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A Bernoulli Mixture Model to Understand and Predict Children's Longitudinal Wheezing Patterns

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Abstract

In this research, we perform discrete unsupervised machine learning through a Bernoulli Mixture Model on data representing the expression of the wheeze phenotype of patients at different stages of their childhood up to age 16. Wheeze is a distinct noise produced while breathing due to narrowed airways, such as asthma or viral chest infections. Due to a study from Henderson et al. (2008), it has been estimated that around 23.5% of U.K. children had at least wheezed once by six years of age, and 6.9% had persistent wheezing problems. The usage of a Bernoulli Mixture Model is new in the field, where previous classification methods used classical unsupervised learning such as K-means, K-medoids, or Latent Class Analyses (Loza et al., 2016; Kurukulaaratchy et al., 2014; Deliu et al., 2016; Brew et al., 2019). In particular, Oksel et al. (2019) found that the Latent Class Analysis has resulted majorly dependent to the sample size, and K-means is largely dependent on the distance measure and so the data-set.

In this research, we estimate that around $27.99(\pm 2.15)\%^1$ of the population has experienced wheezing before turning 1 in the United Kingdom. Furthermore, the Bernoulli Mixture Model classification is found to work best with K=4 clusters in order to better balance the separability of the clusters with their explanatory nature, based on a cohort of N=1184. The probability of the group of parents in the jth cluster to say that their children have wheezed during the ith age is assumed $P_{ij} \sim \text{Beta}(1/2,1/2)$, the probabilities of assignment to each cluster is $R \sim \text{Dirichlet}_K(\alpha)$, the assignment of the nth patient to each cluster is $Z_n \mid R \sim \text{Categorical}(R)$, and the nth patient wheezed during the ith age is $X_{in} \mid P_{ij}, Z_n \sim \text{Bernoulli}(P_{i,Z_n})$; where $i \in \{1,\ldots,6\}$, $j \in \{1,\ldots,K\}$, and $n \in \{1,\ldots,N\}$. The classification is then performed through the E-M optimization algorithm (Bishop, 2006; Saeed et al., 2013). We found that this clustering method groups efficiently the patients with late-childhood wheezing, persistent wheezing, early-childhood wheezing, and none or sporadic wheezing. Furthermore, we found that this method is not dependent on the dataset, and can include data-sets with missing entries.

^{1.} The values in brackets are the differences between the estimated values for the measures listed and the left or right boundary of the 95% confidence interval. The inverse cumulative distribution function value is taken from a t-distribution with n-1 degrees of freedom.

It is hoped this study will give medical staff an understanding of the wheezing patterns in children up to age 16, and so provide an effective treatment.

Keywords: Bayesian Statistics, E-M Optimization, Mixture Models, Bernoulli Mixture Model, Wheeze, Respiratory Problems, Classification

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1. The Cohort & Introduction

Parents of 1184 children residing in the United Kingdom were asked to tell if they had wheeze in the previous year at ages 1, 3, 5, 8, 11, and 16. A positive answer was recorded as a 1 in the registry, while a negative answer was recorded as a 0. Each patient is given a fixed identification number going from 0 to 1183. The data of 537 children was incomplete (45.4% of the data), i.e., the parent did not answer to the question at least once. There were 647 full entries, i.e., parents of 647 children provided the information at every stage described above. The information was later put into a spreadsheet, where each row represented the data collected for each child, and each column the answer for each of the periods as explained above, under "Age 1," "Age 3," "Age 5," "Age 8," "Age 11," and "Age 16." Whenever no information was provided, NaN was recorded.

From this data, we can therefore estimate the number of children within the U.K. population who had wheeze at most a year before turning 1, 3, 5, 8, 11, and 16. We estimate the means by the sample means, and produce a 95% confidence interval with the sample mean and the corresponding critical value from a t-distribution with 647 degrees of freedom. This algorithm can be found in Appendix.

