Searching for genetic interactions in complex disease by using distance correlation

Fernando Castro-Prado,
University and Health Research Institute of Santiago de Compostela, Spain.
E-mail: f.castro.prado@usc.es
Javier Costas
Health Research Institute of Santiago de Compostela, Spain.
and Wenceslao González-Manteiga and David R. Penas
University of Santiago de Compostela, Spain.

Summary. Understanding epistasis (genetic interaction) may shed some light on the genomic basis of common diseases, including disorders of maximum interest due to their high socioeconomic burden, like schizophrenia. Distance correlation is an association measure that characterises general statistical independence between random variables, not only the linear one. Here, we propose distance correlation as a novel tool for the detection of epistasis from case-control data of single nucleotide polymorphisms (SNPs). This approach will be developed both theoretically (mathematical statistics, in a context of high-dimensional statistical inference) and from an applied point of view (simulations and real datasets).

Keywords: Association measures; Distance correlation; Epistasis; Genomics; High-dimensional statistical inference; Schizophrenia

1. Introduction

The application field that motivates the present article is going to be explained hereinafter. The starting point is a genomic problem, whose importance and interest will be addressed. In addition, the state of the art on this field of knowledge will be summarised; underscoring one of the most recent techniques, which has a strong theoretical basis. Upon this, some hypotheses will be made.

1.1. Epistasis in complex disease

The role of heredity in psychiatry has been studied for almost a century, with Pearson (1931) not having “the least hesitation” in asserting its relevance. Today it is known that a majority of psychiatric disorders are multifactorial, complex traits. They occur as a result of a combination of genetic and environmental factors, none of which are necessary or sufficient. Furthermore, the individual effect of each of them is generally trifling. More
precisely, the genome can explain up to 80 % of the susceptibility to suffer some of these diseases, like schizophrenia (Sullivan et al., 2018).

The genetic susceptibility to a psychiatric disorder lies on a large number of variants along the genome. Although the specialised literature usually focuses simply on additive models (Purcell et al., 2009), biological knowledge suggests that gene-gene interactions (or epistasis) could be one of the factors that explain the phenomenon of missing heritability, which contributes to the inefficiency of genome-wide association studies (GWAS) when it comes to explaining causality of complex diseases (Manolio et al., 2009; Gusareva and Van Steen, 2014).

The Psychiatric Genetics Laboratory of the Santiago de Compostela Health Research Institute has produced datasets of case-control GWASs (i.e., they have genotyped “healthy” and “sick” individuals) for schizophrenia. The statistical challenge hinges on using this data to detect pairs of alleles that significantly increase or decrease the susceptibility to develop schizophrenia, to then confirm those findings with biological criteria such as: coincidence on the same metabolic pathway, union of proteins to form complexes, and gene co-expression in space (on the same region of the brain) and time.

This data corresponds to coding single-nucleotide polymorphisms (SNPs), which are variants on one of the “letters” of the DNA regions that are transcribed into messenger RNA, thereby yielding protein products. More specifically, only autosomal variants are considered, which means that each individual can carry 0, 1 or 2 copies of the minor allele (the least frequent of the two variants) on their diploid genome.

The aforementioned setting requires performing statistical inference in a context of high dimension and low sample size, where the covariates are ternary (discrete with support of cardinality 3).

1.2. Statistical approaches to epistasis detection

The recent development of the “-omic” disciplines has been parallel to the creation of bioinformatic tools to process the vast amount of data that these experimental sciences produce. The diversity of the available “-omic” software is so large that it has even been necessary to develop meta-tools to index the existing techniques. For example, the directory of one of them (Henry et al., 2014) contains more than 20 000, 900 of which are designed for GWAS data analyses, which in turn contain a subset of 100 that are suitable for epistasis detection.

The existence of such a wide spectrum of proposed solutions for such a specific task owes to the surprising diversity of statistical methods that are valid for it—e.g. linear models (standard and generalised), logistic regression, tests on Pearson’s correlations, permutation tests, Bayesian nonparametric statistical inference, random forests, Markov chains, co-information indices, graph theory, and maximal entropy probability models.

Another cause of that diversity of alternatives is the fact that some of the available techniques only focus on a specific subproblem (pairwise gene-gene interactions versus higher orders, binary versus continuous response variable, pedigrees, stratified populations and so forth) and on the different computing strategies that they use in order to obtain results within reasonable amounts of time (for instance, biology-based initial filters, code parallelisation, graphical processing units, Boolean operations, machine learning approaches, and ant colony optimisation algorithms).
Finding gene-gene interactions via distance correlation

Table 1 summarises some of the existing methods, including the ones reviewed by Gusareva and Van Steen (2014) and Niel et al. (2015) and some other that are representative.

Anyhow, a thorough discussion of the 100 epistasis detection tools goes beyond the scope of the present article. Instead, only the results and conclusions of each paper were inspected, with the goal of filtering out the less efficient and representative ones. However, this strategy turned out to be scarcely satisfactory because the vast majority of such papers claim that the tool they are presenting performs better than the preexisting ones. Of course, this circumstance does not mean that methodological breakthroughs are being made every few months, but rather that there is no standard way of comparing epistasis detectors.

Firstly, there are differences in the relative importance that is given to speed and accuracy. On top of that, while speed can be measured objectively (quantifying computing time, whose definition is unambiguous), the interpretation of what efficiently detecting epistasis means varies substantially across authors, since there is no consensus on which data or models should be used for validation.

