Clustering parametric models and normally distributed data

Anthony J. Webster

Nuffield Department of Population Health, Big Data Institute, Old Road Campus, University of Oxford, Oxford, OX3 7LF, United Kingdom.

anthony.webster@ndph.ox.ac.uk

Abstract

A recent UK Biobank study clustered 156 parameterised models associating risk factors with common diseases, to identify shared causes of disease. Parametric models are often more familiar and interpretable than clustered data, can build-in prior knowledge, adjust for known confounders, and use marginalisation to emphasise parameters of interest. Estimates include a Maximum Likelihood Estimate (MLE) that is (approximately) normally distributed, and its covariance. Clustering models rarely consider the covariances of data points, that are usually unavailable. Here a clustering model is formulated that accounts for covariances of the data, and assumes that all MLEs in a cluster are the same. The log-likelihood is exactly calculated in terms of the fitted parameters, with the unknown cluster means removed by marginalisation. The procedure is equivalent to calculating the Bayesian Information Criterion (BIC) without approximation, and can be used to assess the optimum number of clusters for a given clustering algorithm. The log-likelihood has terms to penalise poor fits and model complexity, and can be maximised to determine the number and composition of clusters. Results can be similar to using the ad-hoc “elbow criterion”, but are less subjective. The model is also formulated as a Dirichlet process mixture model (DPMM). The overall approach is equivalent to a multi-layer algorithm that characterises features through the normally distributed MLEs of a fitted model, and then clusters the normal distributions. Examples include simulated data, and clustering of diseases in UK Biobank data using estimated associations with risk factors. The results can be applied directly to measured data and their estimated covariances, to the output from clustering models, or the DPMM implementation can be used to cluster fitted models directly.

1 Introduction

Despite some interest in clustering of normally distributed data [1–3], most studies focus on models for clustering such as mixture models or classification-tree based methods [4, 5], and few consider the (usually unknown) distribution of the underlying data. More recently the distribution of data
has been considered through clustering non-normal distributions or assuming distributions with outliers (for example see Refs [6,11]). However, multivariate normal distributions commonly arise, in particular describing the distribution of maximum likelihood estimates (MLEs) of parameterised models. As discussed in Section 2, there are many advantages to fitting a parameterised model to data and clustering the fitted parameters - the original intended application of this work.

Clustering must determine both the number and composition of clusters. When clustering MLEs, clustering must account for uncertainty in the MLEs as characterised by their covariances, and caused for example by different sample sizes or correlations between covariates. This is accomplished here for a simple model whose log-likelihood is calculated in Sections 3, 4, and 5. Results are often qualitatively similar to minimising the within-cluster sum of Mahalanobis distances and using the elbow criterion to determine the number of clusters. A Dirichlet Process Mixture Model (DPMM) implementation of the clustering model is described in Section 6, and when it converges, has been found to give similar results. The clustering model has simple assumptions and leads to additional terms that reflect model complexity, and its maximisation objectively determines both the number and composition of clusters.

Section 2 outlines the advantages of fitting a parameterised model prior to clustering, an approach that is rarely used at present [3,12–16]. Section 3 describes a simple model for clustering multivariate normal distributions that assumes clusters have items with the same mean. The exactly calculated log-likelihood is equivalent to an exact calculation of the Bayesian Information Criterion (BIC) [3,4,17–19], for a particular type of product partition model [20,21]. The resulting likelihood includes a weighted sum of squares term that penalises poor fits, and a term to capture model complexity that has similarities to the equivalent model-complexity terms in AIC [4,22] and BIC [3,4,17–19]. For recent progress on approximate calculations of BIC and a review of related literature, see [3]. Section 5 generalises the calculation in Sections 3 and 4 with a flat prior, to a normally distributed prior. Section 5.2 considers some important limits. Section 6 describes a DPMM implementation of the clustering model. Section 7 provides numerical examples, and Section 8 considers the clustering of diseases that originally motivated this work. Section 9 explores how the model relates to the k-means algorithm. Section 10 discusses the results and highlights topics for future work.

2 Clustering of parametric models

Most parametric models use maximum likelihood estimates (MLEs) to obtain normally distributed estimates of their parameters, specified by a mean \( \mu \) and a covariance matrix \( \Sigma \) [4]. This suggests clustering data by firstly fitting a model to capture relevant information, and then clustering the normally distributed estimates. An example of particular interest is characterisation and classification of diseases using large population datasets and electronic health records [1]. In that case,
survival models were used to estimate the associations of risk factors with disease incidence using epidemiological information about known confounding factors, accounting for truncation and censoring, and the normally distributed estimates for risk-factor associations were then clustered to identify relationships between diseases [1]. There are several advantages to this approach:

1. The distribution of underlying data can be unknown, but under reasonable regularity conditions, MLE estimates are normally distributed [4, 23].
2. Estimates can be stratified and multiply-adjusted for known confounders, helping to extract the information of interest from potentially noisy data [1, 4, 24].
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 [4, 5] 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.

These benefits are increasingly valued [1, 14–16], with similar approaches being used to detect changes in gene expression by clustering Fourier series coefficients [14, 15]. Clustering parameters of linear-models such as a Fourier series, are examples of clustering the normally-distributed MLE estimates of parameterised models. Here we consider the general problem of clustering multivariate normals, to determine both the number and membership of clusters.

3 Clustering multivariate normal distributions

We firstly consider a distribution [25] of identifiable items in identifiable boxes, then use this to consider the likelihood for a partition [25] of identifiable items in unlabelled clusters.\(^1\)

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,

\[
\hat{\mu}_i \sim N \left( \mu_{Z_i}, \hat{\Sigma}_i \right)
\]

with \(\mu_{Z_i} = \mu_{Z_j}\) iff \(Z_i = Z_j\). We will regard \(\hat{\Sigma}_i\) as given, and \(\hat{\mu}_i\) as random variables sampled from Eq. [1]. Write \(X_i = \hat{\mu}_i\), \(\Gamma_i = \hat{\Sigma}_i^{-1}\), and the propositions \(Z = \{Z_i = z_i\}\), \(X = \{X_i = x_i\}\),

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\(^1\) Implicitly, 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.
\( \mathcal{M} = \{ \mathcal{M}_g = \mu_g \} \), where \( \mu_g \) is the mean of cluster \( g \). We will also write \( \mathcal{I} \) to denote both \( \{ \Gamma_i \} \) and any additional implicit information regarding the clustering problem.

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 \( P(Z|X, \mathcal{I}) \) as a product with one term per item to be clustered.

Consider the likelihood of assigning labelled items into a distribution [25] of labelled clusters. Using Bayes theorem and marginalisation [4, 5],

\[
P(Z|X, \mathcal{I}) P(X|Z) = P(X|Z, \mathcal{I}) P(Z|\mathcal{I})
\]

The second line above is read as the probability of observing data \( X \) and clusters with means \( \mathcal{M} \), given the cluster assignments \( Z \), and \( \mathcal{I} \). (This is very different to writing this as the product of probabilities of independent observations \( X_i \), with cluster means \( \mu_{Z_i} = \Pi_{g=1}^m \Pi_{g=g} f(Z_i = g) \).)

