

Interpreting Significance in Nonparametric
Linkage Analysis: The Fuzzy p -Value
Distribution Extended to Multiple Score
Functions

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Abstract

We discuss the concept of fuzzy p -values within the context of nonparametric linkage analysis. Here the fuzziness arises according to ambiguity of true inheritance vectors given marker data, and it evolves into a fuzzy p -value distribution. Inspired by Geyer and Meeden (2005) and Thompson and Geyer (2005) we formulate our own appreciation of this topic and extend the fuzzy p -value distribution to be constructed using linkage evidence originating from using several distinct score functions applied to the same data.

Key words: Nonparametric linkage analysis, score functions, inheritance distribution, significance and power, hypothesis testing, randomized tests, fuzzy p -value, fuzzy p -value distribution.

<i>CONTENTS</i>	1
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Contents

1 Introduction	2
1.1 The Pedigree, Pedigree Set and Inheritance Vector	2
1.2 Allele-Sharing and Score Functions	3
1.3 Test Statistics and Traditional Significance Calculations	5
2 Fuzzy Significance	6
2.1 The Inheritance Distribution	7
2.2 Revisiting the Standard Approach	7
2.3 Randomized Tests	8
2.4 The Inheritance Distribution-Based Fuzzy p -Value	9
3 Fuzzy p-Values in Linkage Analysis	10
3.1 Properties and Interpretations	10
3.2 Summarizing Measures	11
3.3 Extensions	12
4 An Artificial Example	12
References	14
A Types of Significance	17

1 Introduction

Gene mapping through nonparametric linkage analysis (Kruglyak et al., 1996) is based on observing marker data MD, in the form of genotypes, with respect to a set of pedigrees.¹ The actual inheritance of alleles with respect to the pedigree set is compared to what is expected under the null hypothesis H_0 of random inheritance, which corresponds to the concept of no *genetic linkage* or no correkation between genotypes and phenotypes (affection status).

1.1 The Pedigree, Pedigree Set and Inheritance Vector

A pedigree consisting of n individuals includes f founders and $n - f$ non-founders, where the parents of the former are not included in the pedigree. At locus x , the corresponding inheritance of alleles within the pedigree, from the founders to the nonfounders, may be summarized through the binary-valued *inheritance vector* $v(x)$ (Donnelly, 1983),

$$v(x) = (p_1, m_1, p_2, m_2, \dots, p_{n-f}, m_{n-f}), \quad (1)$$

where p_i and m_i correspond to the i^{th} paternal and maternal meioses respectively. In (1) each value may be defined to equal either 0 or 1 depending on whether the corresponding allele originates from the grandfather or the grandmother.

With respect to a genome Ω and assuming fully observable meioses,² the genetic dogma of blockwise inheritance implies that the inheritance process,

$$v(x); x \in \Omega,$$

changes only at so called *crossovers*. In our setting this means that the corresponding meiosis, p_i or m_i for some i , switches between 0 and 1.

Now, simultaneously looking at a sequence of syntenic loci $\mathbf{x} = (x_1, x_2, \dots, x_{|l|})$,³ the corresponding joint inheritance may be described by the $m \times |l|$ *inheritance matrix*,

$$v(\mathbf{x}) = [v(x_1)^T, v(x_2)^T, \dots, v(x_{|l|})^T], \quad (2)$$

¹This is referred to as the *pedigree set*. A pedigree is to be understood as a, possibly multigenerational, tree-wise connected family.

²In other words infinitely many fully informative markers.

³This means that $\forall i, j \in \{1, 2, \dots, |l|\}$, $c(x_i) = c(x_j)$, where $c(x)$ equals the chromosome where x is located.

where the i^{th} row and j^{th} column correspond to the equally indexed meiosis and inheritance vector respectively.

