Bayesian information criteria for clustering normally distributed data

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Abstract

Maximum likelihood estimates (MLEs) are asymptotically normally distributed, and this property is used in meta-analyses to test the heterogeneity of estimates, either for a single cluster or for several sub-groups. More recently, MLEs for associations between risk factors and diseases have been hierarchically clustered to search for diseases with shared underlying causes, but an objective statistical criterion is needed to determine the number and composition of clusters. To tackle this problem, conventional statistical tests are briefly reviewed, before considering the posterior distribution for a partition of data into clusters. The posterior distribution is calculated by marginalising out the unknown cluster centres, and is different to the likelihood associated with mixture models. The calculation is equivalent to that used to obtain the Bayesian Information Criterion (BIC), but is exact, without a Laplace approximation. The result includes a sum of squares term, and terms that depend on the number and composition of clusters, that penalise the number of free parameters in the model. The usual BIC is shown to be unsuitable for clustering applications unless the number of items in each individual cluster is sufficiently large.

Introduction

Despite some interest in clustering data sampled from normal distributions [1,3], most recent work has focussed on clustering distributions of data that are non-normal or containing outliers [4–9], or has focussed on developing methods for clustering data whose underlying distributions are unknown [10,11]. However, multivariate normally distributed data commonly arise, in particular as the asymptotic distribution of maximum likelihood estimates (MLEs). When clustering MLEs, their (estimated) covariances are given and must be accounted for, and these are determined by sample sizes and often strong correlations between covariates. Here the posterior probability for clusters of normally distributed data with known covariances is calculated by marginalising out the unknown cluster centres. The result is equivalent to exactly calculating the Bayesian Information Criterion (BIC) [3,10,12–14], without the Laplace approximation. It includes a weighted sum of squares term to penalise poor fits, and a term equivalent to the $k \log n$ term in BIC [3,10,12–14], where $k$ and $n$ are the number of parameters and data respectively. For recent work on approximate BIC calculations for use with clustering, and a review of related literature, see [3]. The greatest difference to other studies, is that the work here assumes that each data point is sampled from a normal distribution with a known covariance and a mean that is an (unknown) cluster centre.

When the underlying distribution of data are unknown, there are advantages to firstly fitting a parametric model, and then clustering the estimated co-efficients, but the approach is rarely used [3,15–19]. A recent example [1] used this approach to search for shared underlying causes of disease, in a large study using UK Biobank data [20]. In that case, existing epidemiological understanding was incorporated through the selection, truncation, and censoring of data, and through the adjustment for known confounding factors with established survival analysis methods [1]. Advantages of the general approach include:

1. The distribution of underlying data can be unknown, but under reasonable regularity conditions, MLE estimates are normally distributed [10,21].
2. Estimates can be stratified and multiply-adjusted for known confounders, helping to extract the information of interest from potentially noisy data [10,11,22].
3. The fitted models can be more interpretable and familiar to the scientific community. For example, proportional hazards models are commonly used by medical researchers.
4. Marginalisation [10,11] can be used to select parameter subsets of most interest for clustering [1], e.g. risk factors as opposed to confounders, or minimum versus maximum quantiles.
5. By fitting a model, we can build-in prior knowledge through the model.

In addition to clustering of diseases [1], the approach has been used to detect changes in gene expression by clustering Fourier series coefficients [17,18]. Clustering parameters from linear-models such as a Fourier series, are examples of the more general problem of clustering normally-distributed MLE estimates from a parametric model. Here we consider the general problem of clustering data sampled from multivariate normal distributions, with the aim of determining the number and membership of clusters.

A related approach for clustering categorical data with an “exact integrated complete-data likelihood (ICL)”, was developed by Biernacki et al. [23,24], and has been used for model selection in several applications [25–29], including a recent clustering of human population genomic data [30]. An important difference between the model described here, the ICL, and clustering with Gaussian mixture models for example, is that the MLE data studied here each have an (asymptotically) normal distribution with an estimated mean and covariance. As a result, the probability distributions are quite different, despite all three approaches having a wide range of applicability.
The next section briefly reviews statistical tests of heterogeneity, their use in meta-analyses, and their potential use in clustering studies. The formulae involve sums of squares, and similar terms occur in Section 3 that calculates the posterior distribution associated with a partition of data into clusters. Section 4 relates the results to the Bayesian information criterion (BIC), and indicates the conditions when the usual BIC could be used in clustering studies, and how this would be done. It also emphasises that in general, the usual BIC cannot be used in clustering studies. The final Section 6 discusses: limits of the prior distribution, similarities to clustering with k-means, potential uses in meta-analyses, the scope for sensitivity analyses or forming confidence sets, and potential model improvements.

2 Statistical heterogeneity tests

Heterogeneity tests are widely used in meta-analyses, and are intended to assess whether estimates are the same in several different studies [31]. These include multivariate heterogeneity tests [32–35], and the tests can involve both fixed effects and random effects models [31]. A fixed effects model is considered first, that generalises easily to a random effects model.

In a fixed effects model the null hypothesis is that all diseases have the same associations with one or more parameters, such as a drug, or a collection of potential risk factors. These might be a subset of associations, with potential confounders adjusted for, and subsequently removed by marginalisation [1]. Consider m items, such as a collection of diseases, in a cluster labelled by g. Under the null hypothesis the ith item will have,

\[ X_i \sim N(\mu_g, \Gamma^{-1}_i) \] (1)

where \( \Gamma^{-1}_i = \Sigma_i \) is the covariance (\( \Gamma_i \) is the precision matrix), and \( \mu_g \) are an (unknown) vector of the estimated associations, that are assumed to be the same for all items in the cluster (e.g. diseases in a composite endpoint). Eq. 1 requires \([36]\),

\[ (X_i - \mu_g)^T \Gamma_i (X_i - \mu_g) \sim \chi^2_p \] (2)

where \( p \) is the dimension. Therefore because the sum of \( n_g \) random variables that are individually \( \chi^2_p \), distributed is \( \chi^2_{pn_g} \),

\[ \sum_{i \in C_g} (X_i - \mu_g)^T \Gamma_i (X_i - \mu_g) \sim \chi^2_{pn_g} \] (3)

where \( C_g \) is the set of \( n_g \) items in cluster \( g \). For \( p = 1 \) this has,

\[ \sum_{i \in C_g} \left( \frac{X_i - \mu_g}{\sigma_i} \right)^2 \sim \chi^2_{n_g} \] (4)

for standard deviations \( \sigma_i \). Because \( \mu_g \) is unknown and must be estimated, the test statistic is modified, as explained next.

Appendix C uses Bayes theorem with a flat or normal prior for the mean \( \mu_g \), to show that if \( X_i \sim N(\mu_g, \Gamma^{-1}_i) \), then,

\[ \mu_g \sim N(\bar{\mu}_g, \tilde{\Gamma}_g^{-1}) \] (5)

where,

\[ \bar{\mu}_g = \left( \sum_i \Gamma_i \right)^{-1} \left( \sum_i \Gamma_i X_i \right) \] (6)

and,

\[ \tilde{\Gamma}_g = \left( \sum_i \Gamma_i \right) \] (7)

If a normal prior is used then the sum over \( i \) includes the prior’s mean \( \mu_0 \) and covariance \( \Gamma_0 \), and the sum is from \( i = 0 \) to \( i = n_g \). For a flat prior, the sum is from \( i = 1 \) to \( i = n_g \). The subscripts \( g \) will later allow the discussion to include more than one cluster, for example several clusters of diseases as were considered in Webster et al. [1]. For the rest of this section, unless stated otherwise, we consider a single cluster. For \( p = 1 \), Eq. 5 is the well-known inverse-variance weighted estimate of the mean.

