Semiparametric estimation of a two-component mixture model when a component is known

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Abstract

We consider the mixture model $g(x) = (1-p)f_0(x) + pf(x-\mu)$, where the density function f_0 is known and where the unknown parameters are: the mixing proportion $p \in (0,1)$, the non null location parameter μ and the even density function f. These kinds of models were introduced in biology in order to study the differences of expression between genes. The various estimation methods proposed till now assume that f belongs to a parametric family of density functions. We propose in this paper to show how this assumption can be relaxed. First we note that generally the above model is not identifiable, but we show that under moment and symmetry conditions some "almost everywhere" identifiability results can be obtained. When such identifiability conditions are fulfilled we propose an estimation method for the parameter (p, μ, f) which is shown to be strongly consistent under mild conditions. We discuss applications of our method to microarray data analysis and to the training data problem. We compare our method to the parametric approach on simulated data and finally, we apply our method to actual data coming from microarray experiments.

Keywords: Identifiability, microarray data, training data, multiple test hypothesis, mixture, semiparametric.

1 Introduction

In this work we consider the two-component mixture model defined by

$$g(x) = (1-p)f_0(x) + pf(x-\mu), \quad \forall x \in \mathbb{R}, \tag{1}$$

where the probability density function (pdf) f_0 is known and the unknown parameters are the mixing proportion $p \in (0,1)$, the non null location parameter $\mu \in \mathbb{R}$ and an even pdf f. Such mixture models, semiparametric or nonparametric, have been recently studied by Hall and Zhou (2003), Bordes *et al.* (2004), Cruz-Medina and Hettmansperger (2004), Hunter *et al.* (2004) and can be situated between fully parametric mixture models and nonparametric mixture models (for an overview about classical mixture models we refer to McLachlan and Peel, 2000).

The introduction of model (1) is motivated by the problem of detection of differentially expressed genes under two conditions or more in microarray data (examples of such condition can be ”healthy tissue versus diseased tissue”, ”‘brain versus kidney”, etc.). For this purpose a test statistic is built for each gene. Under the null hypothesis, corresponding to a lack of difference of expression, it has a known distribution (in general Student or Fisher). We then observe the response of thousands of genes, which corresponds in practice to thousands of observations of statistical tests. The sample obtained in this way comes from a mixture of two distributions: the known distribution f_0 (for the genes under the null hypothesis) and another distribution corresponding to $f(\cdot - \mu)$, which is the unknown distribution of the test statistics under the alternative hypothesis. Once the parameters p, μ and f are estimated, we can estimate the probability that a gene belongs to the null component of the mixture distribution conditionally on the observations. Therefore, using a classification criterion we allocate each gene to a component and then we distinguish the genes differentially expressed from the genes non differentially expressed.

Model (1) appears as an alternative to parametric mixture models (Delmas, 2005), when the law under the alternative hypothesis is unknown. For a survey on these methods and the stakes dealing with this kind of applications we refer to Dudoit *et al.* (2002) and McLachlan *et al.* (2004).

Another important issue is the *training data* problem. We consider the problem of estimation of all the parameters in (1), *i.e.* p, μ, f and f_0 (which this time is unknown) when in addition to a sample of g-distributed random variables a sample of f_0-distributed random variables is available (training data from the first component). In the classical training data problem, data are available from each component (see e.g. Titterington *et al.*, 1985), thus, the originality here is that training data are available for only one of the two components of model (1).

The paper is organized as follows. The next section is devoted to the identifiability problem. First we show that model (1) is not identifiable in general even if it is locally identifiable. Then we give some sufficient conditions to obtain the identifiability. In Section 3 we propose an inference procedure based on the symmetry of the unknown component of the model whereas in Section 4 we show that solving the moment equations we can also estimate the unknown Euclidean part of the model. In Section 5 we show that if model (1) is identifiable, estimators of unknown parameters are strongly consistent. Section 6 is devoted to a precise description of the two applications we introduced above, whereas in Section 7 are given simulation results and an application to an actual data set. Future issues concerning such kind of semiparametric mixture models are also discussed in Section 8.

2 Identifiability

2.1 Some non-identifiable cases

From a general point of view model (1) is not identifiable as it is shown in the two following examples.

$$\frac{3}{4}u_{-1,1}(x) + \frac{1}{4}u_{-3,3}(x-4) = \frac{2}{3}u_{-1,1}(x) + \frac{1}{3}u_{-4,4}(x-3), \quad \forall x \in \mathbb{R}, \tag{2}$$

where $u_{a,b}$ is the uniform pdf on $]a,b[$ with a and b two real parameters such that $a < b$, and

$$(1-p)\varphi(x) + pf(x-1) = \left(1 - \frac{p}{2}\right)\varphi(x) + \frac{p}{2}\varphi(x-2), \quad \forall x \in \mathbb{R}, \tag{3}$$

where φ is any even pdf, $p \in (0,1)$ and $f(x) = (\varphi(x-1) + \varphi(x+1))/2$.

Clearly, the two above examples show that without any additional assumptions on the model we cannot obtain an identifiability result. In the next section we shall see that however there are some limitations to the non-identifiability.

2.2 Local identifiability via moment equations

Above examples show that identifiability of model (1) can not be expected for $(p, \mu, f) \in]0,1[\times\mathbb{R}^* \times \mathcal{F}$ where $\mathcal{F}$ is the set of even pdf defined on $\mathbb{R}$. However, if we assume that f_0 has a third order moment and that f belongs to $\mathcal{F}_3 = \{f \in \mathcal{F}; \int_{\mathbb{R}} |x|^3 f(x)dx < +\infty\}$, then the moment equations lead to local identifiability of the model. Let us consider the equation

$$(1-p)f_0(x) + pf(x-\mu) = (1-p_1)f_0(x) + p_1 f_1(x-\mu_1), \quad \forall x \in \mathbb{R}, \tag{4}$$

for fixed values of $(p, \mu, f) \in]0,1[\times\mathbb{R}\backslash\{\mu^{(0)}\} \times \mathcal{F}_3$. We denote by $\mu^{(0)}$ the mean of the pdf f_0.

Proposition 1 *The equation (4) has at most two solutions* $(p_1, \mu_1, f_1) \in]0,1[\times\mathbb{R}\backslash\{\mu^{(0)}\} \times \mathcal{F}_3$ *if* f_0 *is a symmetric pdf and at most three solutions otherwise.*

Proof. Note that since f_0 is known we can, up to a translation, assume that f_0 has a null first moment. Therefore we assume from now on that μ and μ_1 belong to $\mathbb{R}^*$. The first three moment equations are:

$$\begin{cases} p\mu = p_1\mu_1 \\ (1-p)\theta_0 + p(\mu^2+\theta) = (1-p_1)\theta_0 + p_1(\mu_1^2+\theta_1) \\ p(3\mu\theta+\mu^3) = p_1(3\mu_1\theta_1+\mu_1^3), \end{cases} \tag{5}$$

where θ_0, θ and θ_1 are respectively the second order moments of f_0, f and f_1. Then, because it is easy to check (see Appendix A for details) that μ_1 is the zero of a two-order polynomial, we obtain that either $(p_1, \mu_1, \theta_1) = (p, \mu, \theta)$ or

$$\begin{cases} p_1 &= p\left(\dfrac{2\mu^2}{3\theta+\mu^2-3\theta_0}\right) \\ \mu_1 &= \mu + \dfrac{3\theta-\mu^2-3\theta_0}{2\mu} \\ \theta_1 &= \theta + \dfrac{(\theta+\mu^2-\theta_0)(3\theta_0+\mu^2-3\theta)}{4\mu^2}. \end{cases} \tag{6}$$

Note that if f_0 is not symmetric with third order moment equal to γ_0, the two first equations in (5) are unchanged whereas the third equation becomes

$$(1-p)\gamma_0 + p(3\mu\theta+\mu^3) = (1-p_1)\gamma_0 + p_1(3\mu_1\theta_1+\mu_1^3).$$

Then, with this new system of equations we obtain that either $\mu = \mu_1$ or

$$-2\mu\mu_1^2 + (3\theta - 3\theta_0 + \mu^2)\mu_1 + \gamma_0 = 0.$$

It follows that there are at most 3 solutions for (p_1, μ_1, θ_1). Because by (1) we have

$$f(x) = \frac{g(x+\mu) - (1-p)f_0(x+\mu)}{p}, \quad x \in \mathbb{R}. \tag{7}$$

the pdf f is uniquely determinated by g, f_0, p and μ. The proposition is proved. □

The above proposition proves that in the above examples (2) and (3), there is no other way to write the mixture, because in the two examples, f_0 is an even pdf. Note also that this proposition leads to a local identifiability result. Indeed, since $(p_1, \mu_1, f_1) = (p, \mu, f)$ is a solution of (4) there exists a neighborhood of (p, μ) where (p, μ, f) is the unique solution of (4). Note also that if $(p, \mu, \theta) = (1/3, 3, 16/3)$ then by (6) we obtain $(p_1, \mu_1, \theta_1) = (1/4, 4, 3)$ which corresponds to the non-identifiability example given in (2).