Age period	Est. mean	LHS CI at 95%	RHS CI at 95%
Age 1	27.99%	25.84%	30.14%
Age 3	23.74%	21.70%	25.78%
Age 5	23.04%	21.02%	25.06%
Age 8	18.05%	16.20%	19.89%
Age 11	18.89%	17.01%	20.76%
Age 16	17.02%	15.22%	18.83%

Table 1: Estimate of the U.K. population having wheezed at different ages with the LHS and RHS of the 95% confidence interval using a t-distribution with 647 degrees of freedom.

From Table 1, we can deduce that approximately $27.99(\pm 2.15)\%$ (with a 95% confidence) of the population has experienced wheezing before turning 1. This seems to corroborate Henderson et al. (2008) findings, where they estimated that 23.5% of U.K. children had at least wheezed once by 6.

The challenge with this data is that 45.5% of it is incomplete. From Fig. 1, the number of parents stopping to provide a status on their child wheeziness increases whenever the latter gets older.

In particular, other papers such as Loza et al. (2016); Kurukulaaratchy et al. (2014); Deliu et al. (2016); Brew et al. (2019); Oksel et al. (2019) have used well known clustering methods such as K-means, K-medoids, as well as Latent Class Analysis. These methods require that no entry be missing or classified as NaN in the data-set, which we have for a large proportion in our case. Furthermore, Oksel et al. (2019) found that the Latent Class Analysis has resulted majorly dependent to the sample size, the frequency, and the timing of data

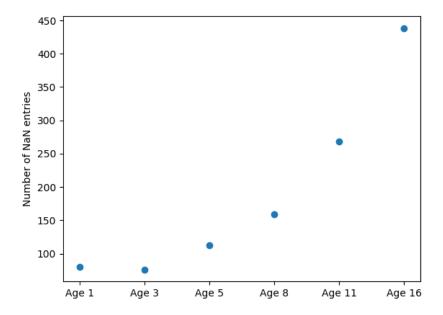


Figure 1: Number of NaN entries per age tranche within the cohort data.

collection.

Therefore, in this paper, we suggest a novel method for classifying the longitudinal wheeze phenotype diagnosed in children aged 1 to 16, using a Bernoulli Mixture Model based on the E-M optimization algorithm. This method can allow missing entries in the data-set, and is generally less dependent on the sample size than other methods.

2. Theory of Bernoulli Mixture Model

In this subsection, we consider the general case of the Bernoulli Mixture Model so that we can apply it in our case later on.

Let X_1, \ldots, X_M be a set of M binary variables where $X_i \sim \text{Bernoulli}(\lambda_i)$ for $\lambda_i \in (0, 1)$, $\forall i \in \{1, 2, \ldots, M\}$. Note that in this case, the marginals of X_i are given by $f_{X_i}(x_i) = \lambda_i^{x_i} (1 - \lambda_i)^{1-x_i}$ where $x_i \in \{0, 1\}, \forall i \in \{1, 2, \ldots, M\}$.

Hence, we have that

$$\Pr(\mathbf{X}|\Lambda) = \prod_{i=1}^{M} f_{X_i}(x_i) = \prod_{i=1}^{M} \lambda_i^{x_i} (1 - \lambda_i)^{1 - x_i}$$

where $\mathbf{X} = (X_1, \dots, X_M)^t$ and $\Lambda = (\lambda_1, \dots, \lambda_M)^t$.