Appendix A shows that,

\[ \sum_i (X_i - \bar{\mu}_g)^T \Gamma_i (X_i - \bar{\mu}_g) \] (8)

and Eq. 5 implies that,

\[ (\mu_g - \bar{\mu}_g)^T \tilde{\Gamma}_g (\mu_g - \bar{\mu}_g) \sim \chi^2_{p} \] (9)

These observations can be used to test the assumption that the normal distributions have the same mean. Using Eqs. 8 and 9,

\[ \sum_{i \in C_g} (X_i - \bar{\mu}_g)^T \Gamma_i (X_i - \bar{\mu}_g) \sim \chi^2_{(n_g-1)p} \] (10)
The left side of Eq. [10] is the Q statistic. It tests the assumption that a set of (approximately) normally distributed estimates \{X_i\} have the same mean. For \( p = 1 \), these expressions give the well known inverse variance weighted heterogeneity test, that is regularly used in meta analyses and 2-sample Mendelian randomisation studies [31, 37]. For the situation described in Webster et al. [11], the aim is to assess the goodness of fit for a clustering of diseases. For this situation, Eq. [10] is modified to sum over all \( m \) clusters, and the Q statistic becomes,
\[
\sum_{g=1}^{m} \sum_{i \in C_g} (X_i - \hat{\mu}_g)^T \Gamma_i (X_i - \hat{\mu}_g) \sim \chi^2_{(n-m)p}
\]
(11)
where we used \( \sum_{g=1}^{m} (n_g - 1)p = (n - m)p \), and \( C_g \) is the set of diseases in cluster \( g \) (composite endpoint \( g \)). If there is a normal prior for the cluster centres, as discussed in Sections 3 and 4, then \( n_g \) will include one extra element for each \( g \). As a consequence, the right sides of Eqs [10] and [11] become, \( \sim \chi^2_{n_g} \) and \( \sim \chi^2_{n_g} \) respectively.

The results above correspond to a fixed effects model where the data are assumed to have the same mean, as opposed to the means being sampled from an underlying distribution (a random effects model). A random effects model firstly assumes that each study has a \( \mu_g \) and the propositions \( \{ \mu_g \} \) asymptotically have,
\[
\hat{\mu}_i \sim N (\mu_{Z_i}, \hat{\Sigma}_i)
\]
(15)
with \( \mu_{Z_i} = \mu_Z \), iff \( Z_i = Z_j \). We will regard \( \hat{\Sigma}_i \) as given, and \( \hat{\mu}_i \) as random variables sampled from Eq. [15]. Write \( X_i = \hat{\mu}_i, \Gamma_i = \hat{\Sigma}_i^{-1} \), and the propositions \( Z = \{ Z_i = z_i \}, X = \{ X_i = x_i \}, M = \{ M_g = \mu_g \} \), where \( \mu_g \) is the mean of cluster \( g \). We will also write \( I \) to denote both \( \{ \Gamma_i \} \) and any additional implicit information regarding the clustering problem.

1Implicitly, a partition’s clusters are labelled by the number of items they contain, but this does not uniquely label the clusters in a partition because more than one cluster can have the same number of elements.

2.1 Heterogeneity and meta-analyses

The traditional measure of heterogeneity is the Q statistic, that was derived above in a multi-variate context. The I-square statistic [38, 39] is closely related to the Q statistic [31], and in the notation above, is for Eq. [11]
\[
I^2 = \frac{Q - (n-m)p}{Q} \times 100
\]
(14)
where \( Q \) is the left side of Eq. [11] and the factor of 100 is conventionally used to express \( I^2 \) as a percentage. \( I^2 \) is usually set to zero if its evaluation is negative. The equivalent expression for a single cluster that uses the left side of Eq. [10] for \( Q \), would replace the number of degrees of freedom \( (n-m)p \), with \( (n_g - 1)p \) in Eq. [14]. If as discussed in Sections 3 and 4, there is a normal prior for the cluster centres, then \( n_g \) will include one extra element for each \( g \), causing \( (n-m)p \) to be replaced by \( np \), and \( (n_g - 1)p \) to be replaced by \( n_g p \). The \( I^2 \) statistic replaces a test with a more nuanced measure of heterogeneity that is useful when some heterogeneity is expected, but it does not provide an objective statistical test.

3 Posterior distribution for clusters of normally distributed data

Firstly consider a distribution [40] of identifiable items in identifiable boxes. Later this will be used this to consider the likelihood for a partition [40] of identifiable items in unlabelled cluster [4].

Notation: The \( i \)th item’s cluster in a distribution of labelled clusters, is \( Z_i \). The MLEs \( \{ \hat{\mu}_i \} \) and their covariances \( \{ \hat{\Sigma}_i \} \), asymptotically have,
\[
\hat{\mu}_i \sim N (\mu_{Z_i}, \hat{\Sigma}_i)
\]
(15)
Note that the proposition \( Z = \{Z_i = z_i\} \) is not simply a conjunction of independent terms. For example, \( Z \) implicitly contains information about the number of clusters \( M = m \), the number of members in each cluster, and the number of \( k \)-element clusters. One consequence is that we cannot directly write \( P(Z|X, I) \) as a product with one term per item to be clustered.

Consider the likelihood of assigning labelled items into a distribution \([40]\) of labelled clusters. Using Bayes theorem and marginalisation \([10, 11]\),

\[
P(Z|X, I) = P(X|Z, I)P(Z|I) = \int_{\infty}^{-\infty} d\mu_1 ... \int_{\infty}^{-\infty} d\mu_m P(X, M, Z, I) P(Z|I)
\]

where \( f_{\infty}^{-\infty} d\mu_i \) denotes \( \int_{-\infty}^{\infty} d\mu_1 ... \int_{-\infty}^{\infty} d\mu_m P(X, M, Z, I) P(Z|I) \) and \( f_{\infty}^{-\infty} d\mu_i \) for components \( 1 \ldots p \) of \( \mu_i \), with each integrated from \(-\infty \) to \( \infty \). The second line above is read as the probability of observing data \( X \) and clusters with means \( M \), given the cluster assignments \( Z, I \). (This is very different to writing this as the product of probabilities of independent observations \( X_i \), with cluster means \( \mu_{Z_i} = \Pi_{g=1}^{m} \mu_g | z_{i=g} \). For independent normally distributed \( \{X_i\} \) with covariances \( \{\Gamma_i^{-1}\} \), sampled from clusters \( g = 1 \ldots m \) with means \( \{\mu_g\} \),

\[
P(X|M, Z, I) = \Pi_{g=1}^{m} \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i)
\]

where \( C_g = \{i : Z_i = g\} \) are the members of the \( g \)th cluster, and,

\[
f(x_i; \mu_g, \Gamma_i) = \frac{1}{\sqrt{(2\pi)^p |\Gamma_i|}} \exp \left( -\frac{1}{2} (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) \right)
\]

Eq. [17] has the form of a product partition model \([41, 42]\). In the following discussions we consider two priors for the means, one a flat prior with \( P(M|Z, I) \) constant, and the other a normal distribution with,

\[
P(M|Z, I) = \Pi_{g=1}^{m} f(\mu_g; \mu_0, \Gamma_0)
\]

We include Eq. [19] in the analysis below. Using Eqs. [17] and [19], Eq. [16] gives,

\[
P(Z|X, I) \propto P(X|Z, I)P(Z|I) \sim \int_{\infty}^{-\infty} d\mu_1 ... \int_{\infty}^{-\infty} d\mu_m \left( \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right) \left( \Pi_{g=1}^{m} f(\mu_g; \mu_0, \Gamma_0) \right) P(Z|I)
\]

Now consider the likelihood for a partition \([40]\) of type \( (N_1, \ldots, N_m) \) with \( m \) clusters, and \( r_1 \ldots r_k \) clusters of size \( 1 \ldots k \). Notice that in Eq. [20] the factor \( P(X|Z, I) \) is invariant to permutations of cluster labels among clusters with the same number of items. In other words, provided \( Z \) is from the same partition, then we can write the probability of a partition \( C \) as,

\[
P(C|X, I) = \sum_{Z:Z \in C} P(Z|X, I) \propto \sum_{Z:Z \in C} P(X|Z, I) P(Z|I) = P(X|Z \in C, I) \sum_{Z:Z \in C} P(Z|I)
\]

Where we used the above observation that \( P(X|Z, I) \) is the same for all \( Z \) such that \( Z \in C \). Noting that the proposition \( Z = \{Z_i = z_i\} \) is the same as \( (Z \text{ and } M(Z) = m) \), where \( M(Z) \) is the number of clusters, given the cluster memberships \( Z \), then,

\[
P(C|I) = \sum_{Z:Z \in C} P(Z|I) = \sum_{Z:Z \in C} P(Z|M = m, I) P(M = m|I)
\]

and assuming that all assignments \( Z \) are equally likely given \( M = m \),

\[
\sum_{Z:Z \in C} P(Z|M = m, I) = \frac{\#(Z:Z \in C,M=m)}{N_1! \ldots N_m! r_1! \ldots r_k! S(n,m)}
\]

where \( \# \) is used to denote “the number of”. Eq. [23] equals the number of partitions of type \( (N_1, \ldots, N_m) \), divided by the total number of partitions of \( n \) identifiable items into \( m \) non-empty clusters (the Stirling numbers of the second kind \( S(n, m) \)). An alternative calculation that leads to the same result is given in Appendix A.

