Brazilian Journal of Probability and Statistics
2012, Vol. 26, No. 2, 123–148
DOI: 10.1214/10-BJPS125

Test, estimation and model comparison for the meiosis I nondisjunction fraction in trisomies

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Abstract. Trisomies are numerical chromosomal anomalies (aneuploidies) which are common causes of mental retardation, pregnancy losses and fetal death. The determination of the meiosis I nondisjunction fraction plays an important role in the identification of possible factors which could generate such aneuploidies. In this article, more flexible misclassification models for the number of peaks in a polymorphic locus of trisomic individuals are considered. They are compared to some others proposed in the literature. Estimation and tests for the nondisjunction fraction in meiosis I and for the misclassification errors are introduced extending previous works. Using the Decision Theory approach, we also build a criterion for making decisions under Jeffreys and Pereira–Stern tests. We apply the results to Down Syndrome data that is the most prevalent trisomy in humans.

1 Introduction

Trisomies are numerical chromosomal anomalies (aneuploidies) that, in general, arise as a consequence of sporadic error in the chromosomal segregation (nondisjunction) during the meiotic process. In humans, trisomies are common causes of mental retardation, pregnancy losses and fetal death. Although the causes of aneuploidies are unknown, it is known that the risk of having children with trisomies 21 (Down Syndrome), 18 (Edward's Syndrome) or 13 (Patou Syndrome) increases with the mother's age (Valero et al., 1999). According to Pena (1998), in trisomy 21, the increase in the rate of nondisjunction in meiosis II is higher than for meiosis I if the mother's age is between 35 and 39 years. For sexual chromosomes, however, high mother age influences only the fraction ϕ of nondisjunction in meiosis I. Thus, the determination of ϕ plays an important role in the identification of possible factors which could generate aneuploidies. See more about these trisomies and other syndromes of genetic origin in the Genetics Home Reference's website (http://ghr.nlm.nih.gov/).

Methods to estimate ϕ which consider information coming from the affected children and their parents are presented in Hassold and Hunt (2001), Nicolaidis and Petersen (1998), Savage et al. (1998), Yoon et al. (1996), Koehler et al. (1996),

Key words and phrases. Aneuploidy, Bayes estimator, Bayes tests, DIC, meiosis, misclassification.

Received July 2009; accepted May 2010.

Griffin (1996), Petersen et al. (1992), Zaragosa et al. (1994), Hassold and Jacobs (1984) along many others. More recently, Bayesian and Classical approaches to infer about ϕ, assuming models that do not take the parental information into consideration, are presented by Franco et al. (2003) and Loschi et al. (2007).

Prenatal diagnosis of aneuploidies can be done by employing the polymerase chain reaction (PCR) based approach followed by a quantitative analysis by computer-assisted laser densitometry. Such procedure provides as a result a graphic in which the peaks represent the different alleles in the loco of interest. Data are obtained from such graphics. Since some other peaks can also be observed as a consequence of residuals generated by the preparation of the genetic material, misclassification can occur. For details, see Pena (1998), Valero et al. (1999), Blake et al. (1999), Schmidt et al. (2000), Pont-Kingdon and Lyon (2003), Ogilvie et al. (2005) among many others.

The model introduced by Franco et al. (2003) took into consideration that, in trisomic patients submitted to such a test, the results display, in informative microsatellite loci, three fragment peaks of equal intensity, two fragments at an average 2:1 dosage or one individual fragment. The relative proportion of the three cases depends on the type of nondisjunction (first or second meiosis division) and on the heterozygosity level. It also considers the perfect classification of all individuals in the sample.

A misclassification model for the number of peaks in a polymorphic locus of trisomic individuals was first considered by Loschi et al. (2008). As in the model introduced by Franco et al. (2003), such a misclassification model is innovative in the analysis of trisomies since its construction does not take into account the parental information. Thus, the use of archive material is possible which is important in studies of rare trisomies. However, it is not flexible enough to accommodate more general situations where the misclassification errors are not equal.

This paper aims at obtaining exact posteriors and predictive distributions under more flexible misclassification models for the number of trisomic individuals with one, two or three peaks. Extensions of Loschi et al. (2008) are twofold: Weaker constraints for the misclassification errors are assumed (say, the errors are assumed being different) and Jeffreys and Pereira–Stern tests under all misclassification models are introduced. Among their other interesting properties, these two test procedures are both Bayes rules, that is, they minimize the risk whenever particular loss functions are assumed. Using such a characteristic, we propose a criteria to obtain the cut points for the acceptance of the null hypothesis. The criterion is building assuming that both procedures have the same prior risk. A case study is presented where we analyze a sample of Brazilian individuals with Down Syndrome using the models introduced here and the ones developed by Franco et al. (2003) and Loschi et al. (2008). The models are compared using the DIC as well as the Bayes factor.

This paper is organized as follows: Section 2 introduces two more flexible misclassification models for the number of individuals with one, two or three peaks, given ϕ. Predictive prior distributions and posteriors for all parameters are presented. We also prove that they are identifiable models. In Section 3 we present procedures for hypotheses tests and model comparisons. A criteria is introduced to define the critical values for tests. In Section 4, we analyze the data from Brazilian patients with trisomy 21. Finally, presented in Section 5 are some conclusions to end the paper.

2 Models description and posterior inferences

The misclassification model introduced by Loschi et al. (2008) is extended by considering more general constraints for the misclassification errors. As in Franco et al. (2003), we assume that the hypothesis of Hardy–Weinberg equilibrium (Hartl and Clark, 1997) has been verified for the population. Thus, we can obtain the relative frequency p_i, $i = 1, \dots, m$, of the allele i in a multiallelic locus of microsatellites.

To establish notation, throughout this paper we denote by Y_l the number of individuals with l peaks pattern, $l = 1, 2, 3$, to be observed in a sample of n trisomic individuals. Denote by $\mathbf{Y}$ the random vector (Y_1, Y_2, Y_3). The misclassification models are constructed following Loschi et al. (2008). It is assumed two auxiliary random variables X and Z, which denote the true (nonobserved) and the observed number of peaks in a trisomic individual, respectively. (See more on misclassification models in Swartz et al. (2004), Paulino et al. (2003) and Viana (1994).) Moreover, denote by $\theta_l(\cdot)$ and $\pi_l(\cdot)$, respectively, the probability of being l, $l = 1, 2, 3$, the true and the observed number of peaks in the microsatellite locus of interest. As proved in Franco et al. (2003), $\theta_l(\phi)$ depends on ϕ, $\phi \in [0, 1]$, and is such that

$$\begin{aligned} \theta_1(\phi) &= a\phi + b(1-\phi), \\ \theta_2(\phi) &= c\phi + d(1-\phi), \\ \theta_3(\phi) &= e\phi, \end{aligned} \tag{2.1}$$

where $a = \sum_{i=1}^m p_i^3$, $b = \sum_{i=1}^m p_i^2$, $c = 3\sum_{i=1}^m \sum_{j=1}^m p_i^2 p_j$, for all $i \neq j$, $d = \sum_{i=1}^m \sum_{j=1}^m p_i p_j$, for all $i \neq j$ and $e = 6\sum_{i=1}^m \sum_{j=1}^m \sum_{k=1}^m p_i p_j p_k$, $\forall i \neq j \neq k$. Notice that $a + c + e = (\sum_{k=1}^m p_k)^3 = 1$ and $b + d = (\sum_{k=1}^m p_k)^2 = 1$.

Let $\eta_{j|k} = P(Z = j|X = k)$, $j, k = 1, 2, 3$, $j \neq k$, be the probability of misclassifying an individual. It follows from probability calculus that the vector of probabilities $\boldsymbol{\pi}(\phi, \boldsymbol{\eta}) = (\pi_1(\phi, \boldsymbol{\eta}), \pi_2(\phi, \boldsymbol{\eta}), \pi_3(\phi, \boldsymbol{\eta}))^t$ is given by

$$\boldsymbol{\pi}(\phi, \boldsymbol{\eta}) = \boldsymbol{\eta}\boldsymbol{\theta}(\phi), \tag{2.2}$$

where $\boldsymbol{\theta}(\phi) = (\theta_1(\phi), \theta_2(\phi), \theta_3(\phi))^t$ and $\boldsymbol{\eta}$ is the following 3×3 matrix

$$\boldsymbol{\eta} = \begin{pmatrix} \eta_{1|1} & \eta_{1|2} & \eta_{1|3} \\ \eta_{2|1} & \eta_{2|2} & \eta_{2|3} \\ \eta_{3|1} & \eta_{3|2} & \eta_{3|3} \end{pmatrix}.$$

Since $\sum_{j=1}^{3} \eta_{j|k} = 1$, for each $k = 1, 2, 3$, it can be proved that $\sum_{j=1}^{3} \pi_j(\phi, \boldsymbol{\eta}) = \sum_{k=1}^{3} \theta_k(\phi) = 1$.