For independent normally distributed \( \{ X_i \} \) with covariances \( \{ \Gamma_i^{-1} \} \), sampled from clusters \( g = 1..m \) with means \( \{ \mu_g \} \),

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

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. [3] has the form of a product partition model [20, 21]. In the following discussions we consider two priors for the means \( \mathcal{M} \), one a flat prior with \( P(\mathcal{M}|Z, \mathcal{I}) \) constant, and the other a normal distribution with,

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

We include Eq. [5] in the analysis below. Using Eqs. [3] and [5], Eq. [2] gives,

\[
P(Z|X, \mathcal{I}) \propto P(X|Z, \mathcal{I}) P(Z|\mathcal{I})
\]

Now consider the likelihood for a partition [25] of type \( (N_1, ..., N_m) \) with \( m \) clusters, and \( r_1 \ldots r_k \) clusters of size \( 1 \ldots k \). Notice that in Eq. [6] the factor \( P(X|Z, \mathcal{I}) \) 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 \( P(X|Z, \mathcal{I}) \) is unchanged. Therefore we can write the probability of a partition \( C \) as,

\[
P(C|X, \mathcal{I}) = \sum_{Z \in C} P(Z|X, \mathcal{I}) \propto \sum_{Z \in C} P(X|Z, \mathcal{I}) P(Z|\mathcal{I}) = P(X|Z \in C, \mathcal{I}) \sum_{Z \in C} P(Z|\mathcal{I})
\]
Where we used the above observation that \( P(X|Z,\mathcal{I}) \) 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,

\[
P(C|\mathcal{I}) = \sum_{Z:Z \in C} P(Z|\mathcal{I}) = \sum_{Z:Z \in C} P(Z|M = m, \mathcal{I}) P(M = m|\mathcal{I}) \tag{8}
\]

and make the prior assumption that all assignments \( Z \) are equally likely given \( M = m \), giving,

\[
\sum_{Z:Z \in C} P(Z|M = m, \mathcal{I}) = \frac{\#(Z:Z \in C, M = m)}{\#(Z:M = m)} \frac{1}{N_1!...N_m!r_1!...r_k! S(N,m)}
\tag{9}
\]

Which equals the number of partitions of type \((N_1, ..., N_m)\), divided by the total number of partitions of \( N \) identifiable items into \( m \) non-empty clusters (the Stirling numbers of the second kind \( S(N,m) \) \([25]\)). An alternative calculation using \( P(Z|\mathcal{I}) \) is given in Appendix A.

For \( P(M = m|\mathcal{I}) \), there are no labels \( \{Z_i\} \) for items, or cluster numbers \( \{N_i\} \). Appendix B considers whether \( P(M = m|\mathcal{I}) \) 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 \( P(M = m|\mathcal{I}) \) might best be informed by the particular application. For the examples here, we will take it as constant \( P(M = m|\mathcal{I}) = 1/N \). Continuing as before,

\[
P(X|Z \in C, \mathcal{I}) = \int_{-\infty}^{\infty} d\mu_1... \int_{-\infty}^{\infty} d\mu_m P(X|M, Z \in C, \mathcal{I}) P(M|Z \in C, \mathcal{I})
\]
\[
= \int_{-\infty}^{\infty} d\mu_1... \int_{-\infty}^{\infty} d\mu_m \left( \prod_{g \in C_g} f(x; \mu_g, \Gamma_i) \right) \left( \prod_{g=1}^{m} f(\mu_g; \mu_0, \Gamma_0) \right)
\tag{10}
\]

Putting Eqs. (7-11) together we have,

\[
P(C|X, \mathcal{I}) \propto P(X|Z \in C, \mathcal{I}) P(C|\mathcal{I}) \]
\[
= P(M = m|\mathcal{I}) \frac{1}{N_1!...N_m!r_1!...r_k! S(N,m)} \times \left( \prod_{g=1}^{m} \frac{1}{(2\pi)^{p_g/2}|\Gamma_g|^{1/2}} \right) \times \left( \prod_{g=1}^{m} \int_{-\infty}^{\infty} d\mu_g f_0(\mu_g) \exp \left\{ -\frac{1}{2} \sum_{i \in C_g} (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) \right\} \right)
\tag{11}
\]

where \( f_0(\mu_g) \) is the prior for \( \mu_g \), for example \( f_0(\mu_g) = f(\mu_g; \mu_0, \Gamma_0) \). The factors group into terms that correspond to the prior probability of splitting \( N \) equivalent items into between 1 and \( N \) non-empty clusters, multiplied by the prior probability of a partition of type \((N_1...N_m)\), given that there are \( m \) clusters and making the prior assumption that all \( Z \) are equally likely, multiplied by the probability of the data given that it has that partition. Eq. (11) has the reassuring quality that we could, quite reasonably, have written it down as the model we were going to study without any further justification.

Compare Eq. (11) 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 \( \{ \Gamma_i \} \) can differ for each data point instead of only between clusters.

4 Evaluating the likelihood - a uniform prior

The (prior) distribution for \( \mu_g \) will usually be unknown. The following Section 5 will show how a normal distribution for \( \mu_g \) with \( \mu_g \sim N(\mu_0, \Gamma_0^{-1}) \), can be incorporated into the analysis. Section 5.2 will show that a “uniform prior” cannot in general be regarded as a limiting case of the normal prior \( N(0, \Gamma_0^{-1}) \), using an example with \( \Gamma_0 = I/\sigma^2 \) where \( I \) is the identity matrix, in the limit where \( \sigma^2 \rightarrow \infty \). However, for simplicity of presentation, firstly consider a uniform prior.

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,

\[
\sum_i (x_i - \mu)^T \Gamma_i (x_i - \mu) = \left( \mu - \left( \sum_i \Gamma_i \right)^{-1} \sum_i \Gamma_i x_i \right)^T \left( \sum_i \Gamma_i \right) \left( \mu - \left( \sum_i \Gamma_i \right)^{-1} \sum_i \Gamma_i x_i \right)
\]

\[
+ \sum_i x_i^T \Gamma_i x_i - \left( \sum_i x_i^T \Gamma_i \right) \left( \sum_k \Gamma_k \right)^{-1} \left( \sum_j \Gamma_j x_j \right)
\]

The terms involving \( \mu \) in (12) factorise in Eq. (13) and lead to Gaussian integrals that integrate to give functions of \( \{ \Gamma_i \} \) that are independent of \( \{ x_i \} \). The remaining terms are,

\[
\sum_i x_i^T \Gamma_i x_i - \left( \sum_i x_i^T \Gamma_i \right) \left( \sum_k \Gamma_k \right)^{-1} \left( \sum_j \Gamma_j x_j \right)
\]

Because \( \Sigma_i \) and their inverses \( \Gamma_i \) are symmetric, then \( C_{ij} = \Gamma_i \left( \sum_k \Gamma_k \right)^{-1} \Gamma_j \) has \( C_{ij} = C_{ji}^T \), as can be seen by taking the transpose of \( C_{ij} \). Using \( C_{ij} = C_{ji}^T \), \( a^T b = b^T a \) for vectors \( a \) and \( b \), and relabeling the indices \( i \) and \( j \),

\[
\frac{1}{2} \sum_{i,j} (x_i - x_j)^T C_{ij} (x_i - x_j)
\]

\[
= \frac{1}{2} \sum_{i,j} x_i^T C_{ij} x_i + \frac{1}{2} \sum_{i,j} x_j^T C_{ij} x_j - \frac{1}{2} \sum_{i,j} x_i^T C_{ij} x_j - \frac{1}{2} \sum_{i,j} x_j^T C_{ij} x_i
\]

\[
= \sum_{i,j} x_i^T C_{ij} x_i - \frac{1}{2} \sum_{i,j} x_i^T C_{ij} x_j - \frac{1}{2} \sum_{i,j} x_j^T C_{ji} x_i
\]

Hence using Eqs. (13) and (14) we have,

\[
\sum_i x_i^T \Gamma_i x_i - \left( \sum_i x_i^T \Gamma_i \right) \left( \sum_k \Gamma_k \right)^{-1} \left( \sum_j \Gamma_j x_j \right)
\]

\[
= \frac{1}{2} \sum_{i,j} (x_i - x_j)^T \Gamma_i \left( \sum_k \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j)
\]
where the sums over $i$, $j$, and $k$ will range over elements in cluster $g$.

