen (Taskesen et al., 2015) and Lee (Lee et al., 2017) for acute myeloid leukaemia and breast cancer respectively. LASSO has also been employed for cancer prognosis (Zhao et al., 2015). Similarly, mRNA – miRNA integration was investigated using Neural Fuzzy Network for colorectal cancer (Vineetha et al., 2013), SVM for pancreatic cancer (Kwon et al., 2015), and RF for cardiac tissue ageing (Dimitrakopoulos et al., 2014) and ovarian cancer (Andël et al., 2015) respectively. SVM has also been used for oral squamous cell carcinoma study by integrating different transcriptomics namely mRNA, miRNA and lncRNA (Li et al., 2017).

Metabolomics and proteomics have been integrated using RF for analysis of prostate cancer (Fan et al., 2011) and thyroid functioning (Pietzner et al., 2017). Similarly, metabolomics is integrated with mRNA for studying ulcerative colitis (Bjerrum et al., 2014) and cancer survival (Kim et al., 2014). On the other hand, glycomics and epigenomics have only appeared once in the multi-omics context (along with mRNA and metabolomics) and used by Zierer (Zierer et al., 2016) for the study of age-related comorbidities using a graphical variant of RF.

Recently, metabolomics and proteomics have also been integrated with lipidomics to evaluate COVID-19 patients using PLS-DA (Partial Least Squares Discriminant Analysis) and Extra Trees (Overmyer et al., 2020; Thomas et al., 2020).

Multi-omics studies have also been successfully conducted in plants (potato (Acharjee et al., 2016, Acharjee et al., 2011)) and animals (such as canine heart disease (Li et al., 2015)).

Overall, the different recent multi-omics studies highlight the superiority of integration methods in understanding the complexity of different diseases and uncovering the underlying abnormalities from the vastly generated multi-omics data, which is not always possible with individual omics analysis.

6. Recommendations

Today a plethora of multi-omic integration methods are available for both supervised and unsupervised learning as evident in the current review. This information can overwhelm interdisciplinary scientists and would require a time-consuming effort to understand the challenging mathematical and computational concepts behind them. Hence, we suggest that interdisciplinary teams working on multi-omics always include ML practitioners to assist with the choice of methods, the development of solutions, the interpretation of results and their significance and limits. Such truly interdisciplinary teams offer real opportunities for better mutual understanding of the different fields, practice and expertise necessary, leading ultimately to more robust conclusions. Also, to facilitate the method selection process, a recommendation flowchart is proposed in Fig. 3. It shows the various decision steps required for choosing an appropriate method (or family of methods) for a given scenario. For example, to choose a method for integrating two omics for unsupervised learning one can choose a model-based method such as 'PSDF or Lemon-Tree' if the two omics are gene expression and CNV, otherwise 'MDI or SNF' can be used. Similarly, 'NEMO' can be used in scenarios where the datasets are partially overlapping, and a transformation approach is required. Hence, it can be used for biomedical analysis, including diagnosis, prognosis and biomarker identification, by posing them as supervised or unsupervised learning problems.

Clearly, a '*one-size-fits-all*' approach is not feasible. Also, unfortunately, the existing literature does not provide many direct comparisons between methods using the same publicly available datasets. Hence, to choose the best method which suits a given dataset and question, an empirical approach that investigates the use of different methods, guided by ML practitioners is recommended.

7. Conclusions

This paper reviewed various ML approaches used for the integration of multi-omics data for analysis. A concise background of multi-omics and ML was presented. It examined the concatenation-, model- and transformation-based integration methods, employed for multi-omics data along with their advantages and disadvantages. Also, various existing multi-omics studies have been summarised. Finally, a recommendation flowchart is presented for interdisciplinary professionals to choose an appropriate method for a multi-omics dataset. Overall, this work showcases the recent findings in the multi-omics domain and signifies the key role of ML in the future of personalised healthcare.

Disclosure

The authors have nothing to disclose.

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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