Omic community detection using multi-resolution clustering

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Abstract

Motivation: The discovery of biologically interpretable and clinically actionable communities in heterogeneous omics data is a necessary first step toward deriving mechanistic insights into complex biological phenomena. Here, we present a novel clustering approach, romeClust, for community detection in omics profiles by simultaneously incorporating similarities among measurements and the overall complex structure of the data.

Results: We show that romeClust outperforms published methods in inferring the true community structure as measured by both sensitivity and misclassification rate on simulated datasets. We further validated romeClust in diverse, multiple omics datasets, revealing new communities and functionally related groups in microbial strains, cell line gene expression patterns and fetal genomic variation. We also derived enrichment scores attributable to putatively meaningful biological factors in these datasets that can serve as hypothesis generators facilitating new sets of testable hypotheses.

Availability and implementation: romeClust is open-source software, and the implementation is available online at http://github.com/omicsEye/omeClust.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Finding biologically meaningful groups exhibiting coherent within-group similarities and between-group differences is often the first critical step in any analysis of modern high-throughput data. An interesting characteristic that real biological networks represent is the clustering or community structure, under which the network topology is organized into modules commonly known as communities or clusters. While clustering and community discovery differ in their representation of detected group entities, they share many commonalities and our use case in this study is based on biological questions benefiting both finding clusters and detecting communities.

Despite being a highly researched unsupervised problem supported by a myriad of algorithms from diverse scientific disciplines, clustering and community structure detection remains computationally and biologically challenging. This is particularly due to the technical nature of the associated data, which are typically noisy and high dimensional with confounding effects unique to individual technology (e.g. platform-specific batch effects). With ever-increasing multi-omics efforts and the associated technology-specific challenges, there is a need for more data-driven methods that are capable of finding biologically meaningful communities in a technology-agnostic manner.

In addition to the omics-specific challenges, there are some long-standing issues shared by most existing clustering (Altman, 1992; Sibson, 1973) and community detection algorithms (Blondel et al., 2008; Bohlin et al., 2014). Clear challenges remain to determine the most appropriate number of clusters as well as the most appropriate distance metric for a particular dataset. For example, a problem akin to hierarchical clustering is the careful tuning of the resolution parameter as well as the selection of appropriate evaluation criteria. When applied in high-throughput biology contexts, these are exacerbated by sparse and highly variable measurements with additional...
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 challenges introduced by the heterogeneity of the associated features. For instance, in metabolomics, some groups of metabolites have greater inter-feature distances than others or in microbial communities, distance between species is often related to sample environment (Lloyd-Price et al., 2017). These, together with the inter-individual differences introduced by the potential confounding factors (e.g. gender and age), calls for an algorithm that detects communities and attributes putatively meaningful biological factors to the detected community structure.

2 Materials and methods

Multi-resolution clustering (omeClust) identifies communities within datasets potentially consisting of heterogeneous ‘features’. Features can be biomarkers from omics molecular profiles (e.g. taxa, genes, pathways, chemicals, etc.) potentially accompanied by the associated metadata (e.g. epidemiological variables, clinical, pharmaceutical and environmental covariates, among others). The relevant features are therefore, specifically defined in a study-specific manner relative to the data and research posed by the individual study. To achieve generality of our approach, a key omeClust input is a distance matrix of features. For an input dataset containing values from samples alongside a pre-calculated distance matrix between points (measurements) (Fig. 1a), the omeClust algorithm proceeds by (i) building a representation of the overall structure of point distances (a hierarchy) using hierarchical clustering (zoom out) (Fig. 1b), (ii) descending the hierarchy to find heterogeneous clusters (zoom in) using a binary-silhouette score, (iii) calculating resolution scores (defined as the harmonic mean of the number of cluster members and the similarity between cluster members) for each cluster to prioritize important clusters and enrichment scores including normalized mutual information (NMI) and frequency-based scores for each metadata to rank the influence of the variable on the detected communities (if provided) and (iv) finally, generating graphic visualizations (Fig. 1c and Supplementary Fig. S1) and reporting interpretable clustering results (Fig. 1d). We cover each of these key workflow elements in more detail below.

### 2.1 Binary-silhouette score

Binary-silhouette, defined in Algorithm 2, is a measurement to quantify how well members within a branch are related compared to the sibling branch in a hierarchy. A hierarchy is a binary tree, and each node has two children nodes. We calculate a binary-silhouette score, which is similar to a silhouette score (Ogbuabor and Ugwoke, 2018), except that, in binary-silhouette scoring, we only consider two clusters, left and right, rather than all clusters, when the score is measured. When we measure the binary-silhouette score for the left child (from: a) in a node, we use the immediate right child as another cluster (to: b) and vice-versa.