As a consequence of the previous assumptions, Loschi et al. (2008) establish that $\mathbf{Y}|\phi, \boldsymbol{\eta} \sim \text{Multinomial}(n, \pi_1(\phi, \boldsymbol{\eta}), \pi_2(\phi, \boldsymbol{\eta}), \pi_3(\phi, \boldsymbol{\eta}))$ which probability function is

$$f(\mathbf{Y}|\phi, \boldsymbol{\eta}) = \frac{n!}{y_1!y_2!y_3!} \prod_{j=1}^{3} [\pi_j(\phi, \boldsymbol{\eta})]^{y_j}, \tag{2.3}$$

where $\sum_{j=1}^{3} y_j = n$. However, to make inference about ϕ, it is assumed that the matrix $\boldsymbol{\eta}$ is such that

$$\eta_{j|k} = \begin{cases} 1 - 2\psi, & \text{for } j = k, \\ \psi, & \text{for } j \neq k. \end{cases} \tag{2.4}$$

This assumption removes the nonidentifiability from the model as has been proven in Loschi et al. (2008). However, it is assumed as equal the probabilities of classifying as having three peaks the individuals for which the true number of different alleles is one or two. It cannot be a realistic assumption since the intensity of peaks displayed in the diagnosis test depends on the number of different alleles in the locos of interest (Valero et al., 1999).

In the following, we present posteriors and posterior moments for all parameters and also predictive prior distributions under more flexible misclassification models. Such models will assume more general constraints on parameters in the matrix $\boldsymbol{\eta}$. Although more general, such new models still remain identifiable (see details in Section 2.5).

Throughout this paper, we assume that a priori the misclassification errors are independent of ϕ. It is also reasonable to assume that the probability of correctly classifying the individual is higher than the total misclassification error. Since there is little information available about the misclassification errors, we considered the Bayes–Laplace approach to build non informative priors for them, say, we assume uniform distributions to describe the prior uncertainty about all misclassification errors. Other procedures such as Jeffreys or Bernardo–Berger approaches (Bernardo and Smith, 1994; Migon and Gamerman, 1999) can also be considered in order to build non-informative priors for the parameters.

Some information about ϕ is available in the literature for other populations. Such pieces of information could be used to build a more informative prior for ϕ. We assume that the prior for ϕ is in the beta family which is very rich in form and can represent well many different prior opinions about ϕ including informative and non-informative ones.

To establish notation consider $I_{1/2}(\alpha, \beta) = \int_0^{1/2} x^{\alpha-1}(1-x)^{\beta-1}\,dx$ which can be approximated by (Abramowitz and Stegun, 1972)

$$I_{1/2}(\alpha, \beta) = \frac{(1/2)^{\alpha+\beta}}{\alpha} \left\{ 1 + \sum_{i=0}^{\infty} \left[\frac{1}{2}\right]^{i+1} \frac{\mathcal{B}(\alpha+1, i+1)}{\mathcal{B}(\alpha+\beta, i+1)} \right\}, \tag{2.5}$$

where $\mathcal{B}(a, b)$ denotes the beta function with parameters $a > 0$ and $b > 0$.

2.1 Bayesian inference under proposed Model 1 (PM1)

In this section, we assume that, given the true number of peaks is k, $k = 1, 2, 3$, the misclassification probabilities are equal for all possible values for the observed number of peaks, say, $\eta_{j|k} = \eta_{i|k} = \psi_k$, for $j \neq i \neq k$, $i, j, k = 1, 2, 3$. Moreover, we consider that the probability of correctly classifying an individual is such that $\eta_{j|k} = \eta_k$, for $j = k$, $j, k = 1, 2, 3$. Since $\sum_{j=1}^{3} \eta_{j|k} = 1$, it follows that $\eta_i = 1 - 2\psi_i$, $i = 1, 2, 3$. Thus, the matrix $\boldsymbol{\eta}$ becomes

$$\boldsymbol{\eta} = \begin{pmatrix} 1-2\psi_1 & \psi_2 & \psi_3 \\ \psi_1 & 1-2\psi_2 & \psi_3 \\ \psi_1 & \psi_2 & 1-2\psi_3 \end{pmatrix}.$$

Consequently, from expressions (2.2) and (2.3) and using the binomial theorem successively, the likelihood function becomes the following finite beta mixture

$$\begin{aligned} f(\boldsymbol{Y}|\phi, \boldsymbol{\eta}) &= n! \sum_{r=0}^{y_1} \sum_{s=0}^{y_2} \sum_{t=0}^{y_3} \sum_{f=0}^{y_1-r} \sum_{g=0}^{r} \sum_{h=0}^{y_1-r-f} \sum_{i=0}^{y_2-s} \sum_{j=0}^{s} \sum_{k=0}^{y_2-s-i} \sum_{l=0}^{y_3-t} \sum_{m=0}^{t} \sum_{q=0}^{y_3-t-l} A_{M_1} \\ &\quad \times \phi^{n-\delta}(1-\phi)^{\delta} \psi_1^{w_1}(1-2\psi_1)^{w_2} \\ &\quad \times \psi_2^{w_3}(1-2\psi_2)^{w_4} \psi_3^{w_5}(1-2\psi_3)^{l} \\ &= n! \sum_{\mathrm{PM}_1} A_{M_1} \phi^{n-\delta}(1-\phi)^{\delta} \psi_1^{w_1}(1-2\psi_1)^{w_2} \\ &\quad \times \psi_2^{w_3}(1-2\psi_2)^{w_4} \psi_3^{w_5}(1-2\psi_3)^{l}, \end{aligned} \tag{2.6}$$

where

$$\begin{aligned} A_{M_1} &= \frac{a^{y_2+y_3+f-s-i-k-t-l-q} b^{g+s+m-j} c^{y_1+i+q-r-f-h}}{f!g!h!i!j!k!l!m!q!(r-g)!(s-j)!(t-m)!} \\ &\quad \times \frac{d^{r+j+t-g-m} e^{w_5+l}}{(y_1-r-f-h)!(y_2-s-i-k)!(y_3-t-l-q)!}, \\ \delta &= r+s+t, \\ w_1 &= y_2+y_3+m-i-j-k-t-l-q, \\ w_2 &= f+g, \\ w_3 &= y_1+t+q-h-m-w_2, \\ w_4 &= i+j, \\ w_5 &= h+k. \end{aligned}$$

We are assuming that the probability of correctly classifying the individual is higher than the total misclassification error which implies that $1 - 2\psi_k > 2\psi_k$, for all $k = 1, 2, 3$. Consequently, $\boldsymbol{\eta} = (\psi_1, \psi_2, \psi_3)$ assume values in the cube $[0, 1/4]^3$ (see Figure 1). Thus, the joint Bayes–Laplace prior for $\boldsymbol{\eta}$ is the following uniform distribution

$$f(\boldsymbol{\eta}) = \begin{cases} 64, & \text{for } (\psi_1, \psi_2, \psi_3) \in [0, 1/4]^3, \\ 0, & \text{otherwise,} \end{cases}$$

which marginals are the independent uniform priors considered in the following proposition.

Proposition 1. *Assume that* $\mathbf{Y}|\phi, \boldsymbol{\psi} \sim \text{Multinomial}(n, \pi_1(\phi, \boldsymbol{\eta}), \pi_2(\phi, \boldsymbol{\eta}), \pi_3(\phi, \boldsymbol{\eta}))$ *which probability function is given in* (2.6). *If, a prior,* $\phi \sim \text{Beta}(\alpha, \beta)$, $\alpha > 0$, $\beta > 0$, *and* $\psi_k \sim \text{Uniform}(0, 1/4)$, $k = 1, 2, 3$, *then it follows that*:

(i) *the predictive distribution of* $\mathbf{Y}$ *is given by*

$$f_{\mathrm{PM}_1}(\mathbf{Y}) = 64n![\mathcal{B}(\alpha; \beta)]^{-1} \sum_{\mathrm{PM}_1} A_{M_1} \mathcal{B}(\alpha + n - \delta; \beta + \delta)\mathcal{I}(\mathbf{w}, l),$$

(ii) *the posterior of* ϕ *is given by*

$$\pi(\phi|\mathbf{Y}) = \frac{\sum_{\mathrm{PM}_1} A_{M_1} \mathcal{I}(\boldsymbol{w}, l)\phi^{\alpha+n-\delta-1}(1-\phi)^{\beta+\delta-1}}{\ker(f_{\mathrm{PM}_1}(\boldsymbol{Y}))},$$

(iii) *the* ξ*th posterior moment of* ϕ *is*

$$E(\phi^{\xi}|\mathbf{Y}) = \frac{\sum_{\mathrm{PM}_1} A_{M_1} \mathcal{I}(\mathbf{w}, l)\mathcal{B}(\xi + \alpha + n - \delta; \beta + \delta)}{\ker(f_{\mathrm{PM}_1}(\mathbf{Y}))},$$

(iv) *the posterior of* ψ_1 *is given by*

$$\pi(\psi_1|\mathbf{Y}) = \frac{\sum_{\mathrm{PM}_1} A_{M_1} \mathcal{J}(w_3, w_4, w_5, l)\psi_1^{w_1}(1 - 2\psi_1)^{w_2}}{\ker(f_{\mathrm{PM}_1}(\mathbf{Y}))},$$

(v) *the* ξ*th posterior moment of* ψ_1 *is*

$$E(\psi_1^{\xi}|\mathbf{Y}) = \frac{\sum_{\mathrm{PM}_1} A_{M_1} \mathcal{J}(w_3, w_4, w_5, l) I_{1/2}(\xi + w_1 + 1; w_2 + 1)2^{-(\xi+w_1+1)}}{\ker(f_{\mathrm{PM}_1}(\mathbf{Y}))},$$

where $\mathcal{I}(\mathbf{w}, l) = I_{1/2}(w_1 + 1; w_2 + 1)I_{1/2}(w_3 + 1; w_4 + 1)I_{1/2}(w_5 + 1; l + 1)2^{-(w_1+w_3+w_5+3)}$, $\mathcal{J}(w_3, w_4, w_5, l) = \mathcal{B}(\alpha + n - \delta; \beta + \delta)I_{1/2}(w_3 + 1; w_4 + 1)I_{1/2}(w_5 + 1; l + 1)2^{-(w_3+w_5+2)}$, $\ker(f_{\mathrm{PM}_1}(\mathbf{Y})) = f_{\mathrm{PM}_1}(\mathbf{Y})\mathcal{B}(\alpha; \beta)[64n!]^{-1}$, *and* A_{M_1}, δ *and* $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5)$ *are given in* (2.6). *The posteriors and posterior moments of* ψ_2 *and* ψ_3 *are obtained similarly.*

The proof of Proposition 1 follows straightforward from Bayes's theorem and some other well-known results of probability calculus. It is similar to the one presented in Loschi et al. (2008) and thus is omitted.