Table 1. Some remarkable epistasis detection tools for GWAS data analysis

| Tool       | Statistical techniques       | Computational tricks                  | Reference                        |
|------------|------------------------------|---------------------------------------|----------------------------------|
| BEAM       | Bayesian MCMC                | None                                  | Zhang and Liu (2007)             |
| BOOST      | Logistic regression          | Boolean operations, parallelisation   | Wan et al. (2010)                |
| BiForce    | Linear regression            | Boolean operations, parallelisation   | Gynesei et al. (2012)            |
| CES        | Evolutionary algorithms      | Artificial intelligence               | Moore and Hill (2015)            |
| EpiGPU     | Linear regression            | GPU architectures                      | Hemani et al. (2011)             |
| EpiACO     | Information theory           | Ant colony optimisation               | Sun et al. (2017)                |
| EpiBlaster | Pearson’s correlations       | GPU architectures                      | Kam-Thong et al. (2011)          |
| GLIDE      | Linear regression            | GPU architectures                      | Kam-Thong et al. (2012)          |
| GWIS       | ROC curve analysis           | GPU architectures                      | Goudey et al. (2013)             |
| IndOR      | Logistic regression          | Pre-filtering                         | Emily (2012)                     |
| MDR        | Combinatorics, resampling    | Pre-filtering                         | Ritchie et al. (2001)            |
| Random Jungle | Random forests             | Parallelisation                        | Schwarz et al. (2010)            |

1.3. Large-scale correlation tests (LCTs)

On Table 1, it is shown that one conspicuous epistasis detector (Kam-Thong et al., 2011) is based on scanning for differential behaviours of (Pearson’s) correlations between cases and controls. This is unsurprising, since several authors (De la Fuente, 2010; Camacho et al., 2005; D’Haeseleer et al., 2000) support the idea of correlation tests in this context when the data is continuous (gene expression, metabolomics and so forth), which however is not the case of SNPs (ternary variables).

Moreover, such techniques usually rely on the normality of the covariates, a hypothesis that turns out to be excessively restrictive in most cases. Therefore, the procedure by Cai and Liu (2016) contains an interesting approach, as they manage to establish a rigorous theoretical framework for the kind of correlation tests that are convenient for epistasis detection. This recent technique is part of the hot topic of hypothesis testing on high-dimensional covariance structure, that has been developed almost from scratch during the past few years (Cai, 2017).
Given \( L \in \mathbb{Z}^+ \) SNPs, let \( X = (X_j)_{j=1}^L \) and \( Y = (Y_j)_{j=1}^L \) be the corresponding random vectors of 0’s, 1’s and 2’s for case and control individuals, respectively. Some authors, like Kam-Thong et al. (2011), argue that treating these clearly discrete data as continuous is an acceptable simplification. Nevertheless, even if that could be anecdotally true in some specific setting, it will be shown below that this it is not the case.

The notation for the correlation matrices for \( X \) and \( Y \) will be:

\[
(\rho_{ij})_{i,j} \in \mathbb{R}^{L \times L} \quad \text{and} \quad (\hat{\rho}_{ij})_{i,j} \in \mathbb{R}^{L \times L}.
\]

The aim is testing:

\[
\begin{align*}
H_{0ij} & : \rho_{ij1} = \rho_{ij2} \\
H_{1ij} & : \rho_{ij1} \neq \rho_{ij2}
\end{align*}
\]

for each pair \((i,j) \in ([1,L] \cap \mathbb{Z})^2\) so that \(i < j\); using samples \(\{X_k\}_{k=1}^{n_1}\) IID \(X\) and \(\{Y_k\}_{k=1}^{n_2}\) IID \(Y\), which are assumed to be independent of each other.

### 1.3.1. LCT: classical approach

A scarcely innovative approach would be to stabilise the variance of the sample correlation coefficients via Fisher’s \(Z\) transformation (\(\text{atanh}\)). One could think of combining this strategy with a procedure that controls the false discovery rate (FDR), such as the ones by Benjamini and Hochberg (1995) or Benjamini and Yekutieli (2001), thus establishing the desired large-scale correlation test (LCT). The main drawback to this idea is that, when normality is not ensured, the behaviour of the test statistic differs from the well-known asymptotic distribution of the Gaussian case. Simulation studies (Cai and Liu, 2016) show that this method performs very poorly (both with Benjamini–Hochberg and Benjamini–Yekutieli), especially when compared to the LCTs that will be introduced next.

### 1.3.2. LCT with normal approximation (LCT-N)

The first test that Cai and Liu (2016) devised, the LCT-N, is based on the test statistic

\[
T_{ij} := \frac{\hat{\rho}_{ij1} - \hat{\rho}_{ij2}}{\sqrt{\hat{s}_{\rho_{ij1}} \left(1 - \hat{\rho}_{ij1}^2\right)^2 + \hat{s}_{\rho_{ij2}} \left(1 - \hat{\rho}_{ij2}^2\right)^2}},
\]

where \(\hat{s}_{\rho_{ij1}}\) and \(\hat{s}_{\rho_{ij2}}\) are the respective sample kurtoses of \(X\) and \(Y\), and \(\hat{\rho}_{ijl}\) is a thresholded version of \(\hat{\rho}_{ijl}\), for \(l \in \{1,2\}\); with \(\hat{\rho}_{ijl}^2 := \max\{\hat{\rho}_{ij1}^2, \hat{\rho}_{ij2}^2\}\).

\(H_{0ij}\) will be rejected when \(|T_{ij}|\) is greater than a certain threshold \(\hat{t}_\alpha \in \mathbb{R}^+\), which depends on the nominal value \(\alpha \in [0,1]\) under which one wants to maintain the FDR. The formula for computing \(\hat{t}_\alpha\) works under the assumption that the initial distributions are Gaussian or are not very far away from being so (elliptical contours). Consequently, the LCT-N should not be used in other contexts.
1.3.3. **LCT with bootstrap (LCT-B)**

If the distributions of $X$ and $Y$ are totally unknown, it is reasonable to use resampling techniques in order to approximate the tail of the distribution of $T_{ij}$, which determines $\hat{t}_\alpha$. The bootstrap scheme that Cai and Liu (2016) built to this purpose is consistent and leads to a threshold $\hat{t}_\alpha^*$, which defines the LCT-B. This test is supported by strong theoretical results, that were proven by the original authors.

1.3.4. **Unsuitability of LCTs for SNP data**

LCTs have been implemented in the $R$ programming language for the purposes of the present article. In order to check the validity of the code, the real-data example on the original article was reproduced step by step, obtaining an adjacency matrix (Fig. 1a) that is identical to the one in Cai and Liu (2016).