Eq. [15] is an intuitively reasonable result, that after marginalisation with respect to the means $\mu_g$, the likelihood will be determined from differences in the estimated means within each cluster with an inverse covariance matrix $\Gamma_i(\sum_{k \in C_g} \Gamma_k)^{-1}\Gamma_j$, that is weighted by the inverse covariances of $x_i$ and $x_j$, and the inverse of the average inverse-covariance of their cluster. Note that the extra factor of $1/2$ prevents double counting in the sum over $i$ and $j$, with $(1/2) \sum_{i,j} F(i,j) = \sum_{i} \sum_{j \geq i} F(i,j)$ for any $F(i,j)$ with $F(i,i) = 0$ and is symmetric with respect to exchange of $i$ and $j$, so that the sum involves exactly one term for every unique combination of $i$ and $j$ in cluster $g$. Using Eqs. [12] and [15] and integrating over $\mu_g$ gives,

$$
\int_{-\infty}^{\infty} d\mu_g \exp \left( -\frac{1}{2} \sum_{i \in C_g} (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) \right)
= \left| 2\pi \left( \sum_{k \in C_g} \Gamma_k \right)^{-1} \right|^{1/2} \times 
\exp \left( -\frac{1}{4} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_i \left( \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j) \right)
\tag{16}
$$

Using Eq. [11] and [16] the log-likelihood has,

$$
\log (P(G|x, \Gamma)) = -\frac{1}{2} \sum_i \log |2\pi \Gamma_i^{-1}| + \frac{1}{2} \sum_{g=1}^{m} \log \left| 2\pi \left( \sum_{k \in C_g} \Gamma_k \right)^{-1} \right| - \frac{1}{4} \sum_{g=1}^{m} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_i \left( \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j) + \log (P(C|I))
\tag{17}
$$

The last term $\log(P(C|I))$ is a prior log-likelihood for the partition based on combinatorial considerations. Comparing it with the observed Fisher information, it is analogous to an observed entropy. The first term on the right side of Eq. [17] is independent of the clustering model, the third term involves a sum of squares that measures the goodness of fit of the data to the model, and the second term captures the model’s complexity. For $\mu$ with dimension $p$, the determinants in the middle term can be considered as a product of $p$ eigenvalues, leading to a sum of $p$ logarithms of the eigenvalues for each cluster. Those $p \times m$ terms are analogous to the number of free parameters in AIC [4], $m$ clusters with $p$ dimensions give $m \times p$ parameters. An MLE’s estimated covariance is roughly proportional to the number of data used to estimate it [4, 23], which adds a (complicated) dependence on the number of data points into Eq. [17] through the second term, that has some similarities to the $\log(n)$ term in BIC [4].

Note that the sum of squares term involves $\left( \sum_{k \in C_g} \Gamma_k \right)$, that uses information from all members of the cluster. As a result, clusters that maximise Eq. [17] will in general differ from clusters that use pair-wise distance based measures. Therefore clusters that maximise Eq. [17] will typically differ from pair-wise distance-based e.g. hierarchical clustering models.
We can use Eq. [17] to evaluate and compare the log-likelihoods of clusterings proposed for example by hierarchical clustering. This allows us to determine the number of clusters that maximise the log-likelihood of the clustering method. Alternately we can directly maximise Eq. [17]. Because the likelihood factorises in terms of the clusters, if Metropolis MCMC were used to generate a sample of clusters, then the change in log-likelihood at each iteration is determined solely by the change in log-likelihood of the clusters whose membership changes.

5 A normal prior

As mentioned earlier, if we had taken a normally distributed prior \( f(\mu_g; \mu_0, \Gamma_0^{-1}) \), with \( \mu_g \sim N(\mu_0, \Gamma_0) \), then there would be an extra term \( (\mu - \mu_0)^T \Gamma_0 (\mu - \mu_0) \) on the left side of Eq. [12].

Taking \( \mu_0 = 0 \) for now, the extra term will cause the \( \sum_i \Gamma_i \) terms on the right side of Eq. [12] to be replaced by \( \Gamma_0 + \sum_i \Gamma_i \), with [2]

\[
\sum_i (x_i - \mu)^T \Gamma_i (x_i - \mu) + \mu^T \Gamma_0 \mu \\
= (\mu - (\Gamma_0 + \sum_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i)^T (\Gamma_0 + \sum_i \Gamma_i) \left( (\mu - (\Gamma_0 + \sum_i \Gamma_i)^{-1} \sum_i \Gamma_i x_i) \right) \\
+ \sum_i x_i^T \Gamma_i x_i - (\sum_i x_i^T \Gamma_i) (\Gamma_0 + \sum_k \Gamma_k)^{-1} \left( \sum_j \Gamma_j x_j \right) \\
\]

Noting that,

\[
\sum_i x_i^T \Gamma_i x_i = \sum_i x_i^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \left( \Gamma_0 + \sum_j \Gamma_j \right) x_i \\
= \sum_i x_i^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_0 x_i \\
+ \sum_{i,j} x_i^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_j x_j \\
\]

and using this with Eq. [14] with \( C_{ij} = \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_j \), we get,

\[
\sum_i x_i^T \Gamma_i x_i - (\sum_i x_i^T \Gamma_i) (\Gamma_0 + \sum_k \Gamma_k)^{-1} \left( \sum_j \Gamma_j x_j \right) \\
= \sum_i x_i^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_0 x_i \\
+ \frac{1}{2} \sum_{i,j} (x_i - x_j)^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_j (x_i - x_j) \\
\]

The first term on the right of Eq. [20] can alternately be written in a symmetrical form with,

\[
\sum_i x_i^T \Gamma_i x_i - (\sum_i x_i^T \Gamma_i) (\Gamma_0 + \sum_k \Gamma_k)^{-1} \left( \sum_j \Gamma_j x_j \right) \\
= \frac{1}{2} \sum_i x_i^T (\Gamma_i + \Gamma_0)^T (\Gamma_0 + \sum_k \Gamma_k)^{-1} (\Gamma_0 + \Gamma_i) x_i \\
- \frac{1}{2} \sum_i x_i^T \Gamma_i^T (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_i x_i - \frac{1}{2} \sum_i x_i^T \Gamma_0^T (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_0 x_i \\
+ \frac{1}{2} \sum_{i,j} (x_i - x_j)^T \Gamma_i (\Gamma_0 + \sum_k \Gamma_k)^{-1} \Gamma_j (x_i - x_j) \\
\]

An alternative way of seeing the calculation below is to consider the addition of a normal prior with zero mean as equivalent to adding an extra term \( k \) into each cluster with \( \Gamma_k = \Gamma_0 \), and setting \( x_k = 0 \). Setting \( x_k = 0 \) in a cluster gives the left side of Eq. [18] and setting \( x_k = 0 \) in Eq. [17] gives the equivalent extra terms in Eq. [17] to those in Eq. [23].
Recalling that,
\[
f(\mu_g; 0, \Gamma_0) = \frac{1}{\sqrt{2\pi\Gamma_0^{-1}}} \exp \left\{ -\frac{1}{2} \mu_g^T \Gamma_0 \mu_g \right\}
\]
and that there is one for each of the \( m \) clusters, then after marginalisation over each \( \mu_g \), the log-likelihood will have,
\[
\log (P(G|x, \Gamma)) = -\frac{m}{2} \log |2\pi \Gamma_0^{-1}| - \frac{1}{2} \sum_i \log |2\pi \Gamma_i^{-1}|
+ \frac{1}{2} \sum_{g=1}^{m} \log \left| 2\pi \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \right|
- \frac{1}{4} \sum_{g=1}^{m} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j)
- \frac{1}{2} \sum_{g=1}^{m} \sum_{i \in C_g} x_i^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_0 x_i
+ \log (P(C|I))
\]
where \( C \) is a constant that ensures correct normalisation of the probability distribution.

