Multiple kernel learning for integrative consensus clustering of genomic datasets

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Abstract.

Summary: Diverse applications – particularly in tumour subtyping – have demonstrated the importance of integrative clustering as a means to combine information from multiple high-dimensional omics datasets. Cluster-Of-Clusters Analysis (COCA) is a popular integrative clustering method that has been widely applied in the context of tumour subtyping. However, the properties of COCA have never been systematically explored, and the robustness of this approach to the inclusion of noisy datasets, or datasets that define conflicting clustering structures, is unclear.

We rigorously benchmark COCA, and present Kernel Learning Integrative Clustering (KLIC) as an alternative strategy. KLIC frames the challenge of combining clustering structures as a multiple kernel learning problem, in which different datasets each provide a weighted contribution to the final clustering. This allows the contribution of noisy datasets to be down-weighted relative to more informative datasets. We show through extensive simulation studies that KLIC is more robust than COCA in a variety of situations.

Availability: R code to run KLIC and COCA can be found at https://github.com/acabassi/klic

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1 Introduction

Thanks to technological advances, both the availability and the diversity of omics datasets have hugely increased in recent years (Manzoni et al., 2016). These datasets provide information on multiple levels of biological systems, going from the genomic and epigenomic level, to gene and protein expression level, up to the metabolomic level, accompanied by phenotype information. Recent high-profile publications have highlighted the importance of integrating information from diverse omics datasets in order to provide novel biomedical insight. For example, numerous studies by The Cancer Genome Atlas (TCGA) consortium have demonstrated the value of combining multiple omics datasets in order to define cancer subtypes (see e.g. The Cancer Genome Atlas Research Network, 2011, 2012).

Many existing statistical and computational tools have been applied to this problem and many others have been developed specifically for this. One of the first statistical methods applied to integrative clustering for cancer subtypes was iCluster (Shen et al., 2009, 2013). iCluster finds a partitioning of the tumours into different subtypes by projecting the available datasets onto a
common latent space, maximising the correlation between data types. Another statistical method for integrative clustering is the Multiple Dataset Integration (MDI) of Kirk et al. (2012). It is based on Dirichlet-multinomial mixture models in which the allocation of observations to clusters in one dataset influences the allocation of observations in another, while allowing different datasets to have different numbers of clusters. Similarly, Bayesian Consensus Clustering (BCC) is based on a Dirichlet mixture model that assigns a different probability model to each dataset. Again, tumour samples belong to different partitions, each given by a different data type, but here they also adhere to a loosely to an overall clustering (Lock and Dunson, 2013). More recently, Gabasova et al. (2017) developed Clusternomics, a mixture model over all possible combinations of cluster assignments on the level of individual datasets that allows to model different degrees of dependence between clusters across datasets.

Integrative clustering methods can be broadly classified as either post-processing or joint modelling approaches. Instead, we consider here the so-called sequential analysis methods (Kristensen et al., 2014), that are composed of two steps: first, the clustering structure in each dataset is analysed independently; then an integration step is performed to find a common clustering structure that combines the individual ones. The advantage of these methods is that the first step, that involves a dimensionality reduction, can be performed independently for each dataset. For this reason, they are particularly suitable for high-dimensional datasets, such as those analysed in genomic applications.

In this context, the Cluster-Of-Clusters Analysis (COCA) method for integrative clustering has grown in popularity since its first introduction in The Cancer Genome Atlas Research Network, 2012. As we explain in Section 2.1, COCA proceeds by first clustering each of the datasets separately, and then building a binary matrix that encodes the cluster allocations of each observation in each dataset. This binary matrix is then used as the input to a consensus clustering algorithm (Monti et al., 2003, Willkerson and Hayes, 2010), which returns a single, global clustering structure, together with an assessment of its stability. The idea is that this global clustering structure both combines and summarises the clustering structures of the individual datasets. Despite its widespread use, to the best of our knowledge the COCA algorithm has never previously been systematically explored. We show that one key limitation is that the combination of the clustering structures from each dataset is unweighted, making the output of the algorithm sensitive to the inclusion of poor quality datasets, or datasets that define unrelated clustering structures.

An alternative class of approaches for integrating multiple 'omic datasets is provided by those based on kernel methods (see, among others, Lanckriet et al., 2004b, Lewis et al., 2006, for 'omics dataset applications). In these, a kernel function (which defines similarities between different units of observation) is associated with each dataset. These may be straightforwardly combined in order to define an overall similarity between different units of observation, which incorporates similarity information from each dataset. Determining an optimal (weighted) combination of kernels is known as multiple kernel learning (MKL); see, for example, Bach et al. (2004), Gonen and Alpaydın (2011), Lanckriet et al. (2004a), Strauß et al. (2019), Wang et al. (2017), Yu et al. (2010). A challenge associated with these approaches is how best to define the kernel function(s), for which there may be many choices.