Remark 1. *In (2) the columns are correlated according to the blockwise inheritance and the assumption of syntenic loci. The strength of the correlations depends on the corresponding genetic distances.*

Given marker data $\text{MD}(x)$ at locus x , if the inheritance vector is fully known or observable one speaks of *fully informative* data at x . Formulation-wise equivalents are *complete* or *perfect* data. Given no or totally noninformative data all inheritance vectors are equally likely under the null hypothesis, which follows from the Mendelian law of random inheritance. To quantify information one introduces *information measures*, usually ranging from 0 (no information) to 1 (complete information). One such locus-specific measure is the *entropy-based information content* presented in Kruglyak et al. (1996). For further discussion on information measures in linkage analysis, see e.g. Teng and Siegmund (1998) and Nicolae and Kong (2004).

Given the complete set of marker genotypes in the pedigree set, there are two distinct ways of extracting inheritance information: (i) Using *single-point analysis*, where for each locus x one uses only $\text{MD}(x)$ when reconstructing the inheritance distribution. (ii) Using *multipoint analysis*, where for each locus x one uses all data $\text{MD}(y)$, $y \in c(x)$, when defining the inheritance distribution.

Remark 2. *Information is lost, i.e. the information measure generally decreases, when facing missing genotypes, marker homozygosity and by using single-point analysis.*

1.2 Allele-Sharing and Score Functions

Nonparametric linkage analysis, as well as some other approaches,⁴ is based on *allele-sharing* between individuals in a pedigree. The actual sharing may be measured using the concepts: (i) Two individuals sharing one allele *identical-by-descent (IBD)* if they have both inherited exactly the same allele, i.e. an identical founder allele, from a common ancestor. (ii) Two individuals sharing one allele *identical-by-state (IBS)* if they have both inherited a common allelic variant.

⁴See, for example, Haines and Pericak-Vance (1998) and Almgren et al. (2003).

One may note that sharing an allele IBD implies sharing one allele IBS. We will exclusively use, as most contemporary test statistics does, the concept of IBD-sharing. Perhaps evidently, one is normally interested in increased allele-sharing within phenotypes⁵ since this generally indicates genetic linkage between the corresponding marker and disease loci.

Remark 3. *Given the inheritance vector and pedigree structure, the IBD-sharing in the pedigree is unambiguous, i.e. known with probability one.⁶ In other words, for a fixed structure, it is completely explained by the corresponding inheritance vector.*

For the one-locus case test statistics may be based on an underlying score function $S(w)$, which assigns a number to each possible IBD-sharing structure (through the inheritance vector). This may be generalized to the two-locus case, where the underlying score function $S(w_1, w_2)$, $(w_1, w_2) \in \mathbb{V} \times \mathbb{V}$, is defined with respect to the joint IBD-sharing through two distinct inheritance vectors.

Remark 4. *Using data mining-terminology, a score function is used for scoring patterns, in this case inheritance patterns (Hand et al., 2001).*

The two most commonly used score functions are: (i) The function S_{pairs} , which is based on summing IBD-sharing among all pairs of affected individuals within a pedigree. (ii) The function S_{all} , which is based on the simultaneous IBD-sharing among all the affecteds in a pedigree.

Given the inheritance vector v , both S_{pairs} and S_{all} (Whittemore and Halpern, 1994; Kruglyak et al., 1996) are calculated using affecteds only. One may refer to such functions as *traditional* score functions. Each traditional score function may be extended in several ways incorporating, for instance, the set of unaffecteds into the analysis. For more information, see Ängquist (2006).

The relative performance of different score functions, in terms of statistical power, depends on the underlying genetic disease model λ and the pedigree set structure. Given λ it is possible to derive different kinds of *optimal* score functions (McPeck, 1999; Hössjer, 2003, 2005) which then implicitly leads to usage of both affecteds and unaffecteds. In applications the genetic model is

⁵Often restricted to increased sharing among affecteds.

⁶Considering locus x , formally $\exists i : P(v(x) = w_i | \text{MD}) = 1$, $w_i \in \mathbb{V}$, where \mathbb{V} is the set of possible inheritance vectors.

most oftenly not fully known leading to extensive usage of, often traditional, score functions which quite widely are accepted as intuitive, computationally feasible and performance-wise robust with respect to λ .