5.1 Prior with \( \mu_0 \neq 0 \)

A prior for \( \mu_g \) with \( \mu_0 \neq 0 \) can be easily incorporated by noting that,
\[
\sum_i (x_i - \mu_g)^T \Gamma_i (x_i - \mu_g) = \sum_i ((x_i - \mu_0) - (\mu_g - \mu_0))^T \Gamma_i ((x_i - \mu_0) - (\mu_g - \mu_0))
\]
So a simple change of variables with \( \tilde{x}_i = x_i - \mu_0 \) and \( \tilde{\mu}_g = \mu_g - \mu_0 \) (that will have a Jacobian of 1 for the change of variables with respect to \( \mu_g \)), will give,
\[
\Pi_{g=1}^{m} \int_{-\infty}^{\infty} d\mu_g f(\mu_g; \mu_0, \Gamma_0) \left( \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right)
= \Pi_{g=1}^{m} \int_{-\infty}^{\infty} d\tilde{\mu}_g f(\tilde{\mu}_g; 0, \Gamma_0) \left( \Pi_{i \in C_g} f(\tilde{x}_i; \tilde{\mu}_g, \Gamma_i) \right)
\]
which is the same form as a normal prior with \( E[\mu_g] = 0 \). So if \( \mu_0 \neq 0 \), then we simply need to offset the data values with \( \tilde{x}_i = x_i - \mu_0 \) and evaluate the log-likelihood with Eq. \( \text{(23)} \) (for \( \mu_0 = 0 \)). For example, most epidemiological studies find that smoking and high BMI increase your risk of disease, so we could include that prior information about \( \mu_0 \) through an offset.

Often data are centred prior to clustering. When data such as fitted models have both estimates and covariances, then instead of simply centring the data, a better estimate can be obtained by using Eq. \( \text{(22)} \) and considering the data as a single cluster to estimate \( \mu_0 \). However it may not be appropriate to centre the data because, as was illustrated above, centring the data is equivalent to using the data to help choose a prior. This is discussed further in Section 10.
5.2 Important limits

A flat prior cannot be considered as a limiting case of a normal prior with, for example, \( \Gamma_0^{-1} = \sigma_0^2 I \) and \( \sigma_0^2 \to \infty \). This can be seen from Eqs. [11] and Eq. [23]. Considering Eq. [23], the first term is \( -(m/2)p \log(2\pi \sigma_0^2) \) and tends to \( -\infty \), the 2nd term is independent of \( \Gamma_0 \), the 3rd term tends to \( \log((\sum_{k \in C_g} \Gamma_k)^{-1}) \), the 4th term has \( (\Gamma_0 + (\sum_{k \in C_g} \Gamma_k)^{-1}) \to (\sum_{k \in C_g} \Gamma_k)^{-1} \), and the final term is proportional to \( \Gamma_0^{-1} = \sigma_0^2 I \) and tends to zero. The behaviour of the 1st term, that ensures \( f(\mu_g; 0, I/\sigma_0^2) \) is correctly normalised, can be understood from Eq. [11]. As \( \sigma_0^2 \) becomes larger, \( P(M_g = 0) \) must become increasingly small to ensure that \( P(M_g = \mu_g) \) is correctly normalised, and there is an extra factor for each cluster. For this example with \( \Gamma_0^{-1} = \sigma_0^2 I \), the first term provides a penalty that is proportional to the number of free parameters \( m \times p \). For the alternative limit with \( \sigma_0^2 \to 0 \), then the first and third terms cancel, but the final term diverges at a rate proportional to \( 1/\sigma_0^2 \).

Often data without covariances are clustered. To explore this limit, take \( \Gamma_i^{-1} = \sigma^2 I \) and let \( \sigma \to 0 \). The final term diverges most rapidly \( (\sim 1/\sigma^2) \), and has,

\[
(x_i - x_j)^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j) \to \frac{1}{\sigma^2} \frac{(x_i - x_j)^T (x_i - x_j)}{n_g}
\]

where \( n_g \) is the number of items in group \( g \). This can be written as,

\[
-\frac{1}{4} \sum_{g=1}^m \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j) \\
\to -\frac{1}{2\sigma^2} \sum_{g=1}^m \frac{1}{2n_g} \sum_{i,j \in C_g} (x_i - x_j)^T (x_i - x_j)
\]

(27)

showing that as the variance in the data becomes increasingly small, the log-likelihood is maximised by the minimum sum of within-group sum of squares.

In practice, data points may be measured along with estimated errors. Their estimated covariances might simply be a diagonal matrix whose diagonal entries are the variances of the measured values. If covariances are entirely unavailable, then competition between terms can be explored by taking a diagonal covariance \( \Omega^2 I \), and treating \( \Omega^2 \) as a temperature-like parameter, with \( P(C|\mathcal{Z}) \) dominating at large \( \Omega^2 \) but \( P(X|Z \in C, \mathcal{Z}) \) dominating at small \( \Omega^2 \). Combined with some prior e.g. expert knowledge, this might be helpful when assessing how many clusters to consider.
Dirichlet process mixture model and estimation of cluster parameters

The number and membership of clusters are determined by maximising the log-likelihood, without the cluster means needing to be estimated. If the cluster means are required then they can be calculated for each cluster \( C_g \) from the data \( \{(X_i, \Gamma_i)\} \) with \( i \in C_g \), using Bayes theorem,

\[
P(\mu_g | X, i \in C_g, \mathcal{I}) = \frac{P(X | \mu_g, i \in C_g, \mathcal{I})P(\mu_g)}{\int P(X | \mu', i \in C_g, \mathcal{I})P(\mu')d\mu'}
\]

(28)

If \( P(\mu_g) \) has a normal distribution, then it is a conjugate prior for the normal distribution \( P(X | \mu_g, i \in C_g, \mathcal{I}) \). Taking a prior with,

\[
\mu'_g \sim N(\mu_0, \Gamma_0^{-1})
\]

(29)

and a likelihood with,

\[
X_i \sim N(\mu'_g, \Gamma_i^{-1})
\]

(30)

then the posterior for a sample of \( n_g \) data in cluster \( g \) has (Appendix C),

\[
\mu_g \sim N\left(\mu_g, \tilde{\Lambda}_g\right)
\]

(31)

with,

\[
\tilde{\mu}_g \overset{\sim}{=} \left(\Gamma_0 + \sum_{i \in C_g} \Gamma_i\right)^{-1}\left(\Gamma_0 \mu_0 + \sum_{i \in C_g} \Gamma_i X_i\right)
\]

(32)

and covariances,

\[
\tilde{\Lambda}_g = \left(\Gamma_0 + \sum_{i \in C_g} \Gamma_i\right)
\]