Here we combine ideas from COCA and MKL in order to propose a new Kernel Learning Integrative Clustering (KLIC) method that addresses the limitations of COCA (Section 2.2). Key to our approach is the result that the consensus matrix returned by consensus clustering is a valid kernel matrix (Section 2.2.4). This insight allows us to make use of the full range of multiple kernel learning approaches in order to combine consensus matrices derived from different omics datasets.

Throughout, we are motivated by tumour subtyping applications. We perform extensive simulation studies to illustrate our proposed approach and compare it to COCA.
2 Methods

2.1 Cluster Of Clusters Analysis

Cluster Of Clusters Analysis (COCA; The Cancer Genome Atlas Research Network, 2012) is an integrative clustering method that was first introduced in a breast cancer study by The Cancer Genome Atlas Research Network, 2012 and quickly became a popular tool in cancer studies (see e.g. Hoadley et al., 2014 and Aure et al., 2017). It is based on Consensus Clustering (CC; Monti et al., 2003), an algorithm that was initially developed to assess the stability of the clusters obtained with any clustering algorithm.

2.1.1 Consensus clustering

We recall here the main features of CC in order to be able to explain the functioning of COCA. As originally formulated, CC is an approach for assessing the robustness of the clustering structure present in a single dataset (Monti et al., 2003, Wilkerson and Hayes, 2010). The idea behind CC is that, by resampling multiple times the items that we want to cluster and then applying the same clustering algorithm to each of the subsets of items, we assess the robustness of the clustering structure that the algorithm detects, both to perturbations of the data and (where relevant) to the stochasticity of the clustering algorithm. To do this, CC makes use of the concepts of co-clustering matrix and consensus matrix, which we recall below:

- Given a set of items $X = [x_1, \ldots, x_N]$ that we seek to cluster and a clustering $c = [c_1, \ldots, c_N]$ such that $c_i$ is the label of the cluster to which item $x_i$ has been assigned, the corresponding co-clustering matrix (or connectivity matrix) is a $N \times N$ matrix $C$ such that

$$C_{ij} = \begin{cases} 1 & \text{if } c_i = c_j, \\ 0 & \text{otherwise.} \end{cases}$$

Moreover, if $I^*$ is a subset of the indices of the observations $I = \{1, 2, \ldots, n\}$, and $X^*$ is the dataset containing only the statistical units corresponding to the indices in set $I^*$, then the co-clustering matrix has $ij$-th element

$$C^*_{ij} = \begin{cases} 1 & \text{if } i, j \in I^* \text{and } c_i = c_j, \\ 0 & \text{otherwise.} \end{cases}$$

- Let $X^{(1)}, \ldots, X^{(H)}$ be a list of perturbed datasets obtained by resampling subsets of items and/or covariates from the original dataset $X$. We denote by $C^{(h)}$ the co-clustering matrix corresponding to dataset $X^{(h)}$ where the items have been assigned to $k$ classes using a clustering algorithm. The consensus matrix $C^k$ is a $N \times N$ matrix with elements

$$C^k_{ij} = \frac{\sum_{h=1}^{H} C^{(h)}_{ij}}{\sum_{h=1}^{H} \mathbb{1}^{(h)}_{ij}}$$

where $\mathbb{1}^{(h)}_{ij} = 1$ if both items $i$ and $j$ are present in dataset $X^{(h)}$.

Thus, CC performs multiple runs of a (stochastic) clustering algorithm (e.g. $k$-means, hierarchical clustering, etc.) to assess the stability of the discovered clusters, with the consensus matrix providing a convenient summary of the CC analysis. If all the elements of the consensus matrix are close to
either one or zero, this means that every pair of items is either almost always assigned to the same cluster, or almost always assigned to different clusters. Therefore, consensus matrices with all the elements close to either zero or one indicate stable clusters. The CC procedure for a fixed number of clusters $K$ is reported in Algorithm 1.

**Algorithm 1: Consensus cluster (CC).**

**Input:** Dataset $X$, number of clusters $K$.

**Initialise:** Consensus matrix $C^K = 0_{N \times N}$.

1. for $h \in \{1, \ldots, H\}$ do
2. $X^{(h)} = \text{resample from the rows and/or columns of } X$
3. $C^{(h)} = \text{divide the items of } X^{(h)} \text{ into } k \text{ clusters}$
4. for $i, j \in \{1, \ldots, n\}$ do
5. $C^K_{ij} = C^K_{ij} + C^{(h)}_{ij} / 1_{ij}$
6. end
7. end

**Output:** Consensus matrix $C^K$.

In the framework of consensus clustering, these matrices can also be used to determine the number of clusters, by computing and comparing the consensus matrices $C^K_k$ for a range of numbers of clusters $K = \{k_{\text{min}}, \ldots, k_{\text{max}}\}$ of interest and then pick the value of $k$ that gives the consensus matrix with the greater proportion of elements close to either zero or one (Monti et al., 2003).