1.3 Test Statistics and Traditional Significance Calculations

In this context, to perform a statistical test the actual IBD-sharing in the pedigree set is calculated and compared, through a properly chosen *test statistic*, with the expected sharing under the null hypothesis. Throughout, we will use and discuss the score function-based *nonparametric linkage (NPL) score* approach described in, for instance, Kruglyak et al. (1996).

To ease interpretation and significance calculations we *standardize*, or alternatively worded *normalize*, the underlying score function under H_0 .⁷ The standardized score function is used to calculate, at locus x , the *pedigree-specific NPL score*,

$$Z(x) = \sum_w p_w(x) S(w), \quad w \in \mathbb{V}, \quad (3)$$

where the probabilities $p_w(x) = P(v(x) = w | MD)$ constitutes the inheritance distribution at x .

Remark 5. In (3) complete data corresponds to the simplified expression,

$$\exists w : Z(x) = S(w); \quad w \in \mathbb{V},$$

i.e. in this case $P(v(x) = w | MD) = 1$ for the only inheritance vector w consistent with marker data MD .

For a pedigree set consisting of N pedigrees all pedigree-specific scores (3) are combined into the (total) *NPL score* as,

$$Z(x) = \sum_{k=1}^N \gamma_k Z_k(x), \quad (4)$$

⁷Formally, $S(v) \mapsto \left(\frac{S(v) - \mu}{\sigma} \right)$, where μ and σ^2 are the mean and variance of S prior to standardization under the null hypothesis H_0 of no linkage. After standardization, we have $E(S|H_0) = 0$ and $V(S|H_0) = 1$.

where γ_k is the k^{th} pedigree weight.⁸

Calculating the NPL score (4) with respect to a set of loci $\mathbf{x} \in \Omega$ leads to the stochastic *NPL process* $Z(\mathbf{x}) = \{Z(x)\}_\Omega$. According to the blockwise inheritance of chromosomal segments, NPL scores at syntenic loci are correlated. Considering a genome scan over Ω , to being able to deal with the issue of inherent *multiple testing* one introduces the NPL process maximum over Ω ,

$$Z_{\max} = \max_{x \in \Omega} Z(x).$$

Now, significance calculations may be formulated and performed in a *point-wise* or *genome-wide* context, using the test statistics $Z = Z(x)$ and $Z = Z_{\max}$ respectively. The actual computations may be based on using either *Monte Carlo simulation* (Terwilliger et al., 1993; Ängquist and Hössjer, 2004) or *analytical approximations* (Tang and Siegmund, 2001; Ängquist and Hössjer, 2005).

Formally, for the score threshold T , we define the *significance level* of a test rejecting H_0 when $Z \geq T$ as,

$$\alpha(T) = P(Z \geq T | H_0), \quad (5)$$

when the null hypothesis is simple. Moreover, the corresponding *power function*,

$$\beta(T) = P(Z \geq T | \lambda); \lambda \in H_1,$$

depends on the genetic model λ . Given a test result $Z = z$, one may calculate the *p-value* associated with this result as $p(z) = \alpha(z)$.

2 Fuzzy Significance

Traditionally, using the rejection-based statistical testing paradigm one aims at, in each case, finding a simple answer like: Does our data support a rejection of our null hypothesis H_0 or not? The same principle underlies the somewhat generalized dogma of always, to almost any extent of effort, trying to find a *single p-value* to represent findings through data.

Our usage of the concepts of *fuzzy significance* or *fuzzy interpretations* corresponds to leaving this paradigm and adopting a more evidence-based

⁸To preserve the standardized properties, given perfect data, the *weighting scheme constraint* $\sum_{k=1}^N \gamma_k^2 = 1$ is used.

data approach. Of course, this comes with both the joy of advantages and at the cost of disadvantages. One may also note that we are not the first to adopt this view in linkage analysis (Thompson and Geyer, 2005; Thompson, 2006). A more general discussion of statistical evidence and evidence-based approaches is given in Taper and Lele (2004).