2.2 Bayesian inference under proposed Model 2 (PM2)

As for PM1, we assume that the probabilities of correctly classifying the individual are $\eta_{j|k} = \eta_k$, for $j = k$ and $j, k = 1, 2, 3$, but now we assume a symmetric relationship among the misclassification errors, say, they are such that $\eta_{j|k} = \eta_{k|j} = \psi_k$ for all $j \neq k$ and $j, k = 1, 2, 3$. Since $\sum_{j=1}^{3} \eta_{j|k} = 1$, it follows that the matrix $\boldsymbol{\eta}$ is given by

$$\boldsymbol{\eta} = \begin{pmatrix} 1-\psi_1-\psi_3 & \psi_1 & \psi_3 \\ \psi_1 & 1-\psi_1-\psi_2 & \psi_2 \\ \psi_3 & \psi_2 & 1-\psi_2-\psi_3 \end{pmatrix}.$$

In this case, the likelihood function is given by

$$\begin{aligned} f(\mathbf{Y}|\phi, \boldsymbol{\eta}) &= n! \sum_{r=0}^{y_1} \sum_{s=0}^{y_2} \sum_{t=0}^{y_3} \sum_{f=0}^{y_1-r} \sum_{g=0}^{r} \sum_{h=0}^{y_1-r-f} \sum_{i=0}^{y_2-s} \sum_{j=0}^{s} \\ &\quad \sum_{k=0}^{y_2-s-i} \sum_{l=0}^{y_3-t} \sum_{m=0}^{t} \sum_{q=0}^{y_3-t-l} \sum_{u=0}^{f+g} \sum_{v=0}^{i=j} \sum_{x=0}^{l} C_{M_2} \\ &\quad \times \phi^{n-\delta}(1-\phi)^{\delta} \psi_1^{z_1}(1-\psi_1)^u \psi_2^{z_2}(1-\psi_2)^v \psi_3^{z_3}(1-\psi_3)^x \\ &= n! \sum_{\mathrm{PM}_2} C_{M_2} \phi^{n-\delta}(1-\phi)^{\delta} \psi_1^{z_1}(1-\psi_1)^u \psi_2^{z_2}(1-\psi_2)^v \psi_3^{z_3}(1-\psi_3)^x, \end{aligned} \tag{2.7}$$

where

$$\begin{aligned} C_{M_2} &= A_{M_1} \binom{w_2}{u} \binom{w_4}{v} \binom{l}{x} (-1)^{w_2+w_4+l-u-v-x}, \\ z_1 &= y_1 + y_2 - w_2 - w_5 - v, \\ z_2 &= k + q + t + l - m - x, \\ z_3 &= w_2 + h + y_3 + m - u - t - l - q, \end{aligned}$$

and A_{M_1} and δ are as defined in (2.6).

The likelihood in (2.7) is also a finite beta mixture. However, it differs from the one obtained in PM1 since the misclassification probabilities ψ_k now have different interpretations. In both cases, however, we have a generalization of previous models. If $\psi_k = 0$, for all $k = 1, 2, 3$, Franco et al.'s model (Franco et al., 2003) is obtained and whenever $\psi_k = \psi$, for all $k = 1, 2, 3$, we get the misclassification model introduced by Loschi et al. (2008).

Since the probability of correctly classifying the individual is assumed to be higher than the total misclassification error, the possible values for $\boldsymbol{\eta} = (\psi_1, \psi_2, \psi_3)$ are in the set $\Psi = \{(\psi_1, \psi_2, \psi_3) \in [0, 1/2]^3 : \psi_1 + \psi_2 < 1/2, \psi_2 + \psi_3 < 1/2, \psi_1 + \psi_3 < 1/2\}$. Thus, the joint Bayes–Laplace prior for $\boldsymbol{\eta}$ is

$$f(\boldsymbol{\eta}) = \begin{cases} 32, & \text{if } (\psi_1, \psi_2, \psi_3) \in V, \\ 0, & \text{otherwise,} \end{cases}$$

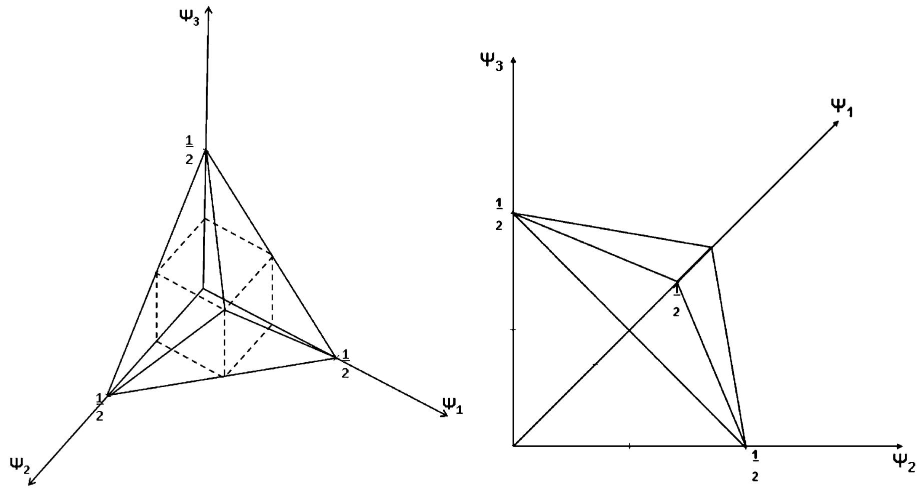

Figure 1 *Prior domain.*

where V is the region pointed out in Figure 1.

We consider an interesting simplification of PM2 (SPM2) which is obtained whenever it is assumed $\psi_1 = \psi_2 = \psi^*$ and $\psi_3 = (\psi^*)^2$. By assuming these constraints we have a more parsimonious model that also assumes $\psi_3 < \psi_1$. In this case, the likelihood becomes

$$\begin{aligned} f(\mathbf{Y}|\phi, \psi^*) &= n! \sum_{f=0}^{y_1} \sum_{g=0}^{y_1-f} \sum_{h=0}^{y_1-f-g} \sum_{i=0}^{f} \sum_{j=0}^{f-i} \sum_{k=0}^{y_2} \sum_{l=0}^{y_2-k} \sum_{p=0}^{k} \sum_{r=0}^{y_3} \sum_{s=0}^{y_3-r} \sum_{t=0}^{y_3-r-s} \sum_{u=0}^{r} A_{\mathrm{SPM}_2} \\ &\quad \times \phi^{n-w_1}(1-\phi)^{w_1}(\psi^*)^{w_2} \qquad (2.8) \\ &= n! \sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} \phi^{n-w_1}(1-\phi)^{w_1}(\psi^*)^{w_2}, \end{aligned}$$

where

$$\begin{aligned} A_{\mathrm{SPM}_2} &= \frac{(-1)^{j+t} a^g b^{f+r-u} c^l d^{p+u} e^s (c-a)^{y_1-f-g-h}(d-b)^{f-i-j}(e-a)^{h+t}}{g!h!i!j!l!p!s!t!u!(k-l)!(r-u)!(f-i-j)!} \\ &\quad \times \frac{(a+e-2c)^{y_2-k-l}(b-2d)^{k-p}(c-e)^{y_3-r-s-t}}{(y_1-f-g-h)!(y_2-k-l)!(y_3-r-s-t)!}, \\ w_1 &= f+k+r, \\ w_2 &= n+h+j+t+r-g-i-l-p-s-u. \end{aligned}$$

By considering the prior conditions on the probability of correctly classifying the individual mentioned previously, it follows that $1-\psi^*-(\psi^*)^2 > \psi^*+(\psi^*)^2$ and $1-\psi^*-\psi^* > \psi^*+\psi^*$. Thus, the support for the prior for ψ^* is also $(0, 1/4)$ which justify the uniform prior used in the following proposition.