As the above expression are written as a separate product of the different probability mass functions of X_1, \ldots, X_M , we have that **X** is independent of Λ . We have $\mathbb{E}(X_i|\lambda_i) = \lambda_i, \forall i \in \{1,\ldots,M\}$ by characteristic of the Bernoulli distribution, so that

$$\mathbb{E}(\mathbf{X}|\Lambda) = \Lambda \in (0,1)^M$$
. (†)

Similarly, by independence we have $cov(X_i, X_j | \lambda_i, \lambda_j) = 0$, $\forall i, j \in \{1, ..., M\}$ such that $i \neq j$, and by property of the Bernoulli distribution, $var(X_i | \lambda_i) = \lambda_i (1 - \lambda_i)$, $\forall i \in \{1, ..., M\}$. Therefore,

$$\Sigma_{ik} := \text{cov}(\mathbf{X}|\Lambda)_{ik} = \delta_{ik}\lambda_i(1-\lambda_i) \in (0,1)^{M \times M} \ (\ddagger)$$

where δ_{ik} is the Kronecker delta, i.e.,

$$\delta_{ik} = \begin{cases} 1 & \text{if } i = k, \\ 0 & \text{if } i \neq k. \end{cases}$$

We now build a finite mixture, with new parameters $\Pi = (\pi_1, \dots, \pi_K)^t$, where $K \leq M$ will be the number of clusters, by

$$\Pr(\mathbf{X}|\tilde{\Lambda},\Pi) := \sum_{j=1}^{K} \pi_j \Pr(\mathbf{X}|\Lambda_j) (\star)$$

where $\tilde{\Lambda} = (\Lambda_1, \dots, \Lambda_K)^t$, the set of parameters of each component (Saeed et al., 2013), where we have

$$\Pr(\mathbf{X}|\Lambda_j) = \prod_{i=1}^M \lambda_{ji}^{x_i} (1 - \lambda_{ji})^{1 - x_i}.$$

For this mixture model, we have

$$\mathbb{E}(\mathbf{X}|\tilde{\Lambda},\Pi) = \sum_{i=1}^{K} \pi_i \mathbb{E}(\mathbf{X}|\Lambda_j) = \sum_{i=1}^{K} \pi_j \Lambda_j \in (0,1)^M \text{ by } (\dagger).$$

Similarly,

$$\operatorname{cov}(\mathbf{X}|\tilde{\Lambda},\Pi) = -\mathbb{E}(\mathbf{X}|\tilde{\Lambda},\Pi)\mathbb{E}(\mathbf{X}|\tilde{\Lambda},\Pi)^t + \sum_{j=1}^K \pi_k(\mathbf{\Sigma}_j + \Lambda_j \Lambda_j^t)$$

where Σ_i is as defined in (‡), i.e.,

$$(\mathbf{\Sigma}_j)_{ik} = \delta_{ik}\lambda_{ji}(1-\lambda_{ji}).$$

For a random sample $\mathbf{X}_1, \dots, \mathbf{X}_N$ which is distributed as in (\star) with respect to $\tilde{\Lambda}$ and Π , the likelihood function for $\mathbf{X}_1, \dots, \mathbf{X}_N | \tilde{\Lambda}, \Pi$ is given by

$$\mathcal{L}(\mathbf{X}_1, \dots, \mathbf{X}_N, \tilde{\Lambda}, \Pi) = \prod_{n=1}^N \sum_{j=1}^K \pi_j \Pr(\mathbf{X}_n | \Lambda_j)$$

so that the log-likelihood ℓ is

$$\ell(\mathbf{X}_1, \dots, \mathbf{X}_N, \tilde{\Lambda}, \Pi) = \sum_{n=1}^N \log \left(\sum_{j=1}^K \pi_j \Pr(\mathbf{X}_n | \Lambda_j) \right) = \sum_{n=1}^N \log \left(\sum_{j=1}^K \left\{ \pi_j \prod_{i=1}^M \lambda_{ji}^{x_{ni}} (1 - \lambda_{ji})^{1 - x_{ni}} \right\} \right).$$

The aim is to generate an algorithm that finds Π , $\tilde{\Lambda}$ which maximize ℓ , which we will call Π_{\max} and $\tilde{\Lambda}_{\max}$ respectively. Unfortunately, due to the shape of ℓ , Π_{\max} and $\tilde{\Lambda}_{\max}$ cannot be found in closed form in that case.

