Bayesian Bi-clustering Methods with Applications in Computational Biology

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Abstract

Bi-clustering is a useful approach in analyzing biology data when observations come from heterogeneous groups and have a large number of features. We outline a general Bayesian approach in tackling bi-clustering problems in high dimensions, and propose three Bayesian bi-clustering models on categorical data, which increase in complexities in terms of modeling the distributions of features across bi-clusters. Our proposed methods apply to a wide range of scenarios: from situations where data are distinguished only among a small subset of features but masked by a large amount of noise, to situations where different groups of data are identified by different sets of features, to situations where data exhibits hierarchical structures. Through simulation studies, we show that our methods outperform existing (bi-)clustering methods in both identifying clusters and recovering feature distributional patterns across bi-clusters. We apply our methods to two genetic datasets, though the area of application of our methods is even broader. Our methods show satisfactory performance in real data analysis, and reveal cluster-level relationships.

Keywords—Bi-clustering, Clustering, Variable Selection, Categorical Data, Model Selection, High Dimensionality, Genetics

1 Introduction

Over the past few decades, the biology community has witnessed an explosion of data due to technology advances. For example, DNA microarrays enable scientists to measure the expression levels of thousands of genes at once; and with next generation technologies, the DNA or RNA of individual cells can now be sequenced. Another example is the Human Genome Project, which sequenced over three billion nucleotide base pairs that make up human DNA. Data collected in these cases are of high dimension in nature. Analyzing such data can reveal important biological functions, identify mutations that are responsible for certain types of diseases, discover human evolutionary history, etc. One useful approach is to cluster data into homogeneous groups. Traditional clustering methods, such as the hierarchical clustering-based UPGMA (Sokal, 1958) and the distance-based K-means method (MacQueen et al., 1967; Hartigan and Wong, 1979) have been successfully applied to gene expression analysis to identify groups of genes or samples that are of biological significance. However, the underlying biological mechanisms and the high dimensional nature of the data both suggest a further examination of the behavior of features while performing clustering. For example, when analyzing the gene expression data across cell types in the same tissue/organ, only a small fraction of genes may be highly expressed and show different expression levels in different cell types. To cluster cells by cell types, it is advised to find out the differentially expressed genes and cluster cells only based on the behavior of those genes. Additionally, different

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biological functions or conditions activate different sets of genes. A gene may be highly expressed for a subset of experiments, while inactive in the rest of conditions. It will be meaningful to identify samples corresponding to different biological conditions and at the same time, for each condition, identify the set of genes that are active. This motivates the idea of bi-clustering, which refers to methods that simultaneously group samples and features.

1.1 A motivating example

To see the need of bi-clustering, we generated 200 discrete random vectors of 400 dimensions from one of 4 distinct groups with equal probability. In each dimension, a sample takes value in \{1, 2, 3, 4, 5\}. The parameters for the categorical distributions in the first 9 dimensions are determined by Table 1. From dimension 10 onwards, parameters for the categorical distributions are generated from a Dirichlet distribution with parameter \((1/5, 1/5, 1/5, 1/5, 1/5)\). In essence, the 4 groups are only distinguished over the first 9 dimensions.

| Group label | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------|---|---|---|---|---|---|---|---|---|
| 1           | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 2           | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3           | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| 4           | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |

Table 1: The data generating mechanism for the first 9 dimensions in the motivating example: in each dimension, groups with entries of 0 share the same probability parameter vector. A group with an entry of 1 has its group-specific probability parameter vector.

We used the K-means method to cluster the 200 samples into 4 clusters based on the first three principal components (PCs) (Jackson, 2005). The result is summarized in Table 2. Each estimated group consists of samples from all 4 underlying groups. Scatter plots (Figure 1) under the first three principal components show that the samples from the 4 groups are not distinguishable based on the first three PCs.

| Estimated cluster label | True cluster label | 1 | 2 | 3 | 4 |
|-------------------------|--------------------|---|---|---|---|
| 1                       | 11                 | 16| 16| 10|
| 2                       | 29                 | 9 | 4 | 3 |
| 3                       | 8                  | 14| 17| 9 |
| 4                       | 9                  | 14| 12| 19|

Table 2: K-means clustering result on the motivating example with the dimension being 400.

We then reduced the dimension to 300, 200, and lastly 100 by deleting noisy columns. Even under the 100-dimension case, the K-means method is still not able to cluster any group cleanly. The clustering error rate is 45%, compared to 60% when dimension is 400. The result is shown in Table 3. As a contrast, the bi-clustering method discussed in Section 3.2 can perfectly recover all the latent groups, and almost perfectly identify the first 9 dimensions that show distinguishing features.
1.2 Literature on bi-clustering methods

The idea of bi-clustering was first introduced in Hartigan (1972). Cheng and Church (2000) pioneered the application of bi-clustering to study gene expression data. They define a bi-cluster as a submatrix of the expression data matrix (possibly transformed and normalized) that have a high similarity score, where their similarity score reflects how well the submatrix can be fitted by a two-way ANOVA model. They use a greedy algorithm to search for bi-clusters that have high scores. In Bergmann et al. (2003), bi-clusters are termed as “transcription modules” that contain co-regulated genes in a set of relevant experimental conditions. Mathematically, a transcription module contains genes whose normalized expression levels exceed a threshold under all conditions that belong to the bi-cluster. Statistical-Algorithmic Method for Bi-cluster Analysis (SAMBA) is a graph based approach proposed by Tanay et al. (2002). They define a bipartite graph whose two stable sets correspond to genes and conditions, with edges for significant expression changes. Bi-clusters correspond to bipartite subgraphs. They assign weights to vertex pairs so that significant bi-clusters have large weights. Ben-Dor et al. (2003) work with the relative ordering of gene expression values, and define bi-clusters to be order-preserving sub-matrices (OPSMs). A submatrix is order preserving if there is a permutation of its columns under which the sequence of values in every row is strictly increasing.

Another set of approaches utilizes singular value decomposition to discover bi-clusters. A rank-
k data matrix \( Y \) with dimensions \( n \) and \( p \) can be decomposed into the sum of \( k \) rank-1 matrices:
\[
Y = U \Lambda V^T = \sum_{i=1}^{k} s_i u_i v_i^T,
\]
where \( \Lambda = \text{diag}(s_1, \ldots, s_k) \), \( s_1 \geq \cdots \geq s_k > 0 \) are \( k \) singular values,
\( U = (u_1, \ldots, u_k) \) are orthonormal left singular vectors and \( V = (v_1, \ldots, v_k) \) are orthonormal right singular vectors. Asgarian and Greiner (2007) use the rank-1 matrix \( s_1 u_1 v_1^T \) to approximate \( Y \). Applying a hinge function, a bi-cluster is extracted by taking out rows and columns whose corresponding entries in \( u_1 \) and \( v_1 \) have large absolute values. Once a bi-cluster is found, the same procedure is applied to the remaining matrix \( Y - s_1 u_1 v_1^T \). Instead of using a hinge function, Lee et al. (2010) directly impose a sparsity constraint on the top singular vector and define a bi-cluster to be rows and columns that have non-zero entries in \( u_1 \) and \( v_1 \).

A useful feature of SVD is that if two columns of \( Y \) are the same, the corresponding columns in \( V^T \) must also be equal. A similar observation applies to the rows of \( Y \). This property can
be used to find bi-clusters that have constant values. Yang et al. (2007) combine this idea with hierarchical clustering to cluster left and right singular vectors. Rows and columns in the same cluster define a constant bi-cluster of the original data matrix.

The plaid model introduced by Lazzeroni and Owen (2002) treats each expression value in a bi-cluster as a sum of the main effect, the gene effect and the condition effect. If a gene-condition pair is in multiple bi-clusters, its expression value is the sum of module effects from all the bi-clusters it falls into. Bi-clusters are found by minimizing mean squared error through an iterative algorithm. Inspired by the plaid model, two Bayesian bi-clustering algorithms were developed about the same time: Gu and Liu (2008) and Caldas and Kaski (2008). The main difference between the two methods is that Gu and Liu (2008) assume that the expression value of a gene in a bi-cluster is centered around the sum of three terms: the bi-cluster-specific main effect, the gene effect, and the condition effect. Those genes that do not fall into any bi-cluster have their expression values following a normal distribution with mean 0. In contrast, in Caldas and Kaski (2008), the cluster-specific main effect term is replaced by a global main effect term that is shared by every observation regardless of whether the data point belongs to any cluster or not.

Most bi-clustering methods mentioned above tackle continuous data. Here are a few methods specifically targeting binary or categorical data. Neuwald et al. (2003) introduce a Bayesian Partition with Pattern Selection model to help cluster aligned protein sequences in a super-family to find functional distinctive protein subfamilies, as well as discover important molecular interactions. Patrikainen and Mannila (2004) formulate a bi-clustering task on binary data through a finite mixture model and term it “subspace clustering”. Postulating that the Bernoulli parameter for each feature equal either a feature-specific background value or a cluster-specific value if the feature is relevant for a bi-cluster $k$, they develop an EM-like algorithm to fit the model and use Chi-squared tests and Bayesian Information Criterion (BIC) (Schwarz et al., 1978) to select features for each bi-cluster and the total number of clusters. Hoff (2005) puts a Bayesian spin on the model of Patrikainen and Mannila (2004) by imposing a Dirichlet process mixture model. A version on continuous data is discussed in Hoff et al. (2006). Labiod and Nadif (2011) propose the SpecCo algorithm to find a pre-specified $K$ number of clusters to partition the input binary data matrix based on a generalized modularity measure.

Some non-probabilistic criterion-based algorithm for bi-clustering of categorical data have been proposed. Pensa et al. (2005) analyze the Boolean context of the data matrix. SUBCAD in Gan and Wu (2004) finds bi-clusters iteratively by optimizing a combination of “compactness” within a bi-cluster and “separation” outside bi-clusters. de França (2016) uses Locality Sensitive Hashing (LSH) to find an initial set of seed clusters and then uses the InClose (Andrews, 2011) algorithm from Formal Concept Analysis to find bi-clusters.

In this article, we use the term “bi-clustering” broadly and do not distinguish between subspace clustering and bi-clustering, thus including both unsupervised learning (aka clustering) with variable selection and clustering with cluster-specific feature selection. For example, BBC2 introduced in Section 3.2 assumes for each feature a feature-specific background distribution and a set of cluster-specific foreground distributions depending on whether the feature is selected by any cluster. Some Bayesian methods for clustering with variable selection have been developed in the early 2000s (Liu et al., 2003; Neuwald et al., 2003; Tadesse et al., 2005; Raftery and Dean, 2006). They are mostly model-based and aim to use a small subset of features to partition objects into different clusters. Each selected feature is usually assumed to follow the same distribution within a cluster but different distributions for different clusters. In contrast, when we allow for cluster-specific feature selection, the goal is to identify subsets of objects and features simultaneously. This strategy may give us more freedom in modeling features and greater interpretability along both dimensions.