2.3 Identifiability and characteristic functions

In this section we investigate identifiability for model (1) when f_0 is a symmetric pdf having a third order moment, or equivalently, when $f_0 \in \mathcal{F}_3$ is an even function (if $\mu^{(0)}$ is the known symmetry point of f_0, then consider $g(\cdot + \mu^{(0)})$). Let us have a look at (4) for (p, μ, f) and (p_1, μ_1, f_1) in $]0, 1[\times\mathbb{R}^* \times \mathcal{F}_3$. Denoting by $\hat{f}$ the Fourier transform (or characteristic function) of a pdf f, we get the following equations by identifying the real and imaginary parts of the Fourier transform of (4):

$$0 = \det\begin{pmatrix} \hat{f}(t) & p_1\sin(\mu_1 t) \\ \hat{f}_1(t) & p\sin(\mu t) \end{pmatrix}, \quad \forall t \in \mathbb{R}, \tag{8}$$

and

$$(p_1 - p)\hat{f}_0(t) = \det\begin{pmatrix} \hat{f}(t) & p_1\cos(\mu_1 t) \\ \hat{f}_1(t) & p\cos(\mu t) \end{pmatrix}, \quad \forall t \in \mathbb{R}. \tag{9}$$

The next proposition gives an identifiability result when $\hat{f}_0 > 0$, which is true e.g. for Gaussian or Student centered distributions.

Proposition 2 *The mixture model (1), with $f_0 \in \mathcal{F}_3$ and $\hat{f}_0 > 0$, is identifiable if*

$$(p, \mu, f) \in]0, 1[\times\mathbb{R}^* \times \mathcal{F}_3 \quad \text{and} \quad \theta \neq \theta_0 + \frac{k \pm 2}{3k}\mu^2, \quad \forall k \in \mathbb{N}^*,$$

where θ and θ_0 are the second order moments of f and f_0 respectively.

Proof. Multiplying (9) by $\sin(t\mu)$ and using (8) we get the following equation

$$(p_1 - p)\sin(\mu t)\hat{f}_0(t) = p_1\hat{f}_1(t)\sin(t(\mu - \mu_1)), \quad \forall t \in \mathbb{R}.$$

Because $\hat{f}_0 > 0$, the above equation implies that $\sin(\mu t) = 0$ whenever $\sin(t(\mu - \mu_1)) = 0$. By considering the particular argument value $t^* = \frac{\pi}{\mu - \mu_1}$ we obtain that:

$$\sin(t^*\mu) = \sin\left(\left[\frac{\mu}{\mu - \mu_1}\right]\pi\right) = 0 \Longrightarrow \frac{\mu}{\mu - \mu_1} \in \mathbb{N}.$$

But according to Proposition 1 there exists at most one other solution $\mu_1 \neq \mu$ to problem (4), which in turn implies that there exists at most a positive integer k_0 such that $|\mu| = k_0|\mu - \mu_1|$. From the last equality it follows that

$$\mu_1 = \frac{k_0 \pm 1}{k_0}\mu.$$

The above equality with the second equality in (6) lead to:

$$\theta = \theta_0 + \mu^2\left(\frac{k_0 \pm 2}{3k_0}\right). \tag{10}$$

Finally, if f belongs to the set of densities that do not satisfy (10), we have $\mu_1 = \mu$ and then, by the first moment equation we obtain $p_1 = p$, and by (8) we obtain $\hat{f}_1 = \hat{f}$ or equivalently $f_1 = f$ almost everywhere on $\mathbb{R}$ (with respect to the Lebesgue measure). □

Using the first order moment and (8) we show that $f = f_1$ almost everywhere (with respect to the Lebesgue measure) whenever $p = p_1$ or $\mu = \mu_1$. It follows that model (1) is identifiable whenever $(\mu, \theta) = (\mu_1, \theta_1)$, i.e. if

$$(\mu, \theta) \in \Phi = \{(\mu, \theta) \in \mathbb{R}^* \times]0, +\infty[\ \} \setminus \bigcup_{k \in \mathbb{N}^*} \{(\mu, \theta_0 + \mu^2(k \pm 2)/3k); \mu \in \mathbb{R}^*\}.$$

Identifiability is therefore obtained on $\mathbb{R}^* \times]0, +\infty[$ except on a set (of uncertainty) with Lebesgue measure equal to 0. We can see in Fig. 1 below the domain of identifiability for $(\mu, \theta) \in (0, +\infty)^2$. Notice that the second non-identifiable case given in (3) (with φ and f symmetric) satisfies $\theta = \theta_0$ which is a particular condition of incertainty since $\theta = \theta_0 + \mu^2\,((2-2)/6)$, corresponding to $k_0 = 2$ in (10).

`Fig. 1 about here`

To conclude this section we propose to remark that there are at least two other cases where identifiability of model (1) holds.

Proposition 3 *(i) The mixture model (1) is identifiable if $f_0 > 0$, f is an even function and both have first order moments and satisfy*

$$\forall \beta \in \mathbb{R}, \qquad \lim_{x \to +\infty} \frac{f(x-\beta)}{f_0(x)} = 0, \quad or \quad \lim_{x \to -\infty} \frac{f(x-\beta)}{f_0(x)} = 0. \tag{11}$$

(ii) The mixture model (1) is identifiable if $f > 0$ has a first order moment, and there exists a real number $a > 0$ such that for all $|x| > a$ we have $f_0(x) = 0$ and $f(x) = f(-x)$.

Proof. (i) If condition (11) is satisfied we have $1 - p = \lim_{x \to +\infty} g(x)/f_0(x)$ (or $1 - p = \lim_{x \to -\infty} g(x)/f_0(x)$ for convenience) and then by (4) we have $p = p_1$. By the first moment equation, denoting by m and m_0 the first order moments of g and m respectively, we have

$$\mu = \frac{m - (1-p)m_0}{p},$$

and thus $\mu = \mu_1$ and by (7) f is unique.

(ii) For all $x \in \mathbb{R}$ such that $|x| > a$ we have by (4)

$$pf(x - \mu) = p_1 f(x - \mu_1).$$

Then, for large values of $|x|$ we obtain

$$pf(x + \mu_1 - \mu) = p_1 f_1(x) = p_1 f_1(-x) = pf(\mu_1 - \mu - x),$$

which is possible only if $\mu = \mu_1$. The end of the proof is the same as for case (i). □

Let us notice that cases (i) and (ii) of Proposition 3 do not require the symmetry of f_0 which can be usefull for microarray data analysis with more than two conditions (see Section 6.1).

3 Estimating the Euclidean parameter by symmetrization

Suppose that we observe n independent and identically distributed (iid) random variables $X_1, \ldots, X_n$ with cumulative distribution function (cdf) G defined by model (1), that is

$$G(x) = (1-p)F_0(x) + pF(x - \mu), \quad \forall x \in \mathbb{R},$$

where G, F_0 and F are cdf's corresponding to pdf's g, f_0 and f respectively. From now on, we assume that f_0 is the density of a centered distribution. If it is not, we have just to change the X_i's into $X_i - m_0$ where $m_0 = \int_{\mathbb{R}} x f_0(x)dx$. Assume that there exists an unique triple (p, μ, F) defining G in the previous equation, then we get

$$F(x) = \frac{1}{p}\left(G(x+\mu) - (1-p)F_0(x+\mu)\right), \quad \forall x \in \mathbb{R}. \tag{12}$$

Since F is the cdf of a symmetric distribution with respect to 0, we have $F(x) = 1 - F(-x)$, for all $x \in \mathbb{R}$. We denote by p_0 and μ_0 respectively the unknown values of p and μ. Defining for all $x \in \mathbb{R}$ the functions

$$H_1(x; \mu, m, G, F_0) = \frac{\mu}{m} G(x+\mu) + \frac{m-\mu}{m} F_0(x+\mu),$$

and

$$H_2(x; \mu, m, G, F_0) = 1 - \frac{\mu}{m} G(\mu - x) + \frac{\mu - m}{m} F_0(\mu - x),$$

where $m = p\mu$ is the first order moment of G, we have, using (12) and the symmetry of F, $H_1(\cdot; \mu_0, m, G, F_0) = H_2(\cdot; \mu_0, m, G, F_0)$. Consequently, if d is a distance measure between two functions, we have $d(H_1(\cdot; \mu_0, m, G, F_0), H_2(\cdot; \mu_0, m, G, F_0)) = 0$.