Hence, we introduce a latent binary variable $\mathbf{Z} = (z_1, \dots, z_K)^t$ associated with each instance of \mathbf{X} (Bishop, 2006). Therefore, the conditional distribution of \mathbf{X} , given the latent variable \mathbf{Z} , is given by

$$\Pr(\mathbf{X}|\mathbf{Z},\tilde{\Lambda}) = \prod_{j=1}^{K} \Pr(\mathbf{X}|\Lambda_j)^{z_j},$$

where the prior for the latent variable is

$$\Pr(\mathbf{Z}|\Pi) = \prod_{j=1}^{K} \pi_j^{z_j}.$$

By considering the random sample $\mathbf{X}_1, \dots, \mathbf{X}_N$, we have the likelihood function \mathcal{G} for $\mathbf{X}_1, \dots, \mathbf{X}_N | \mathbf{Z}$ given by

$$\mathcal{G}(\mathbf{X}_1,\ldots,\mathbf{X}_N,\mathbf{Z},\tilde{\Lambda},\Pi) = \prod_{n=1}^N \Pr(\mathbf{X}_n,\mathbf{Z}|\tilde{\Lambda},\Pi) = \prod_{n=1}^N \prod_{j=1}^K (\pi_j \Pr(\mathbf{X}_n|\Lambda_j))^{z_{nj}},$$

so that, once expanded, we have

$$\mathcal{G}(\mathbf{X}_1,\ldots,\mathbf{X}_N,\mathbf{Z},\tilde{\Lambda},\Pi) = \prod_{n=1}^N \prod_{j=1}^K \left(\pi_j \prod_{i=1}^M \lambda_{ji}^{x_{ni}} (1-\lambda_{ji})^{1-x_{ni}} \right)^{z_{nj}}.$$

Therefore, the log-likelihood g is given by

$$g(\mathbf{X}_1, \dots, \mathbf{X}_N, \mathbf{Z}, \tilde{\Lambda}, \Pi) = \sum_{n=1}^N \sum_{j=1}^K z_{nj} \left(\log(\pi_j) + \sum_{i=1}^M \left\{ x_{ni} \log(\lambda_{ji}) + (1 - x_{ni}) \log(\lambda_{ji}) \right\} \right).$$

Hence, the expectation of the log-likelihood with respect to the marginal distribution of \mathbf{Z} is given by

$$\mathbb{E}_{\Pr(\mathbf{Z}|\Pi)}(g(\mathbf{X}_1,\ldots,\mathbf{X}_N,\mathbf{Z},\tilde{\Lambda},\Pi)) = \sum_{n=1}^N \sum_{j=1}^K \mathbb{E}(z_{nj}) \left(\log(\pi_j) + \sum_{i=1}^M \left\{ x_{ni} \log(\lambda_{ji}) + (1-x_{ni}) \log(\lambda_{ji}) \right\} \right) \cdot (\star \star)$$

By Bayes' Theorem and Saeed et al. (2013); Bishop (2006), we have

$$\mathbb{E}(z_{nj}) = \frac{\pi_j \Pr(\mathbf{X}_n | \Lambda_j)}{\sum_{k=1}^K \pi_k \Pr(\mathbf{X}_n | \Lambda_k)}. \ (\diamond)$$

Let

$$N_j = \sum_{n=1}^N \mathbb{E}(z_{nj}) \text{ and } \overline{\mathbf{X}}_j = \frac{1}{N_j} \sum_{n=1}^N \mathbb{E}(z_{nj}) \mathbf{X}_n.$$

Then one can show that

$$\tilde{\Lambda}_{\max} = (\hat{\Lambda}_1, \dots, \hat{\Lambda}_K)^t$$
 where $\hat{\Lambda}_j = \overline{\mathbf{X}}_j$ and $\hat{\Pi}_{\max} = (\hat{\pi}_1, \dots, \hat{\pi}_K)^t$ where $\hat{\pi}_i = N_i/N$.