(33)

allowing the cluster means to be estimated, and providing covariances for the estimates. Given a new data point \( \tilde{x} \) and its covariance \( \tilde{\Lambda}^{-1} \), such as from a new fitted model, then we can calculate its probability of cluster membership using,

\[
P\left(\tilde{X} = \tilde{x} | X, i \in C_g, \mathcal{I}\right) = \int P\left(\tilde{X} = \tilde{x} | \mu_g, \mathcal{I}\right) P(\mu_g | X, i \in C_g, \mathcal{I}) d\mu_g
\]

(34)

and Eq. 31 for the distribution \( P(\mu_g | X, Z \in C_g, \mathcal{I}) \). Evaluating the integral using the results in Appendix C, then shows,

\[
\tilde{X} \sim N\left(\tilde{\mu}_g, \left(\tilde{\Lambda} + \tilde{\Lambda}_g\right)^{-1}\tilde{\Lambda}_g\right)
\]

(35)
Eqs [28] [35] can be used to formulate the model as a Dirichlet process mixture model (DPMM), that can be solved with a numerical routine such as that implemented by the “dirichletprocess” package [27] in R. The dirichletprocess package is intended to allow modified DPMM to be created without coding the underlying Dirichlet process. Specifically, it requires the user to supply functions to calculate the: A. prior draw, B. likelihood, C. posterior draw, D. marginal predictive distribution of the data given the prior, and to initialise the calculation. A-D respectively code up Eqs. [29] [30] [31] and [35] with $\tilde{\Lambda} = \Gamma$ and $\tilde{\Lambda}_g = \Lambda_0$. Eq. [35] can also be used to select a cluster to assign a new data point to, as discussed in Section [10].

7 Example 1: Simulated data

Figure 1: Test sets were formed for 300 items from 50 clusters, as detailed in the main text. The data were 10 dimensional, and the data were sampled with a signal to noise ratio (SNR) of $\sqrt{\text{tr}(\Sigma_0)/\text{tr}(\Sigma_i)} = \sqrt{5}$. The log-likelihoods were calculated for $N=1$ to 100 clusters using hierarchical clustering with the Bhattacharyya distance and the Ward D2 algorithm in R. Dirichlet Process Mixture Models (DPMM) were also considered, starting from $m = 1$ and $m = N$ initial clusters, and both converged to a solution that maximised the log-likelihood. At the maximum in the log-likelihood, the original clusters of the test data were correctly identified by both methods.

To compare clustering methods, simulated data were created that were expected to be similar to the epidemiological survival data in Ref. [1]. A set of clusters with between 2 and 14 items in each cluster were considered, with $\{N_g\} = \{2, 2, 2, 2, 3, 3, 3, 3, 4, 4, 4, 5, 6, 6, 7, 7, 8, 8, 9, 9, 11, 11, 12, 12, 14\}$, for a total of 300 items in 50 clusters. This was intended to be similar to clustering $\sim 100 - 400$
diseases, (the majority of which were likely to have similar risk factors when present in both men and women). Covariance matrices were sampled by taking,

\[ \Sigma \sim a \text{ diag}(u) + b \text{ outer}(u, u) \]  \hspace{1cm} (36)

where \( u \sim \text{Unif}(1) \) or a vector of 1s with dimension \( p \), “outer()” is the outer product as defined in the R statistical language [28], and \( \Sigma \) was subsequently normalised to have the desired trace. Cluster centres were sampled from a normal distribution with \( \mu_g \sim N(0, \Sigma_0), p = 10 \), and \( tr(\Sigma_0) = 1 \), and \( \mu_g \) were rejected unless a \( \chi^2 \) test was statistically significant at the 0.05 level. Test sets were specified in terms of \( a, b \), where \( u \) was a vector of 1s or sampled from \((0, 1)\), and \( tr(\Sigma_i) = s^2 \) for all clusters in the test data set, so that the signal to noise ratio is \( \sqrt{tr(\Sigma_0)/tr(\Sigma_i)} \sim 1/s \). Data were then sampled as \( X_i \sim N(\mu_g, \Sigma_i) \) for all members of each cluster \( \{N_g\} \).

For comparison with a more traditional statistical test, the null hypothesis of equal means in each group was considered. Data from the same group \( g \) have \( x_i \sim N(\mu_g, \Gamma_i^{-1}) \), so summing over all pairs in all groups gives,

\[ \frac{1}{2} \sum_{g=1}^{m} \sum_{i,j \in C_g} (x_i - x_j)^T \left( \Gamma_i^{-1} + \Gamma_j^{-1} \right)^{-1} (x_i - x_j) \sim \chi^2_{pq} \]  \hspace{1cm} (37)

where \( p \) is the dimension of \( \mu_g \) and \( q = \sum_{g=1}^{m} n_g(n_g - 1)/2 \), with \( n_g \) the number of data points in cluster \( g \), so that \( n_g(n_g - 1)/2 \) is the number of distinct pairs of different diseases in each cluster and \( q \) is the total sum of disease pairs. This provides an approximate statistical test for the null hypothesis of equal means in each group, for comparison with the maximisation of Eqs. 17 or 23. Alternative tests that were originally developed for use with meta-analyses could also be used, these are discussed in Ref. [29].

The example shown in figure 1 took a signal to noise ratio of \( \sqrt{5} \), and assumed a normal prior with \( \sqrt{tr(\Sigma_0)} = 3 \), that should be sufficiently broad to influence clustering only indirectly by favouring fewer clusters. Both DPMM models starting with \( m = 1 \) and \( m = N \) clusters converged to produce the same clustering. Hierarchical clustering using the Bhattacharyya distance (see Appendix D), and the Ward.D2 algorithm from the R software package [28], also correctly identified the test data’s clusters. Similar results were found for an SNR of \( \sqrt{10} \). In another example with SNR=\( \sqrt{2} \), after 60000 iterations the DPMM models did not fully converge, but the hierarchical clustering at the log-likelihood’s maximum correctly identified the test data’s clusters. In these examples, the combination of hierarchical clustering with the Bhattacharyya distance, Ward.D2 algorithm, and maximum log-likelihood, were very effective at finding the original test clusters. It is recognised that for some data, DPMM models will not always converge in an acceptable time [30]. For the examples here, when the DPMM models did converge, they correctly identified the original test clusters. The convergence time increased as the signal to noise ratio (SNR), became less.
A recent epidemiological study using UK Biobank data [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. [1], the code and data are available by application from www.ukbiobank.ac.uk. Diseases with statistically significant differences between men and women after an FDR multiple-testing adjustment [4] 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 associations between exposures and disease incidence, because exposure-disease associations were expected to reflect causal disease pathways. Because the associations between risk factors for disease are often strongly correlated, the covariances of MLEs must be accounted for when clustering. Given the complex exposure-diagnosis pathways and diseases’ different incident rates (sample sizes), the 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 [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 \( \{ \hat{\mu}_i, \hat{\Sigma}_i \} \) into groups with similar \( \{ \mu_g \} \). A simple model that accounts for the uncertainty of estimates \( \{ \hat{\mu}_i \} \) through their covariances, is to take \( \hat{\mu}_i \sim N(\mu_g, \hat{\Sigma}_i) \) for clusters with means \( \{ \mu_g \} \), the model considered here.

An important question was whether associations with a given disease were the same in both men and women. The probability of the same male-female disease pair appearing together in the same cluster by chance is very low for large numbers of e.g. 20 or more clusters. For the 24 clusters studied, the authors found around 83\% of disease pairs appeared together in the same cluster, which would be very unlikely to have occurred by chance. For this example, the number of male-female disease pairs that appear in the same cluster, is likely to give an indication of how well the diseases are clustered.