### 2.1.2 COCA

In contrast to consensus clustering (which we emphasise is concerned with assessing clustering stability when analysing a single dataset), the main goal of COCA is to summarise the clusterings found in different ‘omics datasets, by identifying a “global” clustering across the datasets that is intended to summarise the clustering structures identified in each of the individual datasets. In the first step, a clustering $c^m$ is produced independently for each dataset $X_m$, $m = 1, \ldots, M$, each with a different number of clusters $K_m$. We define $K = \sum_{m=1}^{M} K_m$. Then, the clusters are summarised into a Matrix Of Clusters (MOC) of size $K \times N$, with elements

$$
\text{MOC}_{n,m_k} = \begin{cases} 
1 & \text{if } c^m_n = m_k, \\
0 & \text{otherwise.}
\end{cases}
$$

where by $m_k$ we denote the $k$-th cluster in dataset $m$, $k = 1, \ldots, K_m$ and $m = 1, \ldots, M$. The MOC matrix is then used as input to CC (Algorithm 1) together with a fixed global number of clusters $\bar{K}$. The resulting consensus matrix computed with Algorithm 1 is then used as the similarity matrix for a hierarchical clustering method (or any other distance-based clustering algorithm). The procedure is summarised in Algorithm 2. The global number of clusters $\bar{K}$ is not always known. In The Cancer Genome Atlas Research Network (2012), where COCA was introduced, the global number of clusters was chosen as in Monti et al. (2003), as explained above: CC was performed with different values of $K$ and then the one that gave the “best” consensus matrices were considered. Instead, Aure et al. (2017) suggest to choose the value of $\bar{K}$ that maximises the average silhouette (Rousseeuw, 1987) of the final clustering, since this was found to give more sensible results.

Since the construction of the MOC matrix just requires the cluster allocations, COCA has the advantage of allowing clusterings derived from different sources to be combined, even if the
Algorithm 2: Cluster of clusters analysis (COCA)

Input : \( M \) datasets \( X_m \), number of clusters \( K_m \) in each dataset, global number of clusters \( \tilde{K} \).

Initialise: MOC matrix = \( 0_{K \times N} \).

1. \textbf{for} \( m \in \{1, \ldots, M\} \) \textbf{do}
2. \hspace{1em} \( C^m = \text{cluster the items in dataset } X_m \text{ into } K_m \text{ clusters} \)
3. \hspace{2em} \textbf{for} \( n \in \{1, \ldots, N\}, k \in \{1, \ldots, K_m\} \) \textbf{do}
4. \hspace{3em} set \( MOC_{n,m}^{m,k} = 1 \) if \( C^m_i = k \)
5. \hspace{2em} \textbf{end}
6. \textbf{end}

7. \textbf{for} \( h \in \{1, \ldots, H\} \) \textbf{do}
8. \hspace{1em} MOC\(^{(h)}\) = resample from the rows and/or columns of MOC \( C^{(h)} = \text{divide the items of} \)
9. \hspace{2em} MOC\(^{(h)}\) into \( \tilde{K} \) clusters
10. \hspace{2em} \textbf{for} \( i, j \in \{1, \ldots, n\} \) \textbf{do}
11. \hspace{3em} \( C^{(h)}_{ij} = C^{(h)}_{ij} / \mathbf{1}^{(h)}_{ij} \)
12. \hspace{2em} \textbf{end}
13. \textbf{end}

14. Find final clustering \( c^{\tilde{K}} \) using hierarchical clustering on \( c^{\tilde{K}} \).

Output : Cluster labels \( c^{\tilde{K}} \).

original datasets are unavailable or unwieldy. Moreover, performing CC on the MOC matrix is made straightforward by the availability of the ConsensusClusterPlus Bioconductor package for R Wilkerson and Hayes (2010).

However, the summary of each of the datasets by their clustering structure (in the MOC matrix) inevitably leads to some loss of information. Moreover, this method is unweighted, since all the clusters found in the first step have the same influence on the final clustering. Finally, the objective function that is optimised by the algorithm is unclear.

In what follows, we describe an alternative way of performing integrative clustering, that takes into account not only the clusterings in each dataset, but also the information about the similarities between items that are extracted from different types of data. Additionally, the new method allows to give weights to each source of information, according to how useful it is for recovering the final clustering.

2.2 Kernel learning integrative clustering

Before introducing the new methodology, we recall the main principles behind the methods that we use to combine similarity matrices.