Indeed, such a $\tilde{\Lambda}_{\text{max}}$ makes the derivative with respect to the λ_j s vanish, and such a $\hat{\Pi}_{\text{max}}$ maximizes (**) through a Lagrange multiplier as seen in Saeed et al. (2013); Bishop (2006).

Therefore, the expectation-maximization algorithm for a Bernoulli mixture model first gives initialization values to $\tilde{\Lambda}$ and Π . The algorithm then computes the value of the log-likelihood at the initial values $\tilde{\Lambda}_0$, Π_0 .

On the next step, the algorithm does a loop by evaluating $\mathbb{E}(z_{nj})$ as in (\diamond) , and reevaluates $\hat{\Lambda}_j, \hat{\pi}_j$ as found above. Then, we evaluate the log-likelihood at these values. We stop the loop whenever the log-likelihood meets a convergence criterion.

3. Application to the data-set

Each cluster has a certain probability of a yes answer at the different ages of the children. We assume that they follow a Beta distribution. Hence, let

$$P_{ij} \sim \text{Beta}\left(\frac{1}{2}, \frac{1}{2}\right) \text{ for } i \in \{1, \dots, 6\} \text{ and } j \in \{1, \dots, K\}$$

where K is the number of clusters, as the Beta distribution is well known to represent a distribution of probabilities, and Beta(1/2, 1/2) is more dense around its support boundaries 0 and 1. Hence, this is our prior. That is, given a cluster $j \in \{1, ..., K\}$ and the age tranche of the children $i \in \{1, ..., 6\}$, the group of parents in the jth cluster has a probability of P_{ij} to say that their children have wheezed at (or within a year of) the ith age.

Now, to provide the cluster assignments, we use the Categorical distribution, which is a generalized Bernoulli distribution (in higher dimensions), as each vector in the data either belongs to one of the K clusters or does not. Hence, let

$$Z_n \mid R \sim \text{Categorical}_K(R) \text{ for } n \in \{1, \dots, N\},$$

where R represents the probabilities of the cluster assignments, which we assume follows a Dirichlet distribution, i.e., a generalized Beta distribution (in higher dimensions), so that

$$R \sim \text{Dirichlet}_K(\alpha)$$

for some constant and positive vector α , which we are free to choose as it is an uninformative distribution.

Therefore, for X_{in} the random variable representing the fact that the nth patient wheezed at the ith age tranche, we have

$$X_{in} \mid P_{ij}, Z_n \sim \text{Bernoulli}(P_{i,Z_n}) \text{ for } i \in \{1, \dots, 6\} \text{ and } n \in \{1, \dots, N\}.$$

To sum up, the model is given by

$$P_{ij} \sim \text{Beta}(1/2, 1/2),$$
 $R \sim \text{Dirichlet}_K(\alpha),$
 $Z_n \mid R \sim \text{Categorical}_K(R),$
 $X_{in} \mid P_{ij}, Z_n \sim \text{Bernoulli}(P_{i,Z_n}),$

for $i \in \{1, ..., 6\}, j \in \{1, ..., K\}$, and $n \in \{1, ..., N\}$, where each variable describes the following:

 P_{ij} : probability of the group of parents in the jth cluster to say that their children have wheezed during the ith age,

R: probabilities of assignment to each cluster 1, ..., K,

 Z_n : assignment of the *n*th patient to each cluster 1, ..., K,

 X_{in} : the *n*th patient wheezed during the *i*th age.

The plate diagram for such a configuration can be found in Fig. 2. Note again that α , a K-dimensional vector with $\alpha_j > 0$ for all $j \in \{1, \ldots, K\}$, can be chosen arbitrarily since the distribution of R is uninformative $(Z_n \text{ is latent})$.