Figure 2 shows the log-likelihood for hierarchical clustering with the Bhattacharyya distance (see Appendix D), for a flat prior, and for normal priors with an isotropic covariance \( \Sigma_0 \) with \( \sqrt{tr(\Sigma_0)} \) equal to 2, 3, 4, and 5 (for \( X_i \sim N(\mu_0, \Sigma_0) \), \( E[(X_i - \mu_0)^2] = tr(\Sigma_0) \)). The figure emphasises the importance of the prior. Greater uncertainty about the data is expressed through a prior with greater variance, and this leads to the maxima in the log-likelihood becoming deeper and occurring at a smaller number of clusters, closer to the “elbow” in \( \chi^2 \). The maximum log-likelihood with a flat prior is at \( N = 37 \), but the maxima is very shallow, and would have a very large confidence set. With a normal prior (that is suitable for this example), the maxima is deeper.
and much closer to the “elbow” in $\chi^2$, at similar values of $m = 25$ (for $\sqrt{tr(\Sigma_0)} = 2$) and $m = 22$ otherwise. With a normal prior, the maxima provides a similar result to the “elbow” criteria, but is a less subjective.

For the DPMM model we took a prior with $\sqrt{tr(\Sigma_0)} = 3$, that was expected to be greater than most of the MLE estimates, and clusters were calculated using the dirichletprocess package as described earlier. The results were disappointing in several respects. Firstly, after 160,000 iterations, models starting from $m = 1$ and $m = n$ clusters converged to 37 and 39 clusters respectively, with at most 64% of disease pairs common to the two clustering calculations (see Ref. [1] for details of this comparison). They respectively had a maximum of 59% and 60% of disease pairs common to clusters in the hierarchical clustering model. Secondly, the DPMM results for $m = 1$ and $m = N$ had log-likelihoods that were 28.0 and 37.1 less than the maximum log-likelihood found by hierarchical clustering with the Bhattacharyya distance (see Appendix D), and Ward.D2 algorithm supplied with R software [28]. It is impossible to be certain whether the DPMM model, or maximising the log-likelihood, is more effectively identifying the actual underlying clusters, where they exist. Thirdly, the number of male-female disease pairs clustered together was only 65% and 72% respectively, much less than the 83% clustered together in the 22 clusters selected by hierarchical clustering. The latter remark suggests that the hierarchical model may be finding a more meaningful set of clusters. Reassuringly, a sensitivity analysis with $\sqrt{tr(\Sigma_0)} = 3$ that is discussed in Section [10.3] found that the maximum of the hierarchical clustering’s log-likelihood at $m = 22$ was fairly insensitive to omission of a randomly chosen item of data. However the hclust() algorithm in the R software package [28] that was used, is an agglomerative hierarchical procedure that joins the most similar clusters first. It is possible that clustering the most similar pairs together first, might bias results so that similar pairs are more likely to be clustered together. Despite the differences in results, it is also reassuring that two very different clustering methods are finding large numbers of disease pairs in the same clusters, suggesting it is driven by information in the data. The poor convergence of the DPMM model may correctly reflect insufficient information to clearly determine an optimum clustering, but it was disappointing from a practical perspective, because the DPMM would otherwise directly solve the model for an optimum set of clusters. It is possible that a model that accounts for uncertainty in the estimated covariance matrices might converge in fewer iterations, or perform better. Modifications to the clustering model are discussed further in Section [10.4].

9 Clustering data with equal covariances, and relation to k-means

Consider data points with multivariate normal distributions, whose covariances are all equal, or approximated as being equal. 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. Note that this average over “within-person” covariances 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 this example, we take $\Gamma_i = \Gamma$ for all the data points, and $\Gamma_0 = \alpha \Gamma$ for the prior, with the value of $\Gamma$ determined after collecting the data. Under these conditions the log-likelihood simplifies considerably. Simplifying each term in Eq. 23 in turn:

$$-\frac{m}{2} \log |2\pi \Gamma_0^{-1}| = \frac{m}{2} \log \left| \frac{\alpha \Gamma}{2\pi} \right|$$  \hspace{1cm} (38)

$$-\frac{1}{2} \sum_i \log |2\pi \Gamma_i^{-1}| = \frac{N}{2} \log \left| \frac{\Gamma}{2\pi} \right|$$  \hspace{1cm} (39)

$$\frac{1}{2} \sum_{g=1}^{m} \log \left| 2\pi \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \right| = -\frac{1}{2} \sum_{g=1}^{m} \log \left| \left( \frac{\alpha + N_g}{2\pi} \right)^{-1} \right|$$  \hspace{1cm} (40)

$$-\frac{1}{4} \sum_{g=1}^{m} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_j (x_i - x_j) = -\frac{1}{4} \sum_{g=1}^{m} \frac{1}{\alpha + N_g} \sum_{i,j \in C_g} (x_i - x_j)^T \Gamma (x_i - x_j)$$  \hspace{1cm} (41)

$$-\frac{1}{2} \sum_{g=1}^{m} \sum_{i \in C_g} x_i^T \Gamma_i \left( \Gamma_0 + \sum_{k \in C_g} \Gamma_k \right)^{-1} \Gamma_0 x_i = -\frac{1}{2} \sum_{g=1}^{m} \left( \frac{\alpha}{\alpha + N_g} \right) \sum_{i \in C_g} x_i^T \Gamma x_i$$  \hspace{1cm} (42)

where $N_g$ is the number of items in cluster $g$, and $N = \sum_{g=1}^{m} N_g$. If we diagonalise the inverse-covariance $\Gamma = R^T D R$ and change into “whitened” co-ordinates with $y_i^T = x_i^T R^T D^{1/2}$ and $\mu_g$ replaced by $\mu_g^T R^T D^{1/2}$, then the Jacobians associated with the change of variables in the probability density functions Eqs. 4 and 5, introduce two extra terms $N \log |R^T D^{-1/2}|$ and $m \log |R^T D^{-1/2}|$ into the derivation of the log-likelihood. These give,

$$N \log |R^T D^{-1/2}| + m \log |R^T D^{-1/2}| = -\frac{(N + m)}{2} \log |\Gamma|$$  \hspace{1cm} (43)

where we used $|R| = |R^T| = 1$ for any rotation matrix. Putting all the terms together, then Eq. 43 will partly cancel with Eqs. 38 and 39 to give,

$$\log(C|X, I) = \log P(C|I) - \frac{mp}{2} \log \left( \frac{2\pi}{\alpha} \right) - \frac{Np}{2} \log(2\pi) - \frac{1}{2} \sum_{g=1}^{m} \log \left| \left( \frac{\alpha + N_g}{2\pi} \right)^{-1} \right|$$  \hspace{1cm} (44)

where $p$ is the dimension. If we considered a flat prior the equivalent equation is,

$$\log(C|X, I) = \log P(C|I) - \frac{Np}{2} \log(2\pi)$$  \hspace{1cm} (45)
The sum of squares term might alternately be written as,

\[- \frac{1}{4} \sum_{g=1}^{m} \frac{1}{N_g} \sum_{i,j \in C_g} (y_i - y_j)^T (y_i - y_j) = - \frac{1}{2} \sum_{g=1}^{m} \sum_{i \in C_g} (y_i - \hat{\mu}_g)^T (y_i - \hat{\mu}_g)\]  

(46)

where \( \hat{\mu}_g \equiv (1/N_g) \sum_{j \in C_g} y_j \). As a result, maximising the log-likelihood is similar to applying the k-means algorithm with two extra terms to penalise the model’s complexity. The penalty terms are \( P(C|\mathcal{I}) \), and,

\[- \frac{1}{2} \sum_{g=1}^{m} \log \left| \left( \frac{N_g}{2\pi} \right) \Gamma \right| = - \frac{m}{2} \log |\Gamma| - \frac{p}{2} \sum_{g=1}^{m} \log \left( \frac{N_g}{2\pi} \right)\]  

(47)

The first term’s sign depends on whether \( 0 < |\Gamma| < 1 \) or \( 1 < |\Gamma| \), and can penalise more, or fewer clusters, with large covariances (\( 0 < |\Gamma| < 1 \)) favouring fewer clusters but smaller covariances (\( 1 < |\Gamma| \)) favouring more clusters. The second term is an entropy-like term, and the concave shape of \(- \log(N_g)\) will penalise similarly sized clusters (when summed over \( g \)). Unfortunately, whereas the k-means algorithm simply assigns items to clusters with the nearest mean, the penalty terms will depend on the changes in log-likelihood associated with moving an item between clusters, possibly with a change in the total number of clusters.