Proposition 2. *Assume that* $\mathbf{Y}|\phi, \psi^* \sim \mathrm{Multinomial}(n, \pi_1(\phi, \boldsymbol{\eta}), \pi_2(\phi, \boldsymbol{\eta}), \pi_3(\phi, \boldsymbol{\eta}))$ *which probability function is given in* (2.8). *If, a priori,* $\phi \sim \mathrm{Beta}(\alpha, \beta)$, $\alpha > 0$, $\beta > 0$, *and* $\psi^* \sim \mathrm{Uniform}(0, 1/4)$, *then it follows that*:

(i) *the predictive distribution of* $\mathbf{Y}$ *is given by*

$$\begin{aligned} &f_{\mathrm{SPM}_2}(\mathbf{Y}) \\ &\quad = n![\mathcal{B}(\alpha; \beta)]^{-1} \sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} \mathcal{B}(\alpha + n - w_1; \beta + w_1) 4^{-w_2} [w_2 + 1]^{-1}, \end{aligned}$$

(ii) *the posterior of* ϕ *is given by*

$$\pi(\phi|\mathbf{Y}) = \frac{\sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} 4^{-w_2} [w_2 + 1]^{-1} \phi^{\alpha+n-w_1-1} (1-\phi)^{\beta+w_1-1}}{\ker(f_{\mathrm{SPM}_2}(\mathbf{Y}))},$$

(iii) *the* ξ*th posterior moment of* ϕ *is*

$$E(\phi^{\xi}|\mathbf{Y}) = \frac{\sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} 4^{-w_2} [w_2 + 1]^{-1} \mathcal{B}(\xi + \alpha + n - w_1; \beta + w_1)}{\ker(f_{\mathrm{SPM}_2}(\mathbf{Y}))},$$

(iv) *the posterior of* ψ^* *is given by*

$$\pi(\psi^*|\mathbf{Y}) = \frac{4 \sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} \mathcal{B}(\alpha + n - w_1; \beta + w_1) \psi^{*w_2}}{\ker(f_{\mathrm{SPM}_2}(\mathbf{Y}))},$$

(v) *the* ξ*th posterior moment of* ψ^* *is*

$$E(\psi^{*\xi}|\mathbf{Y}) = \frac{\sum_{\mathrm{SPM}_2} A_{\mathrm{SPM}_2} \mathcal{B}(\alpha + n - w_1; \beta + w_1) 4^{-\xi-w_2} [\xi + w_2 + 1]^{-1}}{\ker(f_{\mathrm{SPM}_2}(\mathbf{Y}))},$$

where $\ker(f_{\mathrm{SPM}_2}(\mathbf{Y})) = f_{\mathrm{SPM}_2}(\mathbf{Y}) \mathcal{B}(\alpha; \beta)[n!]^{-1}$, *and* A_{SPM_2}, δ *and* $\mathbf{w} = (w_1, w_2)$ *are given in* (2.8).

Following, we briefly review some models previously introduced in the literature.

2.3 Bayesian inference under a simplified misclassification model (SMM)

As mentioned before, the model presented by Loschi et al. (2008) is the particular case of both, the PM1 and PM2, where the misclassification errors are those given in (2.4). Under this simplification, the likelihood assumes the following form:

$$\begin{aligned} f(\mathbf{Y}|\phi, \psi) &= n! \sum_{r=0}^{y_1} \sum_{s=0}^{y_2} \sum_{t=0}^{y_3} \sum_{f=0}^{y_1-r} \sum_{g=0}^{y_2-s} A_{\mathrm{SM}} \phi^{\lambda_1} (1-\phi)^{\lambda_2} \psi^{\delta} (1-3\psi)^{n-\delta} \\ &= n! \sum_{\mathrm{SMM}} A_{\mathrm{SM}} \phi^{\lambda_1} (1-\phi)^{\lambda_2} \psi^{\delta} (1-3\psi)^{n-\delta}, \end{aligned}$$

where $A_{\text{SM}} = a^f b^{y_1-r-f} c^g d^{y_2-s-g} e^{y_3-t}[r!s!t!f!g!(y_3-t)!(y_1-r-f)!(y_2-s-g)!]^{-1}$, $\lambda_1 = y_3+f+g-t$, $\lambda_2 = y_1+y_2-r-s-f-g$ and $\delta = r+s+t$.

Assuming that, a priori, $\phi \sim \text{Beta}(\alpha,\beta)$, $\alpha > 0$, $\beta > 0$, and that $\psi \sim \text{Uniform}(0, 1/4)$, Loschi et al. (2008) prove that the predictive distribution and the posteriors for ϕ and ψ are given, respectively, by

$$f_{\text{SMM}}(\mathbf{Y}) = 4n![\mathcal{B}(\alpha,\beta)]^{-1}\sum_{\text{SMM}} A_{\text{SM}} I_{3/4}(\delta+1; n+1-\delta) \times 3^{-(\delta+1)}\mathcal{B}(\alpha+\lambda_1; \beta+\lambda_2),$$

$$\pi(\phi|\mathbf{Y}) = \frac{\sum_{\text{SMM}} A_{\text{SM}} I_{3/4}(\delta+1; n+1-\delta)3^{-(\delta+1)}\phi^{\alpha+\lambda_1-1}(1-\phi)^{\beta+\lambda_2-1}}{\ker(f_{\text{SMM}}(\mathbf{Y}))},$$

$$\pi(\psi|\mathbf{Y}) = \frac{\sum_{\text{SMM}} A_{\text{SM}}\mathcal{B}(\alpha+\lambda_1; \beta+\lambda_2)\psi^{\delta}(1-3\psi)^{n-\delta}}{\ker(f_{\text{SMM}}(\mathbf{Y}))},$$

where $\ker(f_{\text{SMM}}(\mathbf{Y})) = f_{\text{SMM}}(\mathbf{Y})\mathcal{B}(\alpha,\beta)[4n!]^{-1}$. These distributions will be used in the next section for both hypotheses tests and model comparisons.

2.4 Inference under Franco et al's model (FM)

Franco et al.'s (2003) model does not take into consideration the misclassification errors that can occur when data are obtained. Thus, it is a particular case of the models presented previously whenever ψ in (2.4) is equal to zero. Given ϕ, Franco et al. (2003) show that the random vector $\mathbf{Y}$ has a multinomial distribution with parameters n, $\theta_1(\phi) > 0$, $\theta_2(\phi) > 0$ and $\theta_3(\phi) > 0$, denoted by $\mathbf{Y}|\phi \sim \text{Mult}(n, \theta_1(\phi), \theta_2(\phi), \theta_3(\phi))$, which has a probability function given by

$$f(\mathbf{Y}|\phi) = \frac{n!}{y_1!y_2!y_3!}[\theta_1(\phi)]^{y_1}[\theta_2(\phi)]^{y_2}[\theta_3(\phi)]^{y_3}. \tag{2.9}$$

For $\phi \sim \text{Beta}(\alpha,\beta)$, $\alpha > 0$, $\beta > 0$, it follows that the predictive distribution and the posteriori of ϕ are given, respectively, by

$$f_{\text{FM}}(\mathbf{Y}) = \frac{n!}{y_3!\mathcal{B}(\alpha,\beta)}\sum_{k=0}^{y_1}\sum_{t=0}^{y_2} D_{\text{FM}}\mathcal{B}(n+\alpha-k-t, k+t+\beta),$$

$$\pi(\phi|\mathbf{Y}) = \frac{\sum_{k=0}^{y_1}\sum_{t=0}^{y_2} D_{\text{FM}}\phi^{n+\alpha-k-t-1}(1-\phi)^{k+t+\beta-1}}{\ker(f_{\text{FM}}(\mathbf{y}))},$$

where $D_{\text{FM}} = a^{y_1-k}c^{y_2-k}e^{y_3}b^k d^t[k!t!(y_1-k)!(y_2-t)!]^{-1}$ and $\ker(f_{\text{FM}}(\mathbf{Y})) = f_{\text{FM}}(\mathbf{Y})y_3!\mathcal{B}(\alpha,\beta)[n!]^{-1}$.

2.5 On identifiability in PM1 and PM2

Quoting Lindley (1971) "*In passing it might be noted that unidentifiability causes no real difficulty in the Bayesian approach.*" This statement discloses, in fact, a school thought that suggests that noidentifiability is removed with the introduction of priors into the model. However, in the presence of nonidentifiability, data information may not overcome the prior information, even if large samples are available. Thus, a poor posterior inference is obtained. Nonidentifiability in the likelihood may also lead to a poor posterior inference if there is strong posterior correlation among the parameters. If the posterior is obtained throughout MCMC-based methods, the presence of strong correlation can result in poor exploration of the posterior. Discussion about nonidentifiability in the Bayesian context can be found in Dawid (1979), Swartz et al. (2004), Gelfand and Sahu (1999) among many others.

Since we are assuming that the misclassification probabilities are smaller than the probability of correctly classifying the individual, the permutation-type nonidentifiability discussed by Swartz et al. (2004) is removed from the model. This condition corresponds to the second set of constraints suggested by such authors to overcome permutation-type nonidentifiability.

According to Dawid (1979), models are nonidentifiable whenever the posterior and prior full conditionals are equal (see also Gelfand and Sahu, 1999). That corresponds to the nonidentifiability in the likelihood. Let us consider the most controversial case where noninformative priors are assumed for the parameters, say, $\phi \sim \text{Beta}(1,1)$ and $\psi_k \sim \text{Uniform}(0,1/4)$, $k = 1,2,3$. For PM1, for instance, the posterior full conditionals for ϕ and ψ_1 are given respectively by

$$\begin{aligned}
&\pi(\phi|\psi_1,\psi_2,\psi_3,\mathbf{Y})\\
&\quad= \left(\sum_{\text{PM}_1} A_{M_1}\phi^{n-\delta}(1-\phi)^{\delta}\psi_1^{w_1}(1-2\psi_1)^{w_2}\psi_2^{w_3}(1-2\psi_2)^{w_4}\psi_3^{w_5}(1-2\psi_3)^{l}\right)\\
&\qquad\bigg/\left(\sum_{\text{PM}_1} A_{M_1}\mathcal{B}(n+1-\delta,\delta+1)\psi_1^{w_1}(1-2\psi_1)^{w_2}\right.\\
&\qquad\qquad\left.\times\,\psi_2^{w_3}(1-2\psi_2)^{w_4}\psi_3^{w_5}(1-2\psi_3)^{l}\right),\\
&\pi(\psi_1|\phi,\psi_2,\psi_3,\mathbf{Y})\\
&\quad= \left(\sum_{\text{PM}_1} A_{M_1}\phi^{n-\delta}(1-\phi)^{\delta}\psi_1^{w_1}(1-2\psi_1)^{w_2}\psi_2^{w_3}(1-2\psi_2)^{w_4}\psi_3^{w_5}(1-2\psi_3)^{l}\right)\\
&\qquad\bigg/\left(\sum_{\text{PM}_1} A_{M_1}\phi^{n-\delta}(1-\phi)^{\delta}I_{1/2}(w_1+1,w_2+1)\right.\\
&\qquad\qquad\left.\times\,\psi_2^{w_3}(1-2\psi_2)^{w_4}\psi_3^{w_5}(1-2\psi_3)^{l}\right).
\end{aligned}$$