In some studies, data from different sources collected under different conditions need to be integrated. In these cases, bi-clustering may be more appropriate given that certain biological functions are gene-specific and condition-specific. While in other studies, samples are more similar to each other: e.g., experiments conducted under the same condition and from the same tissue. The subset of genes that are active are likely to be the same across groups. Then, one may want to perform a variable selection to identify this subset. BBC1 to be introduced in Section 3.1 falls under clustering with variable selection.

We propose a general framework for bi-clustering problems in the Bayesian context in Section 2. Although our framework works for various data types, we present in Section 3 detailed treatments of a few special twists aiming at different tasks in biology. Specifically, three methods with
increasing complexity are introduced to tackle categorical data. The first method (BBC1) works on binary data, and performs a Bayesian clustering with variable selection. We then model a more complicated situation by allowing a feature to have cluster-specific distributions in only some of the clusters (BBC2). Compared with BBC1, BBC2 is able to identify both features that are unique to a cluster, and clusters that share certain features. We further extend BBC2 to build a hierarchy of clusters (HBBC), which is able to detect finer differences in the distributions of features among clusters compared with BBC1 and BBC2. For continuous data, we elevate the general framework and detect bi-clusters based on independent correlation matrices of the features. This enables us to integrate datasets from different sources and identify consistent patterns among datasets. Applications of the proposed methods on a few genetic and genomic datasets are presented in Section 4. We conclude in Section 5.

2 A general framework for Bayesian bi-clustering

2.1 A statistical model

Let $Y$ denotes the $n \times p$ data matrix. For consistency, we call rows of $Y$ objects, and columns features. The goal is to assign objects into clusters, and for each cluster, find a subset of features that supports the cluster assignment, i.e., features that follow cluster-specific distributions. Objects in the same cluster follow the same distribution, which is different for different clusters. The parameters of interest are: the total number of clusters $K$, the latent cluster assignment vector $C = (C_1, ..., C_n)$, and the binary feature selection matrix $S = (S_{j,k})_{j=1}^n_{k=1}$. Note that $C \in \{0, 1, \cdots, K\}^n$, where 0 represents a null group hosting objects that are not assigned to any cluster and $k > 0$ represents cluster $k$. Notation $S_{j,k} = 1$ means that feature $j$ is included in cluster $k$.

Conditioning on all the parameters, each element of $Y$ follows an assumed parametric model $F$, and we use $\theta_{j,k}$ to denote model parameters for feature $j$ under cluster $k$:

$$Y_{i,j} \mid C, S, \Theta, K \sim F[\theta_{j,c(i)}I(S_{j,c(i)} = 1) + \theta_{j,0}I(S_{j,c(i)} = 0)].$$

This model assumes that the distribution of $Y_{i,j}$ depends on its cluster assignment $C_i$ and whether feature $j$ is selected as a distinguishing feature for cluster $C_i$. Parameter vectors $\theta_{j,c}$ and $\theta_{j,0}$ represent the cluster-specific and feature-specific distributions of feature $j$, respectively. Conjugate priors for elements of $\Theta$ are particularly convenient to work with in this setting since the posterior distributions are still from the same distribution family, and the normalizing constants can be calculated explicitly. The $C_i$’s are often assumed to be independently and identically distributed (iid) as:

$$\Pr(C_i = 0 \mid K) = \gamma_0, \quad \text{and} \quad \Pr(C_i = k \mid K) = (1 - \gamma_0) / K, \quad k = 1, ..., K, \quad (1)$$

where the constant $\gamma_0$ is the prior probability of an object belonging to the null cluster, and can be set to 0 if we wish for a partition of all objects. As a binary variable, we can assume $S_{j,k}$ to be independent Bernoulli a priori:

$$S_{j,k} \mid K \sim \text{Bernoulli}(\pi_S), \quad j = 1, \ldots, p, \quad k = 1, \ldots, K. \quad (2)$$

In (2), all the $S_{j,k}$’s share the same prior distribution. This is reasonable if one does not have any prior belief that a particular subset of features are more likely to be differently distributed across clusters. If one wants to incorporate prior knowledge on feature importance, one can replace $\pi_S$ with feature specific parameters $\pi_{S_j}$, where $\pi_{S_j}$ is set larger for more importance features. The prior in (2) gives rise to all feature distribution patterns across clusters. In the special case of clustering with variable selection, only two patterns are considered for each feature $j$: $S_{j,k} = 0$ for all $k$ and $S_{j,k} = 1$ for all $k$. In this case $S$ reduces to a $p$ dimensional vector. We can assign independent Bernoulli priors to each of its element in such a case.

Similar discrete-data bi-clustering problems and models have also been studied in Neuwald et al. (2003), Guo (2013), and Wu (2017), although in more specific ways. Our general framework here can be viewed as an extension of their framework.
2.2 Posterior inference via Gibbs sampler

It is straightforward to write down the joint posterior distribution of the parameters of interest:

$$P(C, S, K \mid Y) = \frac{P(Y \mid C, S, K)P(C \mid K)P(S \mid K)P(K)}{P(Y)} \propto P(Y \mid C, S, K)P(C \mid K)P(S \mid K)P(K).$$

(3)

It is of interest to make posterior inference of these parameters, such as finding their posterior means or posterior modes. We here will mostly focus on the latter task because of the multimodality of the posterior distribution resulting from near-nonidentifiability of the clustering model. Due to high dimensionality and the complexity of the parameters and latent variables involved in the model, it is infeasible to obtain either an analytical or a guaranteed numerical optimal solution. Instead, we can apply Markov Chain Monte Carlo (MCMC) methods to draw samples from the posterior distribution to find an approximate mode of (3).

Note that the number of clusters $K$ is also unknown, and the dimension of $S$ depends on $K$. Theoretically we can use a reversible jump MCMC algorithm (Green, 1995) for posterior computation, but it is computationally expensive with poor convergence behaviors. We therefore opt for a less principled but computationally more friendly two-step approach: for a range of $K$ values, we make inference on $C$ and $S$ conditional on $K$; and then we choose the optimal $K$ according to a certain criterion, such as maximizing an approximation of $P(K \mid Y)$. In the current subsection, we focus on the inference of $C$ and $S$, and will discuss how to find the optimal $K$ in the next subsection.

Conditioning on $K$, we run a Gibbs sampler to iteratively draw elements in $C$ and $S$ conditional on the rest. By the Bayes rule, the posterior probability of selecting feature $j$ for cluster $k$ is,

$$P(\hat{S}_{j,k} = 1 \mid C, S, Y, K) = \frac{\pi_S P(Y \mid C, \hat{S}_{j,k} = 1, S_{[-j,k]}, K)}{\pi_S P(Y \mid C, \hat{S}_{j,k} = 1, S_{[-j,k]}, K) + (1 - \pi_S) P(Y \mid C, \hat{S}_{j,k} = 0, S_{[-j,k]}, K)}.$$

(4)

where $S_{[-j,k]}$ denotes the feature selection matrix with the $(j, k)$-entry omitted. When $K$ is not too large, we can also calculate $P(S_j \mid C, S_{[-j]}, Y, K)$, where $S_{[-j]}$ refers to $S$ without the $j$-th row, for all configurations of $S_j = (S_{j1}, \ldots, S_{jK})$, and sample from it. The conditional distribution of each element of $C$ is categorical with probability:

$$P(C_i = k \mid C_{[-i]}, S, Y, K) \propto P(Y \mid C_i = k, S, C_{[-i]}, K)P(C_i = k \mid K), \quad k = 0, \ldots, K.$$

(5)

where $C_{[-i]}$ denotes the latent cluster assignment vector without the $i$-th element.

We obtain the maximum a posteriori (MAP) estimate of $(C, S)$ from the MCMC samples. For any given $K$, running the Gibbs sampler $M$ times after burnin gives us $(C^1(K), S^1(K)), \ldots, (C^M(K), S^M(K))$. The MAP estimate is defined as

$$(\hat{C}(K), \hat{S}(K)) = \arg\max_{m=1,\ldots,M} P(C^m(K), S^m(K) \mid Y, K) = \arg\max_{m=1,\ldots,M} P(Y \mid C^m(K), S^m(K), K)P(C^m(K) \mid K)P(S^m(K) \mid K).$$

Besides inferring $C$ and $S$ jointly, we sometimes can integrate out $S$ and calculate the marginal likelihood with only $C$ and $K$ if $K$ is not too large. This marginalization can further improve the efficiency of the Gibbs sampler as suggested in Liu (1994). Since we assume that each feature is independent of the rest and all entries in $S$ are binary, integrating out $S$ gives us:

$$P(Y \mid C, K) = \sum_S P(Y \mid C, S, K)P(S \mid K) = \sum_{j=1}^{p} \prod_{j=1}^{p} P(Y_{i,j} \mid C, S_j, K)P(S_j \mid K) = \prod_{j=1}^{p} \sum_{S_j} P(Y_{i,j} \mid C, S_j, K)P(S_j \mid K).$$

This leads to another MAP estimate of $C$, which can also be approximated using MCMC samples:

$$\hat{C}(K) = \arg\max_{m=1,\ldots,M} P(Y \mid C^m(K), K)P(C^m(K) \mid K).$$
After obtaining $\hat{C}(K)$, we can proceed to get an estimate of $S$:

$$\hat{S}(K) = \arg\max_{m=1,\ldots,M} P(Y \mid S^m(K), \hat{C}(K), K) P(S^m(K) \mid K).$$

or get the posterior mode of $S$ by evaluating $P(Y \mid S(K), \hat{C}(K), K) P(S(K) \mid K)$ for all configurations of $S(K)$.

### 2.3 Inference of number of clusters $K$

To infer the number of clusters $K$, a natural approach is to choose $K$ that maximizes the marginal posterior distribution $P(K \mid Y)$, i.e.,

$$\hat{K} = \arg\max_K P(Y \mid K) P(K),$$

which requires the marginalization computation:

$$P(Y \mid K) = \sum_C \sum_S P(Y \mid C, S, K) P(C \mid K) P(S \mid K).$$

Equation (7) generally does not have an analytical solution. We can approximate it using Chib (1995)’s method, which will be briefly reviewed below, with its specific application to our task deferred to Section 3.2. Using $\theta_K$ to denote the set of parameters in the model, whose dimension may be related to $K$, and letting $Z$ be the latent variable (or missing data) in the model, we can write $P(Y \mid K)$ as

$$P(Y \mid K) = \frac{P(Y \mid \theta_K, K) P(\theta_K \mid K)}{P(\theta_K \mid Y, K)}.$$ (8)

where $P(\theta_K \mid K)$ is the prior density of $\theta_K$, and $P(Y \mid \theta_K, K) = \int P(Y, Z \mid \theta_K, K) dZ$. Equation (8) holds for any $\theta_K$. However, to estimate $P(\theta_K \mid Y, K)$ in the denominator accurately, it is advised to choose a $\theta_K$ with high posterior density, such as the posterior mean or mode computed from the Gibbs outputs. We denote the selected $\theta_K$ value as $\hat{\theta}_K^*$.