## 10 Discussion

### 10.1 Big datasets and cluster assignment

Distance-based measures are unsuitable for clustering large datasets because the distance matrix grows as \( n^2 \), where \( n \) is the number of data points, eventually making computation intractable for large enough \( n \). However, if we can assume that a data subset is sufficiently large and complete to allow all clusters to be found and sufficiently well estimated, then we can assign the remaining points to clusters via,

\[ \argmax_g P \left( \tilde{X}|X, i \in C_g, \mathcal{I} \right) \]  

(48)

with \( P \left( \tilde{X}|X, i \in C_g, \mathcal{I} \right) \) given by Eq. [35]. This offers a pragmatic option to cluster large datasets, or to assign new members to existing cluster sets. Because the number of comparisons needed to assign data values is \( \sim nm \), where \( m \) is the number of clusters, then the number of calculations grow linearly in \( n \). If estimates for \( \{\mu_g\} \) are not updated as items are added to clusters, then the clustering process would also have the benefit of being deterministic and independent of the ordering of the data, given the initial dataset used to estimate cluster centres.
10.2 Centring data

Data are often centred by subtracting the mean $\bar{X} = (1/n) \sum_{i=1}^{n} X_i$, prior to clustering. Here the covariances for each data point are known, and an option is to consider the data as a single cluster ($m = 1$), and use its estimated mean $\mu_1$ to centre the data. Using Eqs 30-33 to estimate $\mu_1$, gives $\mu_1 = (\sum_i \Gamma_i)^{-1} (\sum_i \Gamma_i X_i)$, where $i = 0$ to $n$, so that the estimate includes any assumption for the prior’s $\mu_0$ and $\Gamma_0$. The estimate assumes a single normally distributed dataset, with uncertainty in the individual data points accounted for through their individual covariances.

As was noted in Section 5.1, a prior with non-zero mean is equivalent to offsetting the data by the mean, and taking a prior with zero mean. As a result, centring the data is equivalent to using the data to select a prior with the data’s mean, and the log-likelihood is modified by the centring procedure. This raises questions about whether it is appropriate to centre the data. It certainly suggests that in general, the interpretation of clustering results is complicated when data have been centred using the data itself, as opposed to using a prior estimate.

Many distance-based clustering methods, including those using the Bhattacharyya distance, are invariant to how the data are centred. This contrasts with a DPMM model, that introduces a dependence on centring through the prior. A non-flat prior can also introduce a dependence on centring into the log-likelihood that is used to optimise the number of clusters. This is not the case for a flat prior. Whether it is preferable for clustering to be invariant to centring may depend on the particular problem.

10.3 Statistical tests and confidence sets

Conventional 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. One difficulty is that Eq. 23 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. 23 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 boot-strap sample the underlying data used to generate the MLEs being clustered, and obtain the optimum clustering and log-likelihood for each sample. This will give a log-likelihood $l_i$, and other properties associated with 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 “Jacknife” \[4\] 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. For example, removing one item in turn and determining the optimum number of clusters for the test sets in Section \[7\] always gave the same (correct) number of clusters. In contrast, for the disease clustering example in Section \[8\] there was some variation in the MLE for the number of clusters, as shown in figure \[3\] although the histogram remains strongly peaked around 22 clusters. Although the Jacknife procedure is unsuitable for estimating a confidence interval for the number of clusters, the leave-one-out procedure does provide a valuable sensitivity analysis, that can indicate when there is uncertainty in the MLE for the number of clusters.

10.4 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,

$$P\left(\Sigma_i|\hat{\Sigma}_i, n_i\right) P\left(\hat{\Sigma}_i\right) = W\left(\hat{\Sigma}_i|\Sigma_i/n_i, n_i\right) P\left(\Sigma_i\right)$$

With Jeffrey’s prior $P(\Sigma_i) = |\Sigma_i|^{-p+1/2}$, it can be shown that \[31\],

$$P(X_i|\mu, \hat{\Sigma}_i, n_i) = \frac{c_p}{\sqrt{|\hat{\Sigma}_i|}} \frac{1}{1 + \frac{(X_i-\mu)^T\Sigma_i^{-1}(X_i-\mu)}{n_i}}^{n_i+1/2}$$

where,

$$c_p = \frac{\Gamma((n_i + 1)/2)}{\pi n_i^{p/2} \Gamma\left(\frac{n_i+1-p}{2}\right)}$$
Eq. 50 is a form of multivariate t-distribution, and can be used to form a likelihood for the data. 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 DPMM. This is possible with some additional modifications to the “dirichletprocess” package [27], with the caveat that it is expected to take longer to execute.

11 Conclusions

This article’s purpose was to highlight the benefits of clustering parameterised models, and to develop tools to enable it. Parameters are usually estimated by a maximum likelihood estimate (MLE), and the estimates quantified by covariances. A simple model for clustering MLEs was considered, in which normally distributed MLEs are assumed to belong to clusters of MLEs with the same mean, but to have different covariances, for example due to MLEs being calculated from data of differing sizes. A log-likelihood was calculated for the model, that is a function of the number and composition of clusters, and allows clusterings to be compared. A DPMM was also formulated, and for test cases with known clusters, when it converged the clusters were correctly identified. Unfortunately it did not always converge in a reasonable time. This may reflect insufficient information in the data to identify an optimal estimate, possibly due to a low signal to noise ratio, or noise in the estimated covariances. It is possible that convergence would be improved by a DPMM model that accounts for uncertainty in the estimated covariances.

A log-likelihood allows confidence sets to be formed, for example by bootstrapping the underlying data used to calculate MLEs, before clustering. The size of a confidence set can immediately give some indication of uncertainty about the underlying clusters, but methods will also be needed to meaningfully characterise the confidence sets of clustered data. Ideally, a simpler and less computationally intensive approach could be devised. An alternative approach is to explore the sensitivity of clusterings to small changes in the data. The leave-one-out procedure used to form Jacknife estimates provides a simple sensitivity analysis, that can indicate when clusterings are sensitive to small changes in the data, and are unlikely to be reliable.