2.1 The Inheritance Distribution

When the inheritance distribution at a locus x ,

$$p_w(x) = P(v(x) = w | \text{MD}), \quad w \in \mathbb{V}, \quad (6)$$

is not a one-point distribution⁹ one faces imperfect data or, equivalently, the inheritance vector at x is ambiguous.

In this case, for a single pedigree on a single chromosome, the joint inheritance distribution with respect to the inheritance matrix (2) may be formulated as a *latent variable problem*. Here the marker data $\text{MD}(x)$ is the observable variable and the *true* inheritance vector $v(x)$ is the latent or hidden variable ($x \in \Omega$).

If using the *Haldane map function* (Haldane, 1919) one may interpret this as a time-homogeneous *hidden Markov model (HMM)* (Rabiner, 1989; Cappé et al., 2005). The actual computations of the joint inheritance distribution may be performed using the so called *Lander-Green algorithm* and its extensions (Lander and Green, 1987; Kruglyak et al., 1995; Kruglyak and Lander, 1998; Ziegler and Koenig, 2006).

The approach outlined here is an example of a *multipoint* analysis, i.e. that one, if needed, uses marker data $\text{MD}[c(x)]$ from the whole chromosome $c(x)$ when calculating the distribution $v(x)$. If only using the actual marker data $\text{MD}(x)$ at locus x leads to performing a *single-point* analysis.

2.2 Revisiting the Standard Approach

To be able to perform a statistical test one needs to define a problem-wise well-adjusted test statistic. How is that to be done in NPL-score based NPL analysis when the inheritance distribution shows ambiguity? At locus x , the standard or traditional approach (3) is to take the *expected value* of the

⁹In other words, when *at least* two distinct w -values have a positive probability given marker data MD.

pedigree-specific NPL scores with respect to the inheritance distribution at x , recapitulating (4),

$$Z(x) = \sum_w p_w(x)S(w) = E_w[S(w)], \quad w \in \mathbb{V}, \quad (7)$$

and then perform statistical tests or calculate p -values with respect to this, or functions of this, expected-value based statistic.

Although the procedure in (7) seems reasonable it is to some extent an arbitrary approach since no optimality behaviour is guaranteed. Moreover, the loss of information is, so to speak, masked or hidden through taking the expected value. Generally speaking, it may be argued that keeping the distribution of NPL scores $\{p_w(x), S(w); p_w(x) > 0\}$ in (7) is in this sense an intuitive procedure. One such approach is given in Thompson and Basu (2003), where the distribution of IBD-sharing-based scores are compared between the actually found distribution and a H_0 -simulated distribution conditioned on the same marker model and data availability.

2.3 Randomized Tests

As a preface to the fuzzy p -value discussion we will briefly outline the procedure of *randomized tests* (Lehmann, 1959; Geyer and Meeden, 2005).

When facing discrete-valued data it is only possible to perform *exact* significance tests on a countable number of distinct significance levels.¹⁰ For the complementary set of significance levels one may, in order to achieve exact significance tests, introduce randomness with respect to the testing procedure.

Definition 1 (Randomized Test). *Assume we want to perform a test on significance level α with respect to the test statistic $T(X)$, rejecting the null hypothesis for large values of $T(X)$. Assume that the statistic may attain a finite number of values $t_1 < t_2 \cdots < t_n$. Now, if*

$$P(T(X) \geq t_i) = f_i > \alpha$$

and

$$P(T(X) \geq t_{i+1}) = f_{i+1} < \alpha,$$

¹⁰If the number of distinct outcomes is a finite number n , then the number of possible distinct exact significance levels is n as well.

attaining outcome $T(x) = t_i$ one may, in order to get an exact significance test, reject the null hypothesis with probability $\left(\frac{\alpha - f_i}{f_{i+1} - f_i}\right)$.