### 2.2 Enrichment score

To measure the influence of each metadata on the community structure, omeClust implements two approaches, freq and nmi. While omeClust by default, discretizes the continuous metadata, essentially any metadata that can be converted to a float data type can be used as an input to the omeClust algorithm. For the freq approach, enrichment scores are computed by calculating the number of occurrences of the most frequent category of a metadata in a community, which is then scaled by dividing by the number of community members. The mean enrichment scores for each major cluster are then used to rank the influence of each metadata on the detected community structure. Major clusters with >0.05 enrichment scores are highlighted and returned. The nmi approach, on the other hand, directly uses the NMI (Estevez et al., 2009; Kvalseth, 2017) between the community labels and the metadata values as enrichment scores. NMI is a measure to evaluate the dependency between two variables, and it is a variant of mutual information from information theory which provides an interpretable quantification. If two variables are completely independent (no association) the NMI will be 0, whereas, for two identical variables, the NMI will be 1.

At a deeper level, omeClust uses hierarchical clustering to build an overall structure of potentially heterogeneous features and subsequently detects communities of related features. For hierarchical clustering, by default, omeClust uses a complete-linkage approach (Großwendt and Roegl, 2017); however, the algorithm is robust to the specification of the linkage method (Supplementary Fig. S2) as other well-used approaches, such as single, average, complete, weighted, centroid, median and ward can be provided as options by the user. Specifically, for community detection, omeClust undertakes a top-down recursive approach beginning at the root of the hierarchical tree and descending to a set of nodes within the tree. For descent, omeClust compares a node’s binary-silhouette score with its two direct children. This procedure is repeated until termination, i.e. when the selected nodes represent single features in their respective data trees or the current nodes’ binary-silhouette score is larger than its children. All tips under a node in the hierarchy are considered a cluster if the node has a greater score than its children. Philosophically, omeClust’s approach is similar to a static tree cut (e.g. the cutree function in R) that creates groups from hierarchical clustering using an arbitrary cut threshold and returns groups in branches under the cut level (Langfelder et al., 2008). However, omeClust’s approach differs fundamentally from cutree in that omeClust finds the cut levels adaptively at various distance levels, whereas cutree cuts all the hierarchy at an arbitrary and constant level provided by the user.

3 OmeClust increases community detection power in omics data

When applied to datasets with no clear cluster structure, omeClust reports singleton clusters, as expected, ruling out the possibility of...
data artifacts and false positive findings (results not shown). To determine *omeClust*’s ability to recapitulate true positive clusters, we further validated *omeClust* on datasets with known cluster structure (detailed in Section 3.1). Since *omeClust* coherently looks at multiple resolution levels of the underlying hierarchical structure, it is expected to discover clusters (communities) above and beyond those detectable only by computing average distances between clusters. This is particularly relevant for omics data, where large groups of molecular features (e.g. expression values for genes in a metabolic pathway) form communities with variable mean distances between members and it is desirable to incorporate the entire resolution spectrum of the intra-cluster distances into the clustering algorithm.

### 3.1 Synthetic data validation of *omeClust*

To evaluate *omeClust*, we tested our algorithm along with existing state-of-the-art approaches (You and You, 2018) in a variety of synthetic datasets containing built-in known communities (‘ground truth’) and evaluated their statistical and computational performance across a range of parameters. For generating synthetic clusters with ‘ground truth’ membership information, we used *clusterlab* (John et al., 2020), which is a recent method that allows simulation of Gaussian clusters (Maagis et al., 2009) with controlled spacing, size and variance among the generated clusters. Specifically, we generated 135 synthetic datasets of varying capacity across a range of pairwise combinations of cluster size (4, 6, 8) and per-cluster sample size (10, 20, 40), while also varying the feature dimensions (500, 1000, 1500) and inter-cluster distances (0.05, 0.10, 0.25, 0.5, 1).