2.2.1 Kernel methods

Using kernel methods, it is possible to model non-linear relationships between the data points with a low computational complexity, thanks to the so-called kernel trick. For this reason, these have been widely used to extend many traditional algorithms to the non-linear framework, such as PCA (Schölkopf et al., 1998), linear discriminant analysis (Baudat and Anouar, 2000, Mika et al., 1999, Roth and Steinhage, 2000) and ridge regression (Friedman et al., 2001, Shawe-Taylor and Cristianini, 2004).
A positive definite kernel or, more simply, a kernel δ is a symmetric map \( \delta : \mathcal{X} \times \mathcal{X} \rightarrow \mathbb{R} \) for which for all \( x_1, x_2, \ldots, x_N \in \mathcal{X} \), the matrix \( \Delta \) with entries \( \Delta_{ij} = \delta(x_i, x_j) \) is positive semi-definite. The matrix \( \Delta \) is called the kernel matrix or Gram matrix. Kernel methods proceed by embedding the observations into a higher-dimensional feature space \( \mathcal{X} \) endowed with an inner product \( \langle \cdot, \cdot \rangle_{\mathcal{X}} \) and induced norm \( \| \cdot \|_{\mathcal{X}} \), making use of a map \( \phi : \mathbb{R}^p \rightarrow \mathcal{X} \). Using Mercer’s theorem, it can be shown that for any positive semi-definite kernel function, \( \delta \), there exists a corresponding feature map, \( \phi : \mathbb{R}^p \rightarrow \mathcal{X} \) (see e.g. Vapnik, 1998). That is, for each kernel \( \delta \), there exists a feature map \( \phi \) taking value in some inner product space \( \mathcal{X} \) such that \( \delta(x, x') = \langle \phi(x), \phi(x') \rangle_{\mathcal{X}} \). In practice, it is therefore often sufficient to specify a positive semi-definite kernel matrix, \( \Delta \), in order to allow us to apply kernel methods such as those presented in the following sections. For a more detailed discussion of kernel methods, see e.g. Shawe-Taylor and Cristianini (2004).

### 2.2.2 Kernel k-means clustering

Before moving on to the kernel k-means, we first describe the original k-means clustering algorithm (Steinhaus, 1956). Let \( x_1, \ldots, x_N \) indicate the observed dataset, with \( x_n \in \mathbb{R}^p \) and \( z_{nk} \) be the corresponding cluster labels, where \( \sum_k z_{nk} = 1 \) and \( z_{nk} = 1 \) if \( x_n \) belongs to cluster \( k \), zero otherwise. We denote by \( Z \) the \( N \times K \) matrix with \( ij \)th element equal to \( z_{ij} \). The goal of the k-means algorithm is to minimise the sum of all squared distances between the data points \( x_n \) and the corresponding cluster centroid \( m_k \). The optimisation problem is

\[
\begin{align*}
\text{minimise} & \quad \sum_n \sum_k z_{nk} \| x_n - m_k \|^2_2 \\
\text{subject to} & \quad \sum_k z_{nk} = 1, \forall n, \tag{1a} \\
& \quad N_k = \sum_n z_{nk}, \forall k; \tag{1b} \\
& \quad m_k = \frac{1}{N_k} \sum_n z_{nk} x_n, \forall k. \tag{1c}
\end{align*}
\]

Now we can show how the kernel trick works in the case of the k-means clustering algorithm (Girolami, 2002). Redefining the objective function of Equation (1a) based on the distances between observations and cluster centres in the feature space \( \mathcal{X} \), the optimisation problem becomes:

\[
\begin{align*}
\text{minimise} & \quad \sum_n \sum_k z_{nk} \| \phi(x_n) - \tilde{m}_k \|^2_\mathcal{X} \\
\text{subject to} & \quad \sum_k z_{nk} = 1, \forall n, \tag{2a} \\
& \quad N_k = \sum_n z_{nk}, \forall k, \tag{2b} \\
& \quad \tilde{m}_k = \frac{1}{N_k} \sum_n z_{nk} \phi(x_n), \forall k. \tag{2c}
\end{align*}
\]

where we indicated by \( \tilde{m}_k \) the cluster centroids in the feature space \( \mathcal{X} \). Using this kernel, each term of the sum in Equation (2a) can be written as a function of \( \delta(x_i, x_j) \). Therefore, there is no need to evaluate the map \( \phi \) at every point \( x_i \) to compute the objective function of Equation (2a). Instead, one just needs to know the values of the kernel evaluated at each pair of data points \( \delta(x_i, x_j) \), \( i, j = 1, \ldots, N \). This is what is commonly referred to as the kernel trick.

Defining \( L \) as the \( K \times K \) diagonal matrix with \( k \)th diagonal element equal to \( N_k^{-1} \) and \( \Delta \) the \( N \times N \) matrix with \( ij \)th entry equal to \( \delta(x_i, x_j) \), the optimisation problem (2) can be rewritten as
a trace maximisation problem (Gonen and Margolin, 2014):

\[
\begin{align*}
\text{maximise} & \quad \text{tr}(L_z^T Z' \Delta Z L_z^T) \\
\text{subject to} & \quad Z 1_k = 1_n, \quad \forall n, k.
\end{align*}
\]

(3a)

The integrality constraints make this problem difficult to solve. However, the corresponding linear problem obtained by relaxing the integer constraints of Equation (3c) to \(0 \leq z_{nk} \leq 1\) for all \(n, k\) can be solved by performing kernel PCA on the kernel matrix \(\Delta\) and setting \(H\) to the \(K\) eigenvectors that correspond to \(K\) largest eigenvalues (Schölkopf et al., 1998). The clustering solution can be found by first normalising all rows of \(H\) to be on the unit sphere and then performing \(k\)-means clustering on the normalised matrix. Other possible approaches to derive a final clustering from \(H\) are listed in Shawe-Taylor and Cristianini (2004).