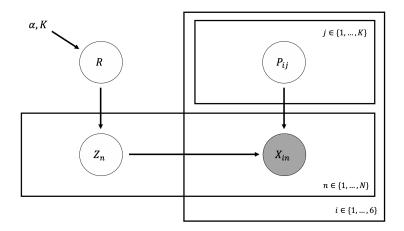


Figure 2: Plate diagram of the considered Bernoulli Mixture Model for the considered cohort.

4. Results

NaN entries.

We then perform the expectation-maximization algorithm on the log-likelihood as explained in the previous section. We can then plot the Hinton plots for R, the P_{ij} s, and the Z_n s. These are visualized in Fig. 3.

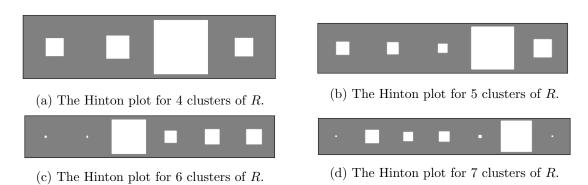


Figure 3: The Hinton plots of R for different number of clusters. Each graph shows the probabilities of being assigned to each cluster. Here, the data used excludes the rows with

Hinton diagrams for R show the number of elements per cluster. The bigger the white square is, the bigger the cluster is. From Fig. 3, we can see that for either setting 4,5,6 or 7 groups, there are 4 dominant clusters. Now, if we set the number of clusters to $64 = 2^6$, which is the number of all possibilities to arrange 0s and 1s in a 6-dimensional vector, i.e., all ways parents can answer to the questionnaire, then we get the Hinton diagram for R as shown in Fig. 4.

Figure 4: The Hinton diagram by setting 64 clusters of R.

We can see from Fig. 4 that there are 4 dominant clusters. Hence, later on for the Bernoulli mixture model we will take 4 different clusters. Note that under the implemented algorithm, although the clusters – of course – do not change by launching again the code, the order of these clusters do change. A choice of 4 clusters give the following Hinton diagram for the P_{ij} s, as seen in Fig. 5, superimposed with the Hinton diagram for R. According to Fig. 5, Cluster 2 is made of the children with high probabilities of late wheezing, Cluster 4 of the children with high probabilities of early wheezing, Cluster 3 of the children with high probabilities of persisting wheezing, and Cluster 1 of the children with probabilities of sporadic and benign wheezing. To give ourselves an idea of the assignments of each cluster for each patient, we can plot the cluster heat map as shown in Fig. 6a. As seen in Fig. 6a, this clustering method seems to be grouping quite efficiently the patients with late-childhood wheezing (blue group), persistent wheezing (green group), early-childhood

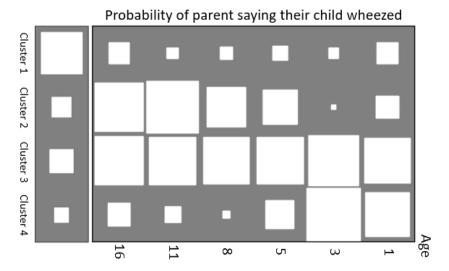
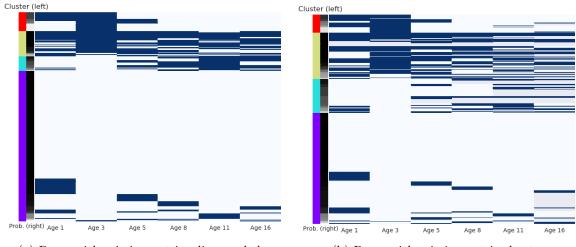


Figure 5: Hinton diagram of the P_{ij} s for $i \in \{1, ..., 6\}$ and $j \in \{1, ..., 4\}$, i.e., the probabilities of the parents saying that their child wheezed at each age tranche separated by cluster. The squares in the lower rectangle show the "sizes" of each cluster (more formally, the probability of belonging to each cluster).

wheezing (red group), and none or sporadic wheezing (purple group).