Similarly, we obtain the posterior full conditionals for ψ_2 and ψ_3. The posterior full conditionals are equal to the prior ones whenever it follows that

$$\phi^{n-\delta}(1-\phi)^{\delta} = \mathcal{B}(n+1-\delta,\delta+1),$$

$$\psi_1^{w_1}(1-2\psi_1)^{w_2} = 2I_{1/2}(w_1+1, w_2+1),$$
$$\psi_2^{w_3}(1-2\psi_2)^{w_4} = 2I_{1/2}(w_3+1, w_4+1),$$
$$\psi_3^{w_5}(1-2\psi_3)^{l} = 2I_{1/2}(w_5+1, l+1),$$

for all $\phi \in (0,1)$ and $\psi_k \in (0, 1/4)$, $k = 1, 2, 3$. But it is equivalent to assume as constant the likelihood. Thus, the Bayesian nonindentifiability defined by David (1979) is also removed from PM1. Similarly, we prove that SPM2 is also identifiable.

3 Selecting a model

Posteriors provide the most complete information about the parameters but posterior summaries, such as posterior evidences for the null hypothesis, the Bayes factors, and so one, make communication with other area researchers easy.

In this section we discuss some techniques that permit us to make decisions about models. Such techniques include Bayesian procedures for hypotheses tests as well as for model comparisons.

It is well known that Bayesian modeling is done in two stages. We build the likelihood expressing the opinion of the researchers about the data behavior and the prior is constructed based on the researcher's knowledge obtained before observing data. Thus, models can differ in their likelihood (as we have in PM1 and PM2) or whenever different prior specifications are assumed (see Section 4). Model comparison procedures (Bayes factor, DIC, etc.) are useful tools in both situations. In the first case, they are used to decide for the likelihood that best fit to data. Model comparison tools are also used in the decision process of "choosing the prior." Sometimes the researcher knows only the prior family of distribution but the prior remains unknown since there is not enough information to define the hyperparameters. A possible strategy is to perform a sensitivity analysis in order to evaluate the effect of different priors in the posterior inferences and to chose the best one.

We start this section presenting some procedures for hypotheses tests. In this paper we consider that the population of interest is compared to another one that is known. In this case, it is assumed that both populations have their behavior described by the same likelihood and we should select the parameters which indexes it.

Assuming Franco et al.'s model, Barros and Franco (2002) introduced bootstrap procedures to test if $\phi = 0.68$ for the Brazilian population with trisomy 21. Later, Bayesian tests for such situation were presented by Loschi et al. (2007). Here, we extend Loschi et al.'s (2007) ideas for all misclassification models discussed in the previous section.

3.1 Bayesian tests for precise hypothesis

Suppose that we are interested in testing the following sharp hypothesis for θ:

$$H_0 : \theta \in \Theta_0 \quad \text{versus} \quad H_1 : \theta \in \Theta_1, \tag{3.1}$$

where $\{\Theta_0, \Theta_1\}$ is a partition of Θ, the parametric space of θ, $\Theta_0 = \{\theta_0\}$ and θ_0 is a known value.

Next we review the usual Bayesian procedures for testing and present the loss functions that confer to them a theoretical decision aspect. We also introduce a criteria for obtaining the cut points for accepting the null hypothesis under both procedures. This criteria assumes that the prior risks under Jeffreys and Pereira–Stern tests are the same.

3.1.1 *Jeffreys test.* The Jeffreys test is by far the most used procedure for testing sharp hypothesis in Bayesian inference. The decision is made based on the posterior of H_0, $P(H_0|\mathbf{x})$, which is a function of the Bayes factor $\mathrm{BF}(H_0, H_1) = f(\mathbf{x}|H_0)/f(\mathbf{x}|H_1) = \mathrm{BF}(H_1, H_0)^{-1}$ (Jeffreys, 1961; Lavine and Schervish, 1999). Denoting by $P(H_i)$ the prior probability for the hypothesis H_i, $i = 0, 1$, the posterior for H_0 is given by

$$P(H_0|\mathbf{x}) = \left[1 + \frac{P(H_1)}{P(H_0)} \mathrm{BF}(H_1, H_0)\right]^{-1}. \tag{3.2}$$

The Jeffreys test is a Bayes rule and it is obtained whenever the following loss function is assumed

$$\begin{cases} \mathrm{L}(\text{Accept } H_0, \theta) = \omega_1 \mathbf{1}\{\theta \in \Theta_1\}, \\ \mathrm{L}(\text{Reject } H_0, \theta) = \omega_0 \mathbf{1}\{\theta \in \Theta_0\}, \end{cases} \tag{3.3}$$

where $\mathbf{1}\{A\}$ denotes the indicator function of event A and $\omega_i > 0$, $i = 1, 2$. We decide for H_0 when the posterior risk of accepting the null hypothesis is the smallest. By assuming this strategy, we accept H_0 whenever

$$P(H_0|\mathbf{x}) > \frac{\omega_1}{\omega_1 + \omega_0}. \tag{3.4}$$

For a more detailed explanation about the Jeffreys test see Migon and Gamerman (1999), Bernardo and Smith (1994) and many others.

For the genetic problem discussed here, the main interest is to test hypotheses about the parameter ϕ. Let us consider the following hypotheses: $H_0 : \phi = \phi_0$ versus $H_1 : \phi \neq \phi_0$, where $\phi_0 \in (0, 1)$ is a known value.

In a general setting, for the misclassifications models, the Bayes factor is obtained as follows:

$$\mathrm{BF}(H_0; H_1) = \frac{\int f(\mathbf{Y}|\phi, \boldsymbol{\psi})\, d\boldsymbol{\psi}}{\int\int f(\mathbf{Y}|\phi, \boldsymbol{\psi})\, d\phi\, d\boldsymbol{\psi}}.$$

Consequently, for the models 1 discussed in Section 2, we have that

$$\mathrm{BF}_{\mathrm{PM1}}(H_0; H_1) = \frac{\mathcal{B}(\alpha;\beta)\sum_{\mathrm{PM}_1} A(r,s,t,f,g,h,i,j,k,l,m,q)\mathcal{I}(\mathbf{w},l)\phi_0^{n-\delta}(1-\phi_0)^{\delta}}{\ker(f_{\mathrm{PM}_1}(\mathbf{Y}))},$$

$$\mathrm{BF}_{\mathrm{SPM}_2}(H_0; H_1) = \Big(\mathcal{B}(\alpha;\beta)\sum_{\mathrm{SPM}_2} A(f,g,h,i,j,k,l,p,r,s,t,u) \times 4^{-w_2}[w_2+1]^{-1}\phi_0^{n-w_1}(1-\phi_0)^{w_1}\Big)\Big/\big(\ker(f_{\mathrm{SPM}_2}(\mathbf{Y}))\big),$$

$$\mathrm{BF}_{\mathrm{SMM}}(H_0; H_1) = \frac{\mathcal{B}(\alpha;\beta)\sum_{\mathrm{SMM}} A(r,s,t,f,g)I_{3/4}(\delta+1;n+1-\delta)3^{-(\delta+1)}\phi_0^{\lambda_1}(1-\phi_0)^{\lambda_2}}{\ker(f_{\mathrm{SMM}}(\mathbf{Y}))},$$

$$\mathrm{BF}_{\mathrm{FM}}(H_0; H_1) = \frac{\mathcal{B}(\alpha;\beta)[\theta_1(\phi_0)]^{y_1}[\theta_2(\phi_0)]^{y_2}[\theta_3(\phi_0)]^{y_3}}{\ker(f_{\mathrm{FM}}(\mathbf{Y}))}.$$

For the misclassification errors, the great interest is to test if the errors are equal to zero. Bayes factors for hypotheses test about the misclassifications errors are obtained similarly. Their formulas will be omitted.

3.1.2 *Pereira–Stern test.* The Pereira–Stern or the full Bayesian significance test (FBST) does not introduce prior probabilities for the hypotheses H_i and makes the test for precise hypotheses simple (Pereira and Stern, 1999; Pereira and Stern, 2001). Besides, it does not lead to the Jeffreys–Lindley paradox (Robert, 1993; Tsao, 2006). The Pereira–Stern measure of evidence for H_0 is based on the posterior distribution for θ. In this case, H_0 is accepted if Θ_0 is in a high posterior probability region of Θ.

Denote by $\pi(\theta|\mathbf{x})$ be the posterior density of θ. Consider the following highest relative surprise (HRS) set

$$T(\mathbf{x}) = \Big\{\theta \in \Theta : \pi(\theta|\mathbf{x}) > \sup_{\Theta_0}\{\pi(\theta|\mathbf{x})\}\Big\}. \tag{3.5}$$

The posterior evidence for the null hypothesis is given by $\mathrm{EV}(H_0, \mathbf{x}) = 1 - \Pr(\theta \in T(\mathbf{x})|\mathbf{x})$. See Madruga et al. (2003) for the FBST in its invariant formulation.