Now, since G and m are unknown, it is natural to replace G and m by their estimators, that is $\hat{G}_n$ and $\hat{m}_n$ defined respectively by

$$\hat{G}_n(x) = \frac{1}{n}\sum_{i=1}^{n} \mathbf{1}(X_i \leq x), \quad \forall x \in \mathbb{R}, \quad \text{and} \quad \hat{m}_n = \frac{1}{n}\sum_{i=1}^{n} X_i,$$

where $\mathbf{1}(\cdot)$ is the indicator function. Therefore we get an empirical version d_n of d defined by

$$d_n(\mu) = d(H_1(\cdot; \mu, \hat{m}_n, \hat{G}_n, F_0), H_2(\cdot; \mu, \hat{m}_n, \hat{G}_n, F_0)), \quad \mu \in \mathcal{X}, \tag{13}$$

where $\mathcal{X}$ is a compact subset of $\mathbb{R}^*$ on which model (1) is identifiable. Therefore it is natural to estimate the unknown parameter μ_0 by

$$\hat{\mu}_n = \arg\min_{\mu \in \mathcal{X}} d_n(\mu), \tag{14}$$

then p_0 is estimated by $\hat{p}_n = \hat{m}_n / \hat{\mu}_n$ (since the first moment equation of g leads to $p = m/\mu$). For d we can choose the $L^q(\mathbb{R})$–norm, defined for $1 \leq q < +\infty$ by

$$d(\mu) = \left(\int_{\mathbb{R}} |H_1(x; \mu, m, G, F_0) - H_2(x; \mu, m, G, F_0)|^q dx\right)^{1/q} \equiv \|H_1 - H_2\|_q.$$

Remark 1 *Replacing μ/m by $1/p$ in H_1 and H_2 we obtain a new contrast function $d(p,\mu;G)$ depending on G and on the unknown parameters p and μ. Replacing G by $\hat{G}_n$ we are lead to an empirical contrast $d_n(p,\mu) = d(p,\mu;\hat{G}_n)$ whose the minimizer $(\hat{p}_n,\hat{\mu}_n)$ is an estimator of (p,μ). This approach should be used when g does not have a first order moment. Note also that when f is not exactly an even function, simulation results show robustness in estimating (p,μ) by using $d_n(p,\mu)$ instead of $d_n(\mu)$.*

Using relation (12) we can estimate F by:

$$\hat{F}_n(x) = \frac{\hat{\mu}_n}{\hat{m}_n}\hat{G}_n(x+\hat{\mu}_n) + \frac{\hat{m}_n - \hat{\mu}_n}{\hat{m}_n}F_0(x+\hat{\mu}_n), \quad \forall x \in \mathbb{R}.$$

Note that generally $\hat{F}_n$ will not be a legitimate cdf since it is not nondecreasing in general, however, the Glivenko-Cantelli strong consistency result obtained in the Section 5 shows that it is not a serious drawback whenever the sample size is large enough.

Again by formula (7) a natural estimator of the pdf f is defined by

$$\tilde{f}_n(x) = \frac{1}{\hat{p}_n}\left(\hat{g}_n(x+\hat{\mu}_n) - (1-\hat{p}_n)f_0(x+\hat{\mu}_n)\right), \quad \forall x \in \mathbb{R},$$

where

$$\hat{g}_n(x) = \frac{1}{nb_n}\sum_{i=1}^{n} q\left(\frac{x-X_i}{b_n}\right), \quad \forall x \in \mathbb{R},$$

with $b_n \to 0$, $nb_n \to +\infty$ and q is a symmetric kernel pdf with finite second order moment. For example we can choose $q(x) = (1-|x|)\mathbf{1}(-1 \le x \le 1)$. Because generally $\tilde{f}_n$ is not a pdf it can be modified into the estimator $\hat{f}_n$ which is itself a pdf

$$\hat{f}_n = \frac{1}{s_n}\tilde{f}_n\mathbf{1}(\tilde{f}_n \ge 0),$$

where $s_n = \displaystyle\int_{\mathbb{R}} \tilde{f}_n(x)\mathbf{1}(\tilde{f}_n(x) \ge 0)dx$. However there are other ways to modifiy kernel estimators to make them non-negative, see Glad *et al.* (2003).

4 Moments method for estimating the Euclidean parameters

Let $\hat{G}_n$ be the empirical cdf obtained from n iid random variables with common cdf G. Let us denote by μ_0, θ_0 and γ_0 the first three moments of f_0. Define $\tilde{g}$ by $\tilde{g}(\cdot) = g(\cdot + \mu_0)$

where g is defined by (1), then we have

$$\tilde{g}(x) = (1-p)\tilde{f}_0(x) + pf(x-\tilde{\mu}), \quad \forall x \in \mathbb{R},$$

where $\tilde{f}_0(\cdot) = f_0(\cdot + \mu_0)$ and $\tilde{\mu} = \mu - \mu_0$. Now we write $\tilde{m}_i = \int_{\mathbb{R}} x^i \tilde{g}(x)dx$ for $i = 1, 2, 3$, and we get

$$\begin{cases} p\tilde{\mu} & = & \tilde{m}_1, \\ (1-p)\tilde{\theta}_0 + p(\theta + \tilde{\mu}^2) & = & \tilde{m}_2, \\ (1-p)\tilde{\gamma}_0 + p(3\theta\tilde{\mu} + \tilde{\mu}^3) & = & \tilde{m}_3, \end{cases} \tag{15}$$

where θ is the second order moment of f and $\tilde{\theta}_0$ and $\tilde{\gamma}_0$ are moments of order two and three of $\tilde{f}_0$. If $\tilde{m}_1 = 0$ and $\tilde{\gamma}_0 \neq 0$, then we have

$$\begin{cases} \mu & = & \mu_0, \\ p & = & \dfrac{\tilde{\gamma}_0 - \tilde{m}_3}{\tilde{\gamma}_0}, \end{cases}$$

whereas if $\tilde{m}_1 = 0$ and $\tilde{\gamma}_0 = 0$ there are infinitely many solutions. Otherwise, if $\tilde{m}_1 \neq 0$ we show that $\tilde{\mu}$ is a zero of the following polynomial

$$\tilde{\mu}^3 + \frac{3(\tilde{\theta}_0 - \tilde{m}_2)}{2\tilde{m}_1}\tilde{\mu}^2 + \frac{\tilde{m}_3 - \tilde{\gamma}_0 - 3\tilde{m}_1\tilde{\theta}_0}{2\tilde{m}_1}\tilde{\mu} + \frac{\tilde{\gamma}_0}{2} = 0.$$

Now, replacing unknown moments $\tilde{m}_k$ by their empirical counterpart $\tilde{m}_k^{(n)}$ defined for $k = 1, 2, 3$ by:

$$\tilde{m}_k^{(n)} = \int_{\mathbb{R}} x^k d\hat{G}_n(x + \mu_0) = \frac{1}{n}\sum_{i=1}^{n}(X_i - \mu_0)^k,$$

we solve the following random polynomial equation

$$\tilde{\mu}^3 + \frac{3(\tilde{\theta}_0 - \tilde{m}_2^{(n)})}{2\tilde{m}_1^{(n)}}\tilde{\mu}^2 + \frac{\tilde{m}_3^{(n)} - \tilde{\gamma}_0 - 3\tilde{m}_1^{(n)}\tilde{\theta}_0}{2\tilde{m}_1^{(n)}}\tilde{\mu} + \frac{\tilde{\gamma}_0}{2} = 0. \tag{16}$$

Then we are lead to at most three solutions written $\hat{\tilde{\mu}}_n^{(i)}$ which in turn lead to three possible estimators for μ. Let us write $\hat{\mu}_n^{(i)} = \mu_0 + \hat{\tilde{\mu}}_n^{(i)}$ $(i = 1, 2, 3)$ these three possible estimators of μ. We finally estimate μ by the value among $\{\hat{\mu}_n^{(1)}, \hat{\mu}_n^{(2)}, \hat{\mu}_n^{(3)}\}$ that minimizes the empirical discrepancy measure d_n defined by (13).

Remark 2 *Solving (16) can be done e.g. by using the function* `polyroot` *of the* `R` *statistical software. Note that (16) can have two conjugate complex roots, because of errors in coefficients of the polynomial. In that case we have to take the real part of the roots.*

Typically, when $\tilde{\gamma}_0 = 0$ and the model is identifiable, the polynomial (16) reduces to a polynomial of degree two, the discriminant of which can be null (if the moment equations give the identifiability). In that case the estimator of the discriminant can be positive or negative and then we can obtain complex roots of (16). However this is not a serious drawback because the more the estimation of moments is precise, the more the estimated value of discriminant will be small and then negligible.

Remark 3 *It is worth to note that the method of moments can give an interesting initial guess value to minimize the discrepancy measure d_n.*

5 Consistency

We denote by (p_0, μ_0) the true value of the unknown Euclidean part (p, μ) of the model (1) and by θ_0 and θ the moments of order 2 of f_0 and f respectively. Let us introduce the set

$$\Phi = \mathbb{R}^* \times]0, +\infty[\setminus \cup_{k \in \mathbb{N}^*} \Phi_k$$

where

$$\Phi_k = \left\{ (\mu, \theta) \in \mathbb{R}^* \times]0, +\infty[; \theta = \theta_0 + \mu^2 \frac{k \pm 2}{3k} \right\}.$$

We consider the following assumptions.

A1. $(f_0, f) \in \mathcal{F}_3^2$, $\hat{f}_0 > 0$ and $(\mu_0, \theta) \in \Phi_c \subset \Phi$, where Φ_c is a compact subset of Φ.

A2. (f_0, f) satisfies the identifiability condition of Proposition 3 (i) and in addition f_0 satisfies the following tail condition:

$$\forall \alpha \in \mathbb{R}, \quad \lim_{x \to +\infty} \frac{f_0(-x + \alpha)}{f_0(x)} = 0, \quad \text{or} \quad \lim_{x \to +\infty} \frac{f_0(x)}{f_0(-x + \alpha)} = 0. \tag{17}$$

A3. (f_0, f) satisfies identifiability condition of Proposition 3 (ii).

