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Data integration and predictive modeling methods for multi-omics datasets†

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Translating data to knowledge and actionable insights is the Holy Grail for many scientific fields, including biology. The unprecedented massive and heterogeneous data have created as many challenges to store, process and analyze as the opportunities and promises they hold. Here, we provide an overview of these opportunities and challenges in multi-omics predictive analytics.

Introduction

Machine learning and multi-omics technologies revolutionize the way we acquire and process data. At their core, machine learning (ML) algorithms dissect the data to learn their structure and associations within, often without the need of specific knowledge on processes and models that generated them.¹ The strength of ML techniques is proportional to the size and quality of the data amassed. At the same time, sequencing and molecular technologies can generate a vast amount of high quality data in an inexpensive, reproducible way and hence they allow an unprecedented system-level view of any organism.² These datasets, which can come from a variety of sources, equipment and experimental settings, are in their majority not ready to serve as training sets to computational models and machine learning methods, as they have not been created with that function in mind. As such, there is a clear need for methods that process, normalize, integrate and transform the plethora of heterogeneous multi-omics data to cohesive compendia that can be used as a training grounds for further analysis and learning.^{3,4}

Here, we review the current methods for preprocessing and analysis of heterogeneous omics data for various problems in computational biology. In line with previous reviews on similar topics in personalized medicine,⁵ genetics,⁶ and bio-imaging analysis,⁷ we extend these efforts to the description of multiple omics-types and to the characterization of the practical aspects

of high-throughput technologies to profile such omics-types. We summarize the data universe for the most data-rich organisms across the five kingdoms and provide an overview of processing procedures for genome-wide raw data profiled from major high-throughput technologies. We then explore methods for integrating heterogeneous omics data and general principles and applications of quality assessment (QA) and quality control (QC) of genome-wide data, as well as the application of machine learning methods to these datasets across a wide spectrum of applications.

The general workflow of multi-omics integration and analysis consists of three major steps (Fig. 1). First, omics data are collected and processed to interrogate genome-wide molecular measurements from isolates. Then, the processed omics data are combined at different levels of depth (prior knowledge and degrees of coverage) and widths (across heterogeneous omics-types) after the quality assurance procedure is performed. On the integrated compendia, machine-learning analytics are applied to learn complex patterns, finally guiding new experimentation based on the model results. This high-level abstraction of the analytic pipeline for predictive biology is applicable to diverse domains including biomedicine,^{5,8} biotechnology,⁹ agriculture,^{10,11} and nutritional science.^{12,13} In the sections below, we review the types of data, preprocessing pipelines, predictive models and applications of omics data.

Omics data types

Overview

There are four main omics-types (genome, transcriptome, proteome, and metabolome) where each represents all molecules of a specific type (DNA, RNA, protein, and metabolite, respectively) within a cell or a group of cells. Here we describe each of the

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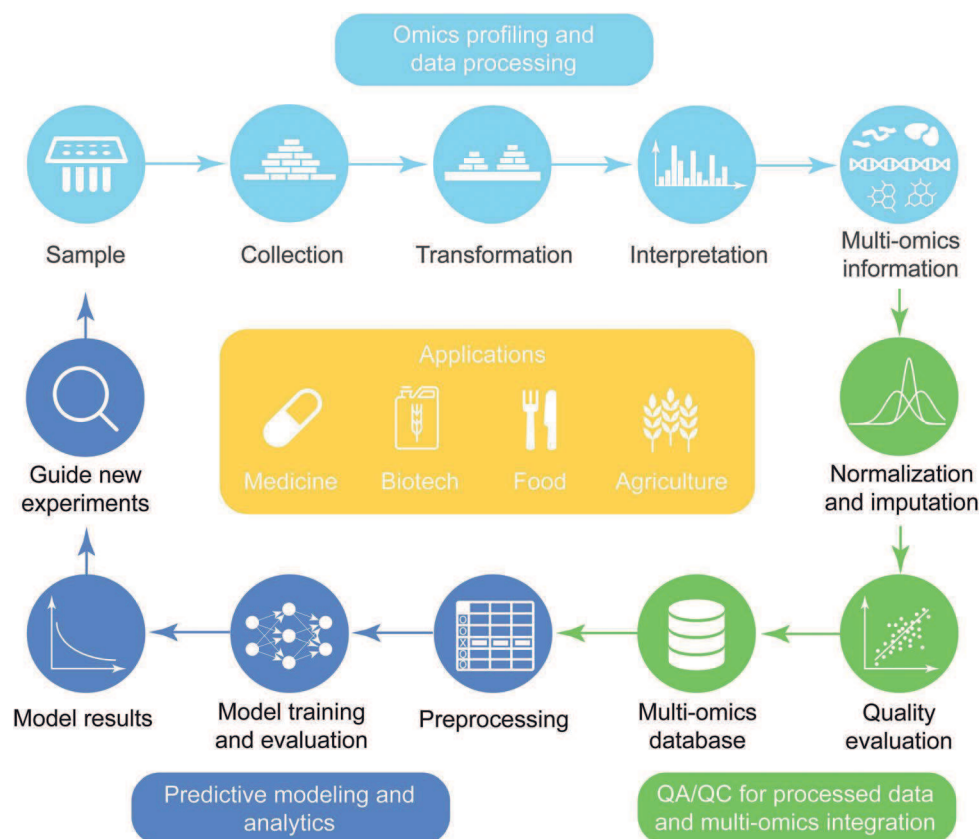


Fig. 1 An end-to-end pipeline for multi-omics data. The three major steps involved are data acquisition, multi-omics integration and predictive modeling. For omics profiling and data processing (cyan icons), samples are collected and profiled using high-throughput technologies. The raw data are then processed, interpreted and translated to knowledge. For QA/QC and multi-omics integration (green icons), the quality of integrated data is ensured by performing normalization, imputation, and quality evaluation. Then, the genome-wide data across different omics-types are integrated into one or more databases. Finally, during predictive modeling and analysis (blue icons), analytics are applied after data have been transformed (pre-processed) to be suitable for training models. Trained models are then evaluated and interrogated to guide further experimentation, either as validation or as hypothesis generation steps for the next iteration of the omics cycle. This pipeline is applied with small variations in a variety of industries, including agriculture, food and nutrition, biotechnology and medicine.

four omics-types and characterize many practical aspects of high-throughput technologies to interrogate such information at the genome scale (Table 1).

Genome

A genome is the complete information of the DNA of an organism. A primary technique to interrogate such information is whole-genome sequencing (DNA-Seq), which can be used for novel assembly and for the discovery of genetic variants for a re-sequenced organism. The quantity and quality of the outcome depends on the read depth (*i.e.* how many reads on average are mapped on the reference genome at a single base position) and it has been extensively reviewed in the past.¹⁴ Two major databases collecting publicly available genomic data are the Sequence Read Archive (SRA), which stores raw sequence data,¹⁵ and the Gene Expression Omnibus (GEO), which stores processed genomic data with characterization metadata.¹⁶ The NCBI dbGaP (The database of Genotypes and Phenotypes) is a public repository for individual-level genotype, sequence data, and phenotype with controlled access.¹⁷

Transcriptome

The transcriptome is the set of all messenger RNA molecules in a cell or a population of cells. The most common high-throughput techniques for transcriptional profiling are micro-arrays and more recently RNA-Seq. Raw data can be used for quantification of mRNAs, novel transcript identification as well as discovery of novel splicing sites.¹⁸ The coverage of genes that can be profiled by RNA-Seq experiments varies from 80% to 99% of the total count depending on the experimental setup.¹⁹ Past reviews have summarized the quality of RNA-Seq data.²⁰ Most publicly available transcriptional profiling datasets can be found in the GEO database,¹⁶ ArrayExpress²¹ and SRA.¹⁵

Proteome

The proteome is the entire universe of proteins that can be expressed by a cell. Mass-spectrometry (MS) is the main platform used for large-scale proteomic profiling. The output processed from mass-spectrometry can be used for quantification of proteins and PTMs (post-translational modifications), as well as for identifying novel proteins.^{22,23} Due to technological

Table 1 Overview of five omics-types and characteristics of relevant high-throughput technologies to profile omics-types. As of 09/05/17, the cost was interrogated from scienceexchange.com and for each instrument, the range shows minimum and maximum cost per sample. As for quantity, coverage was measured based on the depth 35X for genome, transcriptome, ChIP-Seq/-exo.¹⁸⁸ For proteome, 55% for *E. coli*, 80% for human. Isoforms are not counted. MS, mass-spectrometry; Y2H, yeast-two hybrids

Omics-types	Platform	Utility	Cost	Quantity (%)	Quality review	Resources
Genome	DNA-Seq ¹⁸⁷	– Genome assembly – Genetic variant identification	\$250–\$650	~95 ¹⁸⁸	14	GEO ¹⁶ SRA ¹⁵ dbGaP ¹⁷ GEO ¹⁶
Transcriptome	RNA-Seq ¹⁹	– Transcriptome profiling – Novel transcript discovery – Novel splicing event ¹⁸	\$175–\$450	80–99 ¹⁹	20	ArrayExpress ²¹ SRA ¹⁵ PRIDE ²⁷
Proteome	MS ¹⁸⁹	– Proteome profiling – Quantification of PTMs – Novel protein discovery ^{22,23}	\$100–\$171	55–92 ^{24,25}	26	ProteomeXchange ²⁸ ProteomicsDB ²⁴ MetaboLights ³²
Metabolome	MS ⁴⁶	– Metabolome profiling – Novel metabolite discovery ²⁹	\$69–\$90	<20 ³⁰	31	
Interactome	ChIP-Seq ChIP-exo ^{36–38}	– Genome-wide mapping of protein–DNA interactions + Gene-regulatory network + Histone modification maps + Nucleosome maps	\$395–\$415	~95 ¹⁸⁸	38	GEO ¹⁶ SRA ¹⁵ hmChIP ¹⁹⁰
	Y2H ³³	– Protein–protein interaction	—	34–50 ³⁵	191	STRING ³⁹ BioGRID ⁴⁰ PPI database review ⁴¹

limitations, not all proteins can be detected. The coverage of detectable proteins ranges from 55% to 94% of the total proteome, depending on the specific organism.^{24,25} The quality of MS-produced proteome data has been reviewed in ref. 26. The three major repositories that store proteome profiling results are PRIDE,²⁷ ProteomeXchange²⁸ and ProteomicsDB.²⁴

Metabolome

The metabolome is the complete set of small-molecules present within an organism. The typical mass of metabolites in a cell spans from 50 to 1500 daltons (Da). Like the proteome, mass-spectrometry (MS) is a major class of technologies to interrogate genome-wide quantification of metabolites or to discover novel metabolites.²⁹ Detection coverage is still limited to below 20% because of various technological limitations.³⁰ A critical review about quality of MS-produced metabolome data can be found in ref. 31. Compared to other omics-types, the available databases collecting metabolome experiments are scarce. MetaboLights³² is a notable resource, although still with limited data (189 studies so far).

Interactome

The interactome is a map of molecular dependencies in a cell. That is, the interactome can be considered as a collection of genome-wide interplays across genome, transcriptome, proteome, and metabolome. There are many different types of interactions depending on the type of interacting molecules, with protein–protein interaction (PPI) being one of the main ones. PPIs are usually identified by yeast-two hybrid screening³³ and more recently by sequencing technology,³⁴ although the coverage is believed to be limited to around 34–50%.³⁵ Another interaction type is between a protein and DNA, which is typically profiled by ChIP-Seq, and more recently, by ChIP-Exo.^{36–38} The resulting information can be used for revealing the gene regulatory or histone modification maps. The public repositories curating

molecular interactions include STRING³⁹ and BioGRID.⁴⁰ More extensive review on the resources is in ref. 41.

Multi-omics data availability

The estimated availability of multi-omics data across five different kingdoms is shown in Table 2. As expected, genomic information is the most abundant of all omics-types (a total of 891k profiles for the 15 most popular organisms), followed by transcriptional profiling. Interestingly, the metabolome layer is more quantitatively explored than the proteome layer, which might reflect the lower profiling cost as reported in Table 1. As expected, *Homo sapiens* was the organism explored with the largest number of profiles across all omics-types except the fluxome layer, which was second ranked followed by *E. coli*. The number of available flux profiles is estimated to be more abundant in single cell organisms, due to their importance in biotechnology and metabolic engineering.