For \( P(M = m|I) \), there are no labels \( \{Z_i\} \) for items, or cluster numbers \( \{N_i\} \). Appendix B considers whether \( P(M = m|I) \) should reflect the number of ways of partitioning \( n \) identical items into \( m \) clusters, and concludes that this is unlikely to be an appropriate prior in most cases. Instead, the choice of \( P(M = m|I) \) might best be informed by the particular application. For the examples here, we will take it as constant \( P(M = m|I) = 1/n \). Continuing as before,

\[
P(X|Z \in C, I) = \int_{\infty}^{-\infty} d\mu_1 ... \int_{\infty}^{-\infty} d\mu_m P(X|M, Z \in C, I) P(M|Z \in C, I)
\]

\[
\int_{\infty}^{-\infty} d\mu_1 ... \int_{\infty}^{-\infty} d\mu_m \left( \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right) \left( \Pi_{g=1}^{m} f(\mu_g; \mu_0, \Gamma_0) \right)
\]

\[
\Pi_{g=1}^{m} \int_{\infty}^{-\infty} d\mu_g f(\mu_g; \mu_0, \Gamma_0) \left( \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right)
\]

(24)
Putting Eqs. 21–25 together we have,
\[
P(C|X, \mathcal{I}) \propto P(X|Z \in C, \mathcal{I})P(C|\mathcal{I})
\]
\[
= P(M = m|\mathcal{I}) \times \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}}
\]
\[
\times \left( \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right) \times \left( \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right)
\]
\[
\times \prod_{g=1}^{m} \exp \left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \bar{\mu}_g) \Gamma_i (x_i - \bar{\mu}_g) \right\}
\]
(25)

where \(f_0(\mu_g) = f(\mu_g; \mu_0, \Gamma_0)\) is the prior for \(\mu_g\).

The last term gives \(\tilde{\Gamma}\).

To understand the fifth term of Eq. 28 better, and to compare Eq. 28 with the Bayesian Information Criterion (BIC), use Eq. 7 to write,
\[
4 \text{ Bayesian information criteria}
\]
Then for each \(g\) we have,
\[
\tilde{\Gamma}_g = \left( \prod_{i=1}^{n_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right) \times \left( \prod_{i=1}^{n_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right)
\]
\[
\times \prod_{i \in C_g} \exp \left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \bar{\mu}_g) \Gamma_i (x_i - \bar{\mu}_g) \right\}
\]
(26)

where \(\tilde{\Gamma}_g = \sum_{i \in C_g} \Gamma_i\), and \(\tilde{\mu}_g = (\sum_{i \in C_g} \Gamma_i)^{-1} \sum_{i \in C_g} \Gamma_i x_i\) as in Eqs. 4–7

When \(f_0(\mu_g)\) is a flat prior, the integral over \(\mu_g\) involving the last term gives\(\sqrt{2\pi^p \sqrt{\tilde{\Gamma}_g^{-1}}}\) for each \(g\). A normal prior with mean \(\mu_0\) and covariance \(\Gamma_0^{-1}\) has,
\[
f_0(\mu_g) = \frac{1}{\sqrt{2\pi^p \sqrt{\Gamma_0^{-1}}}} \exp \left\{ -\frac{1}{2} (\mu_0 - \mu_g) \Gamma_0 (\mu_0 - \mu_g) \right\}
\]
(27)

Then for each \(g = 1..m\) in Eq. 25, \(f_0(\mu_g)\) leads to an extra factor of \(1/\sqrt{2\pi^p \sqrt{\tilde{\Gamma}_g^{-1}}}\) and each sum over \(C_g\) is modified to include \(i = 0\), with \(x_0 \equiv \mu_0\), and \(\Gamma_0^{-1}\) the covariance of the prior. For this case Eq. 25 becomes,
\[
P(C|X, \mathcal{I}) \propto P(X|Z \in C, \mathcal{I})P(C|\mathcal{I})
\]
\[
= P(M = m|\mathcal{I}) \times \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}}
\]
\[
\times \left( \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right) \times \left( \prod_{g=1}^{n} \prod_{i \in C_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right)
\]
\[
\times \prod_{g=1}^{m} \exp \left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \bar{\mu}_g) \Gamma_i (x_i - \bar{\mu}_g) \right\}
\]
(28)

The first three terms result from the prior \(P(C|\mathcal{I})\) for the partition based on combinatorial considerations. The fourth term on the right side of Eq. 25 is independent of the clustering model, the fifth term depends on the number and size of clusters and is discussed further in the next Section, and the sixth term is a sum of squares term that measures the goodness of fit of the data to the model. If there is a flat prior, the extra factors of \(1/\sqrt{2\pi^p \sqrt{\tilde{\Gamma}_g^{-1}}}\) are no longer present, leaving factors of \(\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}\) in place of \(\sqrt{\tilde{\Gamma}_g^{-1}} / |\Gamma_0^{-1}|\).

Compare Eq. 28 with the equivalent expression for a Gaussian mixture model with cluster means \(\{\mu_g\}\) removed by marginalisation (integrated-out). Key differences are that: (i) a mixture model considers a distribution of named, identifiable clusters, not a partition, (ii) removing \(\mu_g\) by marginalising the joint probability mass/density function in a Gaussian mixture model would lead to \(n\) integrals over \(\mu_g\), instead of just one for each cluster, (iii) here the covariances \(\{\Gamma_i\}\) differ for each data point instead of only between clusters.

4 Bayesian information criteria

To understand the fifth term of Eq. 28 better, and to compare Eq. 28 with the Bayesian Information Criterion (BIC), use Eq. 7 to write,
\[
\tilde{\Gamma}_g = \left( \prod_{i=1}^{n_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right) \times \left( \prod_{i=1}^{n_g} \frac{1}{\sqrt{(2\pi)^p |\Gamma_{g}^{-1}|}} \right)
\]
\[
\times \prod_{i \in C_g} \exp \left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \bar{\mu}_g) \Gamma_i (x_i - \bar{\mu}_g) \right\}
\]
(29)

with \(\tilde{\Gamma}\) now the mean of \(\{\Gamma_i\}\) for the cluster (including \(\Gamma_0\) if there is a normally distributed prior). Using Eq. 29 and \(|A^{-1}| = 1/|A|\), the fifth term of Eq. 28 can be written,
\[
\prod_{g=1}^{m} \sqrt{\tilde{\Gamma}_g^{-1} / \Gamma_0^{-1}} = \left( \prod_{g=1}^{m} \frac{1}{\sqrt{n_g}} \right) \left( \prod_{g=1}^{m} \sqrt{\Gamma_0^{-1} / \tilde{\Gamma}_g^{-1}} \right)
\]
(30)
which is $O((\Pi_{g=1}^m n_g)^{1/\sqrt{n_g}})$ for large $n_g$. Previous authors \cite{43} have argued for and used, an heuristic penalty term equivalent to log of Eq. \ref{bic} when minimising the log-likelihood for clustering. In those studies the term was not derived, but was one of several proposed alternatives \cite{43}. Substituting Eq. \ref{bic} into \ref{bic} then taking the logarithm and multiplying by $-2$, gives

$$-2 \log (P(C|X, \Gamma)) = -2 \log (P(M = m|I)) - 2 \log \left( \frac{1}{\prod_{g=1}^m n_g} \right) + 2 \log (S(n, m)) + \sum_{i=1}^n \log \left( \frac{1}{2\pi \sigma_i^2} \right) + \sum_{g=1}^m \sum_{i \in C_g} (x_i - \bar{\mu}_g)^2 \Gamma_i(x_i - \bar{\mu}_g) + \sum_{g=1}^m p \log n_g - \sum_{g=1}^m \log \left( \frac{1}{\prod_{g=1}^m \Gamma_i} \right)$$