Let us consider $\nu = \xi(\Phi_c)$ under A1, and $\nu = \xi(\Phi_K)$ under A2 or A3, with $\xi(x, y) = x$ and Φ_K denotes any compact subset of $\mathbb{R}^* \times (0, +\infty)$. Therefore we assume that $\hat{\mu}_n$ is defined by

$$\hat{\mu}_n = \arg \min_{\mu \in \nu} d_n(\mu),$$

while estimators $\hat{p}_n$, $\hat{F}_n$ and $\hat{f}_n$ are defined as in Section 3.

Theorem 1 *Assume that one of Assumptions A1–A3 is satisfied. As n tends to infinity we have:*

(i) $(\hat{p}_n, \hat{\mu}_n)$ *converge almost surely to* (p_0, μ_0).

(ii) $\sup_{x\in\mathbb{R}} |\hat{F}_n(x) - F(x)|$ *converges almost surely to 0, if both* F_0 *and* F *are uniformely continuous on* $\mathbb{R}$.

(iii) $\int_{\mathbb{R}} |\hat{f}_n(x) - f(x)|dx$ *converges almost surely to 0 if* $b_n \to 0$, $nb_n \to +\infty$ *and if both* f_0 *and* f *belong to the Besov space*

$$\mathcal{B}^1_{1,\infty} = \left\{ f \in \mathcal{B}(\mathbb{R}) \ : \ \sup_{h\neq 0} \frac{1}{|h|} \int_{\mathbb{R}} |f(x+h) - f(x)|dx < \infty \right\},$$

where $\mathcal{B}(\mathbb{R})$ *denotes the class of Borel measurable functions defined on* $\mathbb{R}$.

(iv) Assume that q *is a symmetric pdf with finite second order moment satisfying the Geffroy properties (see Bosq & Lecoutre, 1987, p.65):*

(a) *the set of discontinuities of* q *has null Lebesgue measure.*

(b) $x \mapsto \sup\{|q(u)|; |u - x| < 1\}$ *is integrable on* $\mathbb{R}$.

In addtition we assume that $b_n \to 0$, $nb_n/\log n \to +\infty$, *and that both* f_0 *and* f *are uniformly continuous on* $\mathbb{R}$. *Then* $\sup_{x\in\mathbb{R}} |\hat{f}_n(x) - f(x)|$ *converges almost surely to 0.*

Remark 4 *Results of Theorem 1 also hold if* $\hat{p}_n$ *and* $\hat{\mu}_n$ *are the estimators of Remark 1.*

Proof. (i) Let $\varepsilon > 0$ be a real number. From Lemma 4 there exists $\delta > 0$ such that

$$\limsup_{n>0} \{|\hat{\mu}_n - \mu_0| > \varepsilon\} \subseteq \limsup_{n>0} \{d(\hat{\mu}_n) > \delta\}.$$

By Lemma 3, the last set has probability zero. The almost sure convergence of $\hat{\mu}_n$ follows, which implies the almost sure convergence of $\hat{p}_n$ since $\hat{p}_n = \hat{m}_n/\hat{\mu}_n$.

(ii) Let us consider, for all $x \in \mathbb{R}$, the inequality:

$$|\hat{F}_n(x) - F(x)| \leq T_1(x) + T_2(x),$$

where

$$\begin{aligned} T_1(x) &= \left| \frac{\hat{\mu}_n}{\hat{m}_n} \hat{G}_n(x + \hat{\mu}_n) - \frac{\mu_0}{m} G(x + \mu_0) \right|, \\ T_2(x) &= \left| \frac{\hat{m}_n - \hat{\mu}_n}{\hat{m}_n} F_0(x + \hat{\mu}_n) - \frac{m - \mu_0}{m} F_0(x + \mu_0) \right|. \end{aligned}$$

For the treatment of T_1 let us remark that

$$T_1(x) \leq \left|\frac{\hat{\mu}_n}{\hat{m}_n}\hat{G}_n(x+\hat{\mu}_n) - \frac{\hat{\mu}_n}{\hat{m}_n}G(x+\hat{\mu}_n)\right| + \left|\frac{\hat{\mu}_n}{\hat{m}_n}G(x+\hat{\mu}_n) - \frac{\mu_0}{m}G(x+\mu_0)\right|.$$

According to the Glivenko-Cantelli Theorem the first term of the right hand side converges almost surely and uniformly in x to 0 as n tends to infinity. Noticing that the second term of the right hand side of the above inequality is very similar to T_2, we propose to consider the following inequality

$$\left|\frac{\hat{\mu}_n}{\hat{m}_n}G(x+\hat{\mu}_n) - \frac{\mu_0}{m}G(x+\mu_0)\right| \leq \left|\frac{\hat{\mu}_n}{\hat{m}_n} - \frac{\mu_0}{m}\right| + \left|\frac{\mu_0}{m}\right| |G(x+\hat{\mu}_n) - G(x-\mu_0)|.$$

The left hand side of the above inequality goes clearly to 0 as n goes to infinity since, as it has been shown in (i), $\hat{\mu}_n \overset{a.s.}{\to} \mu_0$ and $\hat{m}_n \overset{a.s.}{\to} m$, and since G is uniformly continuous. We thus obtain that $\|T_1\|_\infty \overset{a.s.}{\to} 0$ and $\|T_2\|_\infty \overset{a.s.}{\to} 0$ (this result is straightforward by noticing the analogy between T_2 and the last term we discussed) which concludes the proof for (ii).

(iii) Let us notice that

$$\|\tilde{f}_n - f\|_1 \leq \left\|\frac{\hat{\mu}_n}{\hat{m}_n}\hat{g}_n(\cdot - \hat{\mu}_n) - \frac{\mu_0}{m}g(\cdot - \mu)\right\|_1 + \left\|\frac{\hat{m}_n - \hat{\mu}_n}{\hat{m}_n}f_0(\cdot - \hat{\mu}_n) - \frac{m-\mu_0}{m}f_0(\cdot - \mu)\right\|_1.$$

For simplicity we only treat the first term of the right hand (a similar but simpler proof holds for the second one):

$$\begin{aligned}
&\left\|\frac{\hat{\mu}_n}{\hat{m}_n}\hat{g}_n(\cdot - \hat{\mu}_n) - \frac{\mu_0}{m}g(\cdot - \mu)\right\|_1 \\
&\leq \left\|\frac{\hat{\mu}_n}{\hat{m}_n}\hat{g}_n(\cdot - \hat{\mu}_n) - \frac{\hat{\mu}_n}{\hat{m}_n}g(\cdot - \hat{\mu}_n)\right\|_1 + \left\|\frac{\hat{\mu}_n}{\hat{m}_n}g(\cdot - \hat{\mu}_n) - \frac{\mu_0}{m}g(\cdot - \hat{\mu}_n)\right\|_1 \\
&+ \left\|\frac{\mu_0}{m}g(\cdot - \hat{\mu}_n) - \frac{\mu_0}{m}g(\cdot - \mu_0)\right\|_1 \\
&\leq \left|\frac{\hat{\mu}_n}{\hat{m}_n}\right| \|\hat{g}_n - g\|_1 + \left|\frac{\hat{\mu}_n}{\hat{m}_n} - \frac{\mu_0}{m}\right| + \left|\frac{\mu_0}{m}\right| \|g(\cdot - \hat{\mu}_n) - g(\cdot - \mu_0)\|_1.
\end{aligned}$$

From (i) and the Devroye (1983) L^1-consistency result, which establishes that $\|\hat{g}_n - g\|_1 \overset{a.s.}{\to} 0$, we obtain the almost sure convergence to 0 of the two first terms in right hand side of the previous inequality. For the third term we use the fact that g belongs to the Besov space $\mathcal{B}^1_{1,\infty}$, which implies that

$$\begin{aligned}
&\|g(\cdot + \hat{\mu}_n) - g(\cdot + \mu_0)\|_1 \leq |\hat{\mu}_n - \mu_0| \qquad (18)\\
&\times\left((1-p_0)\sup_{h\neq 0}\frac{1}{|h|}\int_{\mathbb{R}}|f_0(x+h) - f_0(x)|dx + p_0\sup_{h\neq 0}\frac{1}{|h|}\int_{\mathbb{R}}|f(x+h) - f(x)|dx\right),
\end{aligned}$$

and proves that $\|\tilde{f}_n - f\|_1 \overset{a.s.}{\to} 0$ from (i). In addition it is straightforward to show that $\|\hat{f}_n - f\|_1 \le \|\tilde{f}_n - f\|_1$, and then we have the almost sure convergence of $\|\hat{f}_n - f\|_1$ to 0. Moreover, under the same assumptions and with $s_n = \int_{\mathbb{R}} \tilde{f}_n(x)dx$, we have

$$|s_n - 1| = \left| \int_{\mathbb{R}} (\tilde{f}_n(x) - f(x))dx \right| \le \|\tilde{f}_n - f\|_1 \to 0, \quad a.s.$$

Therefore, $\hat{f}_n = s_n^{-1}\tilde{f}_n \mathbf{1}(\tilde{f}_n > 0)$ are density functions that satisfy $\|\hat{f}_n - f\|_1 \overset{a.s.}{\to} 0$.