Omics profiling and data processing

In this section, we provide a high-level overview of procedures to process high-throughput raw-data produced from different platforms (Fig. 2). We focus on three major groups of high-throughput technologies (microarray, next generation sequencing, and mass-spectrometry). For more information about each platform, refer to ref. 42 and 43 for microarray, ref. 44 for sequencing technology, and ref. 45 and 46 for mass-spectrometry. Every processing platform can be divided into three phases, each with its own quality control: (i) early stage that directly handles raw data, (ii) middle stage that performs major data processing, and (iii) late stage that executes post-processing to finalize the molecular quantification.

Microarray

Microarray is a technique to probe massive amounts of molecules on a tiny slide based on hybridization principles.^{42,43} This general

Table 2 Estimated availability of multi-omics data across different organisms. Organisms are selected from the review articles.^{192,193} For genome, in the SRA database, we searched the keyword "[organism_name]" and the filter of source type being "DNA". For transcriptome, in google scholar, we searched the keywords "[organism_name] transcriptome profiling". This gives 44 950 search results as of 09/05/17 and 3823 profiles were found. We multiply the ratio ($3823/44\,950 = 0.085$) to other organisms. For proteome, in google scholar, we searched the keywords "[organism_name] proteome profiling mass-spectrometry". This gives 49 200 search results as of 09/05/17 and 137 profiles were found. We multiply the ratio ($137/49\,200 = 0.00273$) to other organisms. For metabolome, in google scholar, we searched the keywords "[organism_name] metabolome profiling mass-spectrometry". This gives 16 220 search results as of 09/05/17 and 696 profiles were found. We multiply the ratio ($696/16\,220 = 0.042$) to other organisms. For fluxome, in google scholar, we searched the keywords "[organism_name] ¹³C fluxome profiling". This gives 1590 search results as of 09/05/17. In-depth investigation shows that there are 43 profiles in the results. We multiply the ratio of true number of profiles to number of google search results ($43/1590 = 0.027$) to other organisms

Kingdom	Species	Layer				
		Genome	Transcriptome	Proteome	Metabolome	Fluxome
Monera	<i>Escherichia coli</i>	35 492	3579	137	696	43
	<i>Bacillus subtilis</i>	445	967	56	180	13
	<i>Salmonella enterica</i>	67 945	459	18	40	4
Protista	<i>Chlamydomonas reinhardtii</i>	749	392	16	68	2
	<i>Emiliana huxleyi</i>	38	45	2	8	0
	<i>Thalassiosira pseudonana</i>	14	83	3	15	0
Fungi	<i>Saccharomyces cerevisiae</i>	39 381	24 392	97	381	20
	<i>Chlamydomonas reinhardtii</i>	744	373	15	75	2
	<i>Schizosaccharomyces pombe</i>	2182	593	25	52	2
Plantae	<i>Arabidopsis thaliana</i>	13 501	30 911	65	518	9
	Maize	1998	10 882	69	381	6
	<i>Oryza sativa</i> (Rice)	40 910	10 472	25	132	1
Animalia	<i>Homo sapiens</i> (Human)	668 718	210 933	691	1519	45
	<i>Caenorhabditis elegans</i>	8291	11 198	64	184	5
	<i>Drosophila melanogaster</i>	12 692	10 918	52	13	2
Total		893 100	316 197	1335	4262	154

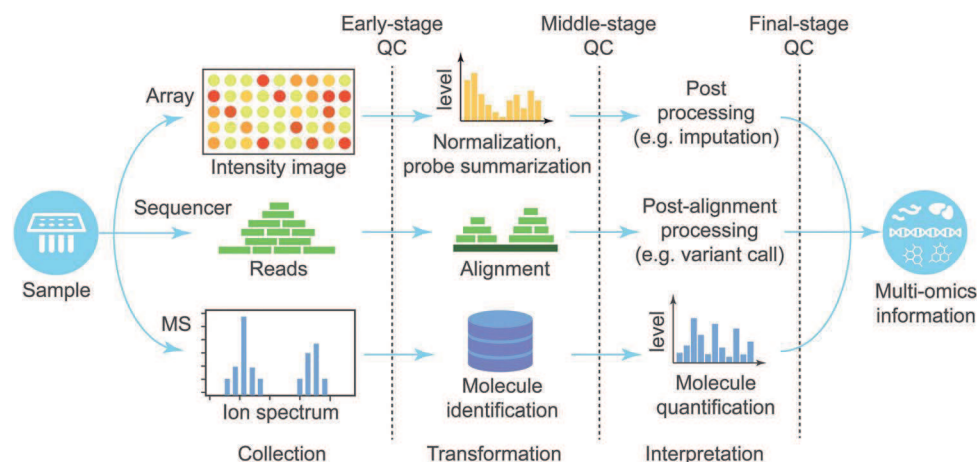


Fig. 2 Omics data processing pipeline. The processing pipelines for three major high-throughput technologies are shown. It is comprised of three distinctive steps: (A) collection step, where the samples are processed and raw data are generated; (B) transformation step, where data are processed, reads mapped and molecules identified; (C) interpretation step, where data are interpreted based on existing knowledge of the corresponding organism. In all cases, quality control (QC) is applied at the end of each stage to ensure high data quality.

principle allows profiling of many different aspects of molecules ranging from genetic variants (DNA microarray) to quantification of transcripts (e.g. cDNA microarray). The raw output is an intensity image, which quantifies information about abundance of hybridized molecules. Higher intensity of molecular hybridization is regarded as that the specific molecule is present in higher abundance. The intensity image is in turn processed in a series of steps

(e.g. background noise removal, normalization, and probe-set summarization). An example of the output is expression levels of molecules in cDNA microarray. Since the introduction of the technology nearly two decades ago, methods to process raw microarray data have been extensively developed and matured. A few suggested reviews on the microarray data processing methods are ref. 47–49 (more information is in Table 3).

Table 3 Review articles on processing methods for each type of high-throughput technologies

High-throughput technologies	Type	Reviews on processing methods
Microarray	General	43–45
	Gene-expression microarray	194
	DNA methylation microarray	195
Sequencing	RNA-Seq	196
	DNA-Seq for genotyping	197
	DNA-Seq for <i>de novo</i> assembly	198
	ChIP-Seq	199
Mass-spectrometry	Protein mass-spectrometry	200
	Metabolite mass-spectrometry	201

Whole-genome sequencing

Whole-genome sequencing technology is a method to interrogate complete information of DNA/RNA of an organism at a single time. The recent advance in this field is the so called next-generation sequencing which has ushered in a new era of genomics by reducing the cost and time to interrogate whole-genome information by profiling short sequence reads in a massively parallel way.⁴⁴ The raw data of short reads from the sequencer are typically aligned on the reference genome to localize short reads. Then the post-alignment step finalizes the output and diverse omics information can be interrogated from the variants of this technology including profiling of protein–DNA binding events (*e.g.* ChIP-Seq and ChIP-exo). Processing methods of sequencing data have been extensively reviewed elsewhere (Table 3).

Mass-spectrometry (MS)

Mass-spectrometry (MS) is a technique where ionization of chemical species is used to sort them based on the mass-to-charge ratio. This technology has been widely used for interrogating quantification of proteins and metabolites, and modification of the sample preparation step (*e.g.* ¹³C labelling) allows profiling of metabolic fluxes.⁵⁰ Unlike metabolites, proteins are usually first digested with a protease (*e.g.* trypsin) into short peptides to lower the mass to be detectable by the instrument. MS produces an ion spectrum which is then used to determine its molecular identity by matching to theoretical spectra measured from the existing databases.^{45,46} In the case of peptides, this step determines the sequences of peptides. Then the next step is to quantify the target molecules based on the amount of identified small molecules. Data processing methods for mass-spectrometry have been extensively reviewed and the suggested articles are in Table 3.

Multi-omics integration

Methods

Omics data integration is not new, with the first review of the field appearing more than a decade ago,^{2,3} in both humans⁵¹ and plants.⁵² Methods for multi-omics integration can be mapped onto a discrete two-dimensional space (Fig. 3). One dimension

represents whether integration is a single or multiple omics-type (breadth). The second dimension captures the depth of integration between data and data, data and knowledge or knowledge and knowledge. As such, multi-omics data integration can be categorized as follows.

Integration within a single omics type

Data-to-data. The integration of data within a layer typically refers to the combination of genome-wide data for the same omics type for a particular organism across different batches, studies and platforms. Most studies along this direction have been focused on the genomic layer and transcriptional layer, as they are the most profiled. SEEK is a transcriptome compendium for human, which provides 150k experiments with platform-adjusted gene correlation measures.⁵³ COLOMBOS is a transcriptome compendium for 19 bacteria where all data are formatted in contrast of two profiles between a test condition and a corresponding control.⁵⁴ Integration of expression profiles across different sources requires special attention in normalization as many artefacts due to lab-to-lab variation may arise.²⁰ For more information, we refer readers to the review on normalization methods.⁵⁵ Integration within the genome layer has been primarily performed across different types of genetic variations to augment the feature set including between SNPs and copy number variations⁵⁶ and between common variants and rare variants.⁵⁷

Data-to-knowledge. Integration of genome-wide omics data and other information about an organism. One notable method in this area is ANNOVAR,⁵⁸ which performs functional annotation of genetic variants including gene annotation (*e.g.* splice site variant, non-synonymous SNP). CEGMA⁵⁹ identifies the exon–intron structure from a novel genome sequence, which is useful for annotating the genome sequence of an unexplored organism. In addition, transcriptome profiles can be functionally annotated to identify novel transcriptional active regions and to reveal alternative splicing patterns.⁶⁰ Interpretation of proteome data can be facilitated by STRAP, which automatically annotates and visualizes user's proteome data.⁶¹ Annotation of metabolomic data is relatively new, compared to genomics and transcriptomics and the tools to facilitate functional interpretation of metabolomic experiments are recently reviewed in ref. 62. A notable tool is MetaboAnalyst, which provides comprehensive characterization of large numbers of metabolites online.⁶³

Knowledge-to-knowledge. Integration of facts about a single omics type of a specific organism that have been compiled and curated by separate groups and projects. Many of the existing biological databases belong to this category, where the primary goal is to curate functional molecular characteristics and their interactions from multiple sources. Molecular characterization is a resource-rich area, where a plethora of gene annotations exist for different organisms including EcoCyc for *E. coli*,⁶⁴ TAIR for *A. thaliana*,⁶⁵ SGD for *S. cerevisiae*,⁶⁶ and NCBI OMIM for human disease genes.⁶⁷ Proteome knowledge has been extensively curated in UniProtKB,⁶⁸ which combines SWISS-PROT that is

manually annotated and reviewed as well as TrEMBL that is automatically annotated and not reviewed.⁶⁹ Another example is the HAMAP project, which combines automated curation and manual curation of the microbial proteome database to facilitate the speed of the curation process while preserving the accuracy of the curated knowledge.⁷⁰ For the metabolome, species-specific databases are available ranging from ECMDDB for *E. coli* and YMDB for Yeast. For a more comprehensive list, refer to ref. 71. In addition, specialized collections based on the type of interaction exist, including protein–protein,⁴¹ gene-regulatory,⁷² and metabolic interactions.⁷³