![Adjacency matrix of the putative epistatic network detected by the LCT-B, for (a) gene expression data for prostate cancer (Broad Institute) and (b) SNP data for schizophrenia (Health Research Institute, Santiago de Compostela)](image)

Namely, the database is the one by Singh *et al.* (2002), in which dimensionality was trimmed down to 500 using the Welch–Satterthwaite test (Behrens–Fisher problem). Since the variables involved are assumed to be continuous, the LCT-B yields believable results; in the sense that the resulting matrix is sparse, but not too much. However, a biological validation of all those results would be extremely difficult to accomplish.

On the other hand, when the schizophrenia SNP data (remarkably discrete) are analysed, the adjacency matrix looks very differently (Fig. 1b) to the previous one (Fig. 1a). The only nonzero elements are close to the diagonal, owing to the fact that the only pairs that are being detected are in linkage disequilibrium (i.e., the frequency of such SNP pairs is significantly different from the product of the marginal frequencies, due to their physical proximity within a certain chromosome). Such findings are useless from the point of view of psychiatric genetics because they do not show an association that is related to schizophrenia, but rather one that is independent of this disease.
The unsatisfactory behaviour of one of the most robust techniques for epistasis detection (when applied to a different setting from the one it was originally intended to) is the main motivation of the present article and, particularly, of its initial hypotheses.

1.4. Motivation
Considering the background that has been given, it is justified to wonder:

(a) Which association measures characterise the independence of ternary variables?
(b) How can the LCTs by Cai and Liu (2016) be extended to less stringent conditions so that they become applicable to SNP data?
(c) Will it be possible to produce a procedure that is adaptable to the kind of interaction that is being searched for?
(d) Will that method perform satisfactorily, both in terms of significance level calibration and of power?
(e) Will any identified (putative) interactions make sense from a biological point of view?

The scope of this work will be address the questions above, using a distance correlation-based approach, aided by high-performance computing techniques. The remainder of the paper is organized as follows. Section 2 summarises the state of the art in the characterisation of independence in metric spaces. Section 3 provides a detailed description of a novel testing procedure for independence in ternary data. The results of a modest simulation study are reported in Section 4. In Section 5, we apply the method to a genomic dataset of schizophrenia. Concluding remarks are given in Section 6.

2. Distance correlation in metric spaces

The energy of data (Székeley and Rizzo, 2017) is a branch of mathematical statistics that has been recently developed and it includes the characterisation of statistical independence in Euclidean spaces via an association measure called distance correlation.

The extension of distance correlation to metric spaces is a nontrivial issue, that will be concisely summarised hereinafter. For a more detailed review of this theoretical framework, please refer to Castro-Prado and González-Manteiga (2020).

2.1. Distance correlation in Euclidean spaces

When two random elements (vectors) \( X \) and \( Y \) are Euclidean-space-valued (let \( X \) be \( L \)-dimensional and \( Y \) be \( M \)-dimensional, for \( L, M \in \mathbb{Z}^+ \)), it is possible to define an association measure that characterises their independence that is called distance correlation (Székeley et al., 2007). Firstly, distance covariance should be defined, as a certain norm of the difference of the joint characteristic function and the product of the marginals:

\[
d\text{Cov}(X, Y) := \| \varphi_{X,Y} - \varphi_X \varphi_Y \|_w = \sqrt{\int_{\mathbb{R}^L \times \mathbb{R}^M} |\varphi_{X,Y}(t,s) - \varphi_X(t)\varphi_Y(s)|^2 w(t,s) \, dt \, ds};
\]
where \(w\) is a weight function which is dependent of the dimension of the Euclidean spaces in which the supports of \(X\) and \(Y\) are contained. As usually:

\[
\varphi_X(t) := E[\exp(i\langle t, X \rangle)], \ t \in \mathbb{R}^L.
\]

Logically, distance correlation is defined as the quotient of variance and the product of standard deviations (as long as none of the latter vanish):

\[
dCor(X, Y) := \frac{dCov(X, Y)}{\sqrt{dCov(X, X) dCov(Y, Y)}},
\]

and so it has no sign. It is an improved version of the square of Pearson’s correlation squared because it has values in \([0,1]\) and, more importantly, it is zero if and only if \(X\) and \(Y\) are (statistically) independent.

However convoluted the initial definition of \(dCor\) is, the sample version can easily be computed. Given a paired sample \((X_1, Y_1), \ldots, (X_n, Y_n)\) IID \((X, Y)\); let \(a_{ij} := d(X_i, X_j)\) be the Euclidean distances between the \(X\)’s with indices \(i,j \in [1,n] \cap \mathbb{Z}\). Then, the doubly-centred distances are:

\[
A_{ij} := a_{ij} - \frac{1}{n} \sum_{k=1}^{n} a_{ik} - \frac{1}{n} \sum_{k=1}^{n} a_{kj} + \frac{1}{n^2} \sum_{k,l=1}^{n} a_{kl}
\]

If \(\{b_{ij}\}_{i,j}\) and \(\{B_{ij}\}_{i,j}\) are analogously defined for \(\{Y_i\}_i\), the empirical distance covariance is the nonnegative square root of:

\[
\widehat{dCov}_n(X, Y)^2 := \frac{1}{n^2} \sum_{i,j=1}^{n} A_{ij} B_{ij}
\]

The above estimator is reminiscent of the following alternative representation of \(dCov^2:\)

\[
dCov(X, Y)^2 = E\left\{ \left( d(X, X') - E[d(X, X'')] - E[d(X', X'')] + E[d(X'', X'')] \right) \right. \\
\times \left. \left( d(Y, Y') - E[d(Y, Y'')] - E[d(Y', Y'')] + E[d(Y'', Y'')] \right) \right\},
\]

which is valid as long as moments of order 2 are finite (Jakobsen, 2017). Primed letters refer to IID copies of the corresponding random vector.