The maximum likelihood estimates for $\{\mu_g\}$ can be found from Eq. \ref{bic} by taking derivatives with respect to the components of each $\mu_g$, and have $\hat{\mu}_g = \bar{\mu}_g$. Hence the fourth and fifth terms are the sum of $-2$ times the maximum-likelihood estimates for the log-likelihood of each cluster $(-2 \log \hat{L}_i)$, the first three terms arise from combinatorial considerations, and the final two terms asymptote to $\sum_{g=1}^m p \log n_g$ as $n_g \to \infty$. For the limit of large $n_g$ this becomes

$$-2 \log (P(C|X, \Gamma)) = -2 \log P(C|I) + \sum_{g=1}^m \left\{ -2 \log (\hat{L}_g) + p \log n_g \right\} + O(1)$$

where the terms involving $\log \left( \frac{1}{\prod_{g=1}^m \Gamma_i} \right)$ are not explicitly included to allow comparison with the Bayesian Information Criterion (BIC). Usually $|\Gamma_0^{-1}| > |\Gamma_i^{-1}|$ and the terms neglected from Eq. \ref{bic} would be positive, the same sign as $p \log(n_g)$ and will penalise larger numbers of clusters, but their size would depend on the details of the clustering. Neglecting these terms will usually underestimate the penalty associated with having more clusters. If there is a normal prior, then $n_g$ equals one plus the number of elements in a cluster, and $\log(n_g) \to 2$ as $m \to n$. The BIC for a parametric model is usually defined as \cite{10}.

$$BIC = -2 \log (\hat{L}) + k \log(n)$$

where $\hat{L}$ is the log-likelihood at the MLE, $k$ is the number of parameters, and $n$ is the number of data. If we were simply studying a single cluster with a flat prior, then Eqs. \ref{bic} and \ref{bic} would be identical, but with $k = p$. If $n_g \gg 1$ for all clusters, then Eqs. \ref{bic} and \ref{bic} are equivalent to the sum of BICs for each cluster, plus a combinatorial term for the probability of sampling the set of clusters by chance that requires a prior for the number of clusters $P(M = m|I)$. Note that in general $n_g$ is not always large, and in many applications a cluster can represent a single item. In clustering applications the usual BIC approximation is not applicable unless all clusters are large with $n_g \gg 1$, but when the data are normally distributed, then the exact posterior distribution can be used (Eqs. \ref{bic} and \ref{bic}).

## 5 Examples

A recent epidemiological study using UK Biobank data \cite{1}, estimated associations with 12 well-known risk factors in over 400 diseases using a proportional hazards survival analysis. Full details of the study and dataset are in Ref. \cite{1}, summary statistics and code are at: osf.io. Diseases with statistically significant differences between men and women after an FDR multiple-testing adjustment \cite{10} were excluded, as were diseases that failed a global $\chi^2$ test of the proportional hazards model using Schoenfeld residuals, and only diseases whose associations remained statistically significant after a Bonferroni adjustment were kept. This left 78 pairs of diseases affecting men and women (156 diseases in total).

The authors wished to cluster diseases using MLEs for associations between exposures and disease incidence, because exposure-disease associations were expected to reflect causal disease pathways. Because associations between diseases and risk factors are often strongly correlated, the covariances of MLEs must be accounted for when clustering. Due to very different incident rates (sample sizes), covariances were expected to differ substantially even if diseases originated from the same cluster. Therefore the authors used the Bhattacharyya distance and hierarchical clustering, the latter allowing easier interpretation of the resulting clusters. A limitation of the approach, is that it did not determine how many clusters to consider. The authors \cite{1} used the ad-hoc elbow criterion to keep 24 clusters, but acknowledged the need for an objective selection criterion. The problem was to cluster $\{\mu_i, \Sigma_i\}$ into groups with similar $\{\mu_i\}$. A simple model that accounts for the uncertainty of estimates $\{\hat{\mu}_i\}$ through their covariances, is to take $\hat{\mu}_i \sim N(\mu_i, \Sigma_i)$ for clusters with means $\{\mu_g\}$; which is the model considered here.

Figure \ref{fig:loglikelihood} shows the log-likelihood for hierarchical clustering with the Bhattacharyya distance (see Appendix D), and a normal prior with an isotropic covariance $\Sigma_0$ with $\sqrt{tr(\Sigma_0)} = 3$ (when $\mu_g \sim N(\mu_0, \Sigma_0)$, $E[(\mu_g - \mu_0)^2] = tr(\Sigma_0)$). The choice of $\sqrt{tr(\Sigma_0)} = 3$ was intended to be large enough to included the largest expected relative risks from smokers and lung-cancer, that has been found to be $45$ of order $20 \simeq \exp(3)$. The figure plots the log-likelihood as calculated using Eq. \ref{bic} whose maximum is at 42 clusters. It also shows

\footnote{Strictly speaking, we are discussing the log of the posterior distribution and the “MLE” is the maximum a posteriori probability (“MAP”) estimate.}
the influence of the combinatorial term \( \log P(C|I) \) (which was small), the penalty term \( \log \Pi_{i=1}^{m} \sqrt{\hat{\Gamma}_{i}^{-1}/|\hat{\Gamma}_{i}|} \), and the log-likelihood using the equivalent term from the usual BIC approximation \(- (1/2) \sum_{i=1}^{m} p \log n_{g}\). As expected, as the number of clusters increases and the typical cluster sizes become smaller, the BIC approximation becomes worse. The p-value for heterogeneity (Eq. 11), rises above 0.05 at 46 clusters. An \( I^{2} \) value less than 40 is usually regarded as a low level of heterogeneity [31], and this occurs for 31 or more clusters, consistent with the maximum log-likelihood at 42. With 42 clusters, 72% of the 78 disease types (78 in men and 78 in women), appeared with their opposite-sex pair in the same cluster. The diseases and their clusters are listed in the Supplementary Material, along with the results from a sensitivity analysis that is described in Section 6.4.

Further examples using simulated data are in the Supplementary Material. These include sensitivity analyses that are described in Section 6.4, some explorations for how results are influenced by noise in the data, and specific numerical test cases.

6 Discussion

6.1 Limits of a normal prior

To better understand the influence of the normal prior \( f_{0}(\mu_{g}) \), take \( \Gamma_{0}^{-1} = I \sigma_{0}^{-2} \) where \( I \) is the identity matrix, and explore the limits of a sharply peaked prior with \( \sigma_{0}^{2} \to 0 \) and of a flat prior with \( \sigma_{0}^{2} \to \infty \). These limits concern the last three terms in Eq. 31.

Firstly consider \( \sigma_{0}^{2} \to \infty \), a limit that emphasises that a flat prior cannot be considered as a limiting case of a normal prior. In the final term \( \sum_{k \in C_{g}} \hat{\Gamma}_{k} \to \sum_{k \in C_{g'}, k \neq 0} \hat{\Gamma}_{k} \). In the fifth term the components of \( \Gamma_{0} = I/\sigma_{0}^{2} \to 0 \), and,

\[
\bar{\mu}_{g} \to \left( \sum_{i \in C_{g}, i \neq 0} \Gamma_{i} \right)^{-1} \sum \sum_{i \in C_{g}, i \neq 0} \Gamma_{i} x_{i}
\]

(34)

and

\[-\log|\hat{\Gamma}_{i}^{-1}| \to -(p/2) \log(2\pi \sigma_{0}^{2}) \]

where \( p \) is the dimension of \( \mu_{g} \) and \( \log(\sigma_{0}^{2}) \to \infty \) as \( \sigma_{0}^{2} \to \infty \). The divergent behaviour arises from requiring that \( f_{0}(\mu_{g}) \) is correctly normalised, and can be understood from Eqs. 25 and 27. As \( \sigma_{0}^{2} \) becomes larger, the maximum of \( f_{0}(\mu_{g}) \) must become increasingly small to ensure that it is correctly normalised, and there is an extra factor for each cluster. For this example with \( \hat{\Gamma}_{0}^{-1} = \sigma_{0}^{2} I \), the first term provides a penalty that is proportional to the number of free parameters \( m \times \hat{\Gamma}_{0} \).