Integration across omics-types

Data-to-data. Integration of genome-wide data for multiple omics types for a particular organism across different batches, studies and platforms. Co-analyses of genomic data with expression profiles from either the transcriptome, proteome, or methylome fall under this category. The main goal of these analyses is to identify the quantitative trait locus, and eQTL, pQTL or mQTL are some techniques that are used for this purpose.⁷⁴ The integration of transcriptome and proteome data has also led to the discovery of post-translational activities and correlation between two omics-types under identical conditions.⁷⁵ Proteogenomics is an emerging field that employs proteomic data to annotate genome sequences.⁷⁶ There has been a growing list of individual studies employing multi-omics data and recent reviews concerning this subject exist. Their focus ranges from grapevines⁷⁷ to microbes,⁷⁸ and single-cell technologies.⁷⁹ Furthermore, there have been recent constructions of large-scale multi-omics compendia. For example, MOPED is a multi-omics compendium of four model organisms of human, mouse, worm and yeast where it collects publicly available transcriptome profiles and proteome profiles.⁸⁰ Ecomics and MyMpn are multi-omics compendia for *E. coli*⁴ and *M. pneumoniae*, respectively.⁸¹

Data-to-knowledge. Integration of genome-wide data for a multiple omics type for a particular organism and relevant facts about the integrated omics type of the organism that have been accumulated by a group of people through time. Many of the studies belonging to this category integrate transcriptome signatures with the protein–protein interaction network. The underlying assumption here is that transcriptional expression is a proxy of protein expression levels although its validity is arguable.⁸² For example, ref. 83 reveals topological features of cancer genes by combining the transcriptome and the interactome. More recently, the genome, transcriptome, and interactome were merged together to process mass-spectrometry data⁸⁴ and plant regulatory networks were inferred by integrating known regulatory bindings, transcriptome, proteome, and metabolome data.⁸⁵

Knowledge-to-knowledge. Integration of facts about a multiple omics type of a specific organism that have been compiled and curated by separate groups and projects. Integration of heterogeneous networks is the focus of the studies in this category. For example, ref. 86 and 87 integrate metabolic, transcriptional regulatory and signal transduction networks for *E. coli* for metabolic flux predictions. Ref. 88 identifies network patterns

in the combined network of protein–protein interactions and transcription regulation for *S. cerevisiae*. Gene-to-phenotype associations in the context of biological networks have also been studied extensively. For example, CIPHER⁸⁹ employed human disease genes and protein–protein interaction map to infer novel biomarkers. Moreover, the power to identify phenotype-associated genes can be improved by integrating findings from genetic association studies and biological networks and pathways.⁹⁰

Challenges and limitations. Despite the growing availability of genome-wide data in multiple omics-types, the limited overlap between different omics-types prevents finding and understanding latent dependencies and mechanisms. For example, in *E. coli*, there are only 6 high-throughput profiles encompassing three omics-types of transcriptome, proteome, and metabolome.⁴ In recent years, a growing number of studies are performing multi-omics exploration under an identical condition (e.g. ref. 91) and even large-scale collaborations are organized to profile massive multi-omics data, which is accelerating to resolve the lack of overlap issue (e.g. TCGA,⁹² hPOP).

Furthermore, biased exploration often subsists in the experimental space of an organism,⁴ which limits our understanding and ability to predictively model an organism. For instance, among the top 5 strains and the top 5 media used for experimenting with *E. coli*, only 6 combinations out of 25 have been explored.⁴ This partial sampling generates knowledge gaps, which increase uncertainty. Computational methods, such as active learning⁹³ and optimal experiment design,⁹⁴ can guide experimentation to lower this uncertainty by selecting the experimental space that we need to explore to inform predictive models and gain a holistic view of an organism's physiological behavior.

Furthermore, the lack of widely adopted standards in metadata characterization prevents the efficient integration of such information across different studies. Often this process requires extensive manual labor to curate literature. There have been suggestions on standardizing the way of describing experimental metadata.^{95,96} Still we are in need of a more structured approach if we aspire to use the resulting datasets for training machine learning algorithms and predictive models. For example, a specific minimal medium called M9 used for growing bacteria can be created with different concentrations of each nutrient, while the meta-data information may not mention it and reading the corresponding publication may be necessary. Similarly, the growth stage in which cultured bacteria are profiled is not mentioned anywhere despite its significance.

Quality assurance and quality control (QA/QC) for processed data

Overview

We provide an overview of the QA/QC procedure at the final stage of omics data processing (Fig. 4). We focus on this stage than the two previous stages because the final stage of QC has a lot more commonalities than earlier QCs, which are heavily dependent on instruments and processing methods that are

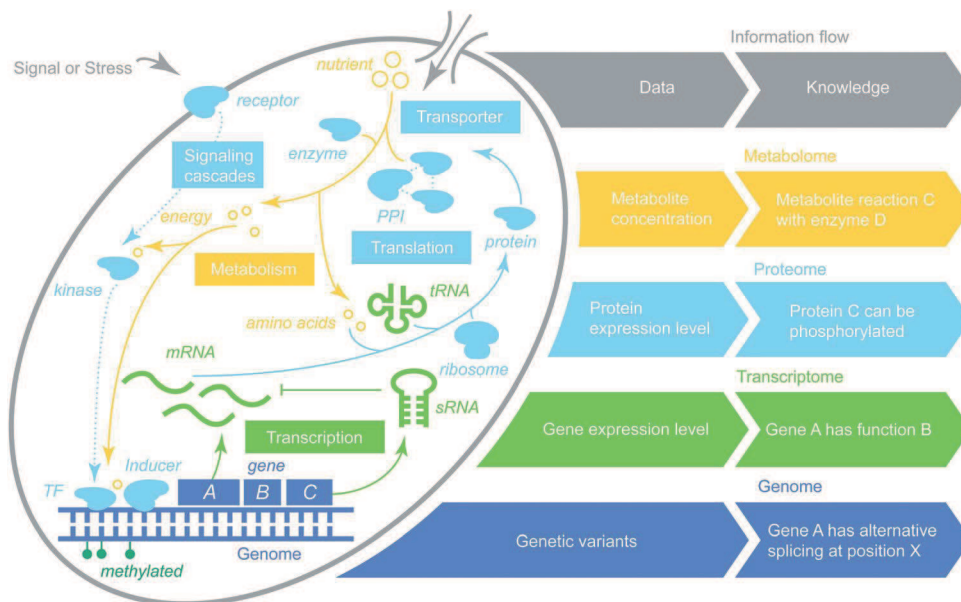


Fig. 3 Multi-omics organization in a cell. Omics data can be integrated within a layer or across multiple layers. Depending on the information and data types involved, integration can be homogeneous (data to data) or heterogeneous (data to knowledge).

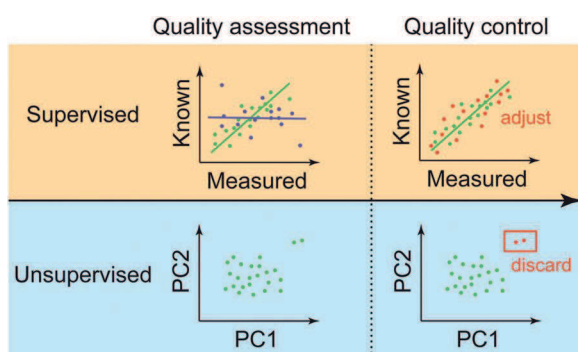


Fig. 4 Quality assessment and quality control. For ensuring data quality, there exist supervised and unsupervised approaches. Supervised approaches rely on control data that can be considered as high-quality measurements (e.g. qPCR). In this way, the quality of data is determined based on how well high-throughput and low-throughput measurements are correlated. Highly correlated data (green points) are further used for bias correction in cases where the corresponding control measurements are missing. In the case of the unsupervised approach, measurements of molecules across multiple profiles are first clustered, as in the case of principal component analysis (PCA). Clustering and dimensionality reduction techniques can reveal outliers (like the two outliers in the figure), i.e. points that are distinctively far away from the clusters, possibly due to low-quality samples. In the quality control step, the outliers can be discarded to avoid any artefactual results arising from the outliers. The PC on the x-axis refers to the corresponding principal component.

used at each step. We can classify the final-stage QA/QC methods based on the availability of control data into supervised and unsupervised.

Supervised QA methods

Supervised approaches rely on control data with known and accurate molecular measurements. In this way, the quality of

data is determined based on the goodness of fit between the processed and known molecular abundances in the control data. As shown in Fig. 4, data exhibiting high correlation (green points) may be used as anchors to adjust measurements of other molecules that don't have corresponding control measurements based on the measured correlation. Typically, two major types of control data are used to assess and to adjust genome-wide measurements. One is called "spike-in control", where known concentrations of selected molecules are profiled together with high-throughput experiments. This approach has been extensively used in different platforms to profile transcripts,⁹⁷ proteins,^{98–101} and metabolites.¹⁰² In the case of genotypes such as SNPs, control data can be samples having known genotypes, for example, of individuals precisely studied from a large consortium (e.g. HapMap or 1000 Genomes Project). Another approach is to generate high-quality measurements of selected molecular species from the same isolate in an independent setting (e.g. qPCR as a control for RNA-Seq datasets).

Unsupervised approach

In the unsupervised approach, the quality of molecular measurements is compared based on "relative" criteria. That is, parameters (e.g. expression levels of genes) consisting of samples are compared with each other to evaluate the data quality. The most popular method in this category is the clustering of multiple genome-wide experiments. This way, the clustering results can show how normal your experiment is compared to other experiments if all experiments arise from the same condition (a combination of environment, genotype, and phenotype). For example, the two outliers in Fig. 4 are distinctively far away from a major group, which "might" be an indication that those are of low-quality. During the quality control step, these outliers can be discarded to avoid any artefactual results. The unsupervised way

of administering the quality of data has been widely used in a variety of omics data ranging from genome (*e.g.* ref. 103 based on PCA), transcriptome (*e.g.* ref. 104 based on clustering), and the integration of multi-omics data with knowledge.¹⁰⁵ One limitation of the unsupervised approach, however, is its sensitivity to noise and bias due to data paucity and process variation.

Predictive modeling and analytics

Overview

Machine learning analytics has been applied in biology to deal with the intrinsic complexity in omics data with a long history and its integration in recent years. The high-level overview of the machine-learning analytic pipeline for integrated multi-omics data is shown in Fig. 5 and consists of data preprocessing, modeling, and active learning. In this review, rather than extensively exploring all steps in the pipeline of predictive analytics, which has been studied elsewhere, we focus on surveying recent applications of machine-learning methods over integrated omics data (Table 4) and organize them based on characteristics of problems in the context of omics integration.

Data preprocessing

First, the multi-omics data are normalized to ensure that the downstream analysis handles data effectively. For example, scaled data are prone to convergence when gradient descent is used. Feature normalization is another important topic and it is covered extensively in ref. 106. The next step is feature selection, which is to decide the subset of features that are useful for modeling. In supervised settings, relevant methods use similarity measures such as mutual information and Pearson correlation coefficient, while unsupervised approaches such as principal component analysis (PCA) are popular. Regularization techniques can supplement these methods¹⁰⁷ and a relevant review on this is ref. 6.

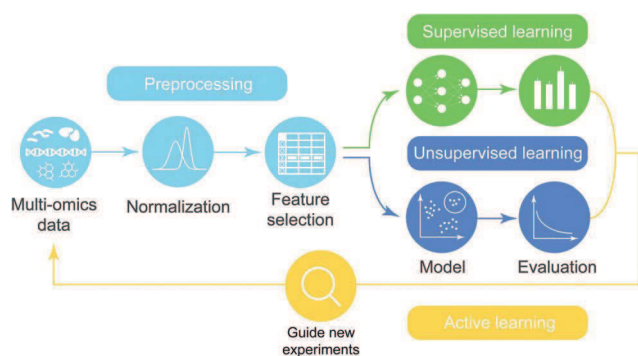


Fig. 5 Iterative framework of predictive analytics over multi-omics data. In the preprocessing step, normalization and feature selection are performed for multi-omics data before model training and evaluation to make models more generalizable, predictive and less vulnerable to noise. Then supervised/unsupervised learning is performed to build a model from training data and then the performance of the model is evaluated by various criteria. The final model is then used to guide new experiments, thereby adding new multi-omics to the original dataset.