We found that *omeClust* vastly outperforms popular community detection methods, such as the Louvain approach (Blondel et al., 2008) and Infomap (Bohlin et al., 2014) in terms of (i) the adjusted Rand index (Fig. 2a), (ii) Jaccard index (Fig. 2b), (iii) Fowlkes–Mallows index (Fig. 2c) and (iv) F1 score (Fig. 2d). While these network community detection approaches tend to perform well in readily distinguishable communities, they suffer in the presence of inherent multicollinearity, noise and overlap as typically observed in omics samples and can in turn give rise to misleading communities (Supplementary Fig. S1). In addition to superseding these more sophisticated methods and improving community detection, *omeClust* further exhibited improved performance as compared to several other state-of-the-art domain-agnostic clustering algorithms, such as the partitioning (e.g. Sincell et al., 2015), pcaReduce (Zurauskiene and Yau, 2016) and Seurat (Satija et al., 2015), network-based (e.g. Infomap (Bohlin et al., 2014) and Louvain (Blondel et al., 2008; Csardi et al., 2006), model-based (e.g. Hcmodel (Fraley et al., 2014), density-based (e.g. DBSCAN (Liu et al., 2007), subspace-based (e.g. Hddc (Bouveyron et al., 2007; Bergé et al., 2013)) and shared nearest neighbor-based (e.g. sNNClust (Ertöz et al., 2003) and ssCllust (Ren et al., 2019)) community detection methods [Supplementary Tables S1 and S2 and Fig. 2a–d]). The superior performance of *omeClust* remained consistent across a range of feature dimensions, inter-cluster distances and linkage methods, which further highlights the flexibility and robustness of *omeClust* in realistically unbalanced community structures. Taken together, these findings confirm that by taking into account the overall high-level structure of diverse features, in addition to feature-wise distances, which alone may not be sufficient to reproducibly recover biologically complex communities, *omeClust* is able to capture biologically relevant communities, missed by other methods, across a broad range of realistically complex scenarios.

### 3.2 Empirical validation and application of *omeClust*

#### 3.2.1 Niche association of human microbial species and strains

We first applied *omeClust* to 2484 metagenomes from the expanded human microbiome project (HMP1-II) (Lloyd-Price et al., 2017). In this application, the ‘features’ included the microbial species inferred from the metagenomic data (Franzosa et al., 2018) as well as clinical metadata for each sample (including body area of the collection site). *omeClust* identified body area as the most influential metadata ($\text{NMI}=0.83$) responsible for the clustering structure (Fig. 3a). *omeClust* also reports four major clusters (resolution score >0.5) each corresponding to a human body site from which samples were collected, confirming the composition structure of microbial species and their niche associations. Two metadata, RANDSID (random ID for patients) and SNPRTN (specimen barcode ID), had the lowest frequency-based enrichment scores (<0.05), as expected. The overlaps of color and shape explain how well our computational approach defines the underlying clustering structure, providing actionable interpretations of the detected clusters or communities. Several ordination plots, such as principal coordinates analysis, $t$-distributed stochastic neighbor embedding and multidimensional scaling were used to visualize the results. We also combined HMP1-II samples with the iHMP (Lloyd-Price et al., 2019) shotgun metagenomic data on the human stool samples, and profiled additional 1149 microbial strains that passed the strain conditions (Truong et al., 2017). *omeClust* detected three communities of Haemophilus parainfluenzae with body site being the most influential metadata, also confirmed with an independent PERMANOVA analysis (Anderson, 2017) using the adonis R function in the vegan package ($P$-value = 0.001 with 999 permutations). These communities largely correspond to two body sites, supragingival plaque (two communities) and tongue dorsum (one community) with NMI of 0.49 (Fig. 3b). Our novel findings thus suggest that microbial species can have more than one strain in each sample. We detected similar patterns for oral microbial species, including *Actinomyces johnsonii* (Fig. 3c), *Rothia mucilaginosa*, *Campylobacter showae* and *Porphyromonas sp* oral taxon 279, and stool microbial species including *Escherichia coli* and *Escherichia coli* that showed evidence of multiple subclades of strains consistent with the literature (Supplementary Fig. S3).
3.2.2 Cross-tissue analysis of gene and protein expression in cell lines

Cell line gene expression has been extensively used to investigate intracellular activities in diseases, such as cancer (Ghandi et al., 2019) and inflammatory bowel disease (Schulze et al., 2008). We applied omeClust to gene expression datasets from three breast cancer studies (McCall et al., 2011, 2014; Zilliox and Irizarry, 2007). In this application, the omics ‘features’ are gene expression and the clinical metadata include cell line type (i.e. kidney versus cerebellum) and spatial information (whether the sample is collected from the left or right side). Cell line gene expression serves as a strong application to validate our technique as we hypothesized these samples to be clustered according to the kind of tissue from which they originated.

omeClust, indeed, found that cells establish communities based on their drawn tissues. Using the high-resolution mode of omeClust, we detected nine communities from seven tissue cell lines with NMI of 0.84 (Fig. 4a). Cell lines from the kidney and cerebellum formed two communities suggesting spatial heterogeneity of these organs (e.g. whether samples have been collected from the left or right side). Although we did not have spatial resolution data to validate this information, this leads to an interesting hypothesis of spatial gene expression patterns of the left and right side of the kidney and cerebellum, which has been indicated in previous animal studies (Evans et al., 2018; Nakamura et al., 2006). This finding also highlights the versatility of omeClust’s clustering capabilities, suggesting that depending on the biological signal present in the dataset, the user may choose the appropriate resolution level. The ability to use multiple resolutions within omeClust allows users the flexibility to interpret communities at multiple vantage points (e.g. specific communities associated with different sets of metadata at various resolution levels).