As proved in Madruga et al. (2001), the FBST or Pereira–Stern test is also a Bayes rule whenever the following loss function is assumed:

$$\begin{cases} \mathrm{L}(\text{Accept } H_0, \theta) = b + c\mathbf{1}\{\theta \in T(\mathbf{x})\}, \\ \mathrm{L}(\text{Reject } H_0, \theta) = a[1 - \mathbf{1}\{\theta \in T(\mathbf{x})\}], \end{cases} \tag{3.6}$$

where b, ξ and c are real, positive numbers. We decide for the acceptance of H_0 whenever

$$\mathrm{EV}(H_0, \mathbf{x}) > \frac{b+c}{c+a}. \tag{3.7}$$

For the genetic problem under consideration in this paper, the posteriors are given in Section 2 and the posterior evidence for H_0 is obtained through numerical approximations.

3.2 Building a criteria for making decisions

When can the posterior evidences for H_0 provided by Jeffreys and Pereira–Stern test procedures be considered strong? The scale of evidence proposed by Jeffreys (1961) has been widely used in the literature as a reference for making decision using the Jeffreys test. However, for the Pereira–Stern test we have not found such a scale.

In order to make the test procedures comparable, we propose finding the values of w_0, w_1, a, b and c such that the prior risk of acceptance of the null hypothesis under Jeffreys and Pereira–Stern test procedures are equal.

Let $\mathrm{Ev}(H_0) \in (0, 1)$ be the prior evidence for the null hypothesis. Assuming as equal the prior risk of acceptance for the two test procedures, we have that

$$c = \frac{w_1(1 - P(H_0)) - b}{(1 - \mathrm{Ev}(H_0))}.$$

Moreover, by considering the risk of rejecting the null hypothesis for the Jeffreys test equal to the one obtained for Pereira–Stern test, it follows that

$$a = \frac{w_0 P(H_0)}{\mathrm{Ev}(H_0)}.$$

The cut points for both test procedures are obtained from (3.4) and (3.7) by arbitrarily specifying $P(H_0)$, w_0,w_1 and b. Particularly, if $P(H_0) = P(H_1) = 0.5$ and $w_0 = w_1 = 1$, then the cut points for Pereira–Stern and Jeffreys test are, respectively, $\mathrm{Ev}(H_0)$ and $P(H_0)$, say, the prior evidences in favor of H_0.

3.3 Model comparison tools

One of the most important characteristics of model comparison tools is that they allow the comparison of models with different complexity degrees. In the following, we briefly present some usual ones.

3.3.1 *Bayes factor.* Bayes factor is also used for model comparison. Let $M_1, \ldots,$ M_k be the models that are being compared. Model M_i has parameter $\theta_{M_i} \in \Theta_{M_i}$.

Denote by $\pi(\theta_{M_i})$ the prior for θ_{M_i}. Thus, Bayes factor in favor of model M_i when compared with model M_j (Kadane and Lasar, 2004) is given by

$$\mathrm{BF}(M_i; M_j) = \frac{\int_{\Theta_{M_i}} p(\mathbf{y}|\theta_{M_i})\pi(\theta_{M_i})\,d\theta_{M_i}}{\int_{\Theta_{M_j}} p(\mathbf{y}|\theta_{M_j})\pi(\theta_{M_j})\,d\theta_{M_j}}.$$

Let $p(M_i) = 1/k$ be the priori for model M_i. Model M_i is preferred to model M_j if $\mathrm{BF}(M_i; M_j) > 1$. However, there is weak evidence in favor of M_i if $\mathrm{BF}(M_i; M_j)$ assume values in the interval $(1, 3)$ and such evidence is considered substantial if $\mathrm{BF}(M_i; M_j)$ is in the interval $(3, 10)$. See more about model selection in Kadane and Lasar (2004).

For the models presented in Section 2, the Bayes factors are

$$\begin{aligned}
\mathrm{BF}(\mathrm{PM}_1, \mathrm{SPM}_2) &= [16\,\mathrm{ker}(f_{\mathrm{PM}_1}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{SPM}_2}(\mathbf{Y}))]^{-1},\\
\mathrm{BF}(\mathrm{PM}_1, \mathrm{SMM}) &= [16\,\mathrm{ker}(f_{\mathrm{PM}_1}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{SMM}}(\mathbf{Y}))]^{-1},\\
\mathrm{BF}(\mathrm{PM}_1, \mathrm{FM}) &= [64\,\mathrm{ker}(f_{\mathrm{PM}_1}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{FM}}(\mathbf{Y}))]^{-1},\\
\mathrm{BF}(\mathrm{SPM}_2, \mathrm{SMM}) &= [\mathrm{ker}(f_{\mathrm{SPM}_2}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{SMM}}(\mathbf{Y}))]^{-1},\\
\mathrm{BF}(\mathrm{SPM}_2, \mathrm{FM}) &= [4\,\mathrm{ker}(f_{\mathrm{SPM}_2}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{FM}}(\mathbf{Y}))]^{-1},\\
\mathrm{BF}(\mathrm{SMM}, \mathrm{FM}) &= [4\,\mathrm{ker}(f_{\mathrm{SMM}}(\mathbf{Y}))][\mathrm{ker}(f_{\mathrm{FM}}(\mathbf{Y}))]^{-1}.
\end{aligned}$$

We consider Gauss–Legendre method to approximate the integrals needed in the calculations of the Bayes factors.

3.3.2 *Deviance Information Criterion* (*DIC*). The Deviance Information Criterion (DIC) was introduced by Spiegelhalter et al. (2002) and can be computed in a simple way from samples of the posterior distributions. Decision is for model M_i, if it presents the smallest DIC.

Let us consider the deviance function $D(\theta_{M_i})$ which depends on the likelihood function associated to the model of interest M_i

$$D(\theta_{M_i}) = -2\log[f(\mathbf{Y}|\theta_{M_i})] + C,$$

where C is a constant. The DIC for model M_i is then given by

$$\mathrm{DIC}(M_i) = -2\log[f(\mathbf{Y}|\overline{\theta}_{M_i})] + 2p_D = \overline{D} + p_D,$$

where $\overline{\theta}_{M_i} = E(\theta_{M_i}|\mathbf{y})$ is the posterior mean of θ_{M_i}, $\overline{D} = E[D(\theta_{M_i})|\mathbf{Y}]$ denotes the posterior mean deviation that measures the model fit quality and $p_D = \overline{D} - D(\overline{\theta})$ is the effective number of parameters in the model M_i.

4 Case study: Down Syndrome data

Trisomy 21 is the most prevalent human genetic disorder and occurs in approximately 1 in 700 births (Valero et al., 1999). It produces Down Syndrome and is the most common cause of mental retardation of a genetic origin. Down Syndrome affects kids' cognitive abilities and around half of them can also have congenital heart defects, problems with hearing and vision and they are prone to developing pulmonary hypertension. Although the causes of Down Syndrome are unknown, scientists do know that in the trisomy of chromosome 21, there is evidence that the rate of nondisjunction increases with the age of the mother (see Pena, 1998). Women age 35 and older have a significantly higher risk of having a child with Down Syndrome. Moreover, the increase in the rate of nondisjunction in meiosis II is higher than for meiosis I if the mother's age is between 35 and 39 years. Thus, the determination of the rate ϕ of nondisjunction in chromosomal segregation, which takes place in meiosis I in each chromosome, plays an important role in understanding aneuploidies. It is useful to identify possible factors, such as geography, nutrition, age and, reproductive practices, among others, which generate such abnormalities.

We analyze the dataset reported in Franco et al. (2003) which consists of a random sample of blood from 34 Brazilian individuals with trisomy of chromosome 21. For this dataset, the observed numbers of patients with one, two and three peaks are 6, 22 and 6, respectively. The hypothesis of the Hardy–Weinberg equilibrium is verified for the Brazilian population and six alleles are found with frequencies 0.12, 0.45, 0.09, 0.31, 0.01 and 0.02.

Several previous works make comparisons between affected individuals and their parents for estimating ϕ. Some of them consider large groups of patients with Down Syndrome, for instance, Lober et al. (1992), Petersen et al. (1992), Zaragosa et al. (1994), Griffin (1996), Koehler et al. (1996), Yoon et al. (1996), Nicolaidis and Petersen (1998) and Savage et al. (1998). Summarizing such estimates of ϕ, we obtained an average of 0.6803 and standard deviation equal to 0.0678. These previous studies help us to construct a more informative prior distribution of ϕ. The priors for ϕ considered in this paper are the beta distributions of which the parameters are pointed out in Table 1. The noninformative Bayes–Laplace prior is also considered for comparison proposes. The only prior information we have about the misclassification errors is that the probability of correctly classifying the individual is higher than the total misclassification error. Thus, for the misclassification errors, we assume the uniform distribution in the interval (0, 1/4).