Modeling

Supervised learning. It is a class of machine-learning methods that infer a function from labeled data. The applications using supervised learning in omics data are substantial than the other classes in machine learning, and therefore, we subgroup methods based on the type of the output layer to predict:

(1) Genome, transcriptome, proteome, metabolome, and epigenome: the problems in predicting a genomic layer include imputation of SNPs, and annotation of a variety characteristics in genome including gene structure,¹⁰⁸ splice site,¹⁰⁹ and promoter binding site.¹¹⁰ Typical input of such problems is either of genome sequences or of genetic variants. Furthermore, essential genes of bacteria are predicted with support-vector machine using sequence characteristics and the co-expression pattern in transcriptome profiles.¹¹¹ With regard to transcriptome output, the problems in predicting the transcriptome layer include prediction of RNA structure¹¹² and prediction of eQTL^{113,114} given genome data. In addition to this, pre-mRNA splicing events were predicted with an ensemble of machine learning methods from genome data.¹¹⁵ Expression levels of transcripts were predicted from genetic and epigenetic signatures using a deep neural network.¹¹⁶ The problems in predicting the proteome layer include prediction of different characteristics of proteins. For example, protein function has been predicted using omics data from different layers,^{117–119} and other examples include secondary structure,¹²⁰ metal binding site,¹²¹ glycosylation site,¹²² subcellular localization,¹²³ and post-translational modification^{124,125} given proteome sequence data. For metabolome prediction, the primary goal is the prediction of metabolite sub-structure and functional type given metabolome information.^{126,127} For epigenome prediction, inferring chromatin state from non-coding variants has been of great interest as characterization of the functional effect remains a challenge. This has been investigated with different methods including deep learning methods^{128,129} and support vector machine.¹³⁰ Furthermore, predicting methylated CpG from genome sequences has been studied with a long history.¹³¹

(2) Interactome: prediction of gene–gene interactions has been studied using many different machine-learning approaches (please see the review in Ref. 132 for more information). Moreover, prediction of protein/DNA binding events given genome sequences has been studied using a kernel-based method¹³³ and a convolutional neural network.¹³⁴ Another network type is a map of transcriptional regulation, which has been inferred based on transcriptome data using ensemble learning.¹³⁵ Protein–protein interaction (PPI) networks have been predicted using random forest trained over previously identified PPIs¹³⁶ and transcriptome dataset.^{137–139} The signaling network and metabolic pathways are predicted using decision tree over transcriptome dataset¹⁴⁰ and a variety of machine learning methods over genome dataset,¹⁴¹ respectively.

(3) Phenome output: phenotype prediction is perhaps one of the most heavily studied subjects among others in this category as understanding genotype–phenotype relationships is a fundamental goal in biology. This can be sub-classified into bacterial phenotype prediction (*e.g.* growth rate prediction from transcriptome¹⁴²),

Table 4 Classification of machine learning methods for biological applications. In input layer, G, genome; T, transcriptome; P, proteome; M, metabolome; E, epigenome; I, interactome

Output layer	Problems	Category	Methods and References	Input omics-types						
				G	T	P	M	E	I	
Genome	– SNP imputation	Supervised	Shallow learning ²⁰²	O						
	– Gene structure annotation	Supervised	108	O						
	– Alternative splicing and splice site	Supervised	109	O						
	– Promoter binding site	Supervised	110	O						
	– Essential genes	Supervised	111	O	O					
Transcriptome	– RNA structure	Supervised	112	O						
	– eQTL	Supervised	113 and 114	O						
	– Pre-mRNA splicing	Supervised	115	O						
	– Gene expression	Supervised	116	O	O					
Proteome	– Protein function	Supervised	118	O						
			117				O			
			119						O	
	– Secondary structure	Supervised	120				O			
	– Metal binding site	Supervised	121				O			
	– Glycosylation site	Supervised	122				O			
	– Subcellular organization	Supervised	123				O			
	– Post-translational modification	Supervised	124 and 125				O			
Metabolome	– Substructure	Supervised	126					O		
	– Metabolite type	Supervised	127					O		
Epigenome	– Chromatin state	Supervised	Deep learning ^{128,129}	O						
			Shallow learning ¹³⁰	O						
	– Methylated CpG	Unsupervised	162 and 163	O						
Interactome	– Gene–gene interaction	Supervised	132	O						
			Deep learning ¹³⁴	O						
			Shallow learning ¹³³	O						
	– Gene-regulatory network	Unsupervised	36						O	
			Supervised	135			O			
			Unsupervised	160			O			
	– Protein–protein interaction	Supervised	Active learning ¹³⁶						O	
			137–139			O				
	– Protein/RNA-binding	Unsupervised	159						O	
			Supervised	Deep learning ¹³⁴			O			
	– Signaling network	Supervised	Shallow learning ²⁰³				O			
			140			O				
	– Metabolic pathway	Supervised	141	O						O
Phenome	– Microbial phenotype prediction	Supervised	Deep learning ²⁰⁴	O						
			Ensemble ⁸	O						
			Shallow ¹⁴²			O				
			Ensemble ²⁰⁵			O				
			10			O				
	– Plant phenotype prediction	Supervised	Ensemble ¹⁴³			O	O	O		
			Ensemble ²⁰⁶	O						
	– Human phenotype prediction	Supervised	Active learning ¹⁶⁷	O						
			144			O				
			145					O		
			146 and 147						O	
			148							O
	– Biomarker	Supervised	149	O	O					
			150				O			
			Unsupervised	158				O		
			Unsupervised	154			O			
			155				O			
– Novel sub-phenotype identification	Unsupervised	156					O			
		157							O	
		207	O	O						
		Bayesian ¹⁵¹	O							
		Unsupervised	161	O						

plant phenotype (e.g. stress prediction from three omics-types using ensemble learning¹⁴³), and human phenotype (e.g. prediction of disease outcome and drug response from different omics-types^{144–148} and from integration¹⁴⁹). Moreover, biomarker

prediction has been studied using support vector machine trained with proteomic data.¹⁵⁰ Finally, phylogenetic relationships between different organisms have been largely investigated based on genome sequences, for example, by the Bayesian approach.¹⁵¹

To investigate how well methods can use different omics data to predict phenotypic characteristics in novel environments, we curated the prediction performance of AUC reported in the literature in recent years and the results (Fig. 6) show that the reported predictability largely fluctuates depending on the types of problems (AUC: 0.81 ± 0.13). The prediction performance of phenotype more dramatically changes with the specific type of phenotype, compared to prediction of other

types of omics data. The most challenging problem is the prediction of Parkinson's disease (AUC: 0.56) and pancreatic cancer (AUC: 0.58) from genomic signatures among the others we compared. Gene–gene interaction (AUC: 0.75) and protein function are some of the hardest problems among the others we curated. Furthermore, several machine learning methods have been used across different prediction problems. The list includes regression-based methods, Naive Bayes, Support Vector Machine, KNN, Ensemble method, and Neural network. The Ensemble method was mostly used among others. This is expected as the prediction based on multiple models is known to outperform one that relies on a single model. Interestingly,

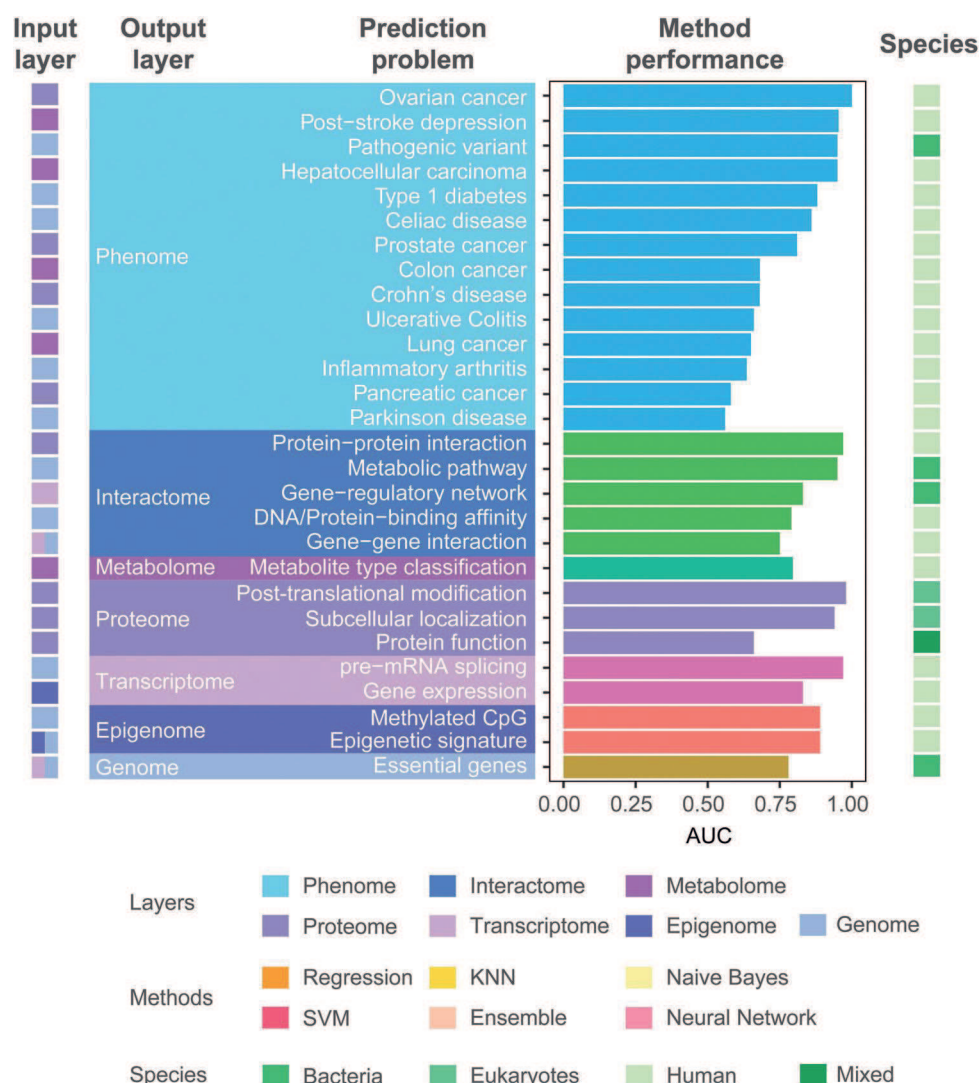


Fig. 6 Prediction performance of multi-omics models. We curated the literature of multi-omics models published between 2007 and 2017 (Table S1, ESI†). We collected the reported AUC values and validated that the reported performance is indeed the highest for that specific problem, by also curating any articles citing the referenced publication. We only investigated the articles providing AUC of their methods. In the case where the authors reported multiple performance results in various settings, the highest AUC was included, while for different sub-tasks of the same prediction problem, we included their average performance. References of the listed prediction problems: colon cancer,²⁰⁸ hepatocellular carcinoma,²⁰⁹ post-stroke depression,²¹⁰ lung cancer,²¹¹ ovarian cancer,²¹² prostate cancer,²¹² pancreatic cancer,²¹² celiac disease,²¹³ Crohn's disease,²¹³ ulcerative colitis,²¹³ type 1 diabetes,²¹⁴ Parkinson's disease,²¹⁵ inflammatory arthritis,²¹⁶ pathogenic variant,²⁰⁴ epigenetic signature,²¹⁷ methylated CpG,¹³¹ DNA/protein-binding affinity,²¹⁸ protein–protein interaction,²¹⁹ gene–gene interaction,²²⁰ gene–regulatory network,²²¹ metabolic pathway,¹⁴¹ post-translational modification (glycosylation site),¹²² protein function,²²² subcellular localization,²²³ metabolite type classification,¹²⁷ essential genes,¹¹¹ pre-mRNA splicing,¹¹⁵ gene expression.¹¹⁶

the regression-based methods (e.g. logistic regression, LASSO) were heavily used in the prediction of phenotype. Recent studies combine complex models for the same prediction problems although without much success, possibly due to the challenges involved in integration of two or more omics data sources.¹⁵²