We also used a dataset of 154 samples with 2845 proteins from the Human Protein Atlas database (Uhlen et al., 2015) and found that samples for Cell RNA, Blood RNA and Brain RNA fall in separate communities, although, tissue RNA falls in two clusters: Blood RNA and Brain RNA (Fig. 4b), suggesting that tissue RNA has a broader transcriptomic community and could potentially have
Finally, we applied omeClust to the NICHD Fetal Growth Studies-Singletons (Grewal et al., 2018) data that included placental samples at delivery from 301 pregnant women from four race/ethnic groups including non-Hispanic white (25.6%), non-Hispanic black (23.9%), Hispanic (33.9%) and Asian/Pacific Islander (16.6%). The samples were genotyped to obtain fetal single nucleotide polymorphisms (SNPs) using HumanOmni2.5 Beadchips (Illumina Inc, San Diego, CA) with ~2 million SNPs (Delahaye et al., 2018). In this application, the SNP data are the genomic ‘features’ and the associated clinical metadata include birth weight, prenatal environment, race, education, etc. Using genetic relationship information among the SNPs as a measure of distance, we set out to detect communities with higher affinity to babies with extremely small or large weight at birth. To this end, we considered several prenatal environments (e.g. maternal age, socio-economic status and parity, among others) as well as low birth weight status (defined as birth weight <2500 g), small for gestational age defined as birth weight less than the 10th percentile for gestational age based on sex-specific birth weight references, and large-for-gestational age defined as birth weight greater than the 90th percentile for gestational age based on sex-specific birth weight references as metadata in the omeClust analysis. omeClust reported four major clusters primarily overlapping with self-identified race/ethnicity (Fig. 5a). The top three most influential metadata were maternal demographic factor (race), socio-economic status (education) and cardiometabolic factors (gestational weight gain), consistent with previous evidence for population differences in size at birth (Buck Louis et al., 2015; Tekola-Ayele et al., 2018; Tekola-Ayele et al., 2019) [Fig. 5b–c]. Specifically, the ordination plots revealed that babies born to self-identified Black mothers had disproportionately smaller weight at birth compared to other races. These findings demonstrate the ability of omeClust to cluster samples based on genetic relatedness information and integrate clinical metadata yielding results consistent with findings from published epidemiological studies.

4 Discussion
omeClust represents a newly developed method to detect clusters and communities in heterogeneous biological datasets. Its validation and applications show that omeClust is well suited for finding biologically meaningful subsets of samples or features in a diverse range of omics studies. Key to our approach is the use of the overall structure of the feature-wise relationships in a dataset that allows capturing biologically relevant communities and clusters in different resolutions of similarity. We optimized and validated omeClust using realistic synthetic datasets of known community structure, where our approach outperformed existing approaches across a range of scenarios. Notably, omeClust remains one of the best-performing methods in the scRNAseq-specific evaluation despite not being optimized for the specific application domain. omeClust can also be used for specific downstream tasks, such as discretizing omics data, dimension reduction, microbial beta-diversity analysis and subclade finding in microbial strains using nucleotide-based distances, among others. Further, our approach can be paired with existing network analysis and community detection methods. For example, omeClust can find an optimal threshold for sparse edge discovery that can be embedded in a network analysis approach, such as Infomap and Louwain to improve their performance. Further, omeClust outputs an enrichment score for each desired metadata that can be used to select the most influential features in any clustering analysis. This arguably leads to more interpretable communities that are potentially explainable by a few metadata, which can also be used as covariates in streamlined downstream discovery (e.g. differential expression and abundance analysis).