Suppose Gibbs sampling can be applied to sample iteratively from conditional densities: $P(\theta_K \mid Y, Z, K)$ and $P(Z \mid Y, \theta_K, K)$. Let $\{\theta_K^{(m)}, Z^{(m)}\}_{m=1}^M$ be $M$ samples drawn from the Gibbs algorithm. Then, we obtain the approximation

$$\hat{P}(\theta_K^* \mid Y, K) = \frac{1}{M} \sum_{m=1}^M P(\theta_K^* \mid Z^{(m)}, Y, K).$$ (9)

Note that the likelihood in the numerator of Equation (8) can be written as

$$P(Y \mid \theta_K, K) = \frac{P(Y, Z \mid \theta_K, K)}{P(Z \mid Y, \theta_K, K)}.$$ In many examples, such as when the missing data distribution $P(Z \mid Y, \theta_K, K)$ and the complete-data likelihood $P(Y, Z \mid \theta_K, K)$ are analytically available, the numerator of Equation (8) can be evaluated exactly at any value of $\theta_K$. Hence Equation (8) can be estimated as $\hat{P}(Y \mid K) = P(Y \mid \theta_K^*, K) P(\theta_K^* \mid K) / P(\theta_K^* \mid Y, K)$. When $P(Z \mid Y, \theta_K, K)$ is not available analytically, for example, we will need to find some way to approximate it (Chib, 1995).

### 3 Bayesian bi-clustering with various data types

There is an abundance of discrete data available in genetic and genomic studies. For example, the Human Genome Project has made available complete or partial DNA sequences and genetic variations of many individuals of different population origins. A major usage of such data is to conduct genome-wide association studies, in which researchers try to link human diseases with the simplest class of genetic variations, single nucleotide polymorphisms (SNPs). In this section we introduce three Bayesian bi-clustering methods with increasing complexity that target discrete datasets.
3.1 Bayesian clustering with variable selection on binary data

Binary data matrices arise in many applications and are also ideal prototypes for developing relevant theories. For example, in text analysis, columns correspond to words (or concepts) and rows correspond to articles. Bi-clustering can provide a complementary view to the classic analysis based on topic models (Blei et al., 2003). Such data can also be generated from single-cell RNA-seq technologies, in which a “1” means that the gene is highly expressed in the cell, and “0” otherwise. Since experimented single cells are often from the same tissue, we usually expect only a small fraction of genes to show different expressed/repressed patterns among cell sub-types. The clustering problem then becomes a bi-clustering one: identifying differently expressed genes and clustering cells based on these genes.

To make our presentation more targeted, we refer rows of $Y$ as “cells”, columns as “genes”, and selected columns as “biomarkers” in the following. Since biomarkers have cluster-specific distributions across all clusters and non-biomarkers assume feature-specific distributions, the feature selection matrix $S$ in the general framework is simplified to a $p$-dimensional vector, $S = (S_1, \ldots, S_p) \in \{0, 1\}^p$, with $S_j = 1$ indicating that gene $j$ is selected as a biomarker, and 0 otherwise. Biomarkers are assumed to have different probabilities of being in the expressed state in each cluster, while non-biomarkers share the same feature-specific background probability across all clusters. The model, termed as “BBC1”, is thus:

$$
\text{BBC1: } Y_{i,j} | C, S, \Theta, K \sim \text{Bernoulli}(\theta_{j,c_i} \mathbb{1}(S_j = 1) + \theta_{j,0} \mathbb{1}(S_j = 0)).
$$

The priors for $C_i$ and $S_j$ follow (1) and (2) and the priors for the $\theta$’s are i.i.d. Beta$(\alpha_\theta, \alpha_\theta$).

The marginal likelihood for BBC1 after integrating out $\Theta$ is,

$$
P(Y | C, S, K) = \prod_{j: S_j = 0} B(\alpha_\theta + n_{j,0}, \alpha_\theta + n_{j,0}) \prod_{j: S_j = 1}^{K} \prod_{k=1} B(\alpha_\theta + n_{j,k,1}, \alpha_\theta + n_{j,k,0})
$$

where $n_{j,0} = \sum_i \mathbb{1}(Y_{i,j} = 0), n_{j,1} = \sum_i \mathbb{1}(Y_{i,j} = 1), n_{j,k,0} = \sum_i \mathbb{1}(C_i = k, Y_{i,j} = 0), n_{j,k,1} = \sum_i \mathbb{1}(C_i = k, Y_{i,j} = 1)$ and $B(\cdot, \cdot)$ is the beta function.

Combined with the priors, we can sample $C$ and $S$ from their posterior distributions using Gibbs sampler. To accelerate the convergence of the Gibbs sampler, we can further integrate out $S$ from the likelihood above if either clustering is the major concern, or we want to get an MAP estimate of $C$ first, and conditioning on it, infer $S$:

$$
P(Y | C, K) = \sum_{S_1 \in \{0, 1\}} \cdots \sum_{S_p \in \{0, 1\}} P(Y | C, S, K)
$$

$$
= \prod_{j=1}^p \left[ (1 - \pi_S) \frac{B(\alpha_\theta + n_{j,1}, \alpha_\theta + n_{j,0})}{B(\alpha_\theta, \alpha_\theta)} + \pi_S \prod_{k=1}^K \frac{B(\alpha_\theta + n_{j,k,1}, \alpha_\theta + n_{j,k,0})}{B(\alpha_\theta, \alpha_\theta)} \right].
$$

Combining Equation (11) with the prior in (1), we have the posterior distribution for $C$, from which we can sample using Gibbs sampling. If a single optimal solution for $C$ is preferred, as it is easier to interpret and proceed to further experimental investigations, the sample MAP estimator can be used. After inferring $C$, we proceed to derive the posterior distribution of $S$:

$$
P(S_j = 1 | C, Y, K) \propto \pi_S \prod_{k=1}^K \frac{B(\alpha_\theta + n_{j,k,1}, \alpha_\theta + n_{j,k,0})}{B(\alpha_\theta, \alpha_\theta)}
$$

$$
P(S_j = 0 | C, Y, K) \propto (1 - \pi_S) \frac{B(\alpha_w + n_{j,1}, \alpha_w + n_{j,0})}{B(\alpha_w, \alpha_w)}, \quad j = 1, \ldots, p.
$$

To infer the number of sub-types, $K$, we select the number that maximizes the marginal likelihood $P(Y | K)$, which can be written as:

$$
P(Y | K) = \frac{P(Y | C, K)P(C | K)}{P(C | Y, K)}.
$$

The two terms on the numerator is readily available from (1) and Equation (11) at any realization of $C$. The denominator can be approximated by the fraction of posterior samples at a given
value. To have a good approximation to the denominator, we evaluate the term at the sample posterior mode $\mathcal{C}^\ast$.

For any $\mathcal{C}$, a permutation of the cluster indices $1, 2, \cdots, K$ generates an equivalent bi-cluster pattern. Denoting the equivalent class as $\tilde{\mathcal{C}}$, we have $P(\mathcal{C} \mid \mathbf{Y}, K) = \frac{1}{K!} P(\tilde{\mathcal{C}} \mid \mathbf{Y}, K)$. Each equivalent pattern in $\tilde{\mathcal{C}}$ is a local mode for the Gibbs sampler. As a result, our sampling result may serve as a representation not for the posterior distribution of $\mathcal{C}$ but for that of $\tilde{\mathcal{C}}$. Let $(\tilde{\mathcal{C}}^m)_{m=1}^M$ be outputs from the Gibbs sampler, and $\tilde{\mathcal{C}}^\ast$ represents the sample posterior mode and its equivalent patterns. We approximate $P(\tilde{\mathcal{C}} \mid \mathbf{Y}, K)$ at $\tilde{\mathcal{C}}^\ast$ by its frequency among the $M$ samples.

To test the method, we simulate datasets from the model in Equation (10) with $n = 200$, $p = 1,000$, and have 20 replications for each setting. We let the simulated data contain $K = 5$ clusters and assign $N_S$ features to be biomarkers, with $N_S = 10, 20, 30, \text{ and } 40$, respectively. For each simulated dataset, we randomly pick $N_S$ biomarkers and assign each sample to one of the $K$ clusters with equal probability. For a non-biomarker feature $j$, we draw $\theta_{j,0} \sim \text{Beta}(1,1)$, and for a biomarker $j$, we draw $\theta_{j,k} \sim \text{Beta}(0.2,0.2)$ for each $k$. We compare the BBC1 approach in (10) to two Latent Class Analysis with variable selection approaches in Marbac and Sedki (2017a) implemented in R package VarSelLCM (Marbac and Sedki, 2017b), which we term “VarSelLCM-BIC” and “VarSelLCM-MICL”, respectively. Given the model parameters and number of clusters, both approaches assume a mixture model. Biomarkers follow cluster-specific distributions and non-biomarkers follow feature-specific distributions in all clusters. “VarSelLCM-BIC” employees a non-Bayesian approach. It obtains the maximum likelihood estimates of model parameters using the EM algorithm (Dempster et al., 1977), and selects the best model based on BIC. “VarSelLCM-MICL” is a Bayesian approach similar to BBC1. Model selection in this case is based on maximizing $P(\mathbf{Y}, \mathcal{C} \mid S, K)$.

The results of the simulation study is shown in Table 4. The clustering error (CE) rate refers to the misclassification error rate after optimal alignment between the inferred and true cluster assignments. BBC1 outperforms VarSelLCM methods. The false positive rate and false negative rate are with respect to features. BBC1 can always find the true number of clusters, with no or very low clustering errors. Most biomarkers and non-biomarkers can be correctly classified. VarSelLCM-BIC almost always estimate the number of clusters to be 2. In many cases, the two estimated clusters have objects from all 5 underlying groups. The high false negative rates indicate that it cannot find biomarkers, and clustering are mostly based on noise. The performance for VarSelLCM-MICL increases significantly as we increase the number of biomarkers. The model for VarSelLCM-MICL is very similar to BBC1 except for some prior and hyper-parameter specifications. However, it employs a different approach to find the optimal $\mathcal{C}$ and $S$ instead of MCMC. It iteratively updates $\mathcal{C}$ and $S$ for each $K$. Conditioning on $\mathcal{C}$, $S$ is set to its posterior mode. Conditioning on $S$, it performs a number of uniform sampling from the elements of $\mathcal{C}$, and each selected $C_i$ is set to the value that maximizes $P(\mathbf{Y}, \mathcal{C} \mid S, K)$. When updating $\mathcal{C}$, without a complete sweep, some elements may seldom get updated, resulting in clustering errors even when $N_s$ is large. When $N_s$ is too small, the algorithm may get stuck in local modes and clustering are largely based on noise.
### Table 4: Simulation results to testing out the effectiveness of Bayesian bi-clustering based on BBC1 for binary data.

| Number of biomarkers | Method       | Number of Clusters | CE Rate | False Positive Rate | False Negative Rate |
|----------------------|--------------|--------------------|---------|---------------------|---------------------|
| Ns = 10              | BBC1         | 5                  | 3.48%   | 0.43%               | 12%                 |
|                      | VarSelLCM-BIC| 2                  | 72.53%  | 2.95%               | 78.5%               |
|                      | VarSelLCM-MICL | 4.6            | 59.45%  | 19.22%              | 40.5%               |
| Ns = 20              | BBC1         | 5                  | 0.025%  | 0.17%               | 2.5%                |
|                      | VarSelLCM-BIC| 2                  | 71.38%  | 2.44%               | 90.75%              |
|                      | VarSelLCM-MICL | 3.85            | 29.1%   | 2.97%               | 9%                  |
| Ns = 30              | BBC1         | 5                  | 0       | 0.14%               | 2.18%               |
|                      | VarSelLCM-BIC| 2                  | 65.33%  | 2.53%               | 95.5%               |
|                      | VarSelLCM-MICL | 4.6            | 20.08%  | 1.59%               | 2.17%               |
| Ns = 40              | BBC1         | 5                  | 0       | 0.13%               | 2.88%               |
|                      | VarSelLCM-BIC| 2                  | 64.83%  | 2.26%               | 99.88%              |
|                      | VarSelLCM-MICL | 6.15            | 8.80%   | 0.79%               | 2%                  |

#### 3.2 Bayesian bi-clustering on categorical data

The model in the previous section deals with binary data, and it assumes a feature follows either a common distribution across clusters, or cluster-specific distributions in different clusters. However, in some scenarios, a feature may follow cluster-specific distributions only in some clusters, and follow the feature-specific background distribution in other clusters. To deal with such scenarios, we introduce here the method BBC2, which is largely based on the framework detailed in Wu (2017).