Regarding the delicate outcome t_i in Definition 1, one may note that this in some sense relates to reversing the interpretation of p -values and dealing with an artificial outcome occurring with probability zero. This outcome may be seen as a hidden variable corresponding to the significance level α that may be seen as having a two-point p -value distribution with respect to f_i and f_{i+1} and their probabilities $\left(\frac{f_{i+1} - \alpha}{f_{i+1} - f_i}\right)$ and $\left(\frac{\alpha - f_i}{f_{i+1} - f_i}\right)$.

Note that statistical testing with a fixed α , i.e. rejection/non-rejection of a null hypothesis, calls for randomization only when having outcome t_i . If instead letting $\alpha \in [0, 1]$ being a variable one defines (two-point) p -value distributions with respect to the complete set of artificial scores corresponding to the whole interval, from 0 to 1, of significance levels α .

2.4 The Inheritance Distribution-Based Fuzzy p -Value

Generally one may generalize the concepts of the preceding subsection as follows:

Definition 2 (Fuzzy p -Value; General Version). *Assume that we want to base p -value calculations on a test statistic $T(X)$, where X is discrete-valued and hidden, but partially observable through Y . This is to be interpreted as that the probability distribution $P(X|Y = y)$ is computable. Now one may calculate a p -value distribution based on the set of scores $T(x_i)$ given that $P(X = x_i|Y = y) > 0$.*

In this paper we will apply Definition 2 to the same context as in Thompson and Geyer (2005) and Thompson (2006). This means that we define X to equal inheritance vectors $v(x)$ in (1) or inheritance matrices $v(\mathbf{x})$ in (2) and Y to equal the marker data $\text{MD}(x)$ or $\text{MD}(\Omega)$.¹¹ In this case the p -value distribution constitutes of the set of conditional p -values,

$$p(z|w) = \alpha [S(w)],$$

which is based on all distinct inheritance vectors w with positive probability given data, i.e the corresponding inheritance distribution (6), and the corresponding conditional scores $S(w)$ applied to the significance level function α given in (5)

¹¹This correspond to *local* and *global* testing respectively.

Alternative descriptions, of more or less similarity to our approach, are given in e.g. the following articles: Filzmoser and Viertl (2004) where the fuzziness arises according to uncertainties (vagueness) in data itself¹² and Geyer and Meeden (2005) which primarily focuses on fuzziness according to discreteness of data.¹³ A somewhat similar context is the construction of Bayesian p -values (Meng, 1994), where the inheritance distribution-equivalent corresponds to an underlying *prior* or *posterior* distribution. This may then be interpreted as a p -value distribution reflecting significance calculations under uncertainties with respect to specific parameters.

3 Fuzzy p -Values in Linkage Analysis

In Section 2.4 we introduced the *fuzzy p -value distribution* in the context of linkage analysis. Here this procedure is outlined in more detail and further extended. Moreover, complementary descriptive measures introduced in order to summarize the distribution in convenient and simple ways are introduced.

3.1 Properties and Interpretations

Given marker data MD, denote the number of consistent inheritance vectors with $|w|$. This gives us a sequence of p -values,

$$p(z|w_1), p(z|w_2), \dots, p(z|w_{|w|}),$$

with corresponding evidence-based weights $p_{w_1}, p_{w_2}, \dots, p_{w_{|w|}}$.¹⁴ Of course, compared to traditional single p -value calculations this p -value distribution gives a different, more abstract and less direct significance answer. Though the interpretation is in this sense vaguer one keeps all the *true* (non-transformed) inheritance information, leading to a more complete picture. This corresponds to a sliding focus from rejection-based hypothesis testing into a more evidence-based data oriented context.

¹²See also, for instance, Grzegorzewski (2000, 2001).

¹³They outline procedures of fuzzy alternatives and interpretations to both hypothesis testing, construction of confidence intervals as well as in the context of p -values. Note the correspondence to the concept of randomized tests in Section 2.3. This work was then applied to several nonparametric tests in Geyer (2005).