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12 Appendices

Appendix A. Prior likelihood for distributions

Recalling the implicit information contained in $Z$, we can expand the prior for cluster membership $P(Z|\mathcal{I})$ as,

$$P(Z|\mathcal{I}) = P(Z, N_1(Z), ..., N_M(Z), M(Z)|\mathcal{I})$$

$$= P(Z, N_1(Z), ..., N_M(Z)|M = m, \mathcal{I})P(M = m|\mathcal{I})$$

Simplifying the expression, we get:

$$P(Z, N_1(Z), ..., N_M(Z)|M = m, \mathcal{I}) = \frac{\#(Z:N_1,...,N_m)}{\#(Z:N_1,...,N_m \geq 1)}$$

$$= \frac{1}{N_1!...N_m! T(N,m)}$$

where $T(N, M)$ is the number of distributions of $N$ identifiable items into $M$ identifiable boxes [25]. 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 $g$. Eq. 53 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 Eq. 53 with Eqs. ?? and ??, gives,

$$P(Z|X, \mathcal{I}) \propto \frac{(N-1)!}{(N-m)!(m-1)!} \frac{1}{2^{N-1} N_1!...N_m! T(N,m)} \frac{1}{\Pi_{g=1}^{m} \int_{-\infty}^{\infty} \mu_g f(\mu_g; \mu_0, \Gamma_0) \left( \Pi_{i \in C_g} f(x_i; \mu_g, \Gamma_i) \right)}$$

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 [25],

$$\left( \begin{array}{c} m = \sum_{j=1}^{k} r_j \\ r_1...r_k \end{array} \right)$$

where as before, $r_j$ can be zero. Each arrangement corresponds to a distribution described by Eq. ?? that is unchanged by a permutation of the cluster labels. Therefore,

$$P(C|\mathcal{I}) = P(Z|\mathcal{I}) \left( \begin{array}{c} m \\ r_1...r_k \end{array} \right)$$

$$= \frac{N!}{N_1!...N_m!r_1!...r_k! S(N,m)} P(M = m|\mathcal{I})$$
where we used Eq. 53 and \( S(N, m) = T(N, m)/m! \). The above Eq. 56 is identical to the combination of Eqs. 8 and 9 of the main text.

### Appendix B. 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,

\[
P(M = m|I) = \frac{\# \text{(Partitions of } N \text{ into } m)}{\# \text{(Partitions of } N)}
\]

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 \[26\], 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,

\[
F_m(N) = \exp \left( -\beta \exp(-k/\beta) \right)
\]

with \( \beta = 2\sqrt{N}/C \). Eq. 59 can in turn be written as,

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

with \( \mu = \beta \log(\beta) \). This is a Gumbell distribution, with mode \( \mu = \beta \log(\beta) \) and variance \( \sigma^2 = \pi^2 \beta^2/6 = N \). For the example 8 of the main text, with \( N = 156 \), this gives \( \mu \simeq 22 \) and \( \sigma \simeq 12 \). 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 when all possible partitions are equally likely, then for large enough datasets, the prior strongly influences the number of clusters to expect. 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 \( P(M = m|I) = 1/N \), and leave a more principled choice of prior as a topic for further study.

### Appendix C. Equations 28-35
Eq. [31] and [35] result from integrals over multivariate normals, that are accomplished by the multivariate equivalent of completing the square. The results can be confirmed by using,

\[
(\tilde{X}^T - \mu^T) \tilde{\Lambda} (\tilde{X} - \mu) + (\mu^T - \mu_N^T) \Lambda_N (\mu - \mu_N)
\]

\[
= (\tilde{X}^T - \mu_N^T) \left( \tilde{\Lambda} (\tilde{\Lambda} + \Lambda_N)^{-1} \Lambda_N \right) (\tilde{X} - \mu_N) +
\]

\[
(\mu^T - (\tilde{X}^T \tilde{\Lambda} + \mu_N^T \Lambda_N) (\tilde{\Lambda} + \Lambda_N)^{-1}) (\tilde{\Lambda} + \Lambda_N) \left( \mu - (\tilde{\Lambda} + \Lambda_N)^{-1} (\tilde{\Lambda} \tilde{X} + \Lambda_N \mu_N) \right)
\]

(61)

as can be seen by expanding the right-side, cancelling terms, and noting that,

\[
\left( \tilde{\Lambda} (\tilde{\Lambda} + \Lambda_N)^{-1} \Lambda_N \right) + \left( \Lambda_N (\tilde{\Lambda} + \Lambda_N)^{-1} \Lambda_N \right) = \Lambda_N
\]

\[
\left( \tilde{\Lambda} (\tilde{\Lambda} + \Lambda_N)^{-1} \Lambda_N \right) + \left( \tilde{\Lambda} (\tilde{\Lambda} + \Lambda_N)^{-1} \tilde{\Lambda} \right) = \tilde{\Lambda}
\]

(62)

Eq. [31] can be understood by firstly substituting \( \mu_N = \mu_0 \), \( \Lambda_N = \Gamma_0 \), \( \tilde{X} = X_1 \), and \( \tilde{\Lambda} = \Gamma_1 \), into Eq. [61]. Adding an additional term \((X_2 - \mu)^T \Gamma_2 (X_2 - \mu)\) to Eq. [61] will cause \( \Gamma_1 + \Gamma_0 \) to be replaced by \( \Gamma_0 + \sum_{i=1}^{2} \Gamma_i \) and the mean to become \( \left( \Gamma_0 + \sum_{i=1}^{2} \Gamma_i \right)^{-1} \left( \Gamma_0 \mu_0 + \sum_{i=1}^{2} \Gamma_i x_i \right) \), and this process can be repeated for additional terms \( X_3, X_4, \ldots \). Eq. [31] results from Eq. [28] by using the above, and cancelling the remaining terms involving \( X \) with those that remain in the denominator after integrating over \( \mu \). Eq. [35] follows from Eq. [34] and Eq. [61] by setting \( \Lambda_N = \hat{\Lambda}_g \), \( \mu_N = \hat{\mu}_g \), \( \mu = \mu_g \), and noting that the terms involving \( \mu = \mu_g \) on the right-side of Eq. [61] will be removed by integration.

Appendix D. Bhattacharyya distance

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

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

(63)

For two multivariate normals we can evaluate this using Eq. [17] with \( m = 1 \) and \( P(C|I) = 1 \). If we replace \( \mu_g \) with \( x, x_1 \) with \( \mu_1 \) and \( x_2 \) with \( \mu_2 \), and take \( k = 1 \ldots 2 \), the exponential of Eq. [17] gives,

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

(64)

Noting that,

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

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

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

(65)
and repeating the calculation with the modifications needed to incorporate the square roots from the definition (Eq. [63]),

\[ \int_{-\infty}^{\infty} dx_1 \ldots \int_{-\infty}^{\infty} dx_p \sqrt{p_1(x)p_2(x)} \]

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

(66)

where with the square root from Eq. [63] the factors of $2\pi$ cancel. Replacing $\Gamma_i^{-1}$ with $\Sigma_i$ gives the Bhattacharyya distance between two multivariate normal distributions in its usual form.

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Figure 2: A recent study \[1\] clustered 78 pairs of diseases (156 in total), that occurred in both men and women. The -log-likelihood is plotted as a function of the number of clusters, for hierarchical clustering of disease data using the Bhattacharyya distance with a flat prior, and normal priors with mean zero and isotropic covariances $\Sigma_0$ with $s = tr(\Sigma_0)$. A $\chi^2$ test for equality of the MLEs in each cluster found statistically significant differences at the 0.05 level, unless there were at least 63 clusters. With a flat prior for $\{\mu_g\}$ the minimum is at 37 clusters, approximately mid-way between 63 clusters and the elbow in $\chi^2$. With a normal prior for $\{\mu_g\}$, the minimum is near the elbow in $\chi^2_{pq}$, at between 22 and 25 clusters, depending on the prior variance for $\{\mu_g\}$. 
Figure 3: The leave-one-out methodology can indicate whether results are sensitive to small changes in the data. For the disease data of Ref. [1], a histogram for the MLE for the number of clusters found after omitting each item of data, is strongly peaked at 22.