Whenever \(\{X, Y\}\) are independent and have finite first moments, the asymptotic distribution of the product of a scaled version of the preceding statistic is a linear combination of independent chi-squared variables with one degree of freedom. More precisely:

\[
n \widehat{dCov}_n(X, Y)^2 \xrightarrow{D} \sum_{j=1}^{\infty} \lambda_j Z_j^2,
\]

where \(\{Z_j\}_j\) are IID \(\mathcal{N}(0, 1)\) and where \(\{\lambda_j\}_j \subset \mathbb{R}^+\). Unfortunately, this null distribution is not useful in practice.

Instead, it is resampling techniques that should be used. The most sensible choice when it comes to approximating the null distribution of the test statistic is to base the design of the resampling scheme on the information that \(H_0\) provides, which in this case (independence) leads to permutation tests.
2.2. The generalised distance covariance

Let $\theta$ be a (Borel) probability distribution on $\mathcal{X} \times \mathcal{Y}$, where $(\mathcal{X}, d_\mathcal{X})$ and $(\mathcal{Y}, d_\mathcal{Y})$ are separable metric spaces. Its distance covariance is defined as:

$$
dcov(\theta) := \int_{(\mathcal{X} \times \mathcal{Y})^2} d_\mu(x, x') d_\nu(y, y') d\theta^2((x, y), (x', y')), $$

where $(\mu, \nu)$ are the marginals of $\theta$ on $(\mathcal{X}, \mathcal{Y})$ and are assumed to both have finite first moments (Lyons, 2013; Jakobsen, 2017). Functions $d_\mu$ and $d_\nu$ are the doubly-centred versions of $d_\mathcal{X}$ and $d_\mathcal{Y}$ respectively:

$$
d_\mu: \mathcal{X} \times \mathcal{X} \to \mathbb{R} \quad (x_1, x_2) \mapsto d_\mathcal{X}(x_1, x_2) - a_\mu(x_1) - a_\mu(x_2) + D(\mu);$$

where:

$$
a_\mu: \mathcal{X} \to \mathbb{R} \quad x \mapsto \int_{\mathcal{X}} d_\mathcal{X}(x, x') d\mu(x');$$

$$
D(\mu) := \int_{\mathcal{X}} a_\mu d\mu = \int_{\mathcal{X}^2} d_\mathcal{X} d\mu \times \mu.
$$

Like ordinary covariance, $dcov$ vanishes under independence as a result of Fubini’s theorem:

$$
dcov(\mu \times \nu) = \{D(\mu) - 2D(\mu) + D(\mu)\}\{D(\nu) - 2D(\nu) + D(\nu)\} = 0.
$$

2.3. Distance covariance in negative type spaces

The fact that:

$$
\theta = \mu \times \nu \Rightarrow dcov(\theta) = 0,
$$

makes it natural to wonder which spaces ensure that the reciprocal implication also holds. The answer is: strong negative type spaces, since in them $dcov(\theta)$ can be presented as an injective function of $\theta - \mu \times \nu$.

A metric space $(\mathcal{X}, d_\mathcal{X})$ is said to be of negative type if and only if:

$$
\forall n \in \mathbb{Z}^+; \forall x, y \in \mathcal{X}^n: \quad 2 \sum_{i,j=1}^{n} d_\mathcal{X}(x_i, y_j) \geq \sum_{i,j=1}^{n} \{d_\mathcal{X}(x_i, x_j) + d_\mathcal{X}(y_i, y_j)\}.
$$

There are many familiar examples of negative type spaces, like the Euclidean ones and, more generally, all Hilbert spaces.

If $(\mathcal{X}, d_\mathcal{X})$ has negative type, the following inequality holds for any probability distributions $\mu_1, \mu_2$ on $\mathcal{X}$ with finite first moments:

$$
D(\mu_1 - \mu_2) \leq 0.
$$

On top of that, if the operator $D$ separates probability measures (with finite first moments) in $(\mathcal{X}, d_\mathcal{X})$, that space is said to have strong negative type:

$$
D(\mu_1 - \mu_2) = 0 \Leftrightarrow \mu_1 = \mu_2.
$$
Whenever $X$ and $Y$ have strong negative type,
\[ \text{dcov}(X,Y) \overset{\text{def.}}{=} \text{dcov}(\theta) = 0 \iff X, Y \text{ independent}, \]
for any random element $(X, Y) \sim \theta$ with values in $\mathcal{X} \times \mathcal{Y}$.

2.4. Nonparametric test of independence in metric spaces
For $n \in \mathbb{Z}^+$, the empirical measure associated to a certain sample
\[ \{(X_i, Y_i)\}_{i=1}^n \overset{\text{IID}}{\sim} (X, Y) \sim \theta \]
is defined as customarily:
\[ \theta_n := \frac{1}{n} \sum_{i=1}^n \delta_{(X_i, Y_i)}, \]
where $\delta_z$ denotes point mass at $z \in \mathcal{X} \times \mathcal{Y}$.

It is easy to see that the natural estimator $\text{dcov}(\theta_n)$ is the $V-$statistic with (nonsymmetric) kernel $h$:
\[ \text{dcov}(\theta_n) = \frac{1}{n^6} \sum_{i=1}^n \sum_{i=1}^n h((X_i, Y_i)_{\lambda=1}^6) \equiv V_n^6(h), \]
with $h$ being given by:
\[ h : (\mathcal{X} \times \mathcal{Y})^6 \rightarrow \mathbb{R} \]
\[ \{(x_i, y_i)\}_{i=1}^6 \mapsto \{d_\mathcal{X}(x_1, x_2) + d_\mathcal{X}(x_3, x_4) - d_\mathcal{X}(x_1, x_3) - d_\mathcal{X}(x_2, x_4)\} \times \{d_\mathcal{Y}(y_1, y_2) + d_\mathcal{Y}(y_5, y_6) - d_\mathcal{Y}(y_1, y_5) - d_\mathcal{Y}(y_2, y_6)\}. \]

If $\theta$ is the product of its marginals and these are nondegenerate, the asymptotic null distribution of the $V-$statistic is:
\[ nV_n^6(h) \xrightarrow{\mathbb{D}} \sum_{i=1}^\infty \lambda_i(Z_i^2 - 1) + D(\mu)D(\nu); \]
where $\{Z_i\}_{i \in \mathbb{N}} \overset{\text{IID}}{\sim} \mathcal{N}(0, 1)$ and where $\{\lambda_i\}_{i \in \mathbb{N}} \subset \mathbb{R}$ are unknown (dependent on $\theta$).