Unsupervised learning. Unsupervised learning approaches do not require class labels and draw inference from data in the absence of answers.¹⁵³ The most common unsupervised learning is clustering, which has been widely used for identifying novel phenotypic groups given expression signatures collected. For example, identifying novel cancer subtypes from transcriptome signatures has been widely investigated using cluster analysis such as hierarchical clustering throughout a variety of cancer types.¹⁵⁴ And this analytical framework has been applied in other omics-types including proteome,¹⁵⁵ metabolome,¹⁵⁶ and epigenome.¹⁵⁷ Furthermore, these methods have also been applied in many other problems including biomarker identification,¹⁵⁸ revealing molecular relationships including protein–protein interaction,^{158,159} and gene-regulatory network,¹⁶⁰ phylogenetics,¹⁶¹ etc.^{162,163}

Model evaluation. In supervised settings, model performance can be evaluated with independent data that are accompanied with labels (*i.e.* answers). A typical way of evaluating model performance is *n*-fold cross-validation. That is, a dataset is divided into *n* folds and *n* – 1 folds are used for training whereas the remaining fold is used for testing. And this procedure is repeated *n* times to iterate testing for all *n* folds. Unlike supervised learning, model results from unsupervised learning are evaluated in completely different ways as exact answers are unavailable. For example, clustering results can be evaluated based on (i) external criteria, which reflects our intuition about the cluster structure, (ii) internal criteria, which involves only quantities and features inherent to the dataset, and (iii) relative criteria, which compares it to other clusters produced from the same algorithm but with different parameter values.¹⁶⁴

Active learning

Once a model is constructed and evaluated, active learning guides what experiments to perform next to minimize uncertainty in the model.⁹³ It was first actively studied in supervised setting, and more methods have been developed in unsupervised setting in recent years.^{165,166} Active learning is particularly a significant problem in the experimental design of genome-wide profiling because of high cost in data generation (Table 1). For example, the human protein–protein interaction network was actively learned based on random forest.¹³⁶ Another example includes ref. 167, which argues that cancer classification can be improved with active profiling of transcriptome signatures based on ML methods such as Support Vector Machines. A recent review covers the topics of active learning on experimental design for uncovering molecular interactions.¹⁶⁸

Other classes of machine learning methods

Semi-supervised learning. It is a class of supervised learning that deals with partially labeled dataset for training. The semi-supervised learning is particularly useful in many real-world scenarios where acquisition of labeled data is expensive or impractical. A variety of methods in this category have been

applied in omics integration, including the detection of disease genes or the integration of protein–protein interaction networks and transcriptome data.¹⁶⁹ Prediction of deleterious SNPs from the combined source of the protein–protein interaction network and genetic variants is explored using low-density separation (LDS).¹⁷⁰ Moreover, semi-supervised learning is used over multi-omics integration for cancer clinical outcome prediction.¹⁷¹

Reinforcement learning. Reinforcement learning is to teach agents how to take actions in an environment to maximize some notion of cumulative reward. This type of methods has been widely used in many real word problems including robot control¹⁷² and medical decision support system¹⁷³ but it has not been extensively studied in biology although many potential applications might exist. One immediate instance is to apply in the context of active learning where it develops a decision support system of experimental design where actions of experimental testing are administered to minimize uncertainty in biological knowledge of an organism.

Deep learning methods. Deep learning is a recent advance in machine learning that efficiently learns convoluted patterns within a dataset by undergoing a series of non-linear computations.¹⁷⁴ The methods have been expanded to all domains of machine learning including supervised, unsupervised, and reinforcement learning. Due to the complexity in high-throughput data, the potential applications of deep-learning methods in biology are considered to be widespread.⁷ As of now, its applications in biology have mostly focused on genomic data for various supervised learning problems including protein-binding site prediction¹³⁴ and chromatin state prediction.¹²⁸ For a comprehensive review on the topic, refer to ref. 7 and 175–177.

Challenges and limitations

There are many caveats in machine learning analytics that must be carefully administered. A wide range of issues have been addressed in past reviews including overfitting, imbalanced class size, and the curse of dimensionality.⁶ To be brief, the overfitting problem arises when too complex a model (*i.e.* with a large number of parameters) is trained over a few data points and the trained model doesn't behave well with unseen objects. This problem is related to the curse of dimensionality because most of the overfitting issues arise from too many parameters to fit compared to given data points, which can be overcome by feature selection before training a model. Moreover, imbalanced class size is a widespread problem in many applications of machine learning to omics data. This refers to the phenomenon that a trained model preferably assigns a specific class label due to highly skewed distribution of class labels. Many computational remedies have been devised to cure such biased prediction including weighting more cost in incorrect predictions to a minor class.¹⁷⁸

Applications

Machine-learning analytics over integrated multi-omics data has the capacity to make far-reaching impacts across multiple industries. In medical applications, finding therapeutic targets

and biomarkers is one of the major issues in human health,⁵ and such efforts are being more and more translated into the real world (e.g. BERG, Eagle Genomics). Antibiotic resistance is of paramount importance as it is considered a global threat and machine learning methods can be applied for predicting antibiotic resistance from the molecular signature of clinical isolates to select effective antibiotics.⁸ Biotechnological applications include optimization of genetic and regulatory processes to produce maximum yield of a certain substance, which can be enabled by a prediction model trained over omics data.⁹ In agriculture, identifying stress response genes is of great significance in crop management and machine learning can accelerate such discovery.^{10,11} Finally, in food and nutrition science, optimizing nutrition treatment for individuals is enabled by machine learning over personal omics data accompanied with dietary information.¹² Furthermore, machine learning and multi-omics analytics can be used in food engineering for producing the best quality of fermentation foods with desired flavors¹³ once genome-wide profiles collected over the course of fermentation process are available.

Next wave and future directions

The ability to generate high-throughput omics data and to build intelligent systems based on large-scale data and convoluted knowledge has revolutionized the way we conduct biology. Most genome-wide technologies provide averages across population of cells, which ignores variability at individual cells.⁷⁹ High-resolution understanding of molecular signatures in a cell is enabled with single-cell assays,¹⁷⁹ which are being expanded to interrogate the multi-omics landscape of a cell.⁷⁹ Furthermore, advances in community-level profiling of molecules (e.g. metagenome sequencing) facilitate the investigation of biodiversity that is directly collected from the environment, which is not possible with conventional cultivation-based technologies, and the type of molecular species that can be profiled by such advancement is becoming more diverse.^{180–183}

Accompanied with the explosion of available data, rapid advances in the development of cognitive systems facilitated by artificial intelligence (AI) are revolutionizing many industries. For example, IBM Watson that was first developed for human-like question-answering is expanding for supporting decision of experts in different domains ranging from healthcare to finance.¹⁸⁴ We believe that biology is not an exception to this ongoing paradigm shifting. That is, we envision building a cognitive system for every single organism that has the ability to process data, transfer information, bring new knowledge, represent a knowledge map of the organism in a structured way and suggest new experiments based on machine-produced hypotheses.^{185,186} We firmly believe that such systems can be a powerful assistant that can empower, rather than replace, humans in their pursuit of scientific knowledge.

Conflicts of interest

There are no conflicts to declare.

References

- 1 P. Simon, *Too Big to Ignore: The Business Case for Big Data*, John Wiley & Sons, 2013, vol. 72.
- 2 A. R. Joyce and B. O. Palsson, The model organism as a system: integrating 'omics' data sets, *Nat. Rev. Mol. Cell Biol.*, 2006, 7(3), 198–210.
- 3 M. Bersanelli, *et al.*, Methods for the integration of multi-omics data: mathematical aspects, *BMC Bioinf.*, 2016, 17(suppl 2), 15.
- 4 M. Kim, *et al.*, Multi-omics integration accurately predicts cellular state in unexplored conditions for *Escherichia coli*, *Nat. Commun.*, 2016, 7, 13090.
- 5 A. Ahmad and H. Fröhlich, Integrating Heterogeneous omics Data via Statistical Inference and Learning Techniques, *Genomics and Computational Biology*, 2016, 2(1), e32.
- 6 M. W. Libbrecht and W. S. Noble, Machine learning applications in genetics and genomics, *Nat. Rev. Genet.*, 2015, 16(6), 321–332.
- 7 C. Angermueller, *et al.*, Deep learning for computational biology, *Mol. Syst. Biol.*, 2016, 12(7), 878.
- 8 J. J. Davis, *et al.*, Antimicrobial Resistance Prediction in PATRIC and RAST, *Sci. Rep.*, 2016, 6, 27930.
- 9 L. J. Sweetlove, R. L. Last and A. R. Fernie, Predictive metabolic engineering: a goal for systems biology, *Plant Physiol.*, 2003, 132(2), 420–425.
- 10 R. Shaik and W. Ramakrishna, Machine learning approaches distinguish multiple stress conditions using stress-responsive genes and identify candidate genes for broad resistance in rice, *Plant Physiol.*, 2014, 164(1), 481–495.
- 11 C. Ma, H. H. Zhang and X. Wang, Machine learning for Big Data analytics in plants, *Trends Plant Sci.*, 2014, 19(12), 798–808.
- 12 D. Zeevi, *et al.*, Personalized Nutrition by Prediction of Glycemic Responses, *Cell*, 2015, 163(5), 1079–1094.
- 13 R. F. Schwan and A. E. Wheals, The microbiology of cocoa fermentation and its role in chocolate quality, *Crit. Rev. Food Sci. Nutr.*, 2004, 44(4), 205–221.
- 14 N. J. Loman, *et al.*, Performance comparison of benchtop high-throughput sequencing platforms, *Nat. Biotechnol.*, 2012, 30(5), 434–439.
- 15 Y. Kodama, *et al.*, The Sequence Read Archive: explosive growth of sequencing data, *Nucleic Acids Res.*, 2012, 40(Database issue), D54–D56.
- 16 E. Clough and T. Barrett, The Gene Expression Omnibus Database, *Methods Mol. Biol.*, 2016, 1418, 93–110.
- 17 M. D. Mailman, *et al.*, The NCBI dbGaP database of genotypes and phenotypes, *Nat. Genet.*, 2007, 39(10), 1181–1186.
- 18 T. Weirick, *et al.*, The identification and characterization of novel transcripts from RNA-seq data, *Briefings Bioinf.*, 2016, 17(4), 678–685.
- 19 Z. Wang, M. Gerstein and M. Snyder, RNA-Seq: a revolutionary tool for transcriptomics, *Nat. Rev. Genet.*, 2009, 10(1), 57–63.
- 20 SeqC/MaqC-Iii Consortium, A comprehensive assessment of RNA-seq accuracy, reproducibility and information

- content by the Sequencing Quality Control Consortium, *Nat. Biotechnol.*, 2014, **32**(9), 903–914.
- 21 N. Kolesnikov, *et al.*, ArrayExpress update-simplifying data submissions, *Nucleic Acids Res.*, 2015, **43**(Database issue), D1113–D1116.
 - 22 E. S. Witze, *et al.*, Mapping protein post-translational modifications with mass spectrometry, *Nat. Methods*, 2007, **4**(10), 798–806.
 - 23 M. Brosch, *et al.*, Shotgun proteomics aids discovery of novel protein-coding genes, alternative splicing, and “resurrected” pseudogenes in the mouse genome, *Genome Res.*, 2011, **21**(5), 756–767.
 - 24 M. Wilhelm, *et al.*, Mass-spectrometry-based draft of the human proteome, *Nature*, 2014, **509**(7502), 582–587.
 - 25 A. Schmidt, *et al.*, The quantitative and condition-dependent *Escherichia coli* proteome, *Nat. Biotechnol.*, 2016, **34**(1), 104–110.
 - 26 J. E. Elias, *et al.*, Comparative evaluation of mass spectrometry platforms used in large-scale proteomics investigations, *Nat. Methods*, 2005, **2**(9), 667–675.
 - 27 P. Jones, *et al.*, PRIDE: a public repository of protein and peptide identifications for the proteomics community, *Nucleic Acids Res.*, 2006, **34**(Database issue), D659–D663.
 - 28 J. A. Vizcaino, *et al.*, ProteomeXchange provides globally coordinated proteomics data submission and dissemination, *Nat. Biotechnol.*, 2014, **32**(3), 223–226.
 - 29 E. J. Want, B. F. Cravatt and G. Siuzdak, The expanding role of mass spectrometry in metabolite profiling and characterization, *ChemBioChem*, 2005, **6**(11), 1941–1951.
 - 30 Z. Lei, D. V. Huhman and L. W. Sumner, Mass spectrometry strategies in metabolomics, *J. Biol. Chem.*, 2011, **286**(29), 25435–25442.
 - 31 J. M. Buscher, *et al.*, Cross-platform comparison of methods for quantitative metabolomics of primary metabolism, *Anal. Chem.*, 2009, **81**(6), 2135–2143.
 - 32 N. S. Kale, *et al.*, MetaboLights: An Open-Access Database Repository for Metabolomics Data, *Curr. Protoc. Bioinformatics*, 2016, **53**, 14.
 - 33 M. Baker, Proteomics: the interaction map, *Nature*, 2012, **484**(7393), 271–275.
 - 34 B. Suter, *et al.*, Next-Generation Sequencing for Binary Protein–Protein Interactions, *Front. Genet.*, 2015, **6**, 346.
 - 35 J. De Las Rivas and C. Fontanillo, Protein–protein interactions essentials: key concepts to building and analyzing interactome networks, *PLoS Comput. Biol.*, 2010, **6**(6), e1000807.
 - 36 T. S. Furey, ChIP-seq and beyond: new and improved methodologies to detect and characterize protein–DNA interactions, *Nat. Rev. Genet.*, 2012, **13**(12), 840–852.
 - 37 D. S. Johnson, *et al.*, Genome-wide mapping of *in vivo* protein–DNA interactions, *Science*, 2007, **316**(5830), 1497–1502.
 - 38 H. S. Rhee and B. F. Pugh, Comprehensive genome-wide protein–DNA interactions detected at single-nucleotide resolution, *Cell*, 2011, **147**(6), 1408–1419.
 - 39 D. Szklarczyk, *et al.*, STRINGv10: protein–protein interaction networks, integrated over the tree of life, *Nucleic Acids Res.*, 2015, **43**(Database issue), D447–D452.
 - 40 A. Chatr-aryamontri, *et al.*, The BioGRID interaction database: 2017 update, *Nucleic Acids Res.*, 2017, **45**(D1), D369–D379.
 - 41 D. Szklarczyk and L. J. Jensen, Protein–protein interaction databases, *Methods Mol. Biol.*, 2015, **1278**, 39–56.
 - 42 M. J. Heller, DNA microarray technology: devices, systems, and applications, *Annu. Rev. Biomed. Eng.*, 2002, **4**, 129–153.
 - 43 Y. F. Leung and D. Cavalieri, Fundamentals of cDNA microarray data analysis, *Trends Genet.*, 2003, **19**(11), 649–659.
 - 44 M. L. Metzker, Sequencing technologies – the next generation, *Nat. Rev. Genet.*, 2010, **11**(1), 31–46.
 - 45 X. Han, A. Aslanian and J. R. Yates, 3rd, Mass spectrometry for proteomics, *Curr. Opin. Chem. Biol.*, 2008, **12**(5), 483–490.
 - 46 K. Dettmer, P. A. Aronov and B. D. Hammock, Mass spectrometry-based metabolomics, *Mass Spectrom. Rev.*, 2007, **26**(1), 51–78.
 - 47 J. Quackenbush, Microarray data normalization and transformation, *Nat. Genet.*, 2002, **32**(suppl), 496–501.
 - 48 H. J. Ruskin, Computational Modeling and Analysis of Microarray Data: New Horizons, *Microarrays*, 2016, **5**, 4.
 - 49 D. B. Allison, *et al.*, Microarray data analysis: from disarray to consolidation and consensus, *Nat. Rev. Genet.*, 2006, **7**(1), 55–65.
 - 50 T. H. Yang, ¹³C-based metabolic flux analysis: fundamentals and practice, *Methods Mol. Biol.*, 2013, **985**, 297–334.
 - 51 M. D. Ritchie, *et al.*, Methods of integrating data to uncover genotype–phenotype interactions, *Nat. Rev. Genet.*, 2015, **16**(2), 85–97.
 - 52 D. Rajasundaram and J. Selbig, More effort – more results: recent advances in integrative ‘omics’ data analysis, *Curr. Opin. Plant Biol.*, 2016, **30**, 57–61.
 - 53 Q. Zhu, *et al.*, Targeted exploration and analysis of large cross-platform human transcriptomic compendia, *Nat. Methods*, 2015, **12**(3), 211–214.
 - 54 M. Moretto, *et al.*, COLOMBOSv3.0: leveraging gene expression compendia for cross-species analyses, *Nucleic Acids Res.*, 2016, **44**(D1), D620–D623.
 - 55 J. Rudy and F. Valafar, Empirical comparison of cross-platform normalization methods for gene expression data, *BMC Bioinf.*, 2011, **12**, 467.
 - 56 S. A. McCarroll, *et al.*, Integrated detection and population-genetic analysis of SNPs and copy number variation, *Nat. Genet.*, 2008, **40**(10), 1166–1174.
 - 57 International HapMap 3 Consortium, Integrating common and rare genetic variation in diverse human populations, *Nature*, 2010, **467**(7311), 52–58.
 - 58 H. Yang and K. Wang, Genomic variant annotation and prioritization with ANNOVAR and WANNOVAR, *Nat. Protoc.*, 2015, **10**(10), 1556–1566.
 - 59 G. Parra, K. Bradnam and I. Korf, CEGMA: a pipeline to accurately annotate core genes in eukaryotic genomes, *Bioinformatics*, 2007, **23**(9), 1061–1067.
 - 60 T. Lu, *et al.*, Function annotation of the rice transcriptome at single-nucleotide resolution by RNA-seq, *Genome Res.*, 2010, **20**(9), 1238–1249.

- 61 V. N. Bhatia, *et al.*, Software tool for researching annotations of proteins: open-source protein annotation software with data visualization, *Anal. Chem.*, 2009, **81**(23), 9819–9823.
- 62 M. Chagoyen and F. Pazos, Tools for the functional interpretation of metabolomic experiments, *Briefings Bioinf.*, 2013, **14**(6), 737–744.
- 63 J. Xia, *et al.*, MetaboAnalyst 3.0-making metabolomics more meaningful, *Nucleic Acids Res.*, 2015, **43**(W1), W251–W257.
- 64 P. D. Karp, *et al.*, The EcoCyc Database, *EcoSal Plus*, 2014, **6**, 1.
- 65 D. Swarbreck, *et al.*, The Arabidopsis Information Resource (TAIR): gene structure and function annotation, *Nucleic Acids Res.*, 2008, **36**(Database issue), D1009–D1014.
- 66 J. M. Cherry, *et al.*, Saccharomyces Genome Database: the genomics resource of budding yeast, *Nucleic Acids Res.*, 2012, **40**(Database issue), D700–D705.
- 67 A. Hamosh, *et al.*, Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders, *Nucleic Acids Res.*, 2005, **33**(Database issue), D514–D517.
- 68 E. Boutet, *et al.*, UniProtKB/Swiss-Prot, *Methods Mol. Biol.*, 2007, **406**, 89–112.
- 69 C. O'Donovan, *et al.*, High-quality protein knowledge resource: SWISS-PROT and TrEMBL, *Briefings Bioinf.*, 2002, **3**(3), 275–284.
- 70 A. Gattiker, *et al.*, Automated annotation of microbial proteomes in SWISS-PROT, *Comput. Biol. Chem.*, 2003, **27**(1), 49–58.
- 71 M. R. Viant, *et al.*, How close are we to complete annotation of metabolomes?, *Curr. Opin. Chem. Biol.*, 2017, **36**, 64–69.
- 72 S. A. Teichmann and M. M. Babu, Gene regulatory network growth by duplication, *Nat. Genet.*, 2004, **36**(5), 492–496.
- 73 J. Schellenberger, *et al.*, BiGG: a Biochemical Genetic and Genomic knowledgebase of large scale metabolic reconstructions, *BMC Bioinf.*, 2010, **11**, 213.
- 74 C. Liu, QTL Mapping of Molecular Traits for Studies of Human Complex Diseases, *Applied Computational Genomics*, Springer, 2012, pp. 61–82.
- 75 D. Kumar, *et al.*, Integrating transcriptome and proteome profiling: strategies and applications, *Proteomics*, 2016, **16**(19), 2533–2544.
- 76 A. I. Nesvizhskii, Proteogenomics: concepts, applications and computational strategies, *Nat. Methods*, 2014, **11**(11), 1114–1125.
- 77 P. Jullian Fabres, *et al.*, A concise review on multi-omics data integration for terroir analysis in *Vitis vinifera*, *Front. Recent Dev. Plant Sci.*, 2017, **8**, 1065.
- 78 D. J. Beale, A. V. Karpe and W. Ahmed, Beyond Metabolomics: A Review of Multi-Omics-Based Approaches, *Microbial Metabolomics*, Springer, 2016, pp. 289–312.
- 79 C. Bock, M. Farlik and N. C. Sheffield, Multi-Omics of Single Cells: Strategies and Applications, *Trends Biotechnol.*, 2016, **34**(8), 605–608.
- 80 E. Montague, *et al.*, Beyond protein expression, MOPED goes multi-omics, *Nucleic Acids Res.*, 2015, **43**(Database issue), D1145–D1151.
- 81 W. H. Chen, *et al.*, Integration of multi-omics data of a genome-reduced bacterium: Prevalence of post-transcriptional regulation and its correlation with protein abundances, *Nucleic Acids Res.*, 2016, **44**(3), 1192–1202.
- 82 C. Vogel and E. M. Marcotte, Insights into the regulation of protein abundance from proteomic and transcriptomic analyses, *Nat. Rev. Genet.*, 2012, **13**(4), 227–232.
- 83 S. Wachi, K. Yoneda and R. Wu, Interactome-transcriptome analysis reveals the high centrality of genes differentially expressed in lung cancer tissues, *Bioinformatics*, 2005, **21**(23), 4205–4208.
- 84 X. Wang and B. Zhang, Integrating genomic, transcriptomic, and interactome data to improve Peptide and protein identification in shotgun proteomics, *J. Proteome Res.*, 2014, **13**(6), 2715–2723.
- 85 M. A. Moreno-Risueno, W. Busch and P. N. Benfey, Omics meet networks-using systems approaches to infer regulatory networks in plants, *Curr. Opin. Plant Biol.*, 2010, **13**(2), 126–131.
- 86 M. W. Covert, *et al.*, Integrating metabolic, transcriptional regulatory and signal transduction models in *Escherichia coli*, *Bioinformatics*, 2008, **24**(18), 2044–2050.
- 87 J. M. Lee, *et al.*, Dynamic analysis of integrated signaling, metabolic, and regulatory networks, *PLoS Comput. Biol.*, 2008, **4**(5), e1000086.
- 88 E. Yeger-Lotem, *et al.*, Network motifs in integrated cellular networks of transcription-regulation and protein-protein interaction, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**(16), 5934–5939.
- 89 X. Wu, *et al.*, Network-based global inference of human disease genes, *Mol. Syst. Biol.*, 2008, **4**, 189.
- 90 Y. V. Sun, Integration of biological networks and pathways with genetic association studies, *Hum. Genet.*, 2012, **131**(10), 1677–1686.
- 91 C. J. Mitchell, *et al.*, A multi-omic analysis of human naive CD4 + T cells, *BMC Syst. Biol.*, 2015, **9**, 75.
- 92 J. N. Weinstein, *et al.*, The Cancer Genome Atlas Pan-Cancer analysis project, *Nat. Genet.*, 2013, **45**(10), 1113–1120.
- 93 B. Settles, *Active learning literature survey*, University of Wisconsin, Madison, 2010, vol. 52(55–66), p. 11.
- 94 M. Alipoor, *et al.*, Optimal Experiment Design for Mono-exponential Model Fitting: Application to Apparent Diffusion Coefficient Imaging, *BioMed Res. Int.*, 2015, **2015**, 138060.
- 95 L. N. Soldatova and R. D. King, An ontology of scientific experiments, *J. R. Soc., Interface*, 2006, **3**(11), 795–803.
- 96 A. Brazma, Minimum information about a microarray experiment (MIAME)-successes, failures, challenges, *Sci. World J.*, 2009, **9**, 420–423.
- 97 J. Loven, *et al.*, Revisiting global gene expression analysis, *Cell*, 2012, **151**(3), 476–482.
- 98 B. Hoekman, *et al.*, msCompare: a framework for quantitative analysis of label-free LC-MS data for comparative candidate biomarker studies, *Mol. Cell. Proteomics*, 2012, **11**(6), M111 015974.
- 99 C. C. Tsou, *et al.*, IDEAL-Q, an automated tool for label-free quantitation analysis using an efficient peptide alignment

- approach and spectral data validation, *Mol. Cell. Proteomics*, 2010, **9**(1), 131–144.
- 100 B. Valot, *et al.*, MassChroQ: a versatile tool for mass spectrometry quantification, *Proteomics*, 2011, **11**(17), 3572–3577.
 - 101 H. P. Benton, *et al.*, XCMS2: processing tandem mass spectrometry data for metabolite identification and structural characterization, *Anal. Chem.*, 2008, **80**(16), 6382–6389.
 - 102 P. Franceschi, *et al.*, A benchmark spike-in data set for biomarker identification in metabolomics, *J. Chemom.*, 2012, **26**(1–2), 16–24.
 - 103 C. A. Anderson, *et al.*, Data quality control in genetic case-control association studies, *Nat. Protoc.*, 2010, **5**(9), 1564–1573.
 - 104 T. Raman, *et al.*, Quality control in microarray assessment of gene expression in human airway epithelium, *BMC Genomics*, 2009, **10**, 493.
 - 105 S. Yoo, *et al.*, MODMatcher: multi-omics data matcher for integrative genomic analysis, *PLoS Comput. Biol.*, 2014, **10**(8), e1003790.
 - 106 S. Aksoy and R. M. Haralick, Feature normalization and likelihood-based similarity measures for image retrieval, *Pattern Recognit. Lett.*, 2001, **22**(5), 563–582.
 - 107 H. Zou and T. Hastie, Regularization and variable selection via the elastic net, *J. R. Stat. Soc. Series B, Stat. Methodol.*, 2005, **67**(2), 301–320.
 - 108 G. Ratsch, *et al.*, Improving the Caenorhabditis elegans genome annotation using machine learning, *PLoS Comput. Biol.*, 2007, **3**(2), e20.
 - 109 S. Sonnenburg, *et al.*, Accurate splice site prediction using support vector machines, *BMC Bioinf.*, 2007, **8**(suppl 10), S7.
 - 110 F. Anwar, *et al.*, Pol II promoter prediction using characteristic 4-mer motifs: a machine learning approach, *BMC Bioinf.*, 2008, **9**, 414.
 - 111 K. Plaimas, R. Eils and R. König, Identifying essential genes in bacterial metabolic networks with machine learning methods, *BMC Syst. Biol.*, 2010, **4**(1), 56.
 - 112 B. A. Shapiro, *et al.*, Bridging the gap in RNA structure prediction, *Curr. Opin. Struct. Biol.*, 2007, **17**(2), 157–165.
 - 113 M. Ackermann, *et al.*, Teamwork: improved eQTL mapping using combinations of machine learning methods, *PLoS One*, 2012, **7**(7), e40916.
 - 114 T. Huang and Y. D. Cai, An information-theoretic machine learning approach to expression QTL analysis, *PLoS One*, 2013, **8**(6), e67899.
 - 115 X. Jian, E. Boerwinkle and X. Liu, *In silico* prediction of splice-altering single nucleotide variants in the human genome, *Nucleic Acids Res.*, 2014, **42**(22), 13534–13544.
 - 116 J. Li, *et al.*, Using epigenomics data to predict gene expression in lung cancer, *BMC Bioinf.*, 2015, **16**(5), S10.
 - 117 L. Han, *et al.*, Recent progresses in the application of machine learning approach for predicting protein functional class independent of sequence similarity, *Proteomics*, 2006, **6**(14), 4023–4037.
 - 118 V. G. Krishnan and D. R. Westhead, A comparative study of machine-learning methods to predict the effects of single nucleotide polymorphisms on protein function, *Bioinformatics*, 2003, **19**(17), 2199–2209.
 - 119 R. Sharan, I. Ulitsky and R. Shamir, Network-based prediction of protein function, *Mol. Syst. Biol.*, 2007, **3**, 88.
 - 120 M. Agathocleous, *et al.*, Protein Secondary Structure Prediction with Bidirectional Recurrent Neural Nets: Can Weight Updating for Each Residue Enhance Performance? in *Artificial Intelligence Applications and Innovations: 6th IFIP WG 12.5 International Conference, AIAI 2010, Larnaca, Cyprus, October 6–7, 2010. Proceedings*, ed. H. Papadopoulos, A. S. Andreou, and M. Bramer, 2010, Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 128–137.
 - 121 M. Brylinski and J. Skolnick, FINDSITE-metal: integrating evolutionary information and machine learning for structure-based metal-binding site prediction at the proteome level, *Proteins*, 2011, **79**(3), 735–751.
 - 122 C. Caragea, *et al.*, Glycosylation site prediction using ensembles of Support Vector Machine classifiers, *BMC Bioinf.*, 2007, **8**(1), 438.
 - 123 Z. Lu, *et al.*, Predicting subcellular localization of proteins using machine-learned classifiers, *Bioinformatics*, 2004, **20**(4), 547–556.
 - 124 S. Li, *et al.*, Predicting O-glycosylation sites in mammalian proteins by using SVMs, *Comput. Biol. Chem.*, 2006, **30**(3), 203–208.
 - 125 G. Bologna, *et al.*, N-Terminal myristoylation predictions by ensembles of neural networks, *Proteomics*, 2004, **4**(6), 1626–1632.
 - 126 J. Hummel, *et al.*, Decision tree supported substructure prediction of metabolites from GC-MS profiles, *Metabolomics*, 2010, **6**(2), 322–333.
 - 127 M. J. Embrechts and S. Ekins, Classification of metabolites with kernel-partial least squares (K-PLS), *Drug Metab. Dispos.*, 2007, **35**(3), 325–327.
 - 128 J. Zhou and O. G. Troyanskaya, Predicting effects of non-coding variants with deep learning-based sequence model, *Nat. Methods*, 2015, **12**(10), 931–934.
 - 129 D. R. Kelley, J. Snoek and J. L. Rinn, Basset: learning the regulatory code of the accessible genome with deep convolutional neural networks, *Genome Res.*, 2016, **26**(7), 990–999.
 - 130 M. Ghandi, *et al.*, Enhanced regulatory sequence prediction using gapped k-mer features, *PLoS Comput. Biol.*, 2014, **10**(7), e1003711.
 - 131 M. Bhasin, *et al.*, Prediction of methylated CpGs in DNA sequences using a support vector machine, *FEBS Lett.*, 2005, **579**(20), 4302–4308.
 - 132 B. A. McKinney, *et al.*, Machine learning for detecting gene–gene interactions: a review, *Appl. Bioinf.*, 2006, **5**(2), 77–88.
 - 133 N. Bhardwaj, *et al.*, Kernel-based machine learning protocol for predicting DNA-binding proteins, *Nucleic Acids Res.*, 2005, **33**(20), 6486–6493.
 - 134 B. Alipanahi, *et al.*, Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning, *Nat. Biotechnol.*, 2015, **33**, 831–838.
 - 135 D. Marbach, *et al.*, Wisdom of crowds for robust gene network inference, *Nat. Methods*, 2012, **9**(8), 796–804.

- 136 T. P. Mohamed, J. G. Carbonell and M. K. Ganapathiraju, Active learning for human protein–protein interaction prediction, *BMC Bioinf.*, 2010, **11**(suppl 1), S57.
- 137 J. D. Han, *et al.*, Evidence for dynamically organized modularity in the yeast protein–protein interaction network, *Nature*, 2004, **430**(6995), 88–93.
- 138 N. Bhardwaj and H. Lu, Correlation between gene expression profiles and protein–protein interactions within and across genomes, *Bioinformatics*, 2005, **21**(11), 2730–2738.
- 139 R. Jansen, *et al.*, A Bayesian networks approach for predicting protein–protein interactions from genomic data, *Science*, 2003, **302**(5644), 449–453.
- 140 S. Hautaniemi, *et al.*, Modeling of signal-response cascades using decision tree analysis, *Bioinformatics*, 2005, **21**(9), 2027–2035.
- 141 J. M. Dale, L. Popescu and P. D. Karp, Machine learning methods for metabolic pathway prediction, *BMC Bioinf.*, 2010, **11**, 15.
- 142 E. M. Airolidi, *et al.*, Predicting cellular growth from gene expression signatures, *PLoS Comput. Biol.*, 2009, **5**(1), e1000257.
- 143 A. Acharjee, *et al.*, Integration of multi-omics data for prediction of phenotypic traits using random forest, *BMC Bioinf.*, 2016, **17**(suppl 5), 180.
- 144 M. Xu, *et al.*, Automated multidimensional phenotypic profiling using large public microarray repositories, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**(30), 12323–12328.
- 145 H. W. Ressom, *et al.*, Classification algorithms for phenotype prediction in genomics and proteomics, *Front. Biosci.*, 2008, **13**, 691–708.
- 146 L. C. Kenny, *et al.*, Novel biomarkers for pre-eclampsia detected using metabolomics and machine learning, *Metabolomics*, 2005, **1**(3), 227–234.
- 147 S. Mahadevan, *et al.*, Analysis of metabolomic data using support vector machines, *Anal. Chem.*, 2008, **80**(19), 7562–7570.
- 148 M. P. Menden, *et al.*, Machine learning prediction of cancer cell sensitivity to drugs based on genomic and chemical properties, *PLoS One*, 2013, **8**(4), e61318.
- 149 L. C. Stetson, *et al.*, Computational identification of multi-omic correlates of anticancer therapeutic response, *BMC Genomics*, 2014, **15**(suppl 7), S2.
- 150 M. Wagner, *et al.*, Computational protein biomarker prediction: a case study for prostate cancer, *BMC Bioinf.*, 2004, **5**, 26.
- 151 G. McGuire, M. C. Denham and D. J. Balding, MAC5: Bayesian inference of phylogenetic trees from DNA sequences incorporating gaps, *Bioinformatics*, 2001, **17**(5), 479–480.
- 152 T. T. Wu, *et al.*, Genome-wide association analysis by lasso penalized logistic regression, *Bioinformatics*, 2009, **25**(6), 714–721.
- 153 H. B. Barlow, Unsupervised learning, *Neural Comput.*, 1989, **1**(3), 295–311.
- 154 J. Lapointe, *et al.*, Gene expression profiling identifies clinically relevant subtypes of prostate cancer, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**(3), 811–816.
- 155 S. J. Deeb, *et al.*, Super-SILAC allows classification of diffuse large B-cell lymphoma subtypes by their protein expression profiles, *Mol. Cell. Proteomics*, 2012, **11**(5), 77–89.
- 156 P. Chinnaiyan, *et al.*, The metabolomic signature of malignant glioma reflects accelerated anabolic metabolism, *Cancer Res.*, 2012, **72**(22), 5878–5888.
- 157 M. E. Figueroa, *et al.*, DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia, *Cancer Cell*, 2010, **17**(1), 13–27.
- 158 M. Lauten, *et al.*, Unsupervised proteome analysis of human leukaemia cells identifies the Valosin-containing protein as a putative marker for glucocorticoid resistance, *Leukemia*, 2006, **20**(5), 820–826.
- 159 C. C. Friedel, J. Krumsiek and R. Zimmer, *Bootstrapping the Interactome: Unsupervised Identification of Protein Complexes in Yeast*, in *Research in Computational Molecular Biology: 12th Annual International Conference, RECOMB 2008, Singapore, March 30 – April 2, 2008. Proceedings*, ed. M. Vingron and L. Wong, 2008, Springer Berlin Heidelberg: Berlin, Heidelberg, pp. 3–16.
- 160 T. Schaffter, D. Marbach and D. Floreano, GeneNetWeaver: *in silico* benchmark generation and performance profiling of network inference methods, *Bioinformatics*, 2011, **27**(16), 2263–2270.
- 161 N. Zamani, *et al.*, Unsupervised genome-wide recognition of local relationship patterns, *BMC Genomics*, 2013, **14**, 347.
- 162 M. M. Hoffman, *et al.*, Unsupervised pattern discovery in human chromatin structure through genomic segmentation, *Nat. Methods*, 2012, **9**(5), 473–476.
- 163 J. Ernst and M. Kellis, Discovery and characterization of chromatin states for systematic annotation of the human genome, *Nat. Biotechnol.*, 2010, **28**(8), 817–825.
- 164 M. Halkidi, Y. Batistakis and M. Vazirgiannis, On clustering validation techniques, *J. Intell. Inf. Syst.*, 2001, **17**(2–3), 107–145.
- 165 S. Berardo, E. Favero and N. Neto, *Active Learning with Clustering and Unsupervised Feature Learning*, Canadian Conference on Artificial Intelligence, Springer, Cham, 2015.
- 166 H. Steck and T. S. Jaakkola, *Unsupervised active learning in large domains*, Proceedings of the Eighteenth conference on Uncertainty in artificial intelligence, Morgan Kaufmann Publishers Inc, 2002.
- 167 Y. Liu, Active learning with support vector machine applied to gene expression data for cancer classification, *J. Chem. Inf. Comput. Sci.*, 2004, **44**(6), 1936–1941.
- 168 Y. Sverchkov and M. Craven, A review of active learning approaches to experimental design for uncovering biological networks, *PLoS Comput. Biol.*, 2017, **13**(6), e1005466.
- 169 T. P. Nguyen and T. B. Ho, Detecting disease genes based on semi-supervised learning and protein–protein interaction networks, *Artif. Intell. Med.*, 2012, **54**(1), 63–71.
- 170 N. Zhao, *et al.*, Determining effects of non-synonymous SNPs on protein–protein interactions using supervised and

- semi-supervised learning, *PLoS Comput. Biol.*, 2014, **10**(5), e1003592.
- 171 D. Kim, *et al.*, Knowledge boosting: a graph-based integration approach with multi-omics data and genomic knowledge for cancer clinical outcome prediction, *J. Am. Med. Inform. Assoc.*, 2015, **22**(1), 109–120.
 - 172 L. P. Kaelbling, M. L. Littman and A. W. Moore, Reinforcement learning: a survey, *J. Intell. Inf. Syst.*, 1996, **4**, 237–285.
 - 173 A. Tsoukalas, T. Albertson and I. Tagkopoulos, From data to optimal decision making: a data-driven, probabilistic machine learning approach to decision support for patients with sepsis, *JMIR Med. Inform.*, 2015, **3**(1), e11.
 - 174 Y. LeCun, Y. Bengio and G. Hinton, Deep learning, *Nature*, 2015, **521**(7553), 436–444.
 - 175 P. Mamoshina, *et al.*, Applications of Deep Learning in Biomedicine, *Mol. Pharmaceutics*, 2016, **13**(5), 1445–1454.
 - 176 S. Min, B. Lee and S. Yoon, Deep learning in bioinformatics, *Briefings Bioinf.*, 2017, **18**(5), 851–869.
 - 177 T. Ching, *et al.*, Opportunities And Obstacles For Deep Learning In Biology And Medicine, *bioRxiv*, 2017, p. 142760.
 - 178 W. Liu and S. Chawla, *Class confidence weighted knn algorithms for imbalanced data sets*, Advances in Knowledge Discovery and Data Mining, Springer, 2011, pp. 345–356.
 - 179 D. Wang and S. Bodovitz, Single cell analysis: the new frontier in ‘omics’, *Trends Biotechnol.*, 2010, **28**(6), 281–290.
 - 180 E. A. Rebollar, *et al.*, Using “Omics” and Integrated Multi-Omics Approaches to Guide Probiotic Selection to Mitigate Chytridiomycosis and Other Emerging Infectious Diseases, *Front. Microbiol.*, 2016, **7**, 68.
 - 181 J. Hultman, *et al.*, Multi-omics of permafrost, active layer and thermokarst bog soil microbiomes, *Nature*, 2015, **521**(7551), 208–212.
 - 182 A. Heintz-Buschart, *et al.*, Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes, *Nat. Microbiol.*, 2016, **2**, 16180.
 - 183 E. A. Franzosa, *et al.*, Sequencing and beyond: integrating molecular ‘omics’ for microbial community profiling, *Nat. Rev. Microbiol.*, 2015, **13**(6), 360–372.
 - 184 Y. Chen, J. D. Elenee Argentinis and G. Weber, IBM Watson: How Cognitive Computing Can Be Applied to Big Data Challenges in Life Sciences Research, *Clin. Ther.*, 2016, **38**(4), 688–701.
 - 185 R. D. King, *et al.*, Functional genomic hypothesis generation and experimentation by a robot scientist, *Nature*, 2004, **427**(6971), 247–252.
 - 186 R. D. King, *et al.*, The automation of science, *Science*, 2009, **324**(5923), 85–89.
 - 187 J. Shendure and H. Ji, Next-generation DNA sequencing, *Nat. Biotechnol.*, 2008, **26**(10), 1135–1145.
 - 188 D. Sims, *et al.*, Sequencing depth and coverage: key considerations in genomic analyses, *Nat. Rev. Genet.*, 2014, **15**(2), 121–132.
 - 189 M. Bantscheff, *et al.*, Quantitative mass spectrometry in proteomics: critical review update from 2007 to the present, *Anal. Bioanal. Chem.*, 2012, **404**(4), 939–965.
 - 190 L. Chen, G. Wu and H. Ji, hmChIP: a database and web server for exploring publicly available human and mouse ChIP-seq and ChIP-chip data, *Bioinformatics*, 2011, **27**(10), 1447–1448.
 - 191 M. E. Cusick, *et al.*, Literature-curated protein interaction datasets, *Nat. Methods*, 2009, **6**(1), 39–46.
 - 192 R. H. Davis, The age of model organisms, *Nat. Rev. Genet.*, 2004, **5**(1), 69–76.
 - 193 S. B. Hedges, The origin and evolution of model organisms, *Nat. Rev. Genet.*, 2002, **3**(11), 838–849.
 - 194 G. Parmigiani, *et al.*, The analysis of gene expression data: an overview of methods and software, *The analysis of gene expression data*, Springer, 2003, pp. 1–45.
 - 195 C. S. Wilhelm-Benartzi, *et al.*, Review of processing and analysis methods for DNA methylation array data, *Br. J. Cancer*, 2013, **109**(6), 1394–1402.
 - 196 M. Garber, *et al.*, Computational methods for transcriptome annotation and quantification using RNA-seq, *Nat. Methods*, 2011, **8**(6), 469–477.
 - 197 R. Nielsen, *et al.*, Genotype and SNP calling from next-generation sequencing data, *Nat. Rev. Genet.*, 2011, **12**(6), 443–451.
 - 198 J. R. Miller, S. Koren and G. Sutton, Assembly algorithms for next-generation sequencing data, *Genomics*, 2010, **95**(6), 315–327.
 - 199 H. Kim, *et al.*, A short survey of computational analysis methods in analysing ChIP-seq data, *Hum. Genomics*, 2011, **5**(2), 117–123.
 - 200 A. I. Nesvizhskii, O. Vitek and R. Aebersold, Analysis and validation of proteomic data generated by tandem mass spectrometry, *Nat. Methods*, 2007, **4**(10), 787–797.
 - 201 M. Katajamaa and M. Oresic, Data processing for mass spectrometry-based metabolomics, *J. Chromatogr. A*, 2007, **1158**(1–2), 318–328.
 - 202 E. Halperin and D. A. Stephan, SNP imputation in association studies, *Nat. Biotechnol.*, 2009, **27**(4), 349–351.
 - 203 Y. D. Cai and S. L. Lin, Support vector machines for predicting rRNA-, RNA-, and DNA-binding proteins from amino acid sequence, *Biochim. Biophys. Acta*, 2003, **1648**(1–2), 127–133.
 - 204 D. Quang, Y. Chen and X. Xie, DANN: a deep learning approach for annotating the pathogenicity of genetic variants, *Bioinformatics*, 2015, **31**(5), 761–763.
 - 205 M. Kim, V. Zorraquino and I. Tagkopoulos, Microbial forensics: predicting phenotypic characteristics and environmental conditions from large-scale gene expression profiles, *PLoS Comput. Biol.*, 2015, **11**(3), e1004127.
 - 206 M. Kim and S. H. Kim, Empirical prediction of genomic susceptibilities for multiple cancer classes, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**(5), 1921–1926.
 - 207 C. Curtis, *et al.*, The genomic and transcriptomic architecture of 2000 breast tumours reveals novel subgroups, *Nature*, 2012, **486**(7403), 346–352.
 - 208 L. Deng, *et al.*, Development and Validation of a High-Throughput Mass Spectrometry Based Urine Metabolomic Test for the Detection of Colonic Adenomatous Polyps, *Metabolites*, 2017, **7**(3), 32.

- 209 R. Gao, *et al.*, Serum metabolomics to identify the liver disease-specific biomarkers for the progression of hepatitis to hepatocellular carcinoma, *Sci. Rep.*, 2015, **5**, 18175.
- 210 J. Xiao, *et al.*, Discriminating poststroke depression from stroke by nuclear magnetic resonance spectroscopy-based metabonomic analysis, *Neuropsychiatr. Dis. Treat.*, 2016, **12**, 1919.
- 211 T. Ligor, Ł. Pater and B. Buszewski, Application of an artificial neural network model for selection of potential lung cancer biomarkers, *J. Breath Res.*, 2015, **9**(2), 027106.
- 212 T. Nguyen, *et al.*, Mass spectrometry cancer data classification using wavelets and genetic algorithm, *FEBS Lett.*, 2015, **589**(24), 3879–3886.
- 213 D. Speed and D. J. Balding, MultiBLUP: improved SNP-based prediction for complex traits, *Genome Res.*, 2014, **24**(9), 1550–1557.
- 214 C. Kooperberg, M. LeBlanc and V. Obenchain, Risk prediction using genome-wide association studies, *Genet. Epidemiol.*, 2010, **34**(7), 643–652.
- 215 F. Mittag, *et al.*, Use of support vector machines for disease risk prediction in genome-wide association studies: concerns and opportunities, *Hum. Mutat.*, 2012, **33**(12), 1708–1718.
- 216 S. J. Schrodi, *et al.*, Genetic-based prediction of disease traits: prediction is very difficult, especially about the future, *Front. Genet.*, 2014, **5**, 162.
- 217 J. Zhou and O. G. Troyanskaya, Predicting effects of non-coding variants with deep learning-based sequence model, *Nat. Methods*, 2015, **12**(10), 931–934.
- 218 B. Alipanahi, *et al.*, Predicting the sequence specificities of DNA-and RNA-binding proteins by deep learning, *Nat. Biotechnol.*, 2015, **33**(8), 831–838.
- 219 Y.-A. Huang, *et al.*, Sequence-based prediction of protein–protein interactions using weighted sparse representation model combined with global encoding, *BMC Bioinf.*, 2016, **17**(1), 184.
- 220 X. Lu, *et al.*, Predicting human genetic interactions from cancer genome evolution, *PLoS One*, 2015, **10**(5), e0125795.
- 221 S. R. Maetschke, *et al.*, Supervised, semi-supervised and unsupervised inference of gene regulatory networks, *Briefings Bioinf.*, 2013, **15**(2), 195–211.
- 222 P. Radivojac, *et al.*, A large-scale evaluation of computational protein function prediction, *Nat. Methods*, 2013, **10**(3), 221–227.
- 223 K. Lee, *et al.*, Protein networks markedly improve prediction of subcellular localization in multiple eukaryotic species, *Nucleic Acids Res.*, 2008, **36**(20), e136.