(iv) For this last point it is enough to remark that since q is a Geffroy kernel, then $\|\hat{g}_n - g\|_\infty \overset{a.s.}{\to} 0$, under the conditions specified in (iv) (see Bosq and Lecoutre, 1987, p.65). In fact, using the analog of the triangular inequalities of the previous proof in supremum norm, the required result holds by replacing the argument in (18) by a uniform continuity argument. □

6 Applications

6.1 Microarray data analysis

Microarrays are technologies that reveal the simultaneous expression levels of a large number of genes in a biological sample. More precisely, a large number (up to several thousands) of gene probes, made of cDNA, are spotted on a membrane. Then the gene targets, in the form of a solution of mRNA, are extracted from a biological tissue and hybridized on this support. The expression level of each gene in the biological tissue is given by the concentration of mRNA hybridized on each probe. The experiments are repeated to assess the experimental variability and conducted under different conditions (different treatments, stages, tissues, etc.). The conditions are compared to detect the differences in expression.

We denote by R the number of repetitions, n the number of genes and J the number of conditions. The data are the random variables (A_{ijr}) corresponding to the rth repetition of the expression level of gene i in condition j. We divide A_{ijr} by the sum of all the expression levels on the membrane to obtain the concentrations:

$$P_{ijr} = \frac{A_{ijr}}{\sum_{i=1}^{n} A_{ijr}}.$$

We consider the following transformation of the P_{ijr}'s:

$$X_{ijr} = \ln\left(\frac{P_{ijr}}{1-P_{ijr}}\right).$$

We write $X_{ij\cdot} = \dfrac{1}{R}\displaystyle\sum_{r=1}^{R} X_{ijr}$, $X_{i\cdot\cdot} = \dfrac{1}{JR}\displaystyle\sum_{j=1}^{J}\sum_{r=1}^{R} X_{ijr}$ and we assume that the data are of good quality and have been correctly normalized to ensure that experimental biases have been removed. We assume that for r in $\{1,\ldots,R\}$, X_{ijr} is normally distributed with mean m_{ij} and variance σ_{ij}^2. Therefore, for i in $\{1,\ldots,n\}$, the null hypothesis $\mathcal{H}_{0,i}$:

"There is no expression difference between the J conditions for gene i",

is equivalent to

$$\left\{ m_{ij} = m_{i\cdot},\ \sigma_{ij} = \sigma_{i\cdot}, \forall j = 1,\ldots,J \text{ where } m_{i\cdot} = \frac{1}{J}\sum_{j=1}^{J} m_{ij}, \text{ and } \sigma_{i\cdot} = \frac{1}{J}\sum_{j=1}^{J}\sigma_{ij} \right\}.$$

In order to compare two conditions ($J = 2$) we can use, for the i-th gene, the test statistic S_i defined by:

$$S_i = \frac{X_{i1\cdot} - X_{i2\cdot}}{\sqrt{\dfrac{\sum_{r=1}^{R}(X_{i1r} - X_{i1\cdot})^2 + \sum_{r=1}^{R}(X_{i2r} - X_{i2\cdot})^2}{R(R-1)}}}. \tag{19}$$

For each i in $\{1,\ldots,n\}$ under the null hypothesis $\mathcal{H}_{0,i} = \{m_{i1} = m_{i2},\ \ \sigma_{i1} = \sigma_{i2}\}$ (that there is no expression difference between the two conditions for gene i) the statistic S_i is Student distributed with $2R-2$ degrees of freedom. Generally speaking when we compare J conditions, we can use for the i-th gene, the test statistic S_i:

$$S_i = \frac{RJ(R-1)}{(J-1)} \times \frac{\sum_{j=1}^{J}(X_{ij\cdot} - X_{i\cdot\cdot})^2}{\sum_{j=1}^{J}\sum_{r=1}^{R}(X_{ijr} - X_{ij\cdot})^2}.$$

Under the null hypothesis $\mathcal{H}_{0,i} = \{m_{ij} = m_{i.},\ \ \sigma_{ij} = \sigma_{i.},\ \forall j = 1,\ldots,J\}$, that there is no expression difference between the J conditions for gene i, the test statistic S_i is Fisher distributed with $(J-1, JR-J)$ degrees of freedom.

Under the alternative hypothesis $\mathcal{H}_{1,i} = \{\exists\ j \in \{1,\ldots,J\} :\ m_{ij} \neq m_{i.},\ \text{ or } \sigma_{ij} \neq \sigma_{i.}\}$ that there is at least one expression difference between the J conditions, the distribution of S_i is unknown. Therefore the S_i's distribution can be modelled by:

$$g(x) = (1-p)f_0(x) + pf(x), \tag{20}$$

where p is the proportion of non-null statistics, f_0 is the null pdf of S_i (Student or Fisher) and f is the unknown non-null pdf.

The estimation of the unknown parameter p and the pdf f allows to obtain an estimation of the probability $\alpha^{(i)}$, that gene i is differentially expressed given $\{S_i = s_i\}$:

$$\alpha^{(i)} = P(\text{gene } i \text{ is differentially expressed } |S_i = s_i) = \frac{pf(s_i)}{(1-p)f_0(s_i) + pf(s_i)}.$$

Under the hypothesis that f is a symmetric pdf on $\mathbb{R}$, model (20) reduces to model (1) and we can estimate p and μ by symmetrization or by the moments method as indicated in Sections 3 and 4 respectively. Then we define natural consistent estimators of f and $\alpha^{(i)}$ given $\{S_i = s_i\}$ by:

$$\begin{aligned}
\hat{f}_n(x) &= \frac{\tilde{f}_n(x)}{\int_{\mathbb{R}} \tilde{f}_n(y)\mathbf{1}(\tilde{f}_n(y) \geq 0)dy}, \\
\hat{\alpha}_n^{(i)} &= \frac{\hat{p}_n \hat{f}_n(s_i - \hat{\mu}_n)}{(1-\hat{p}_n)f_0(s_i) + \hat{p}_n \hat{f}_n(s_i - \hat{\mu}_n)},
\end{aligned}$$

where

$$\tilde{f}_n(x) = \frac{1}{\hat{p}_n}(\hat{g}_n(x+\hat{\mu}_n) - (1-\hat{p}_n)f_0(x+\hat{\mu}_n)).$$

Let us remark that the strong consistency of the $\hat{\alpha}_n^{(i)}$'s to the $\alpha^{(i)}$'s, is insured by Theorem 1. As a consequence, a heuristic way to identify differentially expressed genes, consists in selecting genes i for which the $\hat{\alpha}_n^{(i)}$'s are among the $[n\hat{p}_n]$ greatest values of $\{\hat{\alpha}_n^{(j)}; j = 1, \ldots, n\}$. Identification of differentially expressed genes may also be done using usual classification procedures (see e.g. Benjamini and Hochberg, 1995).

6.2 Mixture model with training data

We still consider model (1) for which both f_0 and f are unknown together with parameters p and μ but for which training data are available for the first component f_0. That is we still have a n–sample from g and in addition a n'–sample from f_0 is given. In classical finite mixture models involving training data, samples from each component are given and then the inference reduces to estimate the mixture proportions (see Titterington, 1983). Following the methodology of Section 3 replacing the unknown cdf F_0 by the empirical cdf $\hat{F}_{0,n'}$ obtained from the training sample, we are able to propose an estimating function similar to (13), defined by

$$d_{n,n'}(\mu) = d(H_1(\cdot;\mu,\hat{m}_n,\hat{G}_n,\hat{F}_{0,n'}), H_2(\cdot;\mu,\hat{m}_n,\hat{G}_n,\hat{F}_{0,n'})), \quad \mu \in \mathcal{X}, \tag{21}$$

where $\mathcal{X}$ is a compact subset of $\mathbb{R}^*$ on which model (1) is identifiable. Therefore it is natural to estimate the unknown parameter μ_0 by

$$\hat{\mu}_{n,n'} = \arg\min_{\mu\in\mathcal{X}} d_{n,n'}(\mu).$$

Therefore, as in Section 3 we can derive natural estimators of the proportion p and the unknown pdf f. Indeed on the one hand we have $p = (m_0 - m)/(m_0 - \mu)$ where m and m_0 are respectively the expectation of g and f_0 (m can be estimated from the g-sample and m_0 can estimated from the f_0-sample). On the other hand, since F can be explicitly expressed as a function of G, F_0, p and μ, it can be estimated by plugging-in estimators of these four quantities in the formula (12). Therefore, smoothing this estimator we can estimate the pdf f as in Section 3.

Note also that the moments method of Section 4 can be used by simply replacing the unknown quantities μ_0, θ_0 and γ_0 by their estimators obtained from the f_0-sample.

Finally, analog consistency results to those of Theorem 1 can be established by assuming that $\min(n, n')$ tends to infinity.

7 Simulations and example

7.1 Simulations

In this section we simulate K samples of n of iid random variables whose the common distribution is given by the following two-component mixture model:

$$(1-p)\mathcal{N}(0,4) + p\mathcal{N}(\mu,1), \tag{22}$$

where $\mathcal{N}(\alpha,\beta)$ denotes the Gaussian distribution with mean α and variance equal to β. For each sample we estimate (p,μ) given that the known component is $\mathcal{N}(0,4)$-distributed. Finally, for different values of n and p, we provide the mean and the standard deviation of the estimates obtained both by the symmetrization method and by the parametric maximum likelihood method.