The most logical approach is, once again, resorting to permutation tests.

3. Distance correlation-based test for epistasis
Thus far, the theoretical basis for the usage of distance correlation within certain metric spaces has been set. Upon this, extensions and applications can be formulated. There are not many examples of this in the literature, the most relevant ones being in the fields of time series (Davis et al., 2018) and of discretised stochastic processes (Dehling et al., 2020).

What is about to be presented is the particularisation of the theoretical framework to spaces of cardinality 3, to then design a procedure that is adapted to epistasis detection and that at the same time solves the inadequacy of the tests by Cai and Liu (2016) to this setting (as shown on Fig. 1).
3.1. Distance correlation in spaces of cardinality 3

Clearly, in a finite space, the finiteness of moments (of any order) and separability are not an issue. Alternatively, one can resort to brute-force and solve the system of inequations that are derived from simply using the definitions (Klebanov, 2005; Lyons, 2013), obtaining a direct—albeit cumbersome—proof of the fact that any 3-point space $(\mathcal{X}, d_{\mathcal{X}})$ is necessarily of strong negative type. Such proof is, in principle, superfluous, as long as one wants to make use of strong theorems, such as Schoenberg’s: $(\mathcal{X}, \sqrt{d_{\mathcal{X}}})$ can clearly be embedded into a Hilbert space, isometric to the vertices of a triangle in $\mathbb{R}^2$ (note that the square root transformation preserves the triangle inequality of the metric). Nevertheless, it is interesting to check that, when the metric structure becomes so simple, abstract arguments (such as the ones that arise in the proof of Schoenberg’s theorem) become unnecessary. In light of this, the study of the mathematical statistics behind energy statistics in the context of 3-point spaces may well be a promising line for future research.

Let $\mathcal{X} := \{0, 1, 2\}$ be the set of the three possible genotypes for each SNP. There is no biological reason to assume that $2 \in \mathcal{X}$ copies of the minor allele affect twice as much as one (Bush and Moore, 2012), neither when it comes to increasing the susceptibility to a psychiatric disorder nor to decreasing it. As a matter of fact, in some cases this susceptibility is maximal under heterozygosis (Costas et al., 2011), which is coded by $1 \in \mathcal{X}$.

Therefore, there is no rationale for prioritising the Euclidean distance:

$$d(0, 2) = 2d(0, 1) = 2d(1, 2),$$

instead of more general (non-“linear”) metric spaces. And this is why distance correlation turns out to be a way to extend the ideas of Cai and Liu (2016). As previously commented, the marked discreteness of SNP data provides another incentive for transcending the idea of linear correlation.

No specific type of interaction is being looked for—the aim is to simply detect epistasis. For this reason, and also for the sake of reducing the computational costs, the equilateral distance will be the one used in every simulation:

$$d(0, 1) = d(1, 2) = d(0, 2) = 1.$$ 

Three further conspicuous distances are to be defined, which are the degenerate ones (in which two of the vertices of the triangle are the same point), that will be especially illustrative in the analysis of real data because they allow a straightforward interpretation of the allelic model that is being studied:

(a) Recessive (distance “0=1”): $d(0, 1) = 0; \ d(0, 2) = d(1, 2) = 1.$

(b) Heterozygous (distance “0=2”): $d(0, 2) = 0; \ d(0, 1) = d(2, 1) = 1.$

(c) Dominant (distance “1=2”): $d(1, 2) = 0; \ d(1, 0) = d(2, 0) = 1.$

3.2. Proposal of a hypothesis test

Searching for epistasis consists in looking for differential dependence structures between the case and control groups, as previously discussed. To simplify notation, let $Z_i$ and $Z_j$
be random variables with support \( Z \in \{ X, Y \} \), corresponding to two different SNPs, for which a joint sample of size \( n \in \mathbb{Z}^+ \) is available:

\[
(Z_{i,1}, Z_{j,1}), \ldots, (Z_{i,n}, Z_{j,n}) \text{ IID } (Z_i, Z_j).
\]

The aim is testing

\[
H_{0ij} : Z_i, Z_j \text{ independent}
\]

or, equivalently,

\[
\begin{cases}
H_{0ij} : \text{dcov}(Z_i, Z_j) = 0 \\
H_{1ij} : \text{dcov}(Z_i, Z_j) \neq 0
\end{cases}
\]

with the philosophy of the large-scale multiple tests by Cai (2017).

In order to approximate the null distribution of the test statistic \( \hat{\text{dcov}}(Z_i, Z_j) \), it is sensible to devise a resampling scheme according to the relevant information that is available under the null hypothesis, which in this case is the independence of \( Z_i \) and \( Z_j \). As a result, the reasonable thing to do is not to resample from \( \{(Z_{i,k}, Z_{j,k})\}_k \), but to do it separately from \( Z_i := \{Z_{i,k}\}_k \) and \( Z_j := \{Z_{j,k}\}_k \) (permutation tests). Thus, it suffices to compute \( B \in \mathbb{Z}^+ \) statistics \( \hat{\text{dcov}}(Z_{i}^{(b)}, Z_{j}^{(b)}) \) to obtain a Monte–Carlo approximation of the sampling distribution of the empirical distance covariance under \( H_{0ij} \).