For the alternative limit with \( \sigma_{0}^{2} \to 0 \), Appendix F shows that the fifth and seventh terms can be combined and will tend to zero, and the sixth term tends to

\[-\frac{1}{2} \sum \sum_{i \in C_{g}} (x_{i} - \bar{\mu}_{g})^{T} \Gamma_{i} (x_{i} - \bar{\mu}_{g}) = -\frac{1}{2} \sum \sum_{i \in C_{g}, i \neq 0} (x_{i} - \mu_{0})^{T} \Gamma_{i} (x_{i} - \mu_{0}) + O(\sigma_{0}^{2})
\]

so that the log-likelihood is equivalent to clusters that all have the same centres \( \mu_{g} = \mu_{0} \), as we might have expected.

6.2 Equal covariances, and relation to k-means

Consider equal covariances for all the data point \( i \) with \( \Gamma_{i}^{-1} = \Gamma^{-1} \) and a flat prior. Using \(|AB| = |A||B| \) and \(|\Gamma^{-1}| = 1/|\Gamma|\), the final term in Eq. 31 simplifies to

\[-\frac{1}{2} \sum (\log |\hat{\Gamma}_{g}^{-1}|) = \frac{1}{2} \sum \log |\Gamma| = \frac{m}{2} \log |\Gamma|
\]

(36)

With \( \Gamma_{i} = \Gamma \) and \( \bar{\Gamma} = n_{g} \Gamma \), then \( \bar{\mu} = \frac{1}{n_{g}} \sum_{i \in C_{g}} x_{i} \), and the fifth term in Eq. 31 is

\[
\sum \sum_{i \in C_{g}} (x_{i} - \bar{\mu}_{g})^{T} \Gamma_{i} (x_{i} - \bar{\mu}_{g}) = \sum \sum_{i \in C_{g}} \left( x_{i} - \frac{1}{n_{g}} \sum_{j \in C_{g}} x_{j} \right)^{T} \Gamma \left( x_{i} - \frac{1}{n_{g}} \sum_{j \in C_{g}} x_{j} \right)
\]

(37)

Eq. 32 shows how Eq. 37 relates to the sum of pairwise within-cluster differences. The log-likelihood is

\[-2 \log (P(C|X, \Gamma)) = -2 \log (P(C|\Gamma)) + \sum \log |2\pi \Gamma^{-1}| + \sum \sum_{i \in C_{g}} \left( x_{i} - \frac{1}{n_{g}} \sum_{j \in C_{g}} x_{j} \right)^{T} \Gamma \left( x_{i} - \frac{1}{n_{g}} \sum_{j \in C_{g}} x_{j} \right) + m \log |\Gamma|
\]

(38)

3For example, this might occur for longitudinal epidemiological data with repeated measurements to allow estimation of either measurement errors or of the intrinsic variation within individuals. An additional set of measurements at a later time allows a covariance to be calculated, and these can be averaged across all individuals to give an estimated covariance for within-person measurements. The average “within-person” covariance is different to the “population” covariance of data for a single time point, for example because the variation within an individual could be less than between individuals.
For a flat prior and equal covariances, maximising the log-likelihood is similar to minimising the sum of squares as for k-means, but with two extra terms to penalise the model’s complexity. The penalty terms for $-2 \times$ the log-likelihood are $-2 \log (P(C|\mathcal{I}))$, and,

$$
\sum_{g=1}^{m} (p \log n_g + \log |\Gamma|)
$$

(39)

The second term’s sign depends on whether $0 < |\Gamma| < 1$ or $|\Gamma| > 1$, and can penalise more, or fewer clusters, with large covariances ($0 < |\Gamma| < 1$) favouring more clusters but smaller covariances ($1 < |\Gamma|$) favouring fewer clusters. Comparison with Eq. 29 indicates that $|\Gamma| > 1$ (that favours fewer clusters), is analogous having a prior with covariance $\Sigma_0$ that has $|\Sigma| < |\Sigma_0|$ (with $|\Gamma| > |\Gamma_0|$), as would usually be the case. The first term is an entropy-like term, and the concave shape of $\log n_g$ will penalise similarly sized clusters (when summed over $g$), with $\frac{1}{m} \sum_{g=1}^{m} \log n_g \leq \log \frac{1}{m} \sum_{g=1}^{m} n_g = \log (n/m)$. Unfortunately the k-means algorithm will not minimise Eq. 38 by assigning items to clusters with the nearest mean, because the penalty terms depend on the number and composition of clusters.

6.3 Heterogeneity, composite endpoints, and sub-group analysis

Composite endpoints consist of several grouped symptoms or diseases, and are intrinsic to how diseases are defined and studied. Since the first statistical studies of disease by John Graunt in the 1600s [46], there has been a trade-off between definitions that are sufficiently specific to distinguish different underlying disease processes, and sufficiently broad to allow a meaningful statistical study. This is particularly apparent in clinical trials and epidemiological studies where data are costly or unavailable. Large population datasets with detailed genetic and biological information are providing new data-driven definitions of disease, identifying distinct subtypes of disease, and collections of diseases with potentially shared underlying causes [1]. Statistical methods can assess whether a composite endpoint consisting of several potentially distinct diseases, is consistent with its assumed properties, such as testing the constituent diseases for heterogeneity of their disease-risk associations.

Heterogeneity is conventionally tested with a Q or $I^2$ statistic [31]. When heterogeneity is anticipated in advance, potential subgroups are often proposed as an alternative to a single cluster. Because the subgroups are pre-specified, as opposed to clustered, the larger number of free parameters does not guarantee a less heterogeneous result. In principle Eq. 31 can, and should, be used in preference to the Q-statistic when deciding whether a proposed sub-group is a better representation of the data than a single cluster, or a different sub-group. However, because the sub-groups are pre-specified in advance, the first three (combinatoric terms) should not be included.

Clustering algorithms usually ensure that the Q or $I^2$ statistics decrease as the number of clusters is increased. In contrast, because Eq. 31 accounts for the number of free parameters, it can have have a minimum at a particular number of clusters. This suggests an alternative approach that does not require pre-specified subgroups, but instead tests if Eq. 31 is minimised by one, or more clusters. The merits of this approach for applications such as meta-analyses, will need exploring in greater detail elsewhere.

6.4 Statistical tests and confidence sets

Maximum likelihood estimates are usually reported with a confidence set to provide a measure of uncertainty in the estimate. In principle this is possible for clusterings, either with confidence sets for the overall configuration of clusters, or for the composition of individual clusters. One difficulty is that Eq. 31 does not have the usual asymptotic properties of log-likelihoods near the maximum likelihood estimate (MLE), that would usually involve a sum over independent random variables, for which the score function asymptotically has a normal distribution. In contrast, Eq. 31 involves a sum over clusters and the cluster’s membership.

In principle, the Bootstrap method offers a simple way to generate confidence sets. Data can be randomly sampled with replacement as usual, and an optimal clustering found by a suitable method. However, a problem with this simple approach, is that the number of clusters can change due to some clusters not being sampled. The underlying issue is that when bootstrap is usually used, each data point contributes information about all the parameters, e.g. the intercept and slope of a line. When clustering, a data point only contributes information about the cluster it belongs to. It might be possible to work around these issues with a more complex sampling method, or a more careful interpretation of results.