From a semiparametric point of view the estimator of μ is given by (14) where we choose the L^2-norm for d; thus, using the first moment equation, we derive an estimator of p (see Section 3). Note that the computation of $d_n(\mu)$ requires an integration step that is performed numerically. Because numerical estimation of the derivatives of $d_n(\mu)$ are quite unstable we do not look for the minimum argument $\hat{\mu}_n$ of d_n by using a standard optimization routine but we simply look for the minimizer of d_n over a parameter space discretization.

Let us mention the following weakness in using $d_n(\mu)$. When f_0 is an even function it is easy to check that $\mu = 0$ is a (non admissible) zero of both d and d_n. Therefore, if the model is identifiable d has two roots (0 and μ) corresponding to two minima. Thus, the approximate d_n should have two minima too. But in practice, if the first moment m is not well estimated (typically when both n and p are small) it may happens that the only minimum of d_n is the non admissible value 0 and in any case we have $d_n(\mu) \geq d_n(0)$. In this case we recommend to estimate (p, μ) by using the two-parameter function d_n given in Remark 1. As just said when both p and n are small the first moment equation can lead to a constraint that is not well satisfied by the data. This fact is illustrated by Fig. 2 where on Fig. 2(a) d_n has only one zero whereas on Fig. 2(b) d_n has two zeros.

`Fig. 2 about here`

$K = 200$	$n = 250$	$n = 1000$
$p = 0.3$ / $\mu = 3$	0.303 (0.057) / 2.963 (0.226)	0.301 (0.029) / 2.976 (0.131)
$p = 0.15$ / $\mu = 3$	0.165 (0.055) / 2.878 (0.418)	0.154 (0.031) / 2.944 (0.272)

Table 1: Mean (standard deviation) of 200 semiparametric estimates of p / μ (obtained by the symmetrization method).

$K = 200$	$n = 250$	$n = 1000$
$p = 0.3$ / $\mu = 3$	0.293 (0.045) / 2.989 (0.058)	0.300 (0.022) / 2.991 (0.041)
$p = 0.15$ / $\mu = 3$	0.156 (0.051) / 2.993 (0.101)	0.152 (0.026) / 2.990 (0.051)

Table 2: Mean (standard deviation) of 200 parametric estimates of p / μ (obtained by the maximum likelihood method).

We can see in Tables 1 and 2 that for the standard deviation criterion the parametric estimates outperform the semiparametric estimates. Although for the smallest sample size performances of semiparametric and parametric estimators are quite close, it should be noted that in the semiparametric symmetrization method, samples for which the empirical contrast function was monotone (as in Fig. 2(a)) were rejected (for $n = 250$ about 10% and 20% for $p = 0.3$ and $p = 0.15$ respectively; very few cases for $n = 1000$). Such drawback does not hold in the parametric setup.

7.2 Actual data: bovine gestation mode comparison

We consider data that have been used to detect genes that are statistically differentially expressed in bovine trophoblast between the artificial insemination (AI) and the vitro fecondation (IVF) gestation modes. The AI mode is the reference gestation mode in animal sciences. This statistical analysis helps the biologist in understanding the biological differences between the two gestation modes and then in improving the IVF techniques to reduce the mortality rate with this gestation mode. Ten macroarrays were obtained, each with $n = 10214$ genes, for each condition (AI and IVF). Let A_{ijr} denotes the mean intensity of the signal for the rth repetition of gene i in condition j, where, following the notations of Section 6.1 we have $(i, j, r) \in \{1, \ldots, n\} \times \{1, \ldots, J\} \times \{1, \ldots, R\}$ with $J = 2$ and $R = 10$. Each S_i is therefore computed by using formula (19) and, under the null hypothesis, it follows a Student distribution with 18 degrees of freedom (denoted by T_{18}).

`Fig. 3 about here`

`Fig. 4 about here`

We assume that the S_i's are iid with common distribution defined by (1) where f_0 is the probability distribution function (pdf) of a T_{18} and p, μ and f are unknown. We estimate the unknown Euclidean parameters p and μ by using the two-parameter contrast function defined in Remark 1 instead of method involving the first moment equation that did not prove to be suitable (the contrast function with only one parameter appears to be more sensitive to the f symmetry).

We obtain $\hat{p} = 0.037$ and $\hat{\mu} = 1.05$ by discretizing the Euclidean parameter space ($[0, 1] \times [\min S_i, \max S_i]$) and taking for $(\hat{p}, \hat{\mu})$ the value that makes the empirical contrast d_n minimum on the discretized space. The graph of the empirical contrast function d_n is given in Fig. 3 (with p and μ restrained to $[0.01, 0.1] \times [0.5, 1.5]$ where d_n reaches its minimum value 0.2257 at $(\hat{p}, \hat{\mu})$; note that $d_n(0.1, 0.5) = 0.3066$).

On Figures 4(a) and 4(b) are respectively given the reconstruction of the mixture density g (defined by model (1)) and the estimate of the unknown density f (not symmetrized). Even if the estimator of f is not really an even function, it allows to reveal the deviations of g with respect to the T_{18} pdf and then, to insure a good reconstruction of g.

Finally, the above identification of model parameters and the heuristic classification method of Section 6.1 allows to detect around 370 genes as possibly differentially expressed.

8 Discussion and concluding remarks

We introduced a new semiparametric finite mixture model that completes the recent semiparametric finite mixture models introduced by Hall and Zhou (2003), Bordes *et al.* (2004) and Hunter *et al.* (2004). We studied the identifiability of our model but we observed that even if one component is completely specified, identifiability is not guaranteed in general. We proposed two types of estimators for the Euclidean part of the model. One is a minimum contrast estimator whereas the other estimator is based on the moments method. These two methods are strongly based on the fact that the pdf of the unknown component is symmetric. In our opinion a challenging problem would be to consider the model (1) without the symmetry assumption on the unknown component. We obtained the consistency of our estimators for several classes of identifiable models. The study of convergence rates and efficiency of our estimators is still an open problem (very little is known about these problems, see Hall and Zhou, 2003; Bordes *et al.* , 2004).

We pointed out two fields of applications for our model: microarray data analysis (that was the initial motivation to introduce the model (1)), see e.g. McLachlan *et al.* (2004), Dudoit *et al.* (2002) and finite mixture models with training data (where our approach provides more flexibility in the sense that it is not necessary to have training data from each component of the model) see e.g. Murray and Titterington (1978), Hall (1981), Titterington (1983) and Qin (1998, 1999).

Another important issue will be to provide efficient algorithms to estimate both the Euclidean and the functional part of these kind of semiparametric model. A promising way is to develop some EM-type algorithms (see Bordes *et al.*, 2006).

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A Inverting the moment equations

Proof of (6). Let us consider the system of moments equations

$$\begin{cases} p\mu & = & p_1\mu_1 & (a) \\ (1-p)\theta_0 + p(\mu^2+\theta) & = & (1-p_1)\theta_0 + p_1(\mu_1^2+\theta_1) & (b) \\ p(3\mu\theta+\mu^3) & = & p_1(3\mu_1\theta_1+\mu_1^3) & (c) \end{cases}$$

With relations (b) and (a) we obtain:

$$\begin{aligned} p_1\theta_1 &= (p_1-p)\theta_0 + p(\theta+\mu^2) - p_1\mu_1^2 \\ &= (p_1-p)\theta_0 + p(\theta+\mu^2) - p\mu\mu_1. \qquad (d) \end{aligned}$$

With (c) and (d) we write

$$\begin{aligned} & 3\mu_1 p_1\theta_1 = 3p\mu\theta + p\mu^3 - p\mu\mu_1^2 \\ \iff & 3p\mu(\theta_0-\theta) - p\mu_3 + \mu_1[3p(\theta+\mu_2-\theta_0)] - 2p\mu\mu_1^2 = 0. \qquad (e) \end{aligned}$$

Equation (e) gives us a polynomial of degree two (in μ_1) which admits $\mu_1 = \mu$ as a trivial zero, hence (e) is equivalent to $(\mu_1-\mu)(a\mu_1+b) = 0$, with

$$a = -2p\mu, \quad \text{and} \quad b = p\mu^2 - 3p(\theta_0-\theta) = p(\mu^2 - 3\theta_0 + 3\theta).$$

Hence the second zero of (e) is

$$\mu_1 = \frac{\mu^2 - 3\theta_0 + 3\theta}{2\mu} = \mu + \frac{+3\theta - 3\theta_0 - \mu^2}{2\mu},$$

which concludes the proof.