Given \( L \) SNPs, \( L^2 - L \) independence tests have to be performed, half of them in the case group (the \( X \)'s) and the other half for the controls (the \( Y \)'s). In a second stage, the absence of epistasis between two SNPs will be rejected whenever the independence is rejected for sick individuals and not for healthy ones, or vice-versa.

Such a two-step procedure requires the significance threshold for the first step to be a modification of the nominal significance level. In order to accomplish such a control of the family-wise error rate (FWER), the Bonferroni correction will be used. The correction by Šidák (1967) could be an alternative, as in practice it performs in a similar fashion.

### 3.3. Methodological discussion of the proposed test

Prior to justifying that the technique that is introduced in this paper is well-behaved, it should be noted that the usage of distance correlation in discrete spaces (in genomics or elsewhere) —and, in particular, its application to the search for SNP-SNP interactions— has no precedents in literature, as it can be checked by going through all the articles that cite Lyons (2013) (more than 100) or Székely et al. (2007) (almost 1000). Moreover, no previously published research has attempted to perform large-scale multiple testing with any of the techniques derived from energy statistics (Székely and Rizzo, 2017).

It is crucial to note that the procedure that has been presented uses a sequential approach instead of directly testing for the equality of distance correlations, as Cai and Liu (2016) did, following the rationale by De la Fuente (2010) and others. In the present article, it has been taken into account that not every significant difference in (distance) correlations reflects epistasis, but only those in which one of the values is close to zero and the other is not. It is especially important not to forget this assumption in the case of distance correlation because, whereas its nullity characterises independence, the interpretation of how large or small its values are does not yield a simple way of analysing the intensity of dependence (unlike in the linear case) and, what is more, it produces some counter-intuitive phenomena (Székely and Rizzo, 2013).
The usage of permutation tests in this context of metric spaces was inspired by the excellent performance of the same scheme in Euclidean spaces (Szekely et al., 2007; Szekely and Rizzo, 2017). It has the drawback that there is not the same kind of fully-fledged formal justification of consistency (as the one by Arcones and Giné [1992] for the naïve bootstrap that Jakobsen [2017, page 100] outlined), which should not be a source of concern in practice, like in the Euclidean case. Some preliminary experimental checks (data not shown) point to a better performance of permutation tests versus the naïve bootstrap approach in the ternary variable setting, but further studies would be needed to verify it.

It should also be clarified that authors such as Cai and Liu (2016) and Szekely et al. (2007) argue that the number of resamples $B$ is relatively unimportant for their methods to work, as long as it is not extremely small. With this in mind, and also taking into account that the execution time is $O(B)$, it has been decided to use a moderate value for $B$ in the present article, namely the one devised by Szekely et al. (2007) as a function of sample size $n$:

$$B(n) = 200 + \lfloor 5000/n \rfloor,$$

where $\lfloor \cdot \rfloor : \mathbb{R} \to \mathbb{Z}$ is the floor function. Some empirical checks confirm that increasing $B$ with respect to the value above causes barely noticeable improvements (if any) both in terms of the calibration of significance levels (as long as the nominal value is not extremely small) and of power.

Nevertheless, if the goal was to control the false discovery rate (FDR), the situation would be quite different: both Benjamini and Hochberg (1995) and Benjamini and Yekutieli (2001) are based on ordering $p$-values and, consequently, $B$ cannot be too small with respect to the number of hypotheses that are tested, in order to avoid an excessive build-up of null $p$-values. Unfortunately, when it comes to analysing real data, this becomes unfeasible (see the empirical issues in Table 2). To tackle this, a FWER approach has been chosen (instead of FDR), which has the slight drawback of neglecting the weak dependencies among the $\binom{L}{2}$ hypothesis tests (both due to one of the SNPs being the same and due to linkage disequilibrium). Despite this, it appears to be the most sensible choice.

3.4. **Computational challenge**

The implementation of the test here presented was an extremely challenging issue from the computational point of view, given the high dimensionality of the data, the amount of samples, and the high number of hypothesis tests. Thus, a quite sophisticated set of computer technologies and strategies was required to obtain results within reasonable computational times.
Table 2. Comparison of running times for the different versions of the code

|                  | Simulation, \( R = 10^3 \) | GWAS, \( L = 1000 \) | GWAS\(^\dagger\), \( L = 4117 \)\(^\ddagger\) |
|------------------|-----------------------------|----------------------|---------------------------------|
| R sequential     | 12 h 10 min                 | 42 days 1 h          | 2 years                         |
| R & C sequential | 3 h 59 min                  | 2 days 1 h           | 29 days 1 h                     |
| R & C parallel   | 50 min                      | 2 h 41 min           | 2 days 1 h                      |

\(^\dagger\)The times for the larger GWAS are estimations.  
\(^\ddagger\)\( L = 4117 \) is the dimensionality of the filtered schizophrenia dataset.

As a general rule, any statistical technique based on GWAS data will suffer from the issues that are inherent to such input (high dimension and low sample size). To illustrate this point, Table 2 compares the running times of the original R code with another one, whose core is implemented in the compiled language C, this way making the numerical crunching far swifter. This second code —labelled “R & C” on the table— also includes some high-performance computing (HPC) improvements and, what is more, it can executed in sequential or in parallel mode (i.e., the workload can be distributed among different processors, decreasing the execution time by a factor that is approximately equal to the number of available processors). For a comparison of performance like the one on Table 2, it is crucial to carry on the experiments in the same environment—in our case, the supercomputer *Finisterrae II* (Galician Supercomputing Centre, CESGA).

Hence, in light of the order of magnitude of these times (the R version would need up to two years in large-scale settings, while the R & C parallel implementation only requires ten hours), it is fully justified to resort to HPC strategies in a compiled language, especially if one takes into account that a GWAS with the same functional filters of the present study can involve up to \( L = 30\,000 \) SNPs, with the running time being a linear and monotonically increasing function of \( \left( \frac{L}{2} \right) \) and, consequently, \( O(L^2) \); as illustrated by the ratio between the GWAS columns of Table 2.