2.2.3 Multiple kernel \(k\)-means clustering

Gonen and Margolin (2014) extended the kernel \(k\)-means approach to the case of multiple kernels. We consider multiple datasets \(X_1, \ldots, X_M\) each with a different mapping function \(\phi_m : \mathbb{R}^P \rightarrow \mathbb{X}_m\) and corresponding kernel \(\delta_m(x_i, x_j) = \langle \phi_m(x_i), \phi_m(x_j) \rangle_{\mathbb{X}_m}\) and kernel matrix \(\Delta_m\). Then, if we define \(\phi_\theta(x_i) = [\theta_1 \phi_1(x_i), \theta_2 \phi_2(x_i), \ldots, \theta_M \phi_M(x_i)]',\) where \(\theta \in \mathbb{R}^*_M\) is a vector of kernel weights such that \(\sum_m \theta_m = 1\) and \(\theta_m \geq 0\), the kernel function of this multiple feature problem is a convex sum of the single kernels:

\[
\delta_\theta(x_i, x_j) = \langle \phi_\theta(x_i), \phi_\theta(x_j) \rangle_{\mathbb{X}_m}
\]

(4)

\[
= \sum_{m=1}^M \langle \theta_m \phi_m(x_i), \theta_m \phi_m(x_j) \rangle_{\mathbb{X}_m}
\]

(5)

\[
= \sum_{m=1}^M \theta_m^2 \delta_m(x_i, x_j).
\]

(6)

We denote the corresponding kernel matrix by \(\Delta_\theta\). The optimisation problem now is

\[
\begin{align*}
\text{maximise} & \quad \text{tr}(H' \Delta_\theta H) - \text{tr}(\Delta_\theta) \\
\text{subject to} & \quad H' H = 1_k, \quad \theta' 1_M = 1, \quad \Delta_\theta = \sum_m \theta_m^2 \Delta_m.
\end{align*}
\]

(7a)

(7b)

(7c)

(7d)

The optimisation strategy proposed by Gonen and Margolin (2014) is based on the idea that, for some fixed vector of weights \(\theta\), the problem is equivalent to the one of Equation (2a), where we had only one kernel. Therefore, they develop a two-step optimisation strategy: (1) given a fixed vector of weights \(\theta\), solve the optimisation problem as in the case of one kernel (Equation 3), with kernel matrix \(\delta_\theta\) and then (2) minimise the objective function with respect to the kernel weights, keeping the assignment variables fixed. This is a convex quadratic programming (QP) problem that can be solved with any standard QP solver up to a moderate number of kernels \(M\). They also generalise this approach to a \textit{localised} multiple kernel \(k\)-means, by assigning sample-specific weights, in order to remove sample-specific noise. This is achieved by defining a matrix of weights \(\Theta\), where
each row corresponds to an observation and each column to one of the datasets. We indicate by \( \theta_{im} \) the weight of observation \( x_i \) in dataset \( m \) and by \( \theta_m = [\theta_{1m}, \ldots, \theta_{Nm}] \) the vector of weights of dataset \( m \). The mapping function is then \( \phi_{\Theta}(x_i) = [\theta_{i1}\phi_1(x_i)', \theta_{i2}\phi_2(x_i)', \ldots, \theta_{iM}\phi_M(x_i)'] \), and the corresponding kernel matrix is

\[
\delta_{\Theta}(x_i, x_j) = \langle \phi_{\Theta}(x_i), \phi_{\Theta}(x_j) \rangle_{\chi_m} = \sum_{m=1}^{M} \theta_{im}\theta_{jm} \langle \phi_m(x_i), \phi_m(x_j) \rangle_{\chi_m} = \sum_{m=1}^{M} \theta_{im}\theta_{jm} \delta_m(x_i, x_j). \tag{8}
\]

Denoting the corresponding kernel matrix by \( K_{\Theta} \), the optimisation problem in this case is analogous to the previous one:

\[
\begin{align*}
\max_{H, \Theta} & \quad \text{tr}(H'\Delta_{\Theta}H) - \text{tr}(\Delta_{\Theta}) \\
\text{subject to} & \quad H'H = 1_k, \\
 & \quad \Theta'1_M = 1, \\
 & \quad \Delta_{\Theta} = \sum_{m=1}^{M} (\theta_m\theta_m') \circ \Delta_m,
\end{align*}
\tag{11a}
\]

where \( \circ \) is the Hadamard product. Again, one can optimise the objective function of Equation (11a) with a two-step procedure, that iteratively (1) solves a standard kernel \( k \)-means problem with kernel \( \delta_{\Theta} \), keeping the weight matrix \( \Theta \) fixed and then (2) optimises the objective function with respect to \( \Theta \). Again, the first step reduces to solving one optimisation problem with a single kernel (Equations 3) and in the second step one just needs to solve a QP problem.

### 2.2.4 Identifying consensus matrices as kernels

We prove that the consensus matrices defined in Section 2.1 are positive semidefinite, and hence that they can be used as input for any kernel-based clustering method, including the integrative clustering method presented in the next section. Given any \( N \times N \) co-clustering matrix \( C \), we can reorder the rows and columns to obtain a block-diagonal matrix:

\[
C = \begin{bmatrix}
J_1 & 0 & 0 & \ldots & 0 \\
0 & J_2 & 0 & \ldots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
0 & 0 & 0 & \ldots & J_K
\end{bmatrix}
\tag{12}
\]

where \( K \) is the total number of clusters and \( J_k \) is an \( n_k \times n_k \) matrix of ones, with \( n_k \) being the number of items in cluster \( k \). It is straightforward to show that the eigenvalues of a block diagonal matrix are simply the eigenvalues of its blocks. Since each block is a matrix of ones, the eigenvalues of each block are nonnegative, and so any co-clustering matrix \( C \) is positive semidefinite. Moreover, given any set of \( \lambda_m \), \( m = 1, \ldots, M \) nonnegative, and co-clustering matrices \( C_m \), \( m = 1, \ldots, M \), then \( \sum_{m=1}^{M} \lambda_m C_m \) is positive semidefinite, because if \( \lambda \) is a nonnegative scalar, and \( C \) is positive semidefinite, then \( \lambda C \) is also positive semidefinite and the sum of positive semidefinite matrices is a positive semidefinite matrix. Since every consensus matrix is of the form \( \sum_{m} \lambda_mC_m \), we can conclude that any consensus matrix is positive semidefinite.
2.2.5 Kernel Learning Integrative Clustering

We recall from Section 2.2.1 that any positive semidefinite matrix defines a feature map \( \phi : \mathbb{R}^p \rightarrow X \) and is therefore a valid kernel matrix. The integrative clustering method that we introduce here is based on the idea that we can identify the consensus matrices produced by Algorithm 1 as kernels. That is, one can perform consensus clustering on each dataset to produce a consensus matrix \( C_m \) for each \( m \in \{1, \ldots, M\} \). This is a kernel \( \Delta_m \), where each element \( \Delta_{ij} \) corresponds to the similarity between items \( i \) and \( j \). Therefore, these matrices \( \Delta_m \) can be combined through the (localised) multiple kernel k-means algorithm described in Section 2.2.3. This allows to obtain a weight for each kernel and a global clustering \( c \) of the items (Algorithm 3). Note that this algorithm works even with more than one similarity matrix per dataset, and also with similarity matrices that are computed using other measures of the similarity between items.

**Algorithm 3: KLIC: Kernel Learning Integrative Clustering**

\[ \text{Input : } M \text{ datasets } X_m, \text{ maximum number of clusters } K. \]
\[ \text{Initialise: Consensus matrices } C_k = 0, k = 2, \ldots, K. \]
1. for \( m \in \{1, \ldots, M\} \) do
2. \hspace{1em} \Delta_m = compute kernel for \( X_m \)
3. end
4. for \( k \in \{1, \ldots, K\} \) do
5. \hspace{1em} \([w_k, c_k] = \text{apply multiple kernel k-means to } \Delta_1, \ldots, \Delta_M\)
6. \hspace{1em} s_k = \text{calculate average silhouette of } c_k
7. end
8. Choose \( k \) such that \( s_k \geq s_j, \forall j \neq k \).
9. return \( k, w_k, c_k \).

\[ \text{Output : Best number of clusters } k, \text{ set of kernel weights } w = [w_1, \ldots, w_M], \text{ cluster labels } c = [c_1, \ldots, c_N] \]

3 Examples

3.1 Simulated data

To assess the KLIC algorithm described in Section 2.2.5 and to compare it to COCA, we perform a range of simulation studies. We generate several synthetic datasets, each composed of data belonging to either three or six different clusters of equal size. Each dataset has total number of observations equal to 300. Each observation \( x_n^{(k)} \) is generated from a bivariate normal with mean \( ks \) for each variable, where \( k \) denotes the cluster to which the observation belongs and \( s \) the separation level of the dataset. Higher values of \( s \) give clearer clustering structures. The variance covariance matrix is the unitary matrix. We consider the following settings:

1. **Similar datasets.** We generate five datasets that have the same clustering structure and cluster separability \( s \). We denote the datasets by A, B, C, D, E. The goal of this experiment is to show that using localised kernel k-means on multiple consensus matrices leads to better results than those obtained using just one consensus matrix.

2. **Datasets with different levels of noise.** In this case we utilise four datasets that have the same clustering structure, but different levels of cluster separability \( s \). We denote the datasets by 0 for “no cluster separability”, 1 “low cluster separability”, 2 “medium cluster separability”,
Figure 1. Consensus matrices of the synthetic data. Blue indicates high similarity and orange low similarity. The colours of the sidebar on the left of each matrix indicate the cluster labels. In the first row are shown the consensus matrices of datasets with different levels of noise, going from dataset 0 on the left (“no cluster separability”) to cluster 3 on the right (“high cluster separability”). In the second row are shown the consensus matrices of two datasets with nested clusters: the one on the left has six clusters, whereas the one on the right has three clusters formed by merging two of the clusters of the dataset with six clusters.
and 3 “high cluster separability” (Figure 1, first row). We use this example to show how the weights are allocated to each consensus matrix and why it is important to assign lower weights to datasets that are noisy or not relevant.

3. Datasets with nested clusters. We also investigate how the algorithm copes with the ambiguous situation of nested clusters. To this end, we generate two datasets with similar cluster separability. The first one has six clusters, while the second one only has three clusters, each of them containing two of the clusters of the other dataset (Figure 1, second row).

We repeat each experiment 100 times. For each synthetic dataset, we use consensus clustering (Algorithm 1) to obtain the consensus matrices. For the number of clusters $K$ we use the true number of clusters (either three or six, depending on the dataset) for simplicity. As for the clustering algorithm, we use $k$-means clustering with Euclidean distance, which we found to work well in practice.

4 Results

4.1 Simulated data

In Section 4.1.1 we apply the developed methods to the synthetic datasets. In Section 4.1.2 we compare the performances of our method for integrative clustering to COCA.

4.1.1 KLIC

We apply KLIC (Algorithm 3) to the synthetic datasets presented in Section 3.1.

Similar datasets. First we run the kernel $k$-means algorithm on each of the consensus matrices that have the same clustering structure and noise level. To assess the quality of the clustering, we compare the clustering found with the true one using the adjusted Rand index (ARI; Rand, 1971), which is equal to one if they are equal and is equal to zero if we observe as many similarities between the two partitions of the data as it is expected by chance. Then we use Algorithm 3 to run unsupervised KLIC on multiple datasets. In particular, on the left side of Figure 2 are reported the box plots of the ARI obtained combining the four datasets together using KLIC (column “A+B+C+D”). On the right side of Figure 2 are reported the box plots of the average weights assigned by the KLIC algorithm to the observations in each dataset. We observe that as expected, combining together more datasets helps recovering the clustering structure better than just taking the matrices one at a time. This is because localised kernel $k$-means allows to give different weights to each observation. Therefore, if data point $n$ is hard to classify in dataset $d_1$, but not in dataset $d_2$, we will have $\theta_{nd_1} < \theta_{nd_2}$. However, on average the weights are divided equally between the datasets. This reflects the fact that all datasets have the same dispersion and, as a consequence, they contain on average the same amount of information about the clustering structure.

Datasets with different levels of noise. Here we use the datasets shown in the first row of Figure 1, that have the same clustering structure (six clusters of the same size each) but different levels of cluster separability. We consider four different settings, each time combining three out of the four synthetic datasets. Figure 3 shows the box plots of the ARI obtained using kernel $k$-means on the datasets taken one at a time (columns “0”, “1”, “2”, “3”) and the ARI obtained using unsupervised KLIC on each subset of datasets (columns “0+1+2”, “0+1+3”, “0+2+3”, “1+2+3”). As expected, the consensus matrices with clearer clustering structure give higher values of the ARI.
Figure 2. Results of applying KLIC to four similar datasets. On the left is the ARI of KLIC applied to each dataset separately (columns “A”, “B”, “C”, and “D”) and to all four datasets together (column “A+B+C+D”). The ARI is higher in the last column because KLIC can combine information from all the datasets to find a global clustering. On the right are the kernel weights associated to each dataset, when applying KLIC to all four datasets together. The algorithm is able to recognise that each dataset contains the same amount of information regarding the global clustering, and therefore assigns on average the same weight to each dataset.

on average. Moreover, the ARI obtained combining three matrices with different levels of cluster separability is on average the same or higher as in the case when only the “best” matrix is considered. This is because larger weights are assigned to the datasets that have clearer clustering structure. In the bottom part of Figure 3 are reported the box plots of the average weights given by the localised multiple kernel $k$-means to the observations in each dataset. It is easy to see that each time the matrix with best cluster separability has higher weights than the other two.