An alternative option when the data and sufficient computing power are available, is to bootstrap sample the underlying data used to generate the MLEs that are subsequently clustered, to obtain the optimum clustering and log-likelihood for each sample. This will give a log-likelihood $l_i$, and other properties for each clustered sample, such as the number of clusters $m_i$. After generating sufficient samples, a confidence set can then be formed using the empirical distribution of the log-likelihoods $\{l_i\}$, and the properties of samples within the confidence set can be studied. For example, the distribution for the number of clusters can then reported with a confidence set.

The “Jackknife” [10] can provide a simple estimate for variances. In practice it is often a poor estimate when a statistic is not smooth, as will be the case for statistics such as the MLE for the number of clusters. However, the variation in statistics under the leave-one-out procedure can provide a simple but useful indication of how sensitive our MLE clustering estimate is to small changes in the data. Although the Jackknife procedure is unsuitable for estimating a confidence interval for the number of clusters, the leave-one-out procedure can provide a valuable sensitivity analysis, that indicates when there is uncertainty in the MLE for the number of clusters. A histogram formed by systematically removing one item at a time before re-clustering using the Bhattacharyya distance, hierarchical clustering, and
Eq. [28] is discussed further in the Supplementary Material. The majority of cases had between 39 and 43 clusters, with a peak at 42. The Supplementary Material includes a more systematic study using simulated data, that explores how the histograms change as noise in the data is gradually increased.

6.5 Model improvements - uncertainty in covariance estimates

The clustering model does not account for uncertainty in the estimated covariances, that for MLEs, are estimated from the underlying data. One model to account for uncertainty, is to model the estimated covariances $\hat{\Sigma}_i$ as sampled from a Wishart distribution $W(\hat{\Sigma}_i|\Sigma_i/n_i, n_i)$, where $n_i$ are the number of data in the estimate for $\hat{\Sigma}_i$, and $\Sigma_i$ is the unknown covariance. Then using Bayes theorem,

$$P(\Sigma_i|\hat{\Sigma}_i, n_i) P(\hat{\Sigma}_i) = W(\hat{\Sigma}_i|\Sigma_i/n_i, n_i) P(\Sigma_i)$$  \hspace{1cm} (40)

With Jeffrey’s prior $P(\Sigma_i) \propto |\Sigma_i|^{-\nu+1/2}$, it can be shown that \[47\],

$$P(X_i|\mu, \hat{\Sigma}_i, n_i) = \frac{c_p}{\sqrt{|\Sigma_i|}} \frac{1}{\left[ 1 + (X_i-\mu)^T \Sigma_i^{-1} (X_i-\mu) \right]^{n_i+\nu/2}}$$  \hspace{1cm} (41)

where,

$$c_p = \frac{\Gamma((n_i + 1)/2)}{\pi^{n_i/2} \Gamma((n_i + 1 - p)/2)}$$  \hspace{1cm} (42)

Eq. [41] is a form of multivariate t-distribution, and can be used to calculate the likelihood. The author is presently unaware of a suitable conjugate prior or generalisation of the log-likelihood calculation of the previous Sections. An option is to formulate a numerical calculation or to implement a Dirichlet Process Mixture Model (DPMM) \[48\].

Conclusions

This research arose from a need to combine the best existing epidemiological methods with clustering techniques, so as to identify shared causes of disease \[1\]. This was accomplished by using established parametric survival models to characterise the data, through MLEs for associations between exposures and disease risks. MLEs are (asymptotically) normally distributed, which led to the general problem of clustering (multivariate) normally distributed data, to determine the number and composition of clusters. The posterior distribution for this model was calculated by marginalising the unknown cluster centres to give Eqs. \[28\] and \[31\], a procedure that is usually combined with a Laplace approximation when calculating the BIC. In the limit where the number of items in each individual cluster is large enough, then Eq. \[31\] will asymptotically agree with an equivalent expression using a sum of the usual BIC estimated for each cluster, plus a combinatoric term. The combinatoric term is intended to indicate the probability of the clusters occurring by chance. In general it is inappropriate to use the usual BIC to compare clusterings, and when used with a normal prior it will usually underestimate the penalty associated with having more clusters, but when the underlying data are normally distributed MLEs then - Eqs. \[28\] and \[31\] can be used.

A Multivariate (inverse variance weighted) sums of squares I

Note that the covariances and their inverses are symmetric, and expand,

\[
\sum_i (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) - \sum_i (\mu_g - \tilde{\mu}_g)^T \Gamma_i (\mu_g - \tilde{\mu}_g)
\]

\[
= \sum_i (x_i - \tilde{\mu}_g)^T \Gamma_i (x_i - \tilde{\mu}_g) + \sum_i (\mu_g - \tilde{\mu}_g)^T \Gamma_i (\mu_g - \tilde{\mu}_g) - 2 (\tilde{\mu}_g - \mu_g)^T \Gamma_i (\mu_g - \tilde{\mu}_g)
\]

\[
= \sum_i (\mu_g - \tilde{\mu}_g)^T (\Gamma_i (x_i - \tilde{\mu}_g) + (\mu_g - \tilde{\mu}_g)^T (\sum_i \Gamma_i (x_i) - (\sum_i \Gamma_i \tilde{x}_i)) - 2 (\mu_g - \tilde{\mu}_g)^T (\sum_i \Gamma_i x_i) - (\sum_i \Gamma_i \mu_g)
\]

where the sums are over all $i$ in cluster $C_g$. If $\tilde{\mu}$ takes the specific form given by Eq. \[6\] with,

\[
\tilde{\mu}_g = \left( \sum_{i \in C_g} \Gamma_i \right)^{-1} \left( \sum_{i \in C_g} \Gamma_i x_i \right)
\]

then the terms $\sum_i \Gamma_i x_i$ and $(\sum_i \Gamma_i) \tilde{\mu}_g$ in the last term of the final line cancel. Writing $\tilde{\Gamma}_g$ as in Eq. \[7\] with,

\[
\tilde{\Gamma}_g = \sum_{i \in C_g} \Gamma_i
\]
Because the terms involving \( \mu \) and their inverses \( \Gamma \) are symmetric, and use this to write,

\[
\begin{aligned}
\sum_{i}(x_i - \mu)\Gamma_i(x_i - \mu) &= \left(\mu - (\Sigma_i \Gamma_i)\right)^T \left(\Sigma_i \Gamma_i\right) \left(\mu - (\Sigma_i \Gamma_i)\right) \\
+ x_i^T \Gamma_i x_i - \left(\sum_i x_i^T \Gamma_i \left(\sum_i \Gamma_i\right)^{-1} \right) (\sum_i x_i \Gamma_i)
\end{aligned}
\]

that can be rearranged to give Eq. 8

**B Multivariate sums of squares II**

To integrate over \( \mu \) write \( \Gamma_i = \Sigma_i^{-1} \) and note that \( \Sigma_i \) and their inverses \( \Gamma_i \) are symmetric, and use this to write,

\[
\begin{aligned}
\sum_{i}(x_i - \mu)^T \Gamma_i(x_i - \mu) &= \left(\mu - (\Sigma_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i\right)^T \left(\Sigma_i \Gamma_i\right) \left(\mu - (\Sigma_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i\right) \\
+ \sum_{i,j} x_i^T \Gamma_i x_i - \left(\sum_i x_i^T \Gamma_i \left(\sum_k \Gamma_k\right)^{-1} \right) (\sum_i x_i \Gamma_i)
\end{aligned}
\]

The terms involving \( \mu \) in (47) will factorise in Eq. 25 and lead to Gaussian integrals that can be integrated to give functions of \{\( \Gamma_i \}\} that are independent of \{\( x_i \}\}. The remaining terms are,

\[
\begin{aligned}
\sum_{i,j} x_i^T \Gamma_i x_i - \left(\sum_i x_i^T \Gamma_i \left(\sum_k \Gamma_k\right)^{-1} \right) (\sum_i x_i \Gamma_i) \\
= \sum_{i,j} x_i^T \Gamma_i x_i - \sum_{i,j} x_i^T \Gamma_i \Gamma_j x_j \\
= \sum_{i,j} x_i^T \Gamma_i x_i - x_i^T \Gamma_i x_j
\end{aligned}
\]

where the last line is the same form as the last line of Eq. 48. Hence using Eqs. 47, 48, and 49, we have,

\[
\begin{aligned}
\sum_{i}(x_i - \mu)^T \Gamma_i(x_i - \mu) &= \left(\mu - (\Sigma_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i\right)^T \left(\Sigma_i \Gamma_i\right) \left(\mu - (\Sigma_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i\right) \\
+ \frac{1}{2} \sum_{i,j} (x_i - x_j)^T \Gamma_{ij} (x_i - x_j)
\end{aligned}
\]

where the sums over \( i, j, \) and \( k \) will range over elements in cluster \( g \).