B Technical results

Lemma 1 *Let H be a cdf such that $\int_{\mathbb{R}} |x| dH(x) < +\infty$. Then, for all $(\alpha,\beta) \in \mathbb{R}^2$ we have :*

$$\int_{\mathbb{R}} |H(x+\alpha) - H(x+\beta)| dx = |\alpha - \beta|.$$

Proof. It is easy to see that it is sufficient to prove the result for $\alpha \geq 0$ and $\beta = 0$. Because $\int_{-\infty}^{0} H(x)dx + \int_{0}^{+\infty}(1 - H(x))dx = \int_{\mathbb{R}} |x|dH(x) < +\infty$, we have

$$\begin{aligned} \int_{\mathbb{R}} |H(x+\alpha) - H(x)|dx &= \int_{\mathbb{R}} (H(x+\alpha) - H(x))dx \\ = \int_{-\alpha}^{0} H(x)dx + \int_{-\alpha}^{+\alpha} H(x)dx &+ \int_{\alpha}^{2\alpha} \bar{H}(x)dx = \alpha, \end{aligned}$$

where $\bar{H}(x) = 1 - H(x)$. □

Lemma 2 *Let H_i $(i = 1, 2)$ be the cdf of two distributions having first order moments. Then for all $(\alpha, \beta) \in \mathbb{R}^2$ we have*

$$\int_{\mathbb{R}} |H_1(x+\alpha) - H_2(x+\beta)|\, dx \leq m_1 + m_2 + |\alpha - \beta|,$$

where $m_i = \int_{\mathbb{R}} |x|dH_i(x)$ for $i = 1, 2$.

Proof. We can consider without loss of generality that $\beta = 0$. Then we have

$$\begin{aligned} & \int_{\mathbb{R}} |H_1(x+\alpha) - H_2(x)|dx \\ \leq & \int_{\mathbb{R}} |H_1(x+\alpha) - H_1(x)|dx + \int_{\mathbb{R}} |H_1(x) - H_2(x)|dx \\ = & \ |\alpha| + \int_{\mathbb{R}} |H_1(x) - H_2(x)|dx, \end{aligned}$$

by Lemma 1. Therefore we have

$$\begin{aligned} & \int_{\mathbb{R}} |H_1(x) - H_2(x)|dx \\ \leq & \int_{-\infty}^{0} H_1(x)dx + \int_{-\infty}^{0} H_2(x)dx + \int_{0}^{+\infty} |1 - H_1(x) - (1 - H_2(x))|dx \\ \leq & \int_{-\infty}^{0} H_1(x)dx + \int_{-\infty}^{0} H_2(x)dx + \int_{0}^{+\infty} (1 - H_1(x))dx + \int_{0}^{+\infty} (1 - H_2(x))dx \\ = & \ m_1 + m_2. \end{aligned}$$

This concludes the proof. □

Lemma 3 *Assume that both F and F_0 have first-order moment. Then, as $n \to +\infty$, we have $d(\hat{\mu}_n) \to 0$ a.s.*

Proof. First remark that

$$d^q(\hat{\mu}_n) \leq d^q(\hat{\mu}_n) - d_n^q(\hat{\mu}_n) + d_n^q(\mu_0) - d^q(\mu_0) \leq 2 \sup_{\mu \in \nu} |d^q(\mu) - d_n^q(\mu)|, \tag{23}$$

because $d_n^q(\hat{\mu}_n) \leq d_n^q(\mu_0)$ and $d^q(\mu_0) = 0$. To simplify our notations we write $H_i(x) = H_i(x; \mu, m, G, F_0)$ and $\hat{H}_i(x) = H_i(x; \mu, \hat{m}_n, \hat{G}_n, F_0)$ for $i = 1, 2$. Let $\hat{c}_n$ be defined by

$$\hat{c}_n = \max\left\{\|H_1\|_\infty + \|H_2\|_\infty, \|\hat{H}_1\|_\infty + \|\hat{H}_2\|_\infty\right\} \leq \frac{c_1}{\min(|m|, |\hat{m}_n|)} + 2,$$

where c_1 is finite and does not depend on μ and $\|\cdot\|_\infty$ denotes the L^∞–norm. Because $||a|^q - |b|^q| \leq q|a-b|$ for $|a| \leq 1$ and $|b| \leq 1$, we have:

$$\begin{aligned} |d^q(\mu) - d_n^q(\mu)| &\leq \left|\int_{\mathbb{R}} \left(|H_1(x) - H_2(x)|^q - |\hat{H}_1(x) - \hat{H}_2(x)|^q\right) dx\right| \\ &\leq q\hat{c}_n^{q-1} \int_{\mathbb{R}} |H_1(x) - H_2(x) - \hat{H}_1(x) + \hat{H}_2(x)| dx. \end{aligned} \tag{24}$$

Straightforward calculations lead to :

$$\begin{aligned} &\int_{\mathbb{R}} |H_1(x) - H_2(x) - \hat{H}_1(x) + \hat{H}_2(x)| dx \\ \leq\ & \frac{2\mu}{\hat{m}_n} \int_{\mathbb{R}} |\hat{G}_n(x) - G(x)| dx + \frac{\mu|\hat{m}_n - m|}{\hat{m}_n m} I(\mu), \end{aligned} \tag{25}$$

where

$$I(\mu) = \int_{\mathbb{R}} |G(x+\mu) + G(\mu - x) - F_0(x+\mu) - F_0(\mu - x)| dx.$$

Using the fact that

$$G(x) = (1-p_0)F_0(x) + p_0 F(x - \mu_0), \quad \forall x \in \mathbb{R},$$

and that both F_0 and F have first-order moment, we show that :

$$I(\mu) \leq 2p_0 \int_{\mathbb{R}} |F(x - \mu_0) - F_0(x)| dx \leq c_2,$$

where c_2 arises from Lemma 2. Finally, the last result with inequalities (24) and (25), give :

$$|d^q(\mu) - d_n^q(\mu)| \leq \hat{K}_n^{(1)} \int_{\mathbb{R}} |\hat{G}_n(x) - G(x)| dx + \hat{K}_n^{(2)} |\hat{m}_n - m|,$$

where $\hat{K}_n^{(1)}$ and $\hat{K}_n^{(2)}$ do not depend on μ and converge almost surely to finite constants when n tends to infinity, $|\hat{m}_n - m|$ converges almost surely to 0 by the strong law of large numbers and, by Hunter et al. (2004), $\int_{\mathbb{R}} |\hat{G}_n(x) - G(x)| dx$ converges almost surely to 0. We finish the proof using (23). □

Lemma 4 *Assume that one of Assumptions A1–A3 is satisfied, then for all $\varepsilon > 0$, there exists $\delta_\varepsilon > 0$, such that:*

$$\forall \mu \in \nu, \quad |\mu - \mu_0| > \varepsilon \Rightarrow d(\mu) > \delta_\varepsilon.$$

Proof. **Step 1.** Let us show that $\mu \mapsto d(\mu)$ is continuous on ν. Following the begining of the proof of Lemma 3 we show that there exists a finite constant c such that

$$\begin{aligned}
& |d^q(\mu) - d^q(\mu')| \\
\leq\ & c \int_{\mathbb{R}} \Big| \frac{\mu}{m} G(x+\mu) - \frac{\mu'}{m} G(x+\mu') + \left(1 - \frac{\mu}{m}\right) F_0(x+\mu) - \left(1 - \frac{\mu'}{m}\right) F_0(x+\mu') \\
& + \frac{\mu}{m} G(\mu - x) - \frac{\mu'}{m} G(\mu' - x) + \left(1 - \frac{\mu'}{m}\right) F_0(\mu' - x) - \left(1 - \frac{\mu}{m}\right) F_0(\mu - x) \Big| dx \\
\leq\ & c \int_{\mathbb{R}} \Big| \frac{\mu}{m} (G(x+\mu) - G(x+\mu')) + \frac{\mu - \mu'}{m} G(x+\mu) \\
& + \frac{m-\mu}{m} (F_0(x+\mu) - F_0(x+\mu')) + \frac{\mu' - \mu}{m} F_0(x+\mu') \\
& + \frac{\mu}{m} (G(\mu - x) - G(\mu' - x)) + \frac{\mu - \mu'}{m} G(\mu' - x) \\
& + \frac{\mu' - m}{m} (F_0(\mu' - x) - F_0(\mu - x)) + \frac{\mu' - \mu}{m} F_0(\mu - x) \Big| dx \\
\leq\ & c_1 |\mu - \mu'| + \frac{c}{m} |\mu - \mu'| \int_{\mathbb{R}} |G(x+\mu') - F_0(x+\mu') + G(\mu' - x) - F_0(\mu - x)| dx,
\end{aligned}$$

where the finite constant c_1 arises from Lemma 1 and the fact that ν is compact. It remains to show that

$$\int_{\mathbb{R}} |G(x+\mu') - F_0(x+\mu') + G(\mu' - x) - F_0(\mu - x)| dx$$

is bounded uniformly with respect to μ. Using (1) for the cdf G we have

$$\begin{aligned}
& \int_{\mathbb{R}} |G(x+\mu') - F_0(x+\mu') + G(\mu' - x) - F_0(\mu - x)| dx \\
\leq\ & \int_{\mathbb{R}} \big| (1-p_0)(F_0(x+\mu) - F_0(x+\mu')) + p_0(F(\mu - \mu_0 + x) - F_0(x - \mu') \\
& + (1-p_0)(F_0(\mu' - x) - F_0(\mu - x)) + p_0(F(\mu' - \mu_0 - x) - F_0(\mu - x) \big| dx \\
\leq\ & 2(1-p_0)|\mu - \mu'| + 2p_0 \left(|\mu| + |\mu'| + |\mu_0| + \int_{\mathbb{R}} |x| dF_0(x) + \int_{\mathbb{R}} |x| dF(x) \right) \\
\leq\ & c_2 < +\infty,
\end{aligned}$$

where we used Lemma 1 and 2 and the compactness of ν. The continuity of d on ν follows.

Step 2. Clearly, if $\mu = \mu_0$ then $d(\mu) = 0$. Let us prove the converse. If $d(\mu) = 0$, then we have $H_1 = H_2$, that is:

$$\mu g(\mu + x) - (\mu - m) f_0(\mu + x) = \mu g(\mu - x) - (\mu - m) f_0(\mu - x), \tag{26}$$

almost everywhere on $\mathbb{R}$.

Under A1. Let us consider the Fourier transform of the above equality. Using the fact that

$$g(x) = (1 - p_0) f_0(x) + p_0 f(x - \mu_0), \quad \forall x \in \mathbb{R}, \tag{27}$$

we get

$$(p - p_0) \sin(t\mu) \hat{f}_0(t) = p_0 \sin(t(\mu_0 - \mu)) \hat{f}(t), \quad \forall t \in \mathbb{R}. \tag{28}$$

Assume that $\mu \neq \mu_0$. On one hand, because $\hat{f}_0 > 0$, the above equality implies that there exists $k_0 \in \mathbb{N}^*$ such that $|\mu| = k_0 |\mu_0 - \mu|$. On the other hand, taking the derivatives of order 1 and 3 of (28) at $t = 0$ we get

$$p_0 \mu_0 = p\mu \quad \text{and} \quad (p - p_0)(\mu^3 + 3\theta_0 \mu) = p_0((\mu_0 - \mu)^3 + 3\theta(\mu_0 - \mu)),$$

where θ_0 and θ denote the moments of order 2 of f_0 and f respectively. The two last equalities with $|\mu| = k_0 |\mu_0 - \mu|$ imply that

$$\theta = \theta_0 + \mu_0^2 \frac{k_0 \pm 2}{3k_0},$$

and then, $(\mu, \theta) \in \cup_{k \in \mathbb{N}^*} \Phi_k$, which in turn implies that $(\mu, \theta) \notin \Phi_c$. It follows that $\mu = \mu_0$.

Under A2. By (26), (27) and the fact that f is an even pdf, we obtain for $x \in \mathbb{R}$:

$$f_0(x + \mu)(m - p_0 \mu) + p_0 \mu f(x + \mu - \mu_0) = f_0(\mu - x)(m - p_0 \mu) + p_0 \mu f(x + \mu_0 - \mu).$$

Dividing the above equality by $f_0(x + \mu)$ (or by $f_0(\mu - x)$ following the tail property of f_0) and making x tend to infinity we obtain $m = p_0 \mu$ that leads to $\mu = \mu_0$.

Under A3. Considering relation (29) for large values of $|x|$, we obtain $f(\mu - \mu_0 + x) = f(\mu - \mu_0 - x)$ which, according to Assumption A3, is possible only if $\mu = \mu_0$.

Step 3. By Step 1 d is continuous on the compact subset $\nu_\varepsilon = \{\mu \in \nu; |\mu - \mu_0| \geq \varepsilon\}$ of ν. Therefore there exists $\mu^* \in \nu_\varepsilon$ such that $d(\mu) \geq d(\mu^*)$ on ν_ε. By Step 2 we have $\delta_\varepsilon = d(\mu^*) > 0$. It follows that the expected result also holds with strict inequalities. □

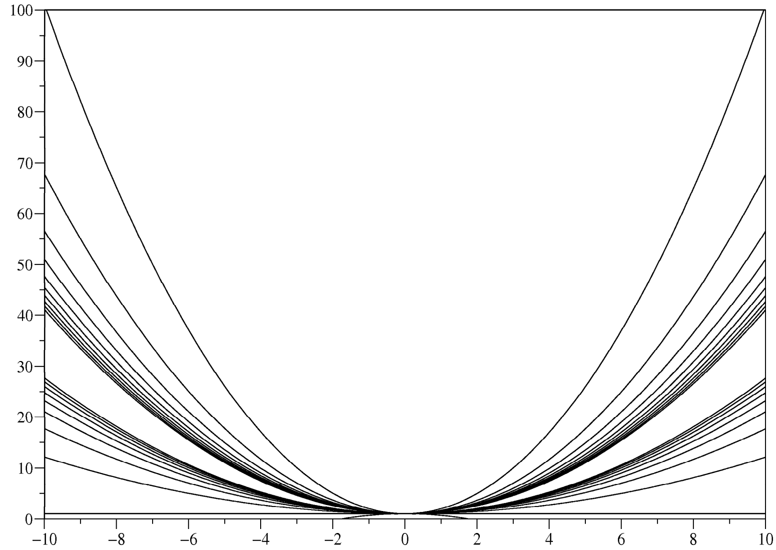
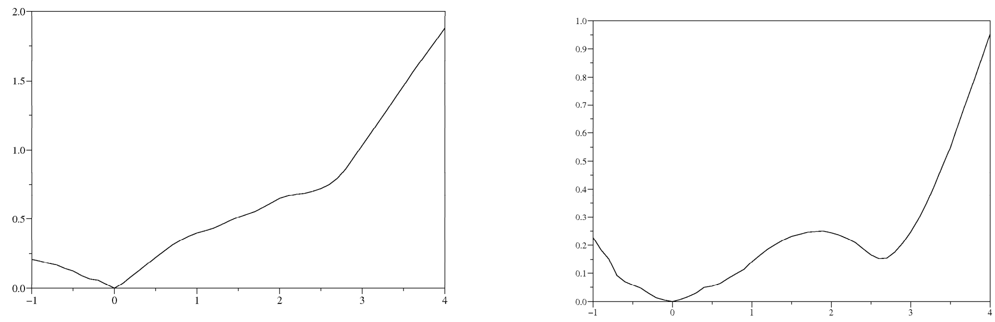


Figure 1: The model (1) is identifiable if (μ, θ) does not belong to one of the curves.



(a) An exemple where μ cannot be estimated from $d_n(\mu)$.

(b) An exemple where μ is estimated from $d_n(\mu)$.

Figure 2: Two exemples of the behavior of the empirical contrast function d_n.

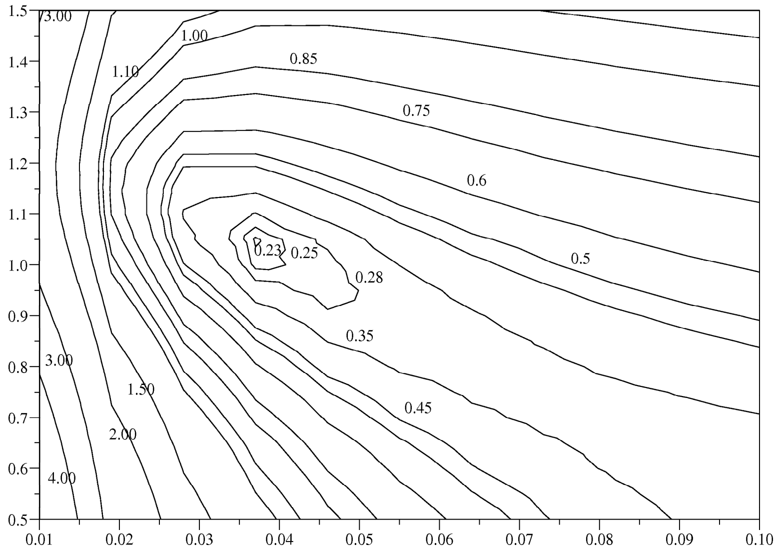
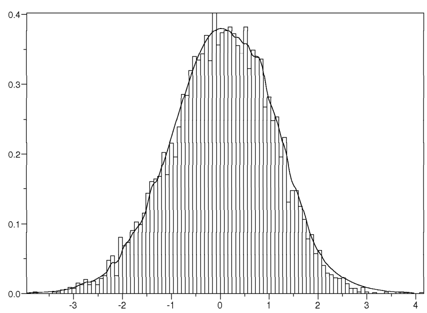
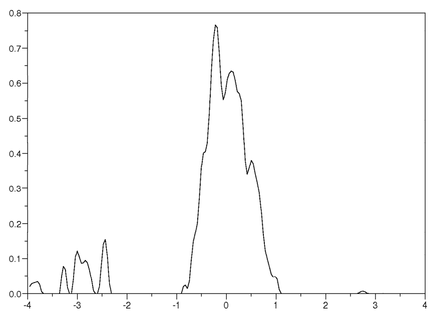


Figure 3: Level curves of $(p, \mu) \mapsto d_n(p, \mu)$ for the actual data set (with $(p, \mu) \in [0.01, 0.1] \times [0.5, 1.5]$).



(a) Histogram of the actual data set compared with $(1-\hat{p})f_0(\cdot) + \hat{p}\hat{f}(\cdot - \hat{\mu})$.



(b) Estimate of the unknown density f.

Figure 4: Estimator of the density f and reconstruction of the mixture distribution using estimates of p, μ and f.