Datasets with nested clusters. We now use the matrices with different numbers of clusters. Since the algorithm works only with a fixed number of clusters, we try both with $k = 3$ and $k = 6$. The ARI and the average weights assigned to each matrix are reported in Figure 4. We observe that both with $k = 3$ and $k = 6$ the algorithm is able to find the “true” clustering structure. However, the weights assigned to each matrix are not as we expected: the matrix with three cluster is always weighted more highly than the other one. To investigate this phenomenon, we introduce an additional way to score how strong the signal is in each dataset. We use the cophenetic correlation coefficient, a measure of how faithfully hierarchical clustering would preserve the pairwise distances between the original data points. Given a dataset $X = [x_1, x_2, \ldots, x_N]$ and a similarity matrix $\Delta \in \mathbb{R}^{N \times N}$, we define the dendrogrammatic distance between $x_i$ and $x_j$ as the height of dendrogram at which these two points are first joined together by hierarchical clustering and we denote it by $\eta_{ij}$. The cophenetic correlation coefficient $\rho$ is calculated as

$$\rho = \frac{\sum_{i<j} (\Delta_{ij} - \bar{\Delta})(\eta_{ij} - \bar{\eta})}{\sqrt{\sum_{i<j} (\Delta_{ij} - \bar{\Delta})^2 \sum_{i<j} (\eta_{ij} - \bar{\eta})^2}},$$

where $\bar{\Delta}$ and $\bar{\eta}$ are the average values of $\Delta_{ij}$ and $\eta_{ij}$ respectively. When we calculate the cophenetic correlation coefficient for each dataset, we find that the consensus matrices with $k = 3$ have higher cophenetic correlation than the ones with $k = 6$. This explains why higher weights are assigned to the former. Indeed, if we generate datasets with $k = 6$ and higher cophenetic correlation, higher
Figure 3. Results of applying KLIC to datasets with different levels of noise (“0” indicates the dataset that has no cluster separability, “1” the dataset with low cluster separability, and so on). On the left is the ARI of KLIC applied to each dataset separately (columns “0”, “1”, “2”, and “3”) and to subsets of three of those datasets (columns “0+1+2”, “0+1+3”, “0+2+3”, and “1+2+3”). On the right are kernel weights associated to each dataset in each of the experiments with multiple datasets, ordered by cluster separability. For example, the first subset is “0+1+2” so the weights marked as “1st” are those assigned to dataset “0”, “2nd” are those assigned to “1” and so on. For each subset of datasets the weights of the noisier datasets (“1st” and “2nd”) are lower than those of the “best” dataset in the subset (“3rd”). This is reflected in an increased ARI in each subset, compared to applying KLIC to those datasets separately.

weights are assigned to those by the algorithm. This means that in general higher weights are given to the datasets that have higher cophenetic correlation.

4.1.2 Comparison between unsupervised KLIC and COCA

We compare the performance of the unsupervised version of KLIC (Algorithm 3) to the one obtained using COCA (Algorithm 2). We use the same synthetic datasets as in the previous section.

For COCA, we use the $k$-means algorithm with Euclidean distance, fixing the number of clusters to be equal to the true one, to find the clustering labels of each dataset. Many other clustering algorithms can be used, but this is the one that gives the best results among the most common ones (hierarchical clustering, $k$-means and partitioning around medoids; see Supplementary Material). We use consensus clustering (Algorithm 1) to find the global clustering. We build the consensus matrices using 1000 resamplings of the data, each time with 80% of the observations and all the features. The final clustering is done using hierarchical clustering with average linkage on the consensus matrix.

Similar datasets. First we compare the algorithm for KLIC and COCA when combining five datasets that have the same clustering structure and cluster separability. In Figure 5 is shown the ARI of the two methods applied to 100 sets of data of this type. The ARI of COCA and KLIC are comparable. This shows that both methods work well in the case of multiple datasets that have the same clustering structure and level of noise.
Datasets with different levels of noise. We also compare the behaviour of KLIC and COCA in the presence of multiple datasets with the same clustering structure, but different levels of cluster separability $s$. The ARI is shown in the second row of Figure 5. We observe that in each of the four simulation settings, KLIC reaches on average higher ARI scores. The reason for this is that COCA is not a weighted method, so its ability to recover the true clustering structure is decreased by adding noisy datasets. Instead, we have shown in the previous section that KLIC allows to give lower weights to the noisiest datasets, achieving better performances.
5 Discussion

In the first part of this work we have given the algorithm for COCA, a widely used method in integrative clustering of genomic data, highlighting the main issues of using this method. We have also presented KLIC, a novel approach to integrative clustering, that allows to combine multiple datasets to find a global clustering of the data and is well-suited for the analysis of large datasets, such as those often encountered in genomics applications. The advantage of using KLIC instead of COCA is that KLIC is able to incorporate more detailed information about the data from each dataset into the final clustering. In fact, while COCA performs a combination of the clusters found in each dataset, KLIC uses the similarities between data points observed in each dataset to perform the integrative step. Moreover, it is not clear how much each dataset influences the final clustering in COCA, whereas the output of KLIC includes a list of weights, one for each dataset. We have shown through simulation studies that, using KLIC, it is possible combine datasets having different levels of noise, assigning higher weights to the most informative ones.
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