Clearly, the development of robust computational and statistical methods for accurate community detection is an ongoing effort. We, therefore, hope that future work could further fine-tune the task of feature selection and dimensionality reduction based on detected communities (e.g. feature engineering and feature extraction for deep learning). Another opportunity for future extension of our method is allowing multiple omics simultaneously especially allowing multiple time points and tissues to comprehensively detect communities in tandem. Combined, such extensions will allow researchers to use other downstream methods in parallel with omeClust, moving toward a robust, unified framework for omics-driven biomarker discovery, development and validation. We believe that the omeClust framework and the improved detection of communities represent an important step in this direction that can ultimately aid in better interpretation and understanding of similar communities as Blood RNA or Brain RNA. In addition, our results using gene expression from 196 520 genes for 1019 cell lines from the CCLE (Cancer Cell Line Encyclopedia) (Ghandi et al., 2019) show that near one major metadata explains the structure underlying the data. In particular, inferred ethnicity (Fig. 4c), histology, pathology and gender were the most influential metadata (in decreasing order) and the least enriched metadata in the communities corresponded to the ID variables (i.e. name and depMapID), as expected. This testing strategy is very similar in spirit to a stand-alone approach like PERMANOVA, where it is possible to attribute the percentage of variation in the distance matrix explained by a metadata of interest. However, unlike PERMANOVA, omeClust explicitly uses the clustering and community results to derive the enrichment scores, providing a sophisticated and biologically balanced information for further follow-up experimentation.

3.2.3 Genetic relatedness in fetal growth outcomes
Finally, we applied omeClust to the NICHD Fetal Growth Studies-Singletons (Grewal et al., 2018) data that included placental samples at delivery from 301 pregnant women from four race/ethnic groups including non-Hispanic white (25.6%), non-Hispanic black (23.9%), Hispanic (33.9%) and Asian/Pacific Islander (16.6%). The samples were genotyped to obtain fetal single nucleotide polymorphisms (SNPs) using HumanOmni2.5 Beadchips (Illumina Inc, San Diego, CA) with ~2 million SNPs (Delahaye et al., 2018). In this application, the SNP data are the genomic ‘features’ and the associated clinical metadata include birth weight, prenatal environment, race, education, etc. Using genetic relationship information among the SNPs as a measure of distance, we set out to detect communities with higher affinity to babies with extremely small or large weight at birth. To this end, we considered several prenatal environments (e.g. maternal age, socio-economic status and parity, among others) as well as low birth weight status (defined as birth weight <2500 g), small for gestational age defined as birth weight less than the 10th percentile for gestational age based on sex-specific birth weight references, and large-for-gestational age defined as birth weight greater than the 90th percentile for gestational age based on sex-specific birth weight references as metadata in the omeClust analysis. omeClust reported four major clusters primarily overlapping with self-identified race/ethnicity (Fig. 5a). The top three most influential metadata were maternal demographic factor (race), socio-economic status (education) and cardiometabolic factors (gestational weight gain), consistent with previous evidence for population differences in size at birth (Buck Louis et al., 2015; Tekola-Ayele et al., 2018; Tekola-Ayele et al., 2019) [Fig. 5b–c]. Specifically, the ordination plots revealed that babies born to self-identified Black mothers had disproportionately smaller weight at birth compared to other races. These findings demonstrate the ability of omeClust to cluster samples based on genetic relatedness information and integrate clinical metadata yielding results consistent with findings from published epidemiological studies.
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Fig. 5. OmeClust reveals communities in fetal growth study. (a) Genome-wide autosomal SNP data were measured for 301 samples from pregnant women in the NICHD Fetal Growth Studies (Grewal et al., 2018). The snp2gsGRM function implemented in SNPRelate (Zheng et al., 2012) was used to calculate the genetic relationship matrix using the correlation method for SNP genotype data between the samples. OmeClust detected four communities and, Maternal Race is the most influential metadata (NMI = 0.51) indicating differences in size of babies at birth for black mothers as compared to other races. (b) Maternal socio-economic status (education) was the second most influential metadata (NMI = 0.16) indicating differences in the socio-economic status for mothers in the black community influencing the size of babies at birth as compared to other races. (c) Maternal cardiometabolic factors (gestational weight gain) was the third most influential metadata indicating differences in cardiometabolic activities of black mothers relating to disproportionate size of babies at birth as compared to other races (NMI = 0.12).

Omics data while also encouraging further methodological advances in this area. An open-source (Python) implementation of OmeClust is freely available at http://github.com/omicsEye/omeClust along with documentation, demo datasets, real-world applications and a user forum.

Author contributions
A.R. conceived the method; A.R. implemented, packaged and provided online documents and software; S.C., A.R. and H.M. prepared synthetic data and evaluated the performance; B.S., A.R., S.C., and F.T.-A. applied the method on real-world applications. A.R., H.M. and S.C. wrote the manuscript. All authors discussed the results and commented on the article.

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