For the parallel version of the R \& C code, in each case, the lowest amount of hardware that yielded results within a reasonable amount of time was used: 12 cores for simulations, and 48 processors for real data analyses. To reduce the times by a factor of \( f \), it would suffice to increase the number of processors \( f \) times, as long as economic and logistic constraints make it possible.

Moreover, the algorithm was parallelised in two alternative ways:

(a) using a shared-memory paradigm via the OpenMP library, distributing the computational effort among the different cores that exist within a processor;  
(b) applying a distributed-memory strategy, where different computational nodes — that belong to various machines— are able to share workload via a message protocol, which in this case is the MPI library.

The first parallelisation (that is very easy to implement in the main loop of the algorithm) was useful to apply the test in simulated data, where the dimensionality was
not too problematic. However, the number of parallel execution threads to add is limited by the number of cores available on a CPU processor chip, which is not enough to address real data examples. For this reason, a distributed-memory parallelisation was developed, with a classical master/slave paradigm, where hundreds of processors can work together to reduce complexity. It consists in:

(a) A processor (master) calls R routines that load the matrices that contain the input, split it and distribute it among several processors (slaves).
(b) Each processor works with one fragment of the matrix, running the iterations that have been assigned to it (i.e., performing independence tests for a fraction of the total of SNP pairs).
(c) Once each slave finishes its part, it sends the results to its master.
(d) Finally, the master builds the final $p$-value matrix, which is later used to wrap up the results in R.

The R & C version combines an interface in the programming language R with a core in C, with the latter being devoted to perform low-level computations in a time-efficient manner. Another important factor that helps to decrease the computational time in our implementation is the use of specific libraries to codify low-level operations that involve large vector and matrices. Namely, the well-known Intel MKL libraries and SIMD (Single Instruction, Multiple Data) techniques have been applied to exploit data-level parallelism — using an extension in the registers and the arithmetic and logic instructions present in modern microprocessors, they can process the same operation simultaneously on the elements of an array through a single instruction. In the present case, it was particularly useful to implement matrix operations.

It was not possible to resort to preexisting software because the most efficient distance-correlation-related algorithms (like the one by Chaudhuri and Hu, 2019) are only designed for the Euclidean case and, therefore, not adaptable to the structure of the 3-point spaces that are the scope of the present article.

4. Simulation study

In this section, some illustrative simulations are shown, including some representative tables and figures. First, the ad hoc statistical models that were created are defined, to then present and discuss the results.

4.1. Design of population models for the validation of the method

The theoretical models that are about to be defined refer to the interaction between an arbitrary pair $\{Z_i, Z_j\}$, where $Z$ is either $X$ or $Y$, depending on the case. When it came to setting the marginal frequencies, instead of allowing for two degrees of freedom on each marginal, a further restriction was introduced (apart from the sum being one): allele and genotype frequencies were constrained to be in Hardy–Weinberg equilibrium (Hardy, 1908), as all the SNPs in the schizophrenia database verify it (it is one of the quality controls that are used). So there is a single free parameter, which is the minor allele frequency, that is sampled from a uniform distribution on $[0.05, 0.2]$. The lower limit mimics standard GWAS quality control filters and the upper one was set so that...
the resulting models are not overly favourable (what would misrepresent the effectiveness of the methodology).

Table 3. Contingency table for model \textit{indep}

| $Z_i \setminus Z_j$ | 0        | 1        | 2        |
|---------------------|----------|----------|----------|
| 0                   | $pr$     | $ps$     | $p(1-r-s)$ |
| 1                   | $qr$     | $qs$     | $q(1-r-s)$ |
| 2                   | $(1-p-q)r$ | $(1-p-q)s$ | $(1-p-q)(1-r-s)$ | $1-p-q$ |

The need for such ad-hoc models owes to the fact that the literature that studies epistasis between SNPs very rarely includes models for simulations and, when it does have some (like in Marchini \textit{et al.} [2005]), they are overly simplistic, e.g. by not allowing to adjust the interaction intensity in order to assess the robustness against different alternatives. More generally, the articles that present epistasis detectors show that there is a blatant lack of consensus on how to compare the effectiveness of such techniques.

The most straightforward model is one in which the probability of each genotype is the product of the marginals (there is independence), as illustrated on the corresponding $3 \times 3$ contingency table (Table 3).

For dependency, two kinds of models will be defined. On the one hand, models \textit{qexp} and \textit{rexp} convey dependence structures that become less intense as parameter $e \in [1, +\infty[$ increases, in the way that Tables 4–5 describe. Note that, for the same value of $e$, the intensity of interaction is higher for \textit{qexp} than for \textit{rexp}, as a result of Hardy–Weinberg equilibrium.

Table 4. Contingency table for model \textit{qexp}

| $Z_i \setminus Z_j$ | 0        | 1        | 2        |
|---------------------|----------|----------|----------|
| 0                   | $pr + q^e s - qs$ | $ps - q^e s + qs$ | $p(1-r-s)$ |
| 1                   | $qr - q^e s + qs$ | $q^e s$ | $q(1-r-s)$ |
| 2                   | $(1-p-q)r$ | $(1-p-q)s$ | $(1-p-q)(1-r-s)$ | $1-p-q$ |

On the other hand, model \textit{qmult} has $g \in [0,1]$ as its free parameter (Table 6). Again, the closer the parameter is to 1, the less notorious the association becomes.
Table 6. Contingency table for model qmult

\[
\begin{array}{c|ccc|c}
Z_i \setminus Z_j & 0 & 1 & 2 & p \\
\hline
0 & pr - (1 - g)qs & ps + (1 - g)qs & p(1 - r - s) & p \\
1 & qr + (1 - g)qs & gqs & q(1 - r - s) & q \\
2 & (1 - p - q)r & (1 - p - q)s & (1 - p - q)(1 - r - s) & 1 - p - q \\
\end{array}
\]

4.2. Results of the simulation study

Given that the data to be analysed represents roughly 4000 SNPs and 1000 individuals, it is not hard to see that computational costs overpass the capacities of domestic computers and even some conventional HPC architectures, which are unable to yield results within a reasonable amount of time (Yang et al., 2015; Kam-Thong et al., 2012).