Using Eqs. 6 and 7, Eq. 50 can alternately be written as,

\[
\begin{aligned}
\sum_{i\in C_g}(x_i - \mu)^T \Gamma_i(x_i - \mu) &= (\mu - \tilde{\mu}_g)^T \tilde{\Gamma}_g (\mu - \tilde{\mu}_g) \\
+ \frac{1}{2} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_{ij} \tilde{\Gamma}_g^{-1} \Gamma_{ij} (x_i - x_j)
\end{aligned}
\]

and comparing with Eq. 46 we can infer that,

\[
\sum_{i\in C_g}(x_i - \tilde{\mu}_g)^T \Gamma_i (x_i - \tilde{\mu}_g) = \frac{1}{2} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_{ij} \tilde{\Gamma}_g^{-1} \Gamma_{ij} (x_i - x_j)
\]

as can be confirmed by expanding out and using the definitions of \( \tilde{\mu} \) and \( \tilde{\Gamma}_g \) given by Eqs. 6 and 7

**C Using Bayes theorem to estimate the cluster mean**

Bayes theorem gives,

\[
P(\mu_g|X) = \frac{P(X|\mu_g)P(\mu_g)}{P(X)}
\]

Because \( \int P(\mu_g|X)d\mu_g = 1 \), this may alternately be written as,

\[
P(\mu_g|X) = \frac{P(X|\mu_g)P(\mu_g)}{\int d\mu_g P(X|\mu_g)P(\mu_g)}
\]
Using Eq. 46 we can write,
\[ P(X|\mu_g)P(\mu_g) \propto \exp\left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) \right\} \]
\[ = \exp\left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \tilde{\mu}_g)^T \Gamma_i (x_i - \tilde{\mu}_g) \right\} \]
\[ \times \exp\left\{ -\frac{1}{2} (\mu_g - \tilde{\mu}_g)^T \tilde{\Gamma}_g (\mu_g - \tilde{\mu}_g) \right\} \]
(55)

The factors involving \( x_i \) are independent of \( \mu_g \), and will cancel each other in the numerator and denominator of Eq. 54 Integrating over \( \mu_g \) in the denominator then leads to,
\[ P(\mu_g|X) = \frac{\exp\left\{ -\frac{1}{2} (\mu_g - \tilde{\mu}_g)^T \tilde{\Gamma}_g (\mu_g - \tilde{\mu}_g) \right\}}{\sqrt{2\pi^p} |\tilde{\Gamma}_g|^{\frac{1}{2}}} \]
(56)
where \( p \) is the dimension of \( \mu_g \).

D Alternative derivation of Eq. 25

Recalling the implicit information contained in \( Z \), we can expand the prior for cluster membership \( P(Z|I) \) as,
\[ P(Z|I) = P(Z, N_1(Z), ..., N_M(Z), M(Z)|I) \]
\[ = P(Z, N_1(Z), ..., N_m(Z)|M = m, I) P(M = m|I) \]
(57)
Assuming all assignments \( Z = \{ Z_i = z_i \} \) are equally likely, then,
\[ P(Z, N_1(Z), ..., N_m(Z)|M = m, I) = \frac{\#(Z,N_1,...,N_m)}{\#(Z,N_1,...,N_m=0)} \]
\[ = \frac{n!}{n_1!...n_m!} T(n,m) \]
(58)
where \( T(n,m) \) is the number of distributions of \( n \) identifiable items into \( m \) identifiable boxes \([40]\). Note that this is different to the multinomial distribution with equal probabilities \( \pi = 1/m \) for bin occupancy, because that allows empty bins with \( N_i = 0 \), whereas \( \{ N_i \} \) are counting the number of assignments of \( Z_i \) to a cluster. Eq. 58 is the probability for a distribution of \( N \) elements into \( 1...m \) bins such that no bins are empty, and all independent assignments \( Z = \{ Z_i = z_i \} \) are equally likely. Combining Eqs. 57, 58 and 20 gives,
\[ P(Z,X|I) \propto \frac{n!}{N_1!...N_m!} \prod_{g=1}^{m} \int_{\Gamma_g = 0}^{\Gamma_g} d\mu_g f(\mu_g; \mu_0, \Gamma_0) \left( \prod_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right) \]
(59)

Now let \( r_j \) be the number of clusters of size \( j \), with \( j = 1..k \), and \( r_j \) can be zero. Then as noted in the main text, there are \( n!/n_1!...n_m!r_1!...r_k! \) partitions of type \( (N_1, ..., N_m) \). A partition is a set of unlabelled clusters, with a form of partial labelling implied by the number of elements in the clusters. The number of equivalent rearrangements of \( m \) unlabelled clusters, with \( \{ r_j \} \) clusters with size \( j \), and \( m = \sum_{j=1}^{k} r_j \), is \([40]\),
\[ \left( \begin{array}{c} m = \sum_{j=1}^{k} r_j \\ r_1 ... r_k \end{array} \right) \]
(60)
where as before, \( r_j \) can be zero. Each arrangement corresponds to a distribution described by Eq. 59 that is unchanged by a permutation of the cluster labels. Therefore,
\[ P(C|I) = P(Z|I) \left( \begin{array}{c} m \\ r_1 ... r_k \end{array} \right) \]
\[ = \frac{n!}{N_1!...N_m!r_1!...r_k!} S(n,m) P(M = m|I) \]
(61)
where we used Eq. 58 and \( S(n,m) = T(n,m)/n! \([40]\).Eq. 61 is identical to the combination of Eqs. 22 and 23 of the main text.

E The prior \( P(M = m|I) \)

The main text suggested that the prior \( P(M = m|I) \), might best be chosen using the prior information for the particular problem being considered. Here we explore the form of \( P(M = m|I) \) that would result from randomly partitioning \( n \) identical items into \( m \) parts. Taking the number of partitions of \( n \) identical items into \( m \) parts as equivalent to the number of partitions of an integer \( n \) into \( m \) parts, and taking all partitions as equally likely,
\[ P(M = m|I) = \frac{\# \{ \text{Partitions of } n \text{ items into } m \text{ non-empty parts} \}}{\# \{ \text{Partitions of } n \text{ items} \}} \]
(62)
This can be approximated by a formula due to Paul Erdos and Joseph Lehner, that gives the distribution for the number of partitions of \( n \) into \( m \) elements or less \([49]\), with as \( n \to \infty \),

\[
F_m(n) \to \exp \left( -\frac{2}{C} \exp \left( -\frac{C}{2} \frac{m}{\sqrt{n}} + \frac{\log(n)}{2} \right) \right)
\]

with \( C = \pi \sqrt{2/3} \). Noting that \( \exp(\log(n)/2) = \sqrt{n} \), this may be written as,

\[
F_m(n) = \exp (-\beta \exp(-k/\beta))
\]

with \( \beta = 2\sqrt{n}/C \). Eq. [64] can in turn be written as,

\[
F_m(n) = \exp \left( - \left( \frac{(m - \mu)}{\beta} \right) \right)
\]

with \( \mu = \beta \log(\beta) \). This is a Gumbel distribution, with mode \( \mu = \beta \log(\beta) \) and variance \( \sigma^2 = \pi^2 \beta^2/6 = n \). However, the distribution is not symmetrical in \( n \), and more importantly, \( \sigma/\mu \sim 1/\log(\sqrt{n}) \to 0 \) as \( n \to \infty \), indicating that the distribution becomes increasingly sharply peaked about its mode as \( n \to \infty \). This would suggest that if all partitions are equally likely, then for large datasets, the prior strongly influences the number of clusters. This would be a surprising result, and needs further consideration. However it would certainly be unsuitable for situations such as a meta-analysis, where we expect that \( m \) is likely to be 1. Therefore for the examples here we will take \( P(M = m|\mathcal{I}) = 1/n \), and leave a more principled choice of prior as a topic for further study.