Let $Y$ be a $n \times p$ matrix with entry $Y_{i,j}$ taking value in $\{1, 2, \ldots, L\}$, where $L$ is the total number of categories. The goal is to partition the $n$ objects into an unknown number, $K$, of clusters and identify a subset of features for each cluster that follow cluster-specific distributions. This problem can clearly be viewed as a special bi-clustering problem, and also as a problem of clustering with variable selection. Compared to SVD-based approaches, an attractive feature of this bi-clustering approach is that its discovered features are more directly interpretable.

Conditioning on all the model parameters, each data entry is assumed to follow a categorical distribution:

$$BBC2: \quad Y_{i,j} \mid C, S, \Theta, K = \begin{cases} \text{Categorical}(\theta_{c(i),j}) & \text{if } S_{j,c(i)} = 1 \\ \text{Categorical}(\theta_{0,j}) & \text{if } S_{j,c(i)} = 0 \end{cases}$$

(13)

The number of clusters $K$ is assumed to follow a truncated Poisson prior with parameter $\alpha$:

$$P(K) \propto \frac{\alpha^{K-1}}{(K-1)!} \exp(-\alpha), \text{ for } K = 1, 2, \ldots, n.$$  

Conditioning on $K$, $C$, and $S_{j,k}$ follows the prior distributions (1) and (2), respectively.

The binary vector $S_j$ has $2^K$ possible configurations. However, the realization $S_j = (1,1, \ldots, 1)^T$ is indistinguishable from any of the $K$ realizations of $S_j$ that have exactly one entry being 0 and the rest being 1, since feature $j$ in cluster $k$ with $S_{j,k} = 0$ follows a distribution not shared by any other cluster. Hence, the total number of configurations of $S_j$ that may lead to different likelihood values is $2^K - K$. We use the all-one vector to denote the all cluster-specific configuration and its $K$ equivalent variants. The prior for $S_j$ conditioning on $K$ is:

$$P(S_j \mid K) = \begin{cases} \sum_{k=1}^{K} \pi_S S_{j,k} (1 - \pi_S)^{K-\sum_{k=1}^{K} S_{j,k}} & \text{if } \sum_{k=1}^{K} S_{j,k} < K \\ \pi_S^K + K \pi_S^{K-1} (1 - \pi_S) & \text{if otherwise.} \end{cases}$$

The probability vectors $\theta_{k,j}, \theta_{0,j}$ in the categorical distributions in (13) are assigned Dirichlet
Similar to Section 3.1, we consider the equivalent class of features whose feature selection vectors are 

\[ \gamma = (\gamma_1, \gamma_2, \ldots, \gamma_L). \]  

Integrating out \( \Theta = \{ (\theta_{0,j})_{j=1:p}, (\theta_{k,j})_{k=1:K,j=1:p} \} \), we can write the posterior distribution as:

\[
P(C, S, K \mid Y) \propto P(K)P(C \mid K)P(S \mid K) \times \frac{1}{B(\gamma)} \prod_{j=1}^{p} \prod_{k=1}^{K} \prod_{j,k=0}^{\infty} B\left( \sum_{k:S_{j,k}=0} n_{j,k} + \gamma_j \right) \cdot \prod_{k:S_{j,k}=1} B(n_{j,k} + \gamma_j) \]  

where \( B(x_1, \ldots, x_L) = \prod_{i=1}^{L} \frac{\Gamma(x_i)}{\Gamma(\sum_i x_i)} \), and \( n_{j,k} = (n_{j,k,1}, \ldots, n_{j,k,L}) \) is the vector recording numbers of occurrences of each categorical value \( l \in \{1, \ldots, L\} \) for feature \( j \) among all objects in cluster \( k \).

As with the previous method, inference on \( C \) and \( S \) becomes more efficient if we condition on \( K \). Given \( K \), Gibbs sampler can be implemented to iteratively draw samples from the conditional posterior distributions of \( C_i \) and \( S_{j,k} \) respectively. The choice of \( K \) is based on its posterior probability \( P(K \mid Y) \propto P(K)P(Y \mid K) \). To approximate the marginal likelihood \( P(Y \mid K) \), we consider a variate of the Chib’s method by making use of the posterior distribution of \( \{C, S, K\} \) in Equation (15). Specifically, the marginal likelihood for any \( K \) can be written as:

\[
P(Y \mid K) = \frac{P(Y \mid C, S, K)P(C \mid K)P(S \mid K)}{P(C \mid Y, K)P(S \mid Y, C, K)} \]  

where the numerator and \( P(S \mid Y, C, K) \) in the denominator can be computed exactly. While \( P(C \mid Y, K) \) is intractable, it can be written as:

\[
P(C \mid Y, K) = \int P(C \mid Y, \Theta, S, K)P(\Theta, S \mid Y, K)d\Theta dS. \]  

Similar to Section 3.1, we consider the equivalent class of \( \{C, S\} \), denoted as \( \{\tilde{C}, \tilde{S}\} \). We have \( P(C \mid Y, K) = \frac{1}{M} \sum_{m=1}^{M} P(\tilde{C} \mid Y, K) \). Let \( \{\tilde{C}^m, \tilde{S}^m, \tilde{\Theta}^m\}_{m=1}^{M} \) be outputs from the Gibbs sampler. Then we approximate \( P(\tilde{C} \mid Y, K) \) at point \( C^* \) (including its equivalent representations) by:

\[
\hat{P}(\tilde{C} \mid Y, K) = \frac{1}{M} \sum_{m=1}^{M} P(C^* \mid Y, \tilde{\Theta}^m, \tilde{S}^m, K). \]  

In the following we use a simulated example to illustrate that modeling the distribution of each feature as a mixture of cluster-specific foreground distributions and feature-specific background distribution can significantly improve performance than that of a model without a background distribution.

We generated a dataset with \( n = 50 \) objects and \( p = 150 \) features. The number of clusters \( k \) is 3 and the numbers of objects in each cluster are 15, 15, and 20, respectively. For each feature, with probability 0.3, it follows a cluster-specific distribution. The parameter for each foreground distribution is independently drawn from Dir(2,1,0.5), and the parameter for each background distribution is drawn from Dir(1,1,1). We compare BBC2 with a method developed in Pritchard et al. (2000) (STRUCTURE). A main difference between STRUCTURE and BBC2 is that STRUCTURE does not assume background distributions for any feature. Each feature follows different distributions in different clusters, which implies that all features are equally important in differentiating clusters. We replicate the experiment 20 times independently. For each method, we record its average predicted number of clusters, clustering error rate, and feature selection accuracy. The feature selection accuracy is only relevant for BBC2. It is computed as the proportion of features whose feature selection vectors \( S_j \)'s are correctly estimated.

From the simulations we can see that BBC2 is able to correctly estimate the number of clusters and fully recover the latent cluster assignment vector in all 20 cases. The highest feature selection accuracy is 67.33% among the 20 experiments. STRUCTURE predicts more clusters than the true number. For example, in one case, 15 units in group 1 are put into 2 clusters of sizes 9 and 6.
Table 5: Simulation results to test the effect of having feature-background distributions in BBC2.

respectively. One unit in group 3 has been singled out. This overestimation may be caused by treating all features as differently distributed across all clusters, which brings in noise to the model.

We also simulated binary outcomes and compared BBC2 with the subspace clustering model in Hoff (2005). We will refer to the later method as “Hoff”. We run two sets of experiments: changing total number of clusters and changing total number of features. For the first experiment, we fix \( n = 200 \), \( p = 300 \) and choose \( K = 2, 4, 6 \), respectively. Given \( K \), objects are randomly sampled into each of the \( K \) clusters. \( S \) and \( \Theta \) are simulated in the same way as above. For the second experiment, we fix \( n = 200 \), \( K = 5 \) and set \( p = 200, 300, 400 \), respectively. For each feature, the probability of being selected into each cluster is 0.25 and is independent of the selection probabilities of other features. We replicate each experiment 20 times.

Both methods are robust to increasing the total number of clusters, which is equivalent to decreasing the number of objects in each cluster. In all cases, both methods correctly estimate the total number of clusters and assign each object into the correct cluster. When it comes to selecting important features for each cluster, performances differ. Results are shown in Table (6). Feature recovery accuracy is always higher for BBC2. The accuracy is always lower than 50% for Hoff. When there is only 2 clusters, BBC2 can achieve 85% accuracy. As \( K \) increases, accuracy starts to decrease. We consider a feature to be correctly recovered only if the method can find all clusters in which this feature follows cluster-specific distributions. As \( K \) increases, it is harder to correctly estimate the feature pattern in all \( K \) clusters.

| Method | Number of Clusters | CE Rate | Feature Selection Accuracy |
|--------|--------------------|---------|-----------------------------|
| BBC2   | 3                  | 0       | 59.4%                       |
| STRUCTURE | 7.8               | 20.1%   | N/A                         |

Table 6: Feature recovery accuracy for BBC2 and Hoff in simulations with different numbers of clusters \( K \).

When we increase the total number of features, performances for both methods stay unchanged. Both have no clustering error. The feature recovery rate stays at 60% for BBC2, and 35% for Hoff. BBC2 is almost twice effective in identifying feature patterns across clusters than Hoff. The stable performance is due to the fact that features are assumed to be independent of each other.

Lastly, we tested BBC2 with the motivating example in the introduction. For all 4 cases, BBC2 correctly estimates the number of clusters and assigns each object into the correct cluster. When \( p \leq 300 \), it also perfectly identifies all features that are active in each of the clusters. When \( p = 400 \), one feature that should follow its background distribution is estimated to have a cluster-specific distribution for one cluster. Other than this false positive case, all other features are correctly classified.

### 3.3 Hierarchical Bayesian bi-clustering

Philosophically, the task of "clustering" (aka *unsupervised learning*) is a very subjective matter and can result in drastically different findings if one focuses on different things, or even different levels of details. For example, given a group of people, one may cluster them into rough racial groups, e.g., Asian, Caucasian, African, etc. However, further dividing them into a finer level of racial groups (e.g., Chinese, Japanese, etc) will need some professional training. Indeed, as shown in the genetics example in Section 4, BBC2 can well separate distant populations, but tends to group
intra-continent sub-populations into the same cluster because it has a hard time re-focusing its attention to more refined details. This observation argues that a unified clustering model might not be able to simultaneously account for both large and subtle differences. A natural solution similar to human’s learning strategy as attempted first in Wu (2017) is to do clustering hierarchically (or recursively), which we term as “hierarchical Bayesian bi-clustering” (HBBC, henceforth). In HBBC, we aim to build a tree structure of data in a divisive manner. As the tree grows, each time, one leaf node is allowed to be further split into two child nodes based on BBC2. The choice of which leaf node to be split and the termination of the tree growth are governed by a Bayesian criterion.

HBBC starts with assigning all objects to one cluster - the root node - at step $t = 0$. Each subsequent step splits an existing cluster and increases the number of clusters by one until the tree stops growing. At the beginning of Step $t$, $t$ clusters have been formed with corresponding data blocks $\{Y^r\}_{r=1}^t$, a row-wise partition of the whole dataset $Y$. We assume that the data of all clusters are mutually independent conditioning on the corresponding hierarchical structure. Denote the current hierarchical structure as model $H_0$, and its “descendant” structure as $H_r$ ($r = 1, 2, \cdots, t$) if node-split takes place at cluster $r$. We assign a prior probability of $q/t$ to each $H_r$ model, and $1 - q$ to model $H_0$, where $0 < q < 1$ is a hyper-parameter. Notice that $H_0$ corresponds to the case that the tree terminates at Step $t$. As the tree grows deeper, it is harder to get split at any node a priori.

To determine whether and where the tree should get split, consider the potential bi-clustering for data block $Y^r$ at step $t$. Let $K_r$ be the number of clusters it can split into. Under $H_0$, $K_r = 1$, and under $H_r$, $K_r = 2$. The model for $Y^r$ and the priors for $K_r$ and latent parameters $C^r$ and $S^r$ all follow BBC2’s setup.

We define $w_r$ to be a step-scaled ratio of model posterior probabilities under $H_r$ and $H_0$:

$$w_r := t \cdot \frac{P(H_r \mid Y)}{P(H_0 \mid Y)} = \frac{q}{1 - q} \frac{P(Y \mid H_r)}{P(Y \mid H_0)} = \frac{q}{1 - q} \frac{\prod_{l=1}^t P(Y^l \mid H_r)}{\prod_{l=1}^t P(Y^l \mid H_0)}$$

$$= \frac{q}{1 - q} \frac{P(Y^r \mid H_r)}{P(Y^r \mid H_0)} = \frac{q}{1 - q} \frac{P(Y^r \mid K_r = 2)}{P(Y^r \mid K_r = 1)},$$

and $w_0 = t$ by default.

To calculate $w_r$, $r = 1, \cdots, t$, the only difficult part is $P(Y^r \mid K_r = 2)$, which corresponds to Equation (16). It has been dealt with in the previous subsection with a variate of the Chib’s method. $P(Y^r \mid K_r = 1)$ corresponds to the case where all data fall under the same cluster. Based on the model defined in (13) and (14), it can be easily computed as

$$P(Y^r \mid K_r = 1) = \int P(Y^r \mid \Theta, K_r = 1)P(\Theta \mid K_r = 1)d\Theta$$

$$= \prod_{j=1}^p P(Y^r_{j, \cdot} \mid \theta_j, K_r = 1)P(\theta_j \mid K_r = 1)d\theta_j = \prod_{j=1}^p \frac{B(n_{j,r} + \gamma)}{B(\gamma)}.$$

At each step, we identify the largest $w_r$, $r = 1, \cdots, t$. If the largest ratio is greater than $w_0 = t$, we split the corresponding node, and go to the next step. Otherwise, the tree stops at level $t$.

### 3.4 Bayesian bi-clustering for (continuous) data integration

Although some Gaussian-based Bayesian bi-clustering models have been developed earlier as reviewed in Section 1.2, they are relatively primitive, mostly used for analyzing “homogeneous” data types (such as gene expression data produced by the same technology from the same lab), and are not sufficiently powerful in handling complex data structures, such as those encountered in integrative genomics tasks. For example, a typical integrative genomic problem is to combine many thousands of published mRNA expression datasets (such as those in GEO and TCGA) to gain deeper biological insights and suggest new biological discoveries. As shown in Li et al. (2017), it is infeasible to impose the simple Bayesian bi-clustering structure developed in Section 2 to the combined dataset since different labs and technologies typically induce different types of error distributions and normalization issues. Instead, one can work on the gene correlation matrices resulting from different datasets, which are more uniform and comparable with each other. The “CLIC” algorithm developed in Li et al. (2017) is based on this observation, of which we here give a generalized formulation.
Let $X_1, \ldots, X_p$ denote $p$ microarray datasets, each of $N$ rows (corresponding to $N$ genes), and let $X_d$ have $l_d$ columns (corresponding to $l_d$ experimental samples). For robustness, we can screen out those datasets with $l_d < 10$. We first convert dataset $X_d$ into a transformed correlation matrix, $Y_d$, whose $(i,j)$-th entry is $Y_{d,i,j} = \frac{1}{2} \log \frac{1 + r_{d,i,j}}{1 - r_{d,i,j}}$, with $r_{d,i,j}$ being the sample correlation coefficient between gene $i$ and $j$ in $X_d$. We are interested in inferring gene co-expression modules among an input list of $n$ genes (a subset of the $N$ genes), and datasets in which these modules are active. Each co-expression module with the relevant datasets forms a bi-cluster. The genes in a module may correspond to, for example, pathways. After identifying co-expression modules, genes not in the input list can be added to these modules based on their co-expression patterns with the input genes in the datasets. Again, we let $C = (C_1, \ldots, C_n)^T$ be the vector of cluster assignment, where $C_i \in \{0 : K\}$ denotes that gene $i$ belongs to cluster $k$, with $k = 0$ indicating the null cluster. The number of clusters $K$ is unknown and estimated from the data. Each cluster $k$ is assumed to be active in only a subset of datasets. Let $S_{d,k} \in \{0, 1\}$ indicates whether dataset $d$ is selected or not for cluster $k$. For a selected dataset $d$ with $S_{d,k} = 1$, genes in cluster $k$ co-express, and their transformed sample correlations follow the same normal distribution with mean $\theta_{d,k}$ and variance $\sigma^2_{d,k}$. If dataset $d$ is not selected ($S_{d,k} = 0$) or gene $i$ and $j$ are not in the same non-null cluster, the corresponding $Y_{d,i,j}$ is normally distributed with dataset-specific mean $\theta_{d,0}$ and variance $\sigma^2_{d,0}$.

In summary,

$$\begin{align*}
[Y_{d,i,j} \mid S_{d,k} = 1, C_i = C_j = k] &\sim N(\theta_{d,k}, \sigma^2_{d,k}), \; k = 1, \ldots, K \\
[Y_{d,i,j} \mid S_{d,k} = 0 \text{ or } C_i \neq C_j \text{ or } C_i = C_j = 0] &\sim N(\theta_{d,0}, \sigma^2_{d,0}).
\end{align*}$$

For computational ease, we adopt the conjugate Normal-Invg-Gamma prior for $\theta_{d,k}$ and $\sigma^2_{d,k}$. Priors for $C$ and $S_{d,k}$ follow (1) and (2). Since the number of genes of a typical gene module is no more than a few hundreds, in most practical cases, the number of gene pairs in which both genes are within the same co-expression module is very small compared to the total number of gene pairs $N(N-1)/2$. We thus fix the dataset-specific background parameters $\theta_{d,0}$ and $\sigma^2_{d,0}$ for two random genes not in the same module at their total-sample estimates for dataset $d$, i.e.,

$$\theta_{d,0} = \frac{2}{N(N-1)} \sum_{1 \leq i < j \leq N} Y_{d,i,j}, \quad \sigma^2_{d,0} = \frac{2}{N(N-1)} \sum_{1 \leq i < j \leq N} (Y_{d,i,j} - \theta_{d,0})^2.$$

Furthermore, we can integrate out $\theta$, $\sigma$ and $S$ to obtain the marginal likelihood $P(Y \mid C, K)$ and implement a Gibbs sampler on the space of $(C, K)$ (see Appendix D for details).

In the above formulation, though bi-clusters correspond to genes-datasets combinations, the actual data we work with are matrices of the transformed gene pairwise correlation coefficients obtained from different datasets. To connect this aspect back to our general framework, we can consider formatting the $p \times n \times n$ array $Y$ into a $n(n-1)/2 \times p$ matrix $\tilde{Y}$, where each row corresponds to an input gene pair, and each column a dataset. Then, we can map the clustering of the original set of genes to the clustering of the rows of $\tilde{Y}$. Specifically, we assign a row of $\tilde{Y}$ to cluster $k \in \{1, \ldots, K\}$ if the two genes whose transformed correlation value this row represents are both in cluster $k$, otherwise the row is assigned to cluster 0. We use $G \in \{0, \ldots, K\}^{n(n-1)/2}$ to represent such an assignment, and with a slight abuse of notation, let element $G_{(i,j)}$ represent the assignment of the row with gene $i$ and $j$. Given $C$, we can write down the prior of $G$

$$[G_{(i,j)} \mid C_i, C_j] \sim \delta(k)(C_i = C_j = k) + \delta(0)(1 - \mathbb{I}(C_i = C_j = k)),$$

where $\delta(k)$ represents a Dirac mass at $k$. Now treating $\tilde{Y}$ as the input data, and $G$ as the latent cluster assignment vector for rows of $\tilde{Y}$, the rest follows Section 2.

### 4 Real-data applications of Bayesian bi-clustering

In this section we apply BBC2 and HBBC to the genetic data collected from the International HapMap Project to identify different populations, and important SNPs. Raw data are downloaded in PLINK format (Purcell et al., 2007) from the HapMap Phase III website. To obtain a set of SNPs that are not in linkage disequilibrium (i.e. mutually independent), we use PLINK to remove correlated SNPs by setting the threshold of $r^2$ as $10^{-6}$. Also, all children individuals from trios-families are dropped, resulting in unrelated individuals. The two filtering steps select 4,217 SNPs and 1,198 individuals from 11 populations based on population origin. A description of the data can be found in Appendix B.
4.1 BBC2 bi-clustering analysis of genetic data

BBC2’s clustering result is shown in Table 7. The method estimates the number of clusters to be 6. Individuals from the ASW group are split into two clusters, mixing with the other African populations. For the rest of the populations, almost all individuals from the same population are grouped together. Populations in mixed groups are close to each other geographically, i.e., from the same continent. Out of the 4217 SNPs, 96.28% show certain extent of diversity cross populations. Especially, 619 SNPs are predicted to have cluster-specific distributions in only one cluster. Table 8 summarizes the number of unique SNPs by cluster. Table 9 summarizes number of SNPs that follow cluster-specific distributions in the specified numbers of clusters. 157 SNPs follow background distributions in all clusters. Most SNPs follow cluster-specific distributions in 2 or 3 clusters. Only 13 SNPs are cluster-specific in all clusters.

When we specify the number of clusters to be 11, the true number of populations, BBC2 still outputs 6 nonempty clusters, and the cluster assignments for the 1,198 individuals are exactly the same as Table 7. We suspect that for populations in the same estimated cluster, the differences in the distributions of SNPs are not big enough for BBC2 to detect, and are far smaller than the differences in the distributions of SNPs in populations under different estimated clusters. Since weak signals does not seem to help in the clustering procedure, we randomly shuffle some columns of the data matrix, and rerun the algorithm. The shuffling percentage ranges from 10% to 90% with step size being 5%. Clustering results stay almost the same when the percentage of shuffled columns is below 75%. When the shuffled percentage is beyond 75%, clustering errors increase to about 54%. The near identical performances indicate that most SNPs carry some amount of information, and when such information is accumulated across a small set (≥ 25%) of SNPs, it is powerful to give clustering information. This supports the previous finding that over 95% of the SNPs are “important”. It also indicates the algorithm is quite robust to noise. Among the shuffled columns, the algorithm correctly estimates 90% of them to follow background distributions across all clusters, i.e., 10% false positive rate. For the majority of the shuffled cases, false positive rates are below 5%. Detailed results on shuffled data is presented in Appendix B.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 31        | 22        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 4         | 152       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 53        | 5         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 7: BBC2’s clustering result on the human genetic dataset: rows correspond to population origins and columns correspond to estimated clusters.

| Cluster Number | 1 | 2 | 3 | 4 | 5 | 6 |
|---------------|---|---|---|---|---|---|
| Number of SNPs| 111| 31| 38| 28| 119| 292|

Table 8: BBC2’s estimate on numbers of unique SNPs for each cluster for the human genetic dataset.
### Table 9: BBC2’s estimate on numbers of SNPs that have the specified numbers of cluster-specific distributions for the human genetic dataset.

| Number of Cluster-Specific Distributions | 0  | 1  | 2  | 3  | 4  | 6  |
|-----------------------------------------|----|----|----|----|----|----|
| Number of SNPs                          | 157 | 619 | 1413 | 1556 | 459 | 13 |

4.2 HBBC bi-clustering result of genetic data

In the previous subsection, individuals are reasonably well separated by continents. However, the grouping of intra-continent sub-populations into the same cluster indicates that intra-continent minor variations across sub-populations have been missed out. HBBC, with its recursive clustering algorithm, is able to resolve this.

From the modeling perspective, focusing on one node each time enables us to detect minor differences between closely related sub-populations. It can also capture the scenario that a feature may have a few background distributions, corresponding to different higher level groups, i.e., continents. The feature can have sub-population-specific distributions in certain continents, and continent-specific background distributions in the rest. From the evolutionary perspective, human population evolution may represent a hierarchical structure: populations are first separated by continents, and then within a continent, sub-populations emerge at different times. Hence, sub-populations within a continent will be genetically closer to each other, and will be on a smaller sub-tree before joining other sub-populations in other continents to form a larger (sub)-tree.

We apply HBBC with hyper-parameter $q = 0.05$, reflecting a fairly conservative prior on developing new clusters. To further alleviate excessive learning, we restrict the minimum size of any node to be 50, which correspond to around 5% of the total number of individuals.

The result is presented in Figure 2. Blue nodes represent internal nodes, orange nodes are leaves and the number inside each node is the number of individuals in the node. The tree starts with all 1,198 individuals in the root node. At the first step, the African populations are the first to get separated from the rest. Next, the Asians are separated from the American and European populations, followed by the further separation of the latter two. Eventually, the two American populations, GIH and MEX, get well separated; and JPT is separated out from the two Chinese populations. Among the African populations, MKK and a small portion of ASW are the first to be separated from the rest. YIH and another subset of ASW are placed in one cluster. LWK makes up the third major cluster for the African populations.

Compared with BBC2, the advantage of HBBC has been demonstrated in this example through its ability to distinguish Japanese from Chinese, and Luhya from Yoruba. The order of the node splitting process is likely to imply the relative genetic proximities of different populations. For example, the splitting at Step 1 indicates that the African populations are genetically most different from the rest of the populations. In terms of selected features, the number of SNPs that have different distributions between the Chinese and Japanese populations is estimated to be 348 (8.25%), while this number is 1038 (24.61%) between GIH and MEX. Thus the difference between the two east Asian populations is estimated to be smaller than the difference between the two American populations. Among the African populations, the MKK-dominate group is most different from the rest of the African populations as it is the first to be split out and is distinguished on 1165 (27.63%) SNPs, while the number is only 306 (7.26%) between the YIH-dominate group and LWK-dominate group.

The minimum node size is a user specified parameter, and requires some judgement. In the current analysis, we restrict it to be 50. We have also tested different numbers: 20, 30 and 40. The result is quite robust (see Appendix C for details). However, when we further decrease the size to 10, the tree grows deeper: there are three further splits at the MKK-dominate node, as shown in Figure 3. Also, 4 LWK individuals in the second leaf node (counted from the top of the figure) are moved to the YRI-dominate cluster, i.e., the first leaf node. Other than these differences, the tree is robust. Relaxing the minimum size requirement, the ASW population gets separated out from the MKK population at the first step on the sub-tree, though they are still mixed with 6 MKK samples. However, the next two steps further split the MKK population. The result indicates that the MKK population exhibits more heterogeneity within the population and the algorithm is able to capture such differences. However, there is the risk that such heterogeneity is only at individual
level, and may not get aggregated into population level differences. In practice, to control the aggressiveness of the algorithm, we can try to control the minimum node size, or impose a higher penalty on node splitting as the tree grows deep.

Figure 2: HBBC’s estimation result on the human genetic data, minimum node size=50. The number in each blue node is the number of individuals assigned to the node. In each orange node, i.e., a leaf node: each population name-number pair indicates for that population, the number of individuals that are assigned to this node. Reading from the left to the right of the figure gives the order of the node splitting process.

Figure 3: HBBC’s partial estimation result on the human genetic data, minimum node size=10: the sub-tree starting from the MKK-dominate node, i.e., the third leaf node (counting from the top of the figure) in Figure 2. Texts inside each node have the same meaning as in Figure 2.

4.3 Cell type clustering with single-cell RNA-seq data

We apply the BBC models described in Section 3 to the dataset in Biase et al. (2014). After binarization, the dataset contains 56 cell samples from 5 cell types: zygote, 2cell, 4cell, inner cell mass (ICM) and Trophoectoderm (TE), and 13889 genes.

The clustering result from BBC1 is shown in Table 10. The algorithm can almost perfectly cluster Zygotes, 2cells, and 4cells into three different clusters. There are some misclassifications of ICMs into TEs. The loss of accuracy may be partly due to the small sample size, and also that ICM and TE are closely related as they both belong to blastocyst. The model identifies 5,317 genes with posterior biomaker selection probability of more than 0.5. Among them, around 4,000 genes have posterior selection probabilities of more than 0.9.
| Cell Type | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Zygote    | 8         | 0         | 0         | 1         | 0         | 0         |
| 2cell     | 0         | 20        | 0         | 0         | 0         | 0         |
| 4cell     | 0         | 0         | 20        | 0         | 0         | 0         |
| ICM       | 0         | 0         | 0         | 0         | 2         | 2         |
| TE        | 0         | 0         | 0         | 0         | 0         | 3         |

Table 10: BBC1’s estimation result on the scRNA-seq data. Columns correspond to estimated clusters.

BBC2 shows a similar result to BBC1. It estimates the number of clusters to be 5, combining cluster 4 with cluster 6 in Table 10. Other than this difference, clustering result is the same as BBC1. The number of genes that have all cluster-specific distributions is estimated to be 10. Among them, 9 are estimated to be biomarkers in BBC1, and 8 of them have posterior probabilities of being a biomarker equal 1. 5685 genes are estimated to be unique to one of the 5 clusters.

Lastly, the result for HBBC is shown in Figure 4. Eight Zygotes are separated from the rest of the cell at the first step, with 5755 genes estimated to be cluster differentiating. The remaining one Zygote that is a singleton in the previous two results is initially mixed with 2cells, but eventually gets singled out. Since 2cell is the next cell stage after Zygote, the mix may because that this Zygote is at its late stage and is on its way differentiating into 2cells. 4cell, ICM and TE are on one sub-tree before joining 2cell. This may indicate that 4cells are biologically more similar to blastocyst than to 2cell, or during the experiment, the 4cells were sampled at times closer to their differentiation into blastocyst than to their parent 2cells. Comparing to BBC1 and BBC2, HBBC gives more cluster-level information. Especially, through the hierarchical structure, we gain insights into the relative closeness of different cell types.

Figure 4: HBBC’s estimation result on the scRNA-seq data. The tree node ordering and interpretation follow from the previous subsection.

### 4.4 Gene clustering analysis based on co-expression patterns

To demonstrate the Bayesian bi-clustering approach described in Section 3.4, we apply the correlation-matrix-based clustering algorithm to a list of 58 genes from two pathways: the DNA replication pathway with 22 genes, and the mitochondrial respiratory chain complex I with 36 genes. The total number of datasets involved is 1774.

Figure 5 displays the clustering result, indicating that the algorithm identifies two nontrivial gene co-expression clusters, CEM1 and CEM2. CEM1 discovered by the algorithm consists of 26 genes from the pathway for mitochondrial respiratory chain complex I (missing 10 genes) and CEM2 consists of 16 genes from the DNA replication pathway (missing 6 genes), with no genes from one pathway mistakenly assigned to the cluster of the other pathway. Those 16 genes missing from the two clusters are identified as singletons.
Figure 5: CLIC's clustering result on the input two pathways. Both rows and columns correspond to the input genes. CEM1 consists of 26 genes from one pathway and is supported by 780 datasets. CEM2 consists of 16 genes from the other pathway and is supported by 785 datasets. Genes that are in neither CEM are identified as singletons.

Genes in CEM1 are estimated to be strongly co-expressed in 780 datasets, and 785 datasets support CEM2. For datasets that support both clusters, different co-expression patterns can occur in the two clusters. As an illustration, we select one such dataset with 49 experimental samples in total, and show its gene expression patterns in Figure 6. In the first 19 samples, genes in CEM1 are all highly expressed, while all genes in CEM2 have low expression values. The pattern is reversed in the next 21 samples. In the last 19 samples, genes in CEM1 show low expression levels, while moderate expression levels are observed among genes in CEM2. The different co-expression patterns across samples in one dataset for one cluster is due to the fact that different samples correspond to different experimental conditions, for example case versus control. Analyzing the expression patterns in the two clusters across datasets tells us when the two pathways will be both activated and work together and when expressions of genes in one pathway will repress the expressions of genes in the other pathway. Examining the selected datasets also reveals information about conditions under which genes in a cluster tend to co-express. For example, among the top 10 datasets selected by CEM1, 5 of them are related to inflammatory process. Two are related to experiments studying rheumatoid arthritis and another two are related to inflammation in liver. An exhaustive analysis of selected datasets by cluster may help categorize conditions under which genes in the cluster co-express, or biological consequences the expressions of these genes can lead to.
Figure 6: Expression levels of genes in CEM1 and CEM2 over samples in one dataset that is selected by both CEMs using CLIC. The top 26 rows correspond to genes in CEM1, and the bottom 16 rows correspond to genes in CEM2. Columns correspond to 49 experimental samples in the dataset.

5 Discussion

Modern high-throughput biomedical technologies have generated massive amount of data. The huge volume of data, complicated by the heterogeneity of data and the complexity of biological systems, posts increasing challenges for discovering hidden patterns and understanding biological functions. Bi-clustering is one way to deal with such challenges by identifying and clustering objects on a subset of features. The goal of bi-clustering, when compared to clustering, is not only to cluster objects, but also to pinpoint important features and model them effectively for each cluster, which reduces the impact of noise and helps unwind hidden structures in the data.

In this paper, we have outlined a general Bayesian framework for tackling bi-clustering problems and described a few variants that target different types of data and attempt for different goals. For categorical data, we start with the basic model that clusters objects on a subset of features, which are assumed to have cluster-specific distributions in every cluster. The method can detect rare signals and has accurate clustering performance. This approach works well when data are more homogeneous, for example, cell sub-types within one tissue/organ. We then extend the model to allow for different features to be used by different bi-clusters. In this way, we are able to identify features that are differently distributed in a subset of bi-clusters, but each follows a common feature-specific distribution in the remaining bi-clusters. We then apply this general approach in a hierarchical fashion to identify bi-clusters in a step-wise manner. The conditional independence assumption enables us to treat each node independently and focus only on the node that shows most heterogeneity within it at each step. This simplifies computation and allows parallel computing. The sequence of node-splitting and the hierarchical structure show the relative heterogeneity among data and enable us to discover cluster-level relationships. As a useful and nontrivial twist of the standard bi-clustering framework, we lastly introduce a data-integration method that imposes a Bayesian bi-clustering structure on the correlation matrices derived from multiple datasets. We show that this approach can effectively extract important gene-module information by combining many publicly available gene expression datasets.

The true number of clusters in a dataset is often unknown. In our general framework, we have discussed inferring $K$ based on its marginal posterior distribution. Another way of simultaneously
inferring bi-cluster memberships and the total number of clusters is to employ a Dirichlet process mixture model. As $K$ will be changing throughout MCMC iterations, algorithms like reversible jump MCMC and split-merge MCMC can be used. Readers can refer to methods in Hoff (2005); Hoff et al. (2006); Kim et al. (2006) for a detailed study on bi-clustering/clustering using Dirichlet process mixture model.

The general framework can be easily extended to deal with data of mixed types. This is likely to occur when we try to combine data from different sources measuring different aspects of a set of objects. The assumption of independence among features in the general framework makes the analysis straightforward. However, in many cases, feature dependency cannot and should not be ignored. For example, genes in a pathway co-express in many biological functions. We have discussed one way to identify bi-clusters based on gene expression correlations. Another way to extend the general framework is to directly impose dependency structures on the observed data. For example, Raftery and Dean (2006) discussed the design and parameterization of the covariance matrix in Gaussian model-based clustering. A potential issue with this more idealistic approach is that the model can be too complex to allow for meaningful inferential results. More research along this direction is certainly warranted.
A Performance of the PCA+K-means method in the motivating example

Figure 7 plots changes in the clustering error rate when we increase the signal to noise ratio for the PCA+K-means method. Figure 8 shows values of the CH index (Caliński and Harabasz, 1974) versus the number of clusters $K$ for various dimensions $p$. In all 4 cases, best number of cluster is estimated to be 2 based on the CH index.

Figure 7: The PCA+K-means method on the motivating example: clustering error rate vs signal/noise ratio, number of clusters $K=4$.

We also list clustering results for $p = 300, 200, 50, 20, 9$ by deleting noisy columns and specify $K = 2$ and 4 in tables 11 to 20. Even when we delete all noisy columns and only keep the first 9 columns, and let $K=4$, the PCA+K-means method still has 12.5% clustering error rate. The result is shown in Table 20. Mis-classification occurs mainly in group 3 and 1.
Table 11: PCA+K-means method’s clustering result on the motivating example when the dimension is 300 and the number of clusters is specified to be 2. Clustering error rate is 59%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 11 26 36 34     |
| 2                       | 46 27 13 7      |

Table 12: PCA+K-means method’s clustering result on the motivating example when the dimension is 300 and the number of clusters is specified to be 4. Clustering error rate is 57%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 9 15 20 7       |
| 2                       | 29 15 5 0       |
| 3                       | 16 14 10 11     |
| 4                       | 3 9 14 23       |

Table 13: PCA+K-means method’s clustering result on the motivating example when the dimension is 200 and the number of clusters is specified to be 2. Clustering error rate is 53.5%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 55 33 20 3      |
| 2                       | 2 20 29 38      |

Table 14: PCA+K-means method’s clustering result on the motivating example when the dimension is 200 and the number of clusters is specified to be 4. Clustering error rate is 48.5%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 18 19 13 4      |
| 2                       | 3 17 20 6       |
| 3                       | 35 14 9 2       |
| 4                       | 1 3 7 29        |
Table 15: PCA+K-means method’s clustering result on the motivating example when the dimension is 50 and the number of clusters is specified to be 2. Clustering error rate is 51%.

| Estimated cluster label | True group label | 1   | 2   | 3   | 4   |
|-------------------------|------------------|-----|-----|-----|-----|
| 1                       |                  | 57  | 50  | 24  | 0   |
| 2                       |                  | 0   | 3   | 25  | 41  |

Table 16: PCA+K-means method’s clustering result on the motivating example when the dimension is 50 and the number of clusters is specified to be 4. Clustering error rate is 37.5%.

| Estimated cluster label | True group label | 1   | 2   | 3   | 4   |
|-------------------------|------------------|-----|-----|-----|-----|
| 1                       |                  | 19  | 28  | 14  | 0   |
| 2                       |                  | 2   | 22  | 21  | 1   |
| 3                       |                  | 0   | 0   | 12  | 40  |
| 4                       |                  | 36  | 3   | 2   | 0   |

Table 17: PCA+K-means method’s clustering result on the motivating example when the dimension is 20 and the number of clusters is specified to be 2. Clustering error rate is 51%.

| Estimated cluster label | True group label | 1   | 2   | 3   | 4   |
|-------------------------|------------------|-----|-----|-----|-----|
| 1                       |                  | 57  | 49  | 26  | 0   |
| 2                       |                  | 0   | 4   | 23  | 41  |

Table 18: PCA+K-means method’s clustering result on the motivating example when the dimension is 20 and the number of clusters is specified to be 4. Clustering error rate is 31.5%.

| Estimated cluster label | True group label | 1   | 2   | 3   | 4   |
|-------------------------|------------------|-----|-----|-----|-----|
| 1                       |                  | 3   | 28  | 27  | 2   |
| 2                       |                  | 47  | 1   | 0   | 0   |
| 3                       |                  | 7   | 24  | 17  | 0   |
| 4                       |                  | 0   | 0   | 5   | 39  |
Table 19: PCA+K-means method’s clustering result on the motivating example when the dimension is 9 and the number of clusters is specified to be 2. Clustering error rate is 51%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 57 49 25 0      |
| 2                       | 0 4 24 41       |

Table 20: PCA+K-means method’s clustering result on the motivating example when the dimension is 9 and the number of clusters is specified to be 4. Clustering error rate is 12.5%.

| Estimated cluster label | True group label |
|-------------------------|-----------------|
| 1                       | 7 52 10 1       |
| 2                       | 50 1 1 0        |
| 3                       | 0 0 33 0        |
| 4                       | 0 0 5 40        |
B Human genetic data description and BBC2’s performance on the same data with shuffled columns

Table 21 summarizes the 11 populations in the human genetic data analyzed in Section 4.1 and 4.2.

| Population Label | Population Description                                | Number of Individuals |
|------------------|-------------------------------------------------------|-----------------------|
| ASW              | African ancestry in Southwest USA                     | 53                    |
| LWK              | Luhya in Webuye, Kenya                                | 110                   |
| MKK              | Maasai in Kinyawa, Kenya                              | 156                   |
| YRI              | Yoruba in Ibadan, Nigeria                             | 147                   |
| GIH              | Gujarati Indians in Houston, Texas                    | 101                   |
| MEX              | Mexican ancestry in LA, California                    | 58                    |
| CHB              | Han Chinese in Beijing, China                         | 137                   |
| CHD              | Chinese in Metropolitan Denver, Colorado              | 109                   |
| JPT              | Japanese in Tokyo, Japan                              | 113                   |
| CEU              | Utah residents with Northern and Western European ancestry | 112                   |
| TSI              | Toscans in Italy                                      | 102                   |

Table 21: A summary of the human genetic data used in Section 4.1 and 4.2.

In the following we present some results on BBC2 on the shuffled data. At each percentage of columns to be shuffled, we repeat the shuffling procedure 10 times, i.e., for each level, 10 datasets are generated. Each dataset contains the specified percentage of columns being shuffled. The actual columns selected for shuffling, and the shuffling are all random in the 10 repeats. Table 22 shows optimal number of clusters and clustering error rates using BBC2 at each pre-specified shuffling level for one shuffled dataset. Results for the rest 9 datasets at each level are very similar to Table 22. Clustering results on the shuffled data at each pre-specified shuffling level are shown in Tables 23 to 39.
| Percentage of shuffled columns | Number of Clusters | CE rate  |
|-------------------------------|-------------------|---------|
| 10%                           | 6                 | 41.40%  |
| 15%                           | 6                 | 41.57%  |
| 20%                           | 6                 | 41.24%  |
| 25%                           | 6                 | 41.32%  |
| 30%                           | 6                 | 41.57%  |
| 35%                           | 6                 | 41.57%  |
| 40%                           | 6                 | 41.74%  |
| 45%                           | 6                 | 41.40%  |
| 50%                           | 6                 | 41.74%  |
| 55%                           | 6                 | 41.74%  |
| 60%                           | 6                 | 41.65%  |
| 65%                           | 6                 | 41.65%  |
| 70%                           | 6                 | 41.57%  |
| 75%                           | 5                 | 53.51%  |
| 80%                           | 7                 | 54.09%  |
| 85%                           | 4                 | 57.76%  |
| 90%                           | 6                 | 53.84%  |

Table 22: A summary of BBC2’s performance on the shuffled human genetic data at different shuffling levels.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 32        | 21        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 3         | 153       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 52        | 6         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 23: BBC2’s clustering result on the shuffled data when 10% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 35        | 18        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 5         | 151       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 52        | 6         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 24: BBC2’s clustering result on the shuffled data when 15% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 32        | 21        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 2         | 154       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 53        | 5         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 25: BBC2’s clustering result on the shuffled data when 20% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 31        | 22        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 4         | 152       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 54        | 4         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 26: BBC2’s clustering result on the shuffled data when 25% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 33        | 20        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 6         | 150       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 53        | 3         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 27: BBC2’s clustering result on the shuffled data when 30% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|------------------------|----------|----------|----------|----------|----------|----------|
| ASW                    | 32       | 21       | 0        | 0        | 0        | 0        |
| LWK                    | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                    | 4        | 152      | 0        | 0        | 0        | 0        |
| YRI                    | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                    | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                    | 0        | 0        | 0        | 51       | 7        | 0        |
| CHB                    | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                    | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                    | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                    | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                    | 0        | 0        | 0        | 0        | 102      | 0        |

Table 28: BBC2’s clustering result on the shuffled data when 35% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|------------------------|----------|----------|----------|----------|----------|----------|
| ASW                    | 33       | 20       | 0        | 0        | 0        | 0        |
| LWK                    | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                    | 5        | 151      | 0        | 0        | 0        | 0        |
| YRI                    | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                    | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                    | 0        | 0        | 0        | 50       | 8        | 0        |
| CHB                    | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                    | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                    | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                    | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                    | 0        | 0        | 0        | 0        | 102      | 0        |

Table 29: BBC2’s clustering result on the shuffled data when 40% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 31        | 22        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 3         | 153       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 52        | 6         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 30: BBC2’s clustering result on the shuffled data when 45% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 33        | 20        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 9         | 147       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 0         | 101       | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 0         | 54        | 4         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 0         | 102       | 0         |

Table 31: BBC2’s clustering result on the shuffled data when 50% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|------------------------|----------|----------|----------|----------|----------|----------|
| ASW                    | 32       | 21       | 0        | 0        | 0        | 0        |
| LWK                    | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                    | 7        | 149      | 0        | 0        | 0        | 0        |
| YRI                    | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                    | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                    | 0        | 0        | 0        | 52       | 6        | 0        |
| CHB                    | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                    | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                    | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                    | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                    | 0        | 0        | 0        | 0        | 102      | 0        |

Table 32: BBC2’s clustering result on the shuffled data when 55% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|------------------------|----------|----------|----------|----------|----------|----------|
| ASW                    | 36       | 17       | 0        | 0        | 0        | 0        |
| LWK                    | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                    | 8        | 148      | 0        | 0        | 0        | 0        |
| YRI                    | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                    | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                    | 0        | 0        | 0        | 54       | 4        | 0        |
| CHB                    | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                    | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                    | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                    | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                    | 0        | 0        | 0        | 0        | 102      | 0        |

Table 33: BBC2’s clustering result on the shuffled data when 60% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|----------|----------|----------|----------|----------|----------|
| ASW                     | 32       | 21       | 0        | 0        | 0        | 0        |
| LWK                     | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                     | 4        | 152      | 0        | 0        | 0        | 0        |
| YRI                     | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                     | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                     | 0        | 0        | 0        | 50       | 8        | 0        |
| CHB                     | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                     | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                     | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                     | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                     | 0        | 0        | 0        | 0        | 102      | 0        |

Table 34: BBC2’s clustering result on the shuffled data when 65% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|----------|----------|----------|----------|----------|----------|
| ASW                     | 36       | 17       | 0        | 0        | 0        | 0        |
| LWK                     | 110      | 0        | 0        | 0        | 0        | 0        |
| MKK                     | 5        | 151      | 0        | 0        | 0        | 0        |
| YRI                     | 147      | 0        | 0        | 0        | 0        | 0        |
| GIH                     | 0        | 0        | 101      | 0        | 0        | 0        |
| MEX                     | 0        | 0        | 0        | 52       | 6        | 0        |
| CHB                     | 0        | 0        | 0        | 0        | 0        | 137      |
| CHD                     | 0        | 0        | 0        | 0        | 0        | 109      |
| JPT                     | 0        | 0        | 0        | 0        | 0        | 113      |
| CEU                     | 0        | 0        | 0        | 0        | 112      | 0        |
| TSI                     | 0        | 0        | 0        | 0        | 102      | 0        |

Table 35: BBC2’s clustering result on the shuffled data when 70% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 53        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         |
| MKK                     | 156       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 100       | 1         | 0         | 0         |
| MEX                     | 0         | 0         | 6         | 52        | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 112       | 0         | 0         |
| TSI                     | 0         | 0         | 102       | 0         | 0         |

Table 36: BBC2’s clustering result on the shuffled data when 75% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 | Cluster 7 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 53        | 0         | 0         | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         | 0         | 0         |
| MKK                     | 156       | 0         | 0         | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 101       | 0         | 0         | 0         | 0         | 0         |
| MEX                     | 0         | 0         | 44        | 10        | 2         | 2         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 112       | 0         | 0         | 0         | 0         |
| TSI                     | 0         | 0         | 102       | 0         | 0         | 0         | 0         |

Table 37: BBC2’s clustering result on the shuffled data when 80% of the columns are shuffled.
| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 |
|-------------------------|-----------|-----------|-----------|-----------|
| ASW                     | 53        | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         |
| MKK                     | 156       | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         |
| GIH                     | 0         | 101       | 0         | 0         |
| MEX                     | 0         | 50        | 8         | 0         |
| CHB                     | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 102       | 0         |

Table 38: BBC2’s clustering result on the shuffled data when 85% of the columns are shuffled.

| Population Abbreviation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| ASW                     | 53        | 0         | 0         | 0         | 0         |
| LWK                     | 110       | 0         | 0         | 0         | 0         |
| MKK                     | 156       | 0         | 0         | 0         | 0         |
| YRI                     | 147       | 0         | 0         | 0         | 0         |
| GIH                     | 0         | 101       | 0         | 0         |
| MEX                     | 0         | 0         | 47        | 5         | 6         | 0         |
| CHB                     | 0         | 0         | 0         | 0         | 137       |
| CHD                     | 0         | 0         | 0         | 0         | 109       |
| JPT                     | 0         | 0         | 0         | 0         | 113       |
| CEU                     | 0         | 0         | 0         | 112       | 0         |
| TSI                     | 0         | 0         | 0         | 102       | 0         |

Table 39: BBC2’s clustering result on the shuffled data when 90% of the columns are shuffled.

Table 40 records false positive rates for shuffled columns at different shuffling levels computed based on BBC2’s outputs. Since for each selected columns, its entries are randomly shuffled, we expect this shuffled column to be a pure noise column and not to be selected by any clusters. Low false positive rates indicate BBC2 is powerful to detect such noise and not use them for clustering.
| Shuffling Level | False Positive Rate | Shuffling Level | False Positive Rate | Shuffling Level | False Positive Rate |
|----------------|---------------------|----------------|---------------------|----------------|---------------------|
| 10%            | 3.55%               | 40%            | 3.79%               | 70%            | 3.15%               |
| 15%            | 4.42%               | 45%            | 3.53%               | 75%            | 6.35%               |
| 20%            | 3.32%               | 50%            | 3.22%               | 80%            | 10.23%              |
| 25%            | 3.22%               | 55%            | 6.21%               | 85%            | 9.93%               |
| 30%            | 3.63%               | 60%            | 3.16%               | 90%            | 7.22%               |
| 35%            | 3.39%               | 65%            | 6.02%               |                |                     |

Table 40: False positive rates among shuffled columns at different shuffling levels computed from BBC2’s outputs.

C  HBBC’s results on the human genetic data with different minimum node sizes

Figure 9 to 11 are HBBC’s results on the human genetic dataset analyzed in Section 4.2 with minimum node size decreasing from 40 to 30 to 20. HBBC is quite robust to minimum node size specifications.

Figure 9: HBBC’s estimation result on the human genetic data, minimum node size=40. Tree and node interpretations follow from Section 4.2.
D  More details on BBC for data integration

We conjugate a Normal-Inverse-Gamma prior for $\theta_{d,k}$ and $\sigma^2_{d,k}$ in Section 3.4

$$\theta_{d,k} \sim N(\mu_\theta, \sigma^2_{d,k}/\kappa_\theta), \quad k = 1, \ldots, K,$$
$$\sigma^2_{d,k} \sim \text{Inv-Gamma}(\alpha_\sigma, \beta_\sigma), \quad k = 1, \ldots, K,$$

where $\mu_\theta$, $\kappa_\theta$, $\alpha_\sigma$ and $\beta_\sigma$ are hyper-parameters.

To enable the Gibbs sampler, we integrate out $\Theta$ and $\Sigma$ to obtain the marginal likelihood
function for $C$ and $S$,

$$P(Y \mid C, S, K) = \int \int P(Y \mid \theta, \sigma, C, S, K) P(\theta \mid C, K) P(\sigma \mid C, K) d\theta d\sigma$$

$$= \prod_{d=1}^{p} \prod_{k=1}^{K} \left\{ \frac{\beta^\alpha_{d}(2\pi)^{-\frac{n_k}{2}}}{\sqrt{1 + \kappa_d^{-1}n_k}} \cdot \left\{ \Gamma \left( \alpha_d + \frac{n_k}{2} \right) / \Gamma (\alpha_d) \right\} \right\}$$

$$\cdot \prod_{d=1}^{p} \prod_{i<j, c_i = c_j} \exp \left\{ \frac{-(Y_{d.i,j} - \theta_{d,0})^2}{2\sigma^2_{d,0}} \right\} S_{d,k} \cdot \prod_{d=1}^{p} \prod_{i<j} \exp \left\{ \frac{-(Y_{d.i,j} - \theta_{d,0})^2}{2\sigma^2_{d,0}} \right\} 1 - S_{d,k},$$

where $n_k$ denotes the number of gene pairs in cluster $k$. We can also integrate out $S$ from the likelihood function $P(Y \mid C, S, K)$ to obtain the marginal distribution of $C$, so that the Gibbs sampler only cycles through $C_1, \ldots, C_n$:

$$P(Y \mid C, K) = \sum_{S_1 \in \{0, 1\}^K} P(S_1 \mid C, K) \cdots \sum_{S_p \in \{0, 1\}^K} P(S_p \mid C, K) P(Y \mid C, S, K)$$

$$= \prod_{d=1}^{p} \prod_{k=1}^{K} \left\{ \frac{\beta^\alpha_{d}(2\pi)^{-\frac{n_k}{2}}}{\sqrt{1 + \kappa_d^{-1}n_k}} \cdot \left\{ \Gamma \left( \alpha_d + \frac{n_k}{2} \right) / \Gamma (\alpha_d) \right\} \right\}$$

$$\cdot \prod_{d=1}^{p} \prod_{i<j, c_i = c_j} \exp \left\{ \frac{-(Y_{d.i,j} - \theta_{d,0})^2}{2\sigma^2_{d,0}} \right\} \left( 1 - \pi_s \right) \cdot \prod_{i<j} \exp \left\{ \frac{-(Y_{d.i,j} - \theta_{d,0})^2}{2\sigma^2_{d,0}} \right\} \right\}.$$

We run the sampler for a range of cluster numbers, $K = 1, \ldots, K$, and obtain the point estimator of number of clusters $\hat{K}$ and cluster assignment $\hat{C}$ by the MAP estimator. Let $C^{(1)}(K), \ldots, C^{(M)}(K)$ denote MCMC samples of $C$ with the number of clusters $K$. The MAP estimator for $K$ and $C$ is defined as

$$\left( \hat{K}, \hat{C} \right) = \arg \max_{K, C^{(m)}(K)} P \left( C^{(m)}(K) \mid Y \right).$$

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