In light of this, and to ease the interpretation of results, each simulation consisted in the study of one of the models for a SNP pair. This is an acceptable simplification because the current setting is a problem of multiple testing and not a single high-dimensional test (see Cai [2017] for a discussion of the methodological and conceptual differences), that is, there are no underlying asymptotic results when \( L \rightarrow \infty \) that require a matrix to be built and replicated.

Tables 7a–7b show the calibration of significance for some usual nominal levels. In turn, the empirical power is represented on Fig. 2. In all cases, \( R = 1000 \) replications were carried out.

| Nominal significance level (\( \alpha \)) versus empirical power under the null hypothesis (\( \hat{\alpha} \)), for two different models |
|---|---|---|---|---|
| (a) indep | (b) rexp with \( e = 10 \) |
| \( \alpha \) | 0.01 | 0.02 | 0.05 | 0.10 | \( \hat{\alpha} \) | 0.01 | 0.02 | 0.04 | 0.07 |
| \( \hat{\alpha} \) | 0.01 | 0.02 | 0.04 | 0.07 | \( \hat{\alpha} \) | 0.01 | 0.02 | 0.04 | 0.08 |

On the basis of the aforementioned tables, it can be concluded that the calibration of significance is acceptable or even good for low levels of nominal \( \alpha \). In addition, the plots on Fig. 2 show that the power is very satisfactory and that, as expected, it increases as one gets further away from the null hypothesis. This last part is unsurprising, since the only critique to the power of independence tests via distance correlation that can be found in the literature (Ramdas et al., 2015) refers only to simple tests for high dimension and not to large-scale multiple testing.

All in all, the procedure here presented does not suffer from the same issues as the one by Cai and Liu (2016), at least from the theoretical point of view.

5. Application to a case-control study of schizophrenia

To begin with, the genomic database that motivates this article will be introduced. Then, the results of their analyses will be presented and discussed.
Finding gene-gene interactions via distance correlation

5.1. Genomic database

The SNP data around which the whole present article pivots comes from a case-control study of schizophrenia, that was performed on \(n_1 = 585\) patients and \(n_2 = 573\) healthy individuals, all of them of Galician origin, as previously described (Rodríguez-López et al., 2020). The sampling of each group was independent from the other one: the control samples come from the Galician Blood Transfusion Centre, while the cases come from a years-long effort of the Clinical University Hospital of Santiago de Compostela.

For each individual, 588,628 SNPs were initially genotyped, using the microarray PsychArray-24 BeadChip (Illumina, San Diego, California). After genotyping, several conventional quality controls were performed. Namely, to avoid experiment-derived problems, it was decided to leave out from the database every SNP that verified any of the following conditions:

(a) The minor allele frequency (MAF) is less than 1 %.
(b) The genotype proportions differ significantly from Hardy–Weinberg equilibrium in the control sample, when \(\alpha = 0.05\).
(c) The call rate (proportion of non-missing data) is under 95 %, or either it is significantly different between cases and controls.

Had not the previous restrictions been imposed, many badly-behaved SNPs would remain in the database, that is, for many SNPs it would not be possible to clearly discriminate between the two possible alleles.

After all this process, among the remaining autosomal SNPs, only the exonic missense SNPs (i.e., those that induce a change in the aminoacid sequence of a protein) are
considered, as they are the ones that can potentially present epistasis. This yields a reduction of dimensionality by a factor of roughly 100, since the exome accounts for approximately 1% of the human genome.

The final SNP count is $L = 4117$ for the schizophrenia database, with this number being remarkably lower than the usual amount of covariates in GWASs because two last requisites are to be met by the polymorphisms:

(a) MAF > 10%. This reduces dimensionality to an extent that computational times are less of an issue, but not to the point that it becomes impossible to discover interactions, given the remarkably high sparsity of the adjacency matrices of epistatic networks (Cai, 2017).

(b) Belonging to one of the genes that are contained in any of the 35 spatiotemporal co-expression modules of the human brain that are known (Fromer et al., 2016). This will enable to biologically validate the results: in a favourable scenario, it is expected that the pairs of variants in which interactions are detected lay on the same module in a proportion that is significantly higher than what would be achieved by choosing random SNP pairs (equiprobably).

With the same goal of unveiling interactions more easily, the lower limit for MAF was set higher than what is strictly necessary for a quality control, since it is believed that the genetic basis of complex (non-Mendelian) diseases is the combination of multiple common variants, each of which has a low marginal effect (Bush and Moore, 2012). Another argument to avoid low-MAF SNPs is that they would cause the minor allele to be observed very rarely in homozygosis and, given that sample sizes are not extremely high, the power of the test could be an issue in that case.

Moreover, the most relevant discoveries will be checked by investigating the literature.

5.2. Results of the application to SNP data

For the analysis of genomic data, the computational costs are extremely high (see Table 2), what makes it advisable to further reduce the schizophrenia database. On top of that, given that the aim is just to confirm the usefulness of the method by means of biological knowledge, the database can be reduced from $L = 4117$ to $L = 1000$ SNPs, which will notably speed up the computations because the time is $O(L^2)$. To prevent any possible bias, these 1000 SNPs were randomly (equiprobably) selected.

5.2.1. Study by co-expression modules

The four distances that had previously been defined were used to examine the schizophrenia database, in each case computing the proportion of the putative discovered SNP-SNP interactions in which both polymorphisms lay on the same of the 35 spatiotemporal co-expression modules of the human brain that were described by Fromer et al. (2016).

Only for one of the distances, the one coded as “0=1”, that proportion was significantly higher than what would be expected with random (equiprobable) choices: 0.085 versus 0.071, with a $p$-value lower than any of the usual nominal significance levels. This justifies that only this metric will be used hereinafter.
5.2.2. Particularisation of the results for the SLC39A8 gene

Finally, the results for a specific SNP will be dealt with in detