OmicsView: Omics data analysis through interactive visual analytics

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\textbf{A B S T R A C T}

With advances in NGS technologies, transcriptional profiling of human tissue across many diseases is becoming more routine, leading to the generation of petabytes of data deposited in public repositories. There is a need for bench scientists with little computational expertise to be able to access and mine this data to understand disease pathology, identify robust biomarkers of disease and the effect of interventions (\textit{in vivo} or \textit{in vitro}). To this end we release an open source analytics and visualization platform for expression data called OmicsView, http://omicsview.org.

This platform comes preloaded with 1000 s of samples across many disease areas and normal tissue, including the GTEx database, all processed with a harmonized pipeline. We demonstrate the power and ease-of-use of the platform by means of a Crohn’s disease data mining exercise where we can quickly uncover disease pathology and identify strong biomarkers of disease and response to treatment.

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1. Introduction

Comprehensive omics profiling of patients is fundamental for understanding the molecular mechanism of diseases as well as drug discovery in the era of precision medicine. Modern technologies have enabled the generation of terabytes of RNA-seq and microarray data across all disease areas, and typically they are deposited into public repositories from both academia and industry. However, the deposited data are heterogeneous, and analysed using highly customized pipelines against a variety of annotations, making it a formidable task to make comparisons across projects and diseases. Interpretation and visualization of high-dimensional omics data sets is another daunting task that requires considerable computational training and practice. Although web portals have been developed to analyze publicly available and proprietary datasets [1–4], the analytical capacity is either limited or specialized to the disease of interest, e.g., oncology. Thanks to major breakthroughs in data generation, especially Next Generation Sequencing (NGS), there is a booming demand for advanced tools providing comprehensive visualizations as well as analytical capabilities for biological interpretation of data. Here, we make the public release of OmicsView (https://omicsview.org), an open source solution that is designed to be data type agnostic with all visualization modules easily adaptable to new data types and has a straightforward user data upload process. Furthermore, we provide sample level gene expression data sets across ten disease areas from a curation effort in collaboration with Qiagen to demonstrate the versatile functionalities of the system with an emphasis on accessibility of advanced visual and analytical capabilities and cross study meta-analyses. With OmicsView, every bench scientist, regardless of their computational skill level, can carry out in-depth data analysis and interpretation.

2. Material and methods

OmicsView was developed as an independent interactive web application with backend database support that uses multiple underlying libraries and tools for visualizations. The interactive plots have been generated with a diverse array of JavaScript libraries like CanvasXpress, D3, Plotly and Highcharts running within the web browser. Additionally, R packages, specifically from Bioconductor have been used to create some specific plots like KEGG pathways with a gene highlighting feature. JavaScript and PHP were the underlying programming languages for the web
framework and to tie the visualizations together. Finally, MySQL was used for data storage and management.

2.1. Data processing

To demonstrate the utility of the web-based application, a subset of curated data from DiseaseLand (https://www.qiagenbioinformatics.com/disease_land/) is accessible through OmicsView. The DiseaseLand data service uses common analysis pipelines to quantify and normalize publicly available microarray and RNA-seq expression data from raw files. For each project, and each sample, metadata are curated to apply controlled vocabularies and ensure consistent formatting of metadata fields. Information on the data processing pipeline and the DiseaseLand product is available at the following links: http://www.arrayserver.com/wiki/index.php?title=DiseaseLand_Curation_Pipeline, http://www.arrayserver.com/wiki/index.php?title=Omicsoft_Affymetrix_Microarray_Preprocessing, http://www.arrayserver.com/wiki/index.php?title=RNA-Seq_Normalized_FPKM_Values_in_Land.

The data in OmicsView was exported from DiseaseLand prior to 8/27/2019. None of the preloaded curated data can be exported from the portal, distributed with a software package, or otherwise redistributed without express permission from QIAGEN.

2.2. Plotting and visualization

OminsView offers two main ways to visualize datasets: through a gene-centric or a dataset-centric way. The gene-centric way shows expression of a single or multiple candidate genes across the datasets available in OmicsView (see Supplemental text: Section 2. Visualize Gene expression, https://bit.ly/3sYIJMo). On the other hand, the dataset-centric way is based on one or more candidate datasets, and plots expression of all genes within them (see Supplemental text: Section 3. Visualize Comparison data, https://bit.ly/3pVnOJ). OmicsView offers a variety of plotting types like Bubble Plots, PCA Plots, Volcano Plots, Heatmaps, Pathway plots etc, that are highly customizable. These visualization options are data-type agnostic enabling plotting of micro-array, RNA-seq and proteomic datasets together for comparative analysis (Supplemental text, section 3.12). This is possible because of the uniform way the datasets are analysed, normalized and stored in OmicsView.

2.3. Functional and pathway enrichment

The functional enrichment algorithms implemented in OmicsView come in two flavours. The first is based on hypergeometric enrichment of differentially expressed genes (DEGs) against a number of knowledge databases, based on the HOMER package (https://homer.salk.edu/homer/microarray/go.html). This requires a significance p-value cutoff to be applied to the two group comparison expression data in order to select a set of genes that is unregulated and downregulated, i.e. differentially expressed genes. The HOMER package comes with pre-compiled collections of gene knowledge databases that we use for enrichment. The second approach is based on a variant of the Gene Set Enrichment Analysis (GSEA) approach called PAGE (Parametric Analysis of Gene Set Enrichment) which is faster than the original GSEA approach and more sensitive. We use an implementation of PAGE [5] included in the R piano package (https://www.bioconductor.org/packages/release/bioc/html/piano.html). GSEA based approaches just require a ranked list of genes (genes with a numeric quantity for ranking them that shows how different they are between groups in the comparison, usually logFC values) and are typically more sensitive in detecting pathway enrichment. Both, HOMER and PAGE packages come pre-built with a set of known functions/pathways in the form of gene sets, against which we look for enrichment in the comparison of interest. The enrichment tools are run against differential expression data as they are being imported into OmicsView, so the end user is presented with pre-computed results readily. We describe both enrichment approaches in the subsequent sections.

2.4. HOMER workflow

The HOMER workflow is our first enrichment tool that enables pathway analysis on differentially expressed genes (DEGs) in two ways. The first step is selection of differentially expressed genes (DEGs) for enrichment analysis. For each comparison, a list of the up- and down-regulated genes are selected as input for functional enrichment analysis. We use a dynamic cutoff of logFC and AdjustedPValue / pValue to aim for 200–2000 genes in each list. To achieve this, we start with a stringent cutoff of adjusted p-value of 0.05, and 2-fold change up or down. Getting a list of greater than 200 genes is ideal for the downstream analysis. If there are fewer, we drop the nominal p-value to 0.01 (with 2-fold up or down), and subsequently if 200 is not reached we drop the fold change to 1.2 in either direction or increase the adjusted p-value to 0.1. If the most relaxing cutoff doesn’t generate a list of at least 50 dysregulated genes, we select the top 50 genes ranked by absolute logFC values to generate the lists for enrichment analysis. The second step is functional enrichment of the DEG list against the genome. In this workflow the findGo.pl function from the Homer package implements the hypergeometric test and is used to analyse the functional enrichment for each DEG list. There are several different “ontologies”, or libraries of gene groupings that come with the Homer package. We used Homer version v4.8.3, human-o v5.8 and mouse-o v5.8 libraries (current as of Dec 6, 2016). The HTML output from HOMER is further enhanced by a custom php script for a cleaner display of browsable results.

2.5. Gene set enrichment analysis (GSEA) and PAGE workflow

For our second enrichment tool, we used a variation of the GSEA method, PAGE (Parametric Analysis of Gene Set Enrichment) [5] to process the DEG data, as PAGE is much faster than GSEA and more sensitive. For each comparison, we produce a rank file with gene symbol and logFC values. If a gene symbol appears multiple times in the same comparison, the average logFC is used. Human gene sets were downloaded from MSigDB, version 5.2 (msigdb.v5.2.symbols.gmt). Mouse gene sets were downloaded from Bader Lab from Univ. of Toronto (https://baderlab.org/GeneSets), version from December 2016 (Mouse_GO_AllPathways_with_GO_iea_December_01_2016_symbol.gmt). This gmt file contains special characters that cannot be used by the R piano package, therefore we manually replaced special characters to either forward slash or underscore. In addition, some mouse gene sets have the same name, so we added suffix “_altSetX” to make all the names unique. For the PAGE workflow, the R piano package was used for all the rank files. To simplify the piano output, we combined down-regulated and up-regulated gene sets into a single table for each gene set. From the piano results, we extracted out the p-value, FDR, and Z-score.

2.6. Meta-analysis

The meta-analysis functions allow a user to combine expression data from multiple studies to find changes that are robust across datasets and much less likely to be due to batch differences. OmicsView offers two ways to perform meta-analysis. The first method works on comparison data. The system uses the comparison data (logFC, p-value) to compute a combined p-value and rank product (product of ranks for each gene across the comparisons of interest). This method is fast and can be applied to any type of comparison
data. However, it does not use the individual sample data, nor does it consider the number of samples in each comparison. The second method uses per sample gene expression data. The user inputs a list of factors that indicate comparisons across or within studies and then gene level significant changes are recomputed by extracting expression data from all samples for each comparison, and then applying the RankProd (https://bioconductor.org/packages/release/bioc/html/RankProd.html) [6] and/or MetaDE (https://github.com/metaOmics/MetaDE) [7] packages to perform meta-analysis. Limma is also applied to get statistics for each individual comparison. This analysis takes much longer (10 min to an hour for a typical analysis, even longer if number of samples are very large), and it has more strict sample requirements (no samples can occur in two different comparisons). Statistically, the second method is more robust but both methods should detect consistently changed genes.

2.6.1. Meta-analysis statistics

For comparison data, the combined p-value is computed using Fisher’s method, that is $-2^\text{sum of ln(p-value)}$ is compared against a Chi-squared distribution with N degrees of freedom, where N is the number of p-values being combined. This is carried out for every gene and yields a combined p-value that is reported. Another simpler approach is to report the maximum p-value for the gene across all the comparisons – a much more stringent measure of overall significance. This approach to combining p-values is implemented in the MetaDE R package [7]. Note MetaDE will not produce results if more than 30% of the comparisons for a gene have missing p-values. In addition, with this approach, the p-value combination does not account for the direction of the fold change (up or down), so the up regulated & down regulated percentage summaries need to be referred to for interpretation.

The RankProd method converts log2 fold changes across all genes in a comparison to ranks and then computes a meta-statistic per gene which is the geometric mean of the ranks across comparisons. It is a non-parametric approach, and computes statistical significance based on permutations. Permutations also account for the multiple testing aspect of looking for significance within the set of all genes in the transcriptome.

Fig. 1. Schematic view of main analytical functionalities in OmicsView on Data Exploration by PCA, heatmap analysis, Biological Interpretation by pathway mapping and comparison, and Meta-Analysis by bubble and forest plots.
3. Results

Currently, OmicsView is published with the entire database from the Genotype-Tissue Expression project (GTEx) [8] and a disease database containing samples from highly studied disease areas, both processed with the same computational pipeline and extracted from QIAGEN DiseaseLand. The web-based portal provides an easy-to-use framework for wet-lab biologists to interactively explore, compare and analyze data and produce publication-quality figures in SVG format, Fig. 1. In addition, the user has the option of uploading their own datasets (see Supplementary Material for instructions), and by following the installation guide they can create their own private instance of the OmicsView application to store proprietary data.

Users can easily search genes (using gene symbols, descriptions, alias or database IDs) and samples for detailed annotations in the database. By providing a list of gene names, users can compare expression of multiple genes between multiple samples within and across tissue types, disease states and disease categories. Differential gene expression between relevant groups is pre-computed along with pathway enrichment results. Gene, sample and pathway level plots are readily visualized in interactive JavaScript based views including PCA, Volcano, Multiple Gene Boxplot, Pathway Heatmap and Pathway Overlay and many more options (see Supplementary Material for user guide with all functionality).

In addition to gene expression and differential gene expression data, OmicsView’s powerful pathway analysis module pre-computes and stores pathway enrichment results for popular pub-
lic databases from the Gene Ontology Consortium [9], WikiPathways [10], Gene Set Enrichment Analysis (GSEA – MsigDB) [11], Kyoto Encyclopedia of Genes and Genomes (KEGG) [12], and Reactome [13].

3.1. Feature comparison of tools

We conducted a comprehensive comparison of OmicsView and 11 other tools for analyzing omics data, including ARCHS4 [14], Bgee [15], BIOMEX [16], DEE2 [17], Gemma [17], GEPIA [18], GXD [19], OASIS [2], PaintOmics 3 [20], PulmonDB [21], and recount3 [22]. Specifically, the functionality, software usage, data source, disease focus, and analytical output of these software tools have been summarized in Supplementary Table 1 available at https://bit.ly/3HY9ox5, thereby assisting users in selecting appropriate tools in their research and distinguishing OmicsView. The strengths of OmicsView lie in versatile interactive visualization modules, cross-dataset pathway enrichment analysis and mapping, and meta-analysis on summary statistics, which will be showcased in the following use cases.

3.2. Exploration of Crohn’s disease pathology and identification of TNFalpha signalling pathway dysregulation

Crohn’s disease datasets

To demonstrate the power of OmicsView in discovering underlying disease pathology with minimal effort, we mine Crohn’s disease datasets that are available from QIAGEN’s DiseaseLand. The dashboard interface allows you to quickly see the distribution of disease types and determine that the current database has a good

Fig. 4. (A) GSE52746 study: Pathway scores for an anti-TNF expression profile compared to baseline untreated. On a selected set of immunologic pathways, including TNFalpha signalling (top row in the heatmap) we see a very strong reversal of the disease signature (red – upregulated) compared to TNF treated (blue – downregulated). (B) The PCA tool in OmicsView allows us to examine GSE52746 samples individually where we can see baseline disease (blue circles), normal control (red circles) and the 12 week treated samples which show an intermediate profile and are returning to control. Interestingly the two outlier treated samples are non-responders. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. Gene level drill down into selected genes for inflammatory mediators in Crohn’s disease from GSE52746. A select set of genes from the original publication are viewed in a volcano plot for anti-TNF response (A) and as boxplots partitioned by gene and grouped by response category (NA response means baseline samples, prior to treatment). The responders (red triangles) clearly show much more pronounced cytokine suppression towards normal levels compared to non-responders (red squares). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
representation of Crohn’s disease datasets where several disease-versus-normal comparisons are available, see Fig. 2. We then select out the comparisons directly from the dashboard by selecting relevant categories. We retrieve 8 comparisons in ileum or colon tissue across several GEO studies which enables a robust meta-analysis. This can be saved to a comparison list for easy access.

We next pass that through a pathway meta-analysis by using the “Pathway Heatmap” tool against all PAGE gene sets to get a sense of what the general disease pathology is in Crohn’s disease. We find very strong upregulation in a number of inflammatory gene sets – many of these are oncology related or computationally predicted but one canonical pathway that appears in the top 5 is TNFalpha signalling which is strongly enriched (z-score greater than 10 in all comparisons tested), Fig. 3A. To further probe this, by clicking directly on the enrichment heatmap, we can overlay the gene-expression for each comparison onto the TNF signalling pathway from KEGG where we can identify genes that are consistently upregulated in comparisons, including TNF, CEBP and many downstream cytokines and chemokines, Fig. 3B. We believe this is a novel approach to pathway enrichment visualization as it points to key genes in the pathway that are consistently dysregulated in a meta-analysis, and the overlaid network structure can suggest potential targets for modulation.

Then, by browsing and searching comparisons in the “Review Comparisons” interface we find that there is a GEO study, GSE52746 [23], that includes colon gene expression after anti-TNF treatment. This comparison can be added to the disease versus control list, and on a selected set of immunologic pathways (including TNFalpha signalling) we see a striking reversal of the disease signature when comparing treatment at 12 weeks versus...
baseline groups, Fig. 4A. A sample level representation of the full gene expression profiles can be generated from the PCA tool for this study, Fig. 4B, which shows very clearly disease samples returning to normal in gene expression space, and interestingly two annotated non-responders in the study are outliers at 12 weeks.

To query the magnitude of fold changes of the anti-TNF response, we can apply annotated volcano plots, Fig. 5A where we have highlighted the genes of interest from the GSE52746 study showing the relative strength of the effect compared to the full transcriptome. Alternatively we can readily generate multi-gene boxplots where we can group and colour by relevant patient groups, Fig. 5B.

We may also want to look for novel biomarkers of disease independent of prior biological knowledge or pathway enrichment, so we can ask “What is the most significantly dysregulated genes across the whole transcriptome in Crohn’s disease?”. The Meta-Analysis (Comparisons) tools will apply several statistics to rank genes (see Methods) by level of dysregulation across studies. To carry out the analysis, we need merely re-load the previously saved comparison list, and in Fig. 6A and 6B we see the results of such an analysis on Crohn’s disease comparisons. Most of these genes can be related back to IBD, colitis or colonic epithelial cell homeostasis [24–26]. MLKL itself is in the TNF signalling pathway as can be seen in Fig. 3B and has been noted as a biomarker for intestinal inflammation in IBD [25]. For a more complete step-by-step recreation of plots for this Crohn’s disease exploration see Supplementary Section 7 available at https://bit.ly/3Ikqt5z.

The power of OmicsView is in these meta-analyses across studies and diseases. Another cross-disease use case is a new indication search for a given target gene. For example, motivated by the Crohn’s disease analysis, we may want to ask, “In what other indications may TNF be a good target?”. This is readily answered by creating a Bubble Plot for TNF where its fold changes across many diseases and comparisons can be shown, and the top 10 can be highlighted, Fig. 7. In this analysis we see, along with the consistent TNF upregulation in Crohn’s disease versus normal, there also appears to be significant TNF upregulation in psoriasis and ulcerative colitis. These validate the approach, as anti-TNF treatments (e.g., infliximab, adalimumab) are approved for both conditions [27,28].

3.3. Integrative analysis of RNAseq and proteomics data

An extension to OmicsView’s powerful meta-analysis is the ability to perform joint analysis of RNAseq and Proteomics datasets. This can be especially useful in projects where RNAseq and Liquid chromatography/mass spectrometry assays (LC-MS), or another proteomic assays, are performed on the same samples and common gene and pathways between these assays are to be investigated. To demonstrate this capability, we have uploaded RNAseq and LC-MS datasets of diseased and normal iPSCs from Connor-Robson et al. [29] at 2 timepoints of differentiation, D35 and D56. For the proteomic dataset, the protein ID was converted to the gene ID. To identify top pathways dysregulated across the pathways we used the pathway heatmap tool to pull out KEGG terms that are upregulated and downregulated. Fig. 8A shows the top Upregulated pathways to be Lysosome and ECM-receptor interaction, and Fig. 8B shows the top down-regulated pathways to be Axon guidance and Glutamatergic synapse. To understand each gene’s role in the pathway context, we used the KEGG visualisation tool and selected “ECM-receptor interaction” in Fig. 8C and “Glutamatergic synapse” in Fig. 8D. Interestingly many of the ECM genes like COL1A1 and LAMA2 are upregulated across RNAseq and

Fig. 8. Integrative analysis of RNAseq and Proteomics data in iPSCs from Connor-Robson et al. [29] shows KEGG pathways that are dysregulated across RNAseq and Proteomics assays. Upregulated terms (A) and Downregulated terms (B) show that many pathways are significant across the Proteomics and RNAseq assays. “ECM-receptor interaction” was selected in (C) from the Up-regulated terms to probe each individual gene within the pathway across the RNAseq and proteomics comparisons. “Glutamatergic synapse” was selected in (D) from the Down-regulated terms. Panel (E) shows the Endocytosis pathway in more detail. An interactive version created by bioInfograph [31] is available at https://bit.ly/3MrT3I for enlarged view.
Proteomics assay. For Glutamatergic synapse, GRM6 and GRM7 are downregulated across the assays. The authors in Connor-Robson et al. [29] discuss the role and impact of LRRK2 mutations in the endocytic pathway and here we confirm the downregulation of each component of the pathway in the RNAseq and Proteomics dataset (Fig. 8D).

4. Discussion

The combined user-friendly experience, accessibility and functionality of the OmicsView pathway analysis module improves upon popular web portals like GSEA and DAVID [30] in terms of comprehensiveness and interactivity.

Other omics results can also be overlaid along with transcriptomics for integrated data analysis with appropriate name mapping in the input dataset, and by means of the metanalysis features. By combining the latest advancement of visualization, harmonized state-of-the-art bioinformatics analysis and a large publicly available expression dataset, OmicsView is an easy-to-use powerful platform that can benefit all scientists, especially ones with limited programming skills in the biomedical research field. The entire system is released as open source for wide adoption and further enhancement. The Supplementary Material outlines the detailed steps for interacting with the system and generating plots and analyses of interest.

5. Source code availability

OmicsView is released under MIT open-source license with HTML based tutorial and installation guide available at https://github.com/interactivereport/OmicsView. A publicly hosted demo instance of OmicsView, preloaded with GTEx and selected DiseaseLand studies is available at http://omicsview.org. To ease guidance seeking, a “Tutorial” icon linking to corresponding section of the HTML tutorial (https://interactivereport.github.io/OmicsView/tutorial/docs) is provided underneath the title of each tool in the demo application.

CRediT authorship contribution statement

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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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Appendix A. Supplementary data

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