Besides estimates for ϕ and for the misclassification errors, we are also interested in testing the following hypotheses:

$$H_0 : \phi = 0.68 \quad \times \quad H_1 : \phi \neq 0.68,$$
$$H_0 : \psi = 0\ (\psi_k = 0) \quad \times \quad H_1 : \psi > 0\ (\psi_k > 0).$$

Table 1 *Prior distribution for ϕ and their summaries*

Prior parameters		Summaries	
α	β	Mean	Variance
1	1	0.5000	0.0833
2	1	0.6667	0.0556
4	2	0.6667	0.0317
20	10	0.6667	0.0072

Table 2 *Cut points for Jeffreys and Pereira–Stern tests for parameters ϕ and ψ's*

Parameter	Prior	Pereira–Stern test	Jeffreys test
ϕ	Beta(1, 1)	0.0003	0.5000
	Beta(2, 1)	0.4637	
	Beta(4, 2)	0.7213	
	Beta(20, 10)	0.9877	
ψ_k	Uniform(0, 1/4)	0.9997	0.5000

This hypotheses test for ϕ was also considered by Loschi et al. (2007) assuming Franco et al.'s model. To obtain the cut points for Jeffreys and Pereira–Stern tests presented in Section 4, we assume $P(H_0) = 0.5$, $b = 10^{-6}$ and $w_0 = w_1 = 1$. Table 2 presents the cut points for Jeffreys and Pereira–Stern tests whenever the prior specifications in Table 1 are assumed.

4.1 Estimate and test for ϕ

Table 3 shows some posterior summaries for ϕ and the posterior evidences for H_0 provided by Jeffreys and Pereira–Stern tests. Franco et al.'s model provides the highest posterior mean and median and the smallest variance, for all prior specifications. It is followed by the simplification of PM2 considered here. The PM1 tends to present the smallest posterior mean and the highest variance. Except for the less informative priors, all four models provide similar mean, median and mode. In these cases, the posterior means under the three misclassification models are close to the maximum likelihood estimates (MLE) for ϕ obtained by Franco et al. (2003) (MLE = 0.6552 and asymptotic variance = 0.0481). Figures 2 and 3 show that the posteriors have unique modes and are asymmetric. However, the degree of skewness in such distributions tends to be smaller for more informative priors.

Table 3 *Posterior summaries and hypothesis test for ϕ*

Prior			Posterior summaries					Tests	
α	β	Model	Mean	Variance	Median	Mode	95% HPD interval	$\text{Ev}(H_0, \mathbf{y})$	$P(H_0\|\mathbf{y})$
1	1	PM1	0.5483	0.0652	0.5605	0.5920	(0.1025; 0.9955)	0.7683	0.5539
		SPM2	0.5898	0.0493	0.6008	0.6201	(0.2060; 0.9988)	0.8100	0.6196
		SMM	0.5703	0.0569	0.5848	0.6088	(0.1383; 0.9957)	0.7963	0.5930
		FM	0.6596	0.0307	0.6621	0.6551	(0.3539; 0.9832)	0.9040	0.6699
2	1	PM1	0.6663	0.0482	0.6907	0.8345	(0.2655; 1.0000)	0.4840	0.5331
		SPM2	0.6724	0.0364	0.6907	0.7223	(0.3335; 0.9999)	0.8250	0.5771
		SMM	0.6665	0.0409	0.6841	0.7321	(0.3084; 0.9990)	0.8207	0.5625
		FM	0.7043	0.0274	0.7107	0.7243	(0.4179; 0.9991)	0.8167	0.6077
4	2	PM1	0.6583	0.0290	0.6738	0.7162	(0.3368; 0.9519)	0.8460	0.5185
		SPM2	0.6680	0.0241	0.6760	0.6953	(0.3871; 0.9511)	0.9367	0.5455
		SMM	0.6589	0.0261	0.6681	0.6976	(0.3436; 0.9467)	0.9190	0.5365
		FM	0.6798	0.0202	0.6875	0.7012	(0.4224; 0.9562)	0.8913	0.5673
20	10	PM1	0.6654	0.0073	0.6691	0.6750	(0.4986; 0.8224)	0.9567	0.5031
		SPM2	0.6649	0.0062	0.6691	0.6728	(0.5017; 0.8108)	0.9337	0.5092
		SMM	0.6633	0.0069	0.6645	0.6728	(0.5094; 0.8272)	0.9397	0.5070
		FM	0.6697	0.0062	0.6711	0.6753	(0.5225; 0.8263)	0.9573	0.5163

Table 3 also provides the posterior evidence for $H_0 : \phi = 0.68 \times H_1 : \phi \neq 0.68$. The Jeffreys test and the 95% HPD intervals lead to the acceptance of the null hypothesis for all models and prior specifications. The same conclusion can be drawn from the Pereira–Stern test, except when we assume that $\phi \sim$ Beta(20, 10). In this case, we reject H_0 for all models. Notice, that for such a prior, $P(H_0|\mathbf{y})$ is close to 0.5, say, the posterior evidence for the null hypothesis provided by the Jeffreys test is weak.

4.2 Estimate and test for the misclassification errors ψ's

Table 4 shows some results related to the estimation and test for the misclassification errors. Taken into consideration the posterior modes, we conclude that, under the SMM and the SPM2, the misclassification errors ψ and ψ^* are very close to zero, for all prior specifications, which means that these models are almost equivalent to Franco et al.'s model. Similar conclusions can be drawn whenever we consider both test procedures presented in this paper. For PM1 and all priors for ϕ, the misclassification errors ψ_1 and ψ_3 are high (higher than 0.189) and ψ_2 is moderate assuming values between 0.0238, whenever $\phi \sim$ Beta(20, 10), and 0.0377, whenever it has been elicited a noninformative prior for ϕ. That is a reasonable result since, for this model, $\psi_k = P(Z = i|X = k) = P(Z = j|X = k)$, $k \neq j \neq i$. For all models and prior specifications, the posterior means and medians assume similar values. From Table 4 we can also observe that, for PM1, the Jeffreys test

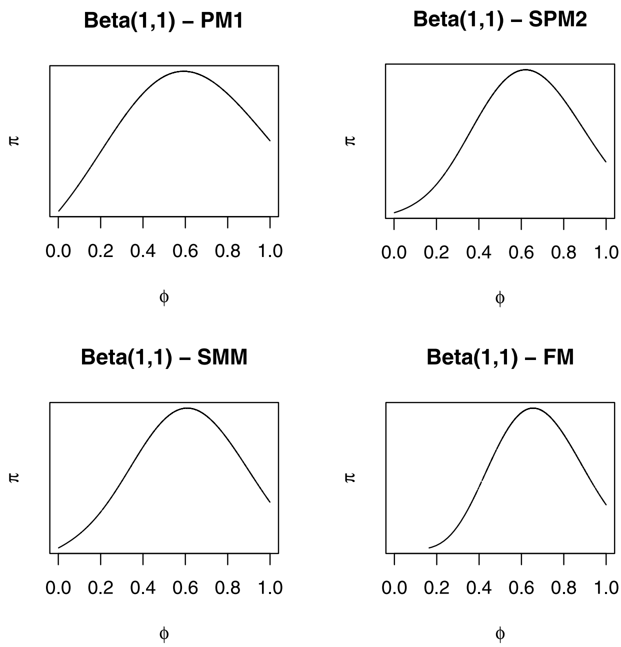

Figure 2 *Posteriors for ϕ under all models*, *case* Beta(1, 1).

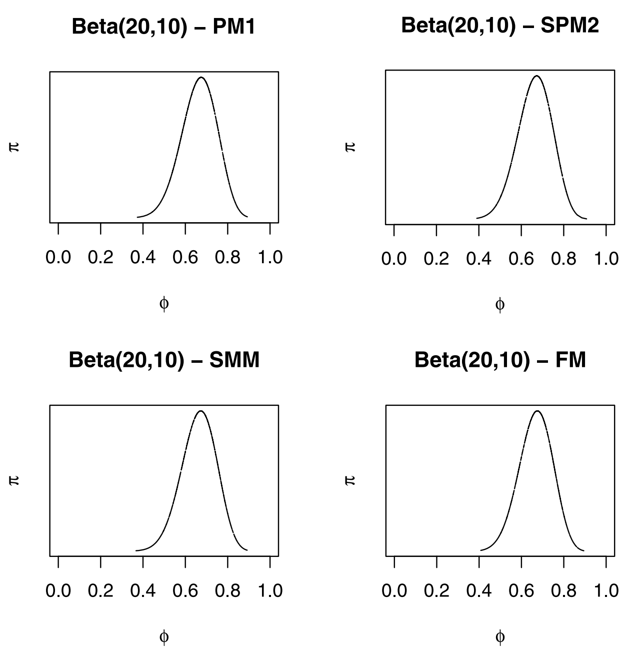

Figure 3 *Posteriors for ϕ under all models*, *case* Beta(20, 10).