**F Sharply peaked prior**

The limit of a prior that is sharply peaked around \( \mu_0 \) can be considered by writing \( \Gamma_0^{-1} = I\sigma_0^2 \), \( (\Gamma_0 = I/\sigma_0^2) \), with \( I \) the identity matrix, and taking the limit \( \sigma_0^2 \to 0 \). Firstly expand \( \Gamma_g^{-1} = (\sum_{i\in C_g} \Gamma_i)^{-1} \) in terms of \( \sigma_0^2 \),

\[
\left( \sum_{i\in C_g} \Gamma_i \right)^{-1} = \left( \frac{1}{\sigma_0^2} I + \sum_{i\in C_{g,i\neq0}} \Gamma_i \right)^{-1} = \sigma_0^2 \left( I + \sigma_0^2 \sum_{i\in C_{g,i\neq0}} \Gamma_i \right)^{-1} = \sigma_0^2 \left( I - \sigma_0^2 \sum_{i\in C_{g,i\neq0}} \Gamma_i \right) + \sigma_0^4 \sum_{i\in C_{g,i\neq0}} \Gamma_i \sum_{j\in C_{g,j\neq0}} \Gamma_j + \ldots
\]

Then expand \( \tilde{\mu}_g \) in terms of \( \sigma_0^2 \),

\[
\tilde{\mu}_g = \left( \sum_{i\in C_g} \Gamma_i \right)^{-1} \sum_{j\in C_g} \Gamma_j x_j = \sigma_0^2 \left( I - \sigma_0^2 \sum_{i\in C_{g,i\neq0}} \Gamma_i + O \left( \sigma_0^4 \right) \right) \left( \frac{\mu_0}{\sigma_0^2} + \sum_{j\in C_{g,j\neq0}} \Gamma_j x_j \right)
\]

Taking the limit \( \sigma_0^2 \to 0 \),

\[
\sum_{i\in C_g} (x_i - \tilde{\mu}_g) \Gamma_i (x_i - \tilde{\mu}_g) = (\mu_0 - \tilde{\mu}_g)^T \Gamma_0 (\mu_0 - \tilde{\mu}_g) + \sum_{i\in C_{g,i\neq0}} (x_i - \tilde{\mu}_g)^T \Gamma_i (x_i - \tilde{\mu}_g)
\]

where the last line used Eq. [67] to substitute for \( \tilde{\mu}_g \), and \( \Gamma_0 = I/\sigma_0^2 \).

Using Eq. [30] the other term involving \( \Gamma_0 \) in Eq. [51] may be written as,

\[
\sum_{g=1}^{m} p \log n_g - \sum_{g=1}^{m} \log \left| \frac{\Gamma_0^{-1}}{\Gamma_g^{-1}} \right| = \sum_{g=1}^{m} \log \left| \frac{\Gamma_0^{-1}}{\Gamma_g^{-1}} \right|
\]

where \( \hat{\Gamma}_g = \frac{1}{n_g} \sum_{i\in C_g} \Gamma_i \) and \( \tilde{\Gamma}_g = \sum_{i\in C_g} \Gamma_i \). Using \( |AB| = |A||B| \) and \( |B^{-1}| = 1/|B| \), this can be written as,

\[
\sum_{g=1}^{m} \log \left| \frac{\Gamma_0^{-1}}{\Gamma_0^{-1}} \sum_{i\in C_g} \Gamma_i \right| = \sum_{g=1}^{m} \log \left| I + \sum_{i\in C_{g,i\neq0}} \Gamma_i \right|
\]

Noting that \( \Gamma_0^{-1} = I/\sigma_0^2 \), then as \( \sigma_0^2 \to 0 \), the determinant on the right-side of Eq. [70] tends to 1, and its logarithm tends to zero. Therefore as \( \sigma_0^2 \to 0 \), the only remaining terms that originally involved \( \Gamma_0 \) are the right-side of Eq. [68].

12
G  Bhattacharyya distance

The Bhattacharyya distance between two probability densities \( p_1(x) \) and \( p_2(x) \) is,

\[
D_{BC} = \int_{-\infty}^{\infty} dx_1 ... \int_{-\infty}^{\infty} dx_p \sqrt{p_1(x)p_2(x)}
\]  
(71)

For two multivariate normals as in Eq. 71 with \( \mu_g \) replaced by \( x \), \( x_1 \) replaced by \( \mu_1 \), and \( x_2 \) replaced by \( \mu_2 \), this can be integrated analytically. Using Eq. 51 with \( C_g = \{1, 2\} \) and \( \mu \) replaced by \( x \), then evaluating the normal integral involving \( x \) gives,

\[
= \sqrt{\frac{2\pi \Gamma(1+\Gamma_2^{-1})}{2\pi \Gamma_1^{-1}||2\pi \Gamma_2^{-1}}} \exp \left\{ -\frac{1}{4} (\mu_1 - \mu_2)^T \Gamma_1 (\Gamma_1 + \Gamma_2)^{-1} \Gamma_2 (\mu_1 - \mu_2) \right\}
\]  
(72)

Noting that,

\[
\Gamma_1 (\Gamma_1 + \Gamma_2)^{-1} \Gamma_2 = (\Gamma_2^{-1}(\Gamma_1 + \Gamma_2)\Gamma_1^{-1})^{-1} = (\Gamma_2^{-1}\Gamma_1\Gamma_1^{-1} + \Gamma_2^{-1}\Gamma_2\Gamma_1^{-1})^{-1} = (\Gamma_1^{-1} + \Gamma_2^{-1})^{-1} = (\Gamma_1^{-1} + \Gamma_2^{-1})^{-1}
\]

and repeating the calculation with the modifications needed to incorporate the square roots from the definition (Eq. 71),

\[
= \sqrt{\frac{2\pi \Gamma(1+\Gamma_2^{-1})}{2\pi \Gamma_1^{-1}||2\pi \Gamma_2^{-1}}} \exp \left\{ -\frac{1}{8} (\mu_1 - \mu_2)^T \left( \frac{\Gamma_1^{-1} + \Gamma_2^{-1}}{2} \right)^{-1} (\mu_1 - \mu_2) \right\}
\]  
(74)

where with the square root from Eq. 71 the factors of \( 2\pi \) cancel. Note that a factor of \( 1/2 \) has been incorporated into \( \left( \frac{\Gamma_1^{-1} + \Gamma_2^{-1}}{2} \right)^{-1} \).

Replacing \( \Gamma_i^{-1} \) with \( \Sigma_i \) gives the Bhattacharyya distance between two multivariate normal distributions in its usual form.

Data and code availability

Summary data [1], test data, and code used to produce the figures and tables will be made publicly available after publication.

Acknowledgements

AJW thanks Geoff Nicholls for helpful discussions about Section 3 and advice about previous versions of this article. Anthony Webster was supported by a fellowship from the Nuffield Department of Population Health, University of Oxford, UK. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The results arose from research detailed in Webster et al. [1], that was conducted using data from UK Biobank, a major biomedical database, under application number 42583.

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Figure 1: Using Eq. 28 log-likelihoods are calculated and their maxima subtracted (top left): all terms (black), without the combinatorial term $\log P(C|I)$, without the penalty term $\log \Pi_{g=1}^{m} \sqrt{|\tilde{\Gamma}^{-1}|/|\Gamma^{-1}_0|}$, and with the penalty term replaced by the usual BIC approximation $-\sum_{g=1}^{m} p \log n_g$. Individual terms are plotted in the bottom three figures, including the sum of squares term $-(1/2) \sum_{q=1}^{m} \sum_{i \in C_g} (x_i - \tilde{\mu}_g)^2 \Gamma_i(x_i - \tilde{\mu}_g)$. The p-value for heterogeneity and the $I^2$ statistic Eqs 11 and 14 are the top-right figures. The data describe associations between common risk factors and 156 diseases [1], hierarchically clustered to search for shared aetiologies.