¹⁴Vaguely speaking, the weights are *evidence-based* in the sense of facilitating views as: 'With probability p_{w_i} the finding $p(z|w_i)$ is a valid or *true* interpretation.'

Remark 6. One may note that if $\min_i p(z|w_i) > \alpha$ or $\max_i p(z|w_i) \leq \alpha$ standard interpretations as non-rejection and rejection of corresponding statistical tests on level α is permissible.

3.2 Summarizing Measures

Given the p -value distribution one may construct *summarizing measures* based on this distribution in order to produce more easily interpretable complements to the distribution in itself. An unlimited number of alternatives exists. Examples include:

- Calculating the p -value *mean*, $\sum_{i=1}^{|w|} p(z|w_i)p_{w_i}$. This is similar but not equivalent to (7). Note the correspondence to the Bayesian formation of posterior means.
- Calculating specific *quantiles* of the p -value distribution, for instance, the median or the first/third quartile. Due to discreteness one may use, if needed, the randomization procedure previously described.
- Given a specific predefined *probability level* α , calculating $\sum_{w_i \in A} p_{w_i}$, where $A = \{w_i; p(z|w_i) \leq \alpha\}$.

	p_{w_i}	$p(z^1 w_i)$	$p(z^2 w_i)$	$p(z^3 w_i)$
w_1	1/16	0.150	0.040	0.100
w_2	1/16	0.150	0.035	0.010
w_3	1/16	0.150	0.030	0.100
w_4	2/16	0.100	0.025	0.050
w_5	2/16	0.100	0.020	0.005
w_6	2/16	0.100	0.015	0.050
w_7	3/16	0.050	0.010	0.050
w_8	4/16	0.010	0.005	0.005

Table 1: An artificial example of constructing an overall p -value distribution based on three distinct score functions and 8 distinct inheritance vectors, more or less probable, consistent with data.

3.3 Extensions

Using the fuzzy p -value approach, i.e. the full p -value distribution, we do not remove the uncertainty with respect to the evidence for linkage from our findings. Apart from this uncertainty the final evidence also clearly depends on the source responsible for producing them, i.e. the choice of score function. The performance of a specific score function varies across true, but hidden, genetic disease models. With this in mind it might seem appealing to merge the p -value distributions produced using several distinct score functions into an overall distribution.

Algorithm 1 (Overall p -Value Distribution). *Assume $|S|$ distinct score functions.*

Step 1 *For each score function S^j , $j = 1, 2, \dots, |S|$, divide all corresponding p -value weights with $|S|$. Explicitly, $p_{w_i}^j \mapsto p_{w_i}^j/|S|$, $i = 1, 2, \dots, |w|$.*

Step 2 *Merge all previously found p -values into an overall distribution. Explicitly, this distribution is based on $p(z^j|w_i)$, $j = 1, 2, \dots, |S|$ and $i = 1, 2, \dots, |w|$, with the corresponding new weights from Step 1.*

One might note that: (i) The inheritance distribution is the same though the score functions, and therefore the results, changes. This implies that exactly the same inheritance vectors $w_1, w_2, \dots, w_{|w|}$, and weights, are used throughout Algorithm 1. (ii) Of course, not all p -values or corresponding weights are numerically distinct. If not, the distribution is formed by summing the appropriate weights corresponding to similar p -values.

4 An Artificial Example

Next, we will give an artificial example in order to show how the techniques outlined in this section works. The basic data in the form of p -values and corresponding weights is given in Table 1 and the three individual, as well as the overall, p -value distributions are displayed in Figure 1. Note that in this case $|S| = 3$ and $|w| = 8$.

Using some of the summarizing measures previously described in Section 3.2 on these distributions gives: (i) The minimum p -values $\min_i p(z|w_i)$ are 0.01, 0.005 and 0.005 in the three individual cases. (ii) The maximum p -values $\max_i p(z|w_i)$ are similarly 0.15, 0.04 and 0.10. Here the second

score functions produces results that may be interpreted as clear evidence for rejecting a standard test for no linkage on the 5%-level. (iii) The mean p -values $\sum_i p(z|w_i)p_{w_i}$ are 0.0775, 0.0172 and 0.0369 respectively. The overall mean is 0.0439. (iv) Given the probability level $\alpha = 0.05$ and letting $A = \{w_i; p(z|w_i) \leq \alpha\}$ the probabilities $\sum_{w \in A} p_w$ are 0.4375, 1 and 0.8750. The overall probability is 0.7708.

In this case the three score functions provide us with quite similar results, though the evidence for linkage is strongest using S^2 , followed by using S^3 and S^1 . The overall evidence indicates, but is not truly convincing, possible linkage at this (artificial) locus.

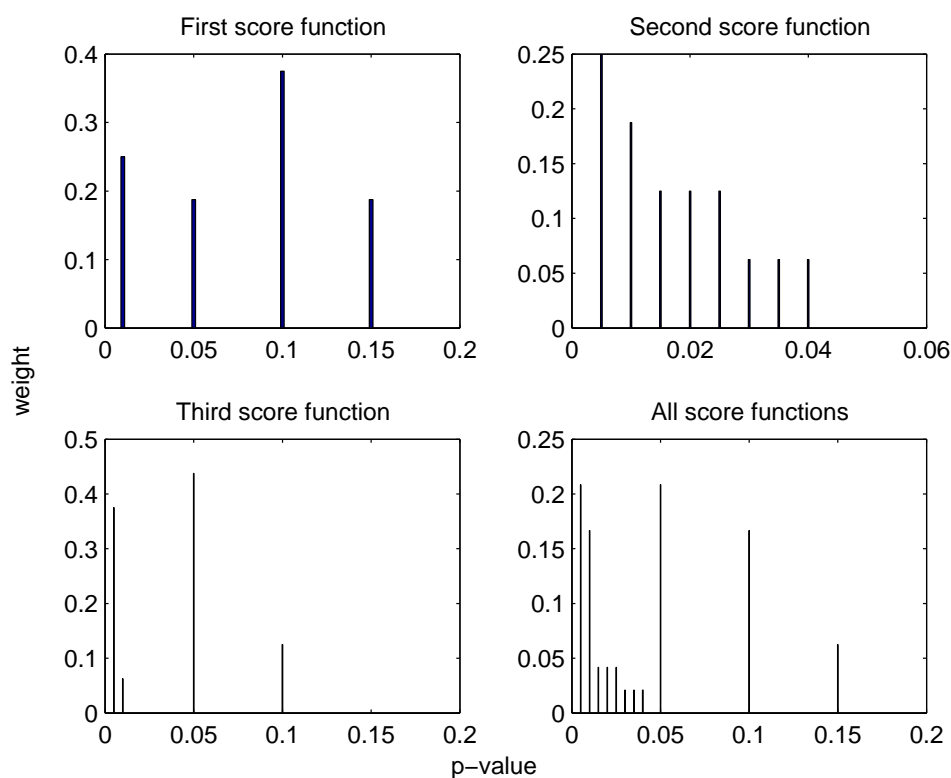


Figure 1: The three individual, and the merged overall, p -value distributions with respect to the data given in Table 1.

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A Some Notes on Types of Significance Calculations

In this text we have not explicitly suggested *which type* of significance calculations to perform. For instance one may: (i) Calculate p -values at all included markers and then draw evidential conclusions. (ii) Choose one marker according to some summarizing criterion, for instance using the standard genome-wide maximum Z_{\max} based on (4), and then produce p -value distributions at this marker.¹⁵

One may also note that the actual significance figures may be presented on either a *pointwise* or a *genome-wide* scale. We suggest the latter approach which in a general sense, more or less, corrects for multiple testing according to scanning through multiple markers.

¹⁵One may also use several *interesting* markers by adjusting the criterion to choose markers corresponding to, for instance, the k largest standard NPL scores.