We can also perform the Bernoulli process on the full data, i.e., also on the parents that did not say if their child wheezed at all age tranches, since P_{ij} is a probability assigned to each answer individually. The aim is to compare whether the change of grouping of the data with answers for each age tranche changes whether or not we add up this new incomplete data. Ideally, it does not so that the prediction is accurate. The heat map of the clustering via Bernoulli mixture of all the data, including the missing one, is shown in Fig. 6b.



- (a) Rows with missing entries disregarded.
- (b) Rows with missing entries kept.

Figure 6: Heat map of the answers of the parents and their respective cluster (the cluster they have been assigned with highest probability) where (6a) the rows with missing entries were disregarded, and where (6b) the rows with missing entries were all kept. Each dark blue entry represents a positive answer by the parents that their child had wheezed, while a light blue entry is a negative answer. From Fig. 5, Cluster 1 is here the purple group, Cluster 2 is the blue group, Cluster 3 is the green group and Cluster 4 is the red group. The gray-scaled bar represents the probability of assignment to this cluster, going from 0.4 (white) to 1 (black). Each missing answer for Fig. 6b from the parents is shown in gray.

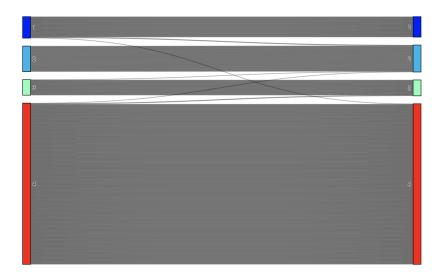


Figure 7: Sankey diagram showing the patients flow between Bernoulli mixture models with the complete data only (left) and all the data including rows with missing entries (right). Note that the clusters here may not have the same labels and color as before since the algorithm was called another time here.

Comparing the sizes of the clusters in Fig. 6a and Fig. 6b, adding the data with missing entries has increased the sizes of the green and blue clusters. We can here plot a Sankey diagram, as seen in Fig. 7 showing to which clusters the entries with complete data are mapped from a Bernoulli mixture with only complete data to a Bernoulli mixture with all the data available. From Fig. 7, we can see that the model for full entries remains stable with only seven swing patients, of which one of type α (Yes, No, Yes, No, Yes, Yes), two of type β (Yes, Yes, No, No, Yes, No), one of type γ (Yes, No, Yes, No, No, Yes), two of type ξ (No, No, No, Yes, No, Yes), and one of type λ (No, Yes, No, No, No, Yes).

Those swing patients are shown in Table 2. The "biggest" swing is made by the two patients of type β (see Table 2), where they have above 60% of probability to be assigned different clusters when the missing entries from the full set of data is added up. This is due to the fact that the expression of the wheeze phenotype of these patients is very unpredictable and do not show any pattern – the parents answered (Yes, Yes, No, No, Yes, No).

Patient type	Cl L	Pr L	Cl R	Pr R
α	3	51%	2	55%
β	1	67%	2	65%
γ	4	64%	2	40%
ξ	4	56%	3	57%
λ	1	41%	4	54%

Table 2: Allocations of the swing patients from a Bernoulli mixture with only the clean data (assigned to the cluster C_L L with probability P_R L) to all the data (assigned to the cluster C_L R with probability P_R R), where each cluster number is as shown in Fig. 7.

The Bernoulli Mixture Model is advantageous in practice because it allows practitioners to add up data throughout the childhood of a patient. E.g., if the parents have a child aged 3 and gave answers to the questionnaire (whether or not the child wheezed before 1, and around 3), the data can still be clustered through the Bernoulli Mixture Model, so that the practitioner can look at complete past entries in this group ("neighboring data") and predict future wheezing patterns of this child. As seen in Fig. 6b, the Bernoulli Mixture Model generally assumes higher probabilities of wheeze if no entry is given, unless if it is sporadic. This method might be more accurate if the parents are asked if their children wheezed during smaller age intervals, such as yearly.

5. Conflicts of interest

The author(s) note no known conflict of interest by undertaking this research.

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