Table 4 *Posterior summaries and hypothesis test for* $\boldsymbol{\psi}$

	Prior		Posterior summaries					Tests	
Param.	α	β	Mean	Var	Median	Mode	95% HPDI	$\text{Ev}(H_0.\mathbf{y})$	$p(H_0\|\mathbf{y})$
Proposed Model 1									
ψ_1	1	1	0.1433	0.0050	0.1509	0.2499	(0.0190; 0.2498)	0.0000	0.3554
	2	1	0.1346	0.0048	0.1385	0.2237	(0.0174; 0.2500)	0.0000	0.4111
	4	2	0.1323	0.0050	0.1365	0.2085	(0.0144; 0.2488)	0.0000	0.4109
	20	10	0.1321	0.0049	0.1360	0.1916	(0.0146; 0.2480)	0.0000	0.4148
ψ_2	1	1	0.0713	0.0024	0.0634	0.0377	(0.0000; 0.1647)	0.4057	0.6373
	2	1	0.0639	0.0021	0.0546	0.0275	(0.0000; 0.1520)	0.4917	0.6695
	4	2	0.0644	0.0021	0.0572	0.0261	(0.0001; 0.1506)	0.5313	0.6744
	20	10	0.0647	0.0021	0.0568	0.0238	(0.0001; 0.1517)	0.5727	0.6815
ψ_3	1	1	0.1284	0.0051	0.1302	0.1963	(0.0141; 0.2495)	0.0000	0.4537
	2	1	0.1343	0.0049	0.1384	0.2205	(0.0189; 0.2499)	0.0000	0.4108
	4	2	0.1337	0.0051	0.1398	0.2059	(0.0067; 0.2420)	0.0000	0.4177
	20	10	0.1329	0.0049	0.1391	0.1891	(0.0163; 0.2486)	0.0000	0.4208
Simplified Proposed Model 2									
ψ^*	1	1	0.0755	0.0030	0.0644	0.0001	(0.0001; 0.1804)	1.0000	0.6724
	2	1	0.0729	0.0029	0.0625	0.0000	(0.0001; 0.1737)	1.0000	0.6926
	4	2	0.0707	0.0028	0.0590	0.0001	(0.0001; 0.1731)	1.0000	0.7007
	20	10	0.0686	0.0028	0.0570	0.0001	(0.0000; 0.1729)	1.0000	0.7131
Simplified Misclassification Model									
ψ	1	1	0.0815	0.0033	0.0726	0.0122	(0.0001; 0.1913)	0.8183	0.6474
	2	1	0.0730	0.0028	0.0629	0.0001	(0.0002; 0.1761)	1.0000	0.6797
	4	2	0.0724	0.0028	0.0623	0.0000	(0.0000; 0.1739)	1.0000	0.6931
	20	10	0.0670	0.0026	0.0562	0.0000	(0.0000; 0.1708)	1.0000	0.7112

leads to the acceptance of the null hypothesis about ψ_2, for all prior specifications. In these cases, posteriors do not provide the same evidence (see also Figure 5). On the other hand, the Pereira–Stern test and the 95% HPD interval provide evidence that the misclassification errors ψ_1, ψ_2 and ψ_3 in PM1 are all different from zero.

Figures 4–6 show that the posteriors for the misclassification errors have unique modes and are strongly asymmetric. The common misclassification errors in SMM and SPM2 put most of their mass in small values. Similar behavior is observed for ψ_2 in PM1.

4.3 Model comparison

Tables 5 and 6 show, respectively, the DIC and the Bayes factor for all models presented in Section 2 and for all prior specifications. From Table 5 we concluded that Franco et al.'s model is the best and SPM2 tends to be the worst. PM1 should be preferred to the SMM except when $\phi \sim \text{Beta}(20, 10)$. From Table 6 we also notice that the strongest evidence is for the Franco et al. model. The Bayes factors for

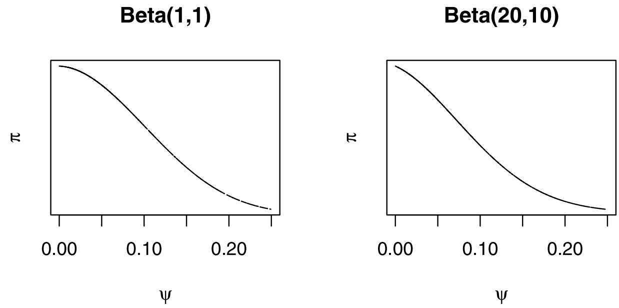

Figure 4 *Posteriors for* ψ^*, *Simplified Proposed Model* 2, *cases* Beta(1, 1) *and* Beta(20, 10).

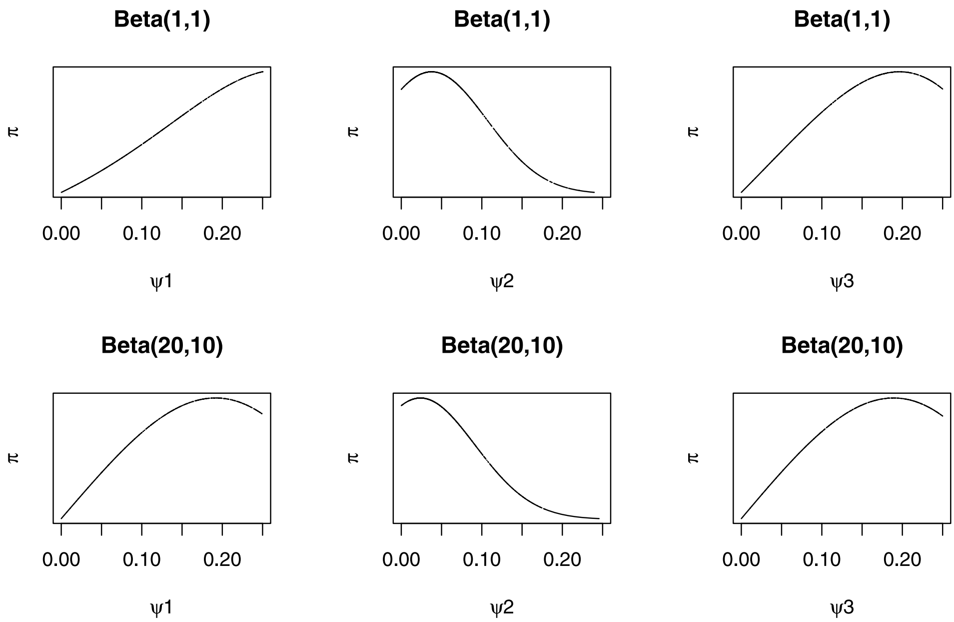

Figure 5 *Posteriors for* ψ_1, ψ_2 *and* ψ_3, *Proposed Model* 1, *cases* Beta(1, 1) *and* Beta(20, 10).

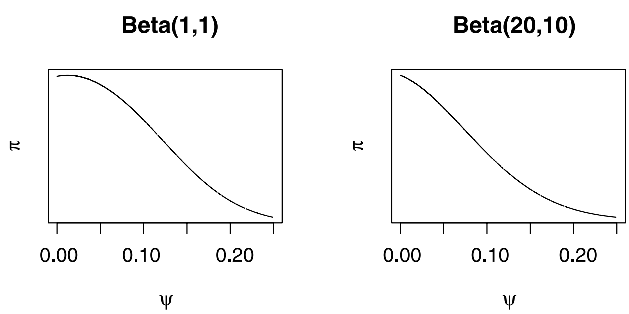

Figure 6 *Posteriors for* ψ, *Simplified Misclassification Model*, *cases* Beta(1, 1) *and* Beta(20, 10).

Table 5 *Model comparison—DIC*

Prior		DIC			
α	β	PM1	SPM2	SMM	FM
1	1	9.272	9.903	9.692	8.378
2	1	8.991	9.487	9.327	8.187
4	2	8.879	9.135	9.041	7.822
20	10	8.685	8.602	8.569	7.230

Table 6 *Model comparison—Bayes factor*

Prior		Bayes factor		
α	β	(PM1, SPM2)	(PM1, SMM)	(PM1, FM)
1	1	1.277	1.142	0.545
2	1	1.163	1.095	0.471
4	2	1.085	1.046	0.443
20	10	0.998	0.988	0.406
		(SPM2, SMM)	(SPM2, FM)	(SMM, FM)
1	1	0.894	0.487	0.545
2	1	0.942	0.444	0.471
4	2	0.964	0.427	0.443
20	10	0.991	0.402	0.406

such a model assume values between 1.84 and 2.49. For comparisons among the other models such evidence is not strong. In fact, the models are almost comparable since the Bayes factors are close to one. Comparing only the misclassification models, we conclude that PM1 is better than both, the SMM and SPM2, except whenever $\phi \sim \text{Beta}(20, 10)$. The SMM is better than SPM2. In general, the Bayes factor and the DIC lead to similar conclusions even when the Bayes–Laplace prior was elicited.

5 Concluding remarks

We extended previous works by considering more general misclassification models for the number of trisomic individuals with 1, 2 or 3 peaks. Such models are more flexible than models introduced in the literature and also identifiable. Posteriors and their moments were exactly obtained. Jeffreys and Pereira–Stern procedures were considered for testing hypotheses about the meiosis I nondisjunction fraction and the misclassification errors. Bayes factor and DIC were considered for model comparison.

In summary, for the dataset analyzed in this paper we concluded that the PM1 brings some improvement to the analysis if compared to the SMM introduced by Loschi et al. (2008). Jeffreys and Pereira–Stern test procedures provided evidence that the common misclassification errors included in the SMM and SPM2 can be considered equal to zero, thus it is comparable to the Franco et al. model. However, that is not the rule for PM1, that is, such tests indicated that the presence of misclassification errors in the model is significant. Thus, in other situations in which the misclassification error is high, the proposed models could bring some advantages to the analysis.

More importantly, we concluded that for the Brazilian population the meiosis I nondisjunction fraction in Down Syndrome can be considered equal to the average of the estimates of the nondisjunction fraction obtained in the literature for other populations.

Acknowledgments

The authors would like to express their gratitude to the editor and the referees for the careful refereeing of the paper. Their suggestions and constructive criticisms, mainly in the presentation of the models, led us to improve the paper substantially. We acknowledge that the simplification of proposed model 2 was suggested by one of the reviewers. We also thank Professor Sergio D. J. Pena and Flavia C. Parra (UFMG), for providing the dataset, and Ricardo H. C. Takahashi for suggestions. V. L. Silva received financial support from CNPq (*Conselho Nacional de Desenvolvimento Científico e Tecnológico*) of the Ministry for Science and Technology of Brazil, via PIBIC program. R. H. Loschi has her research supported in part by CNPq, Grants 306085/2009-7, 304505/2006-4, 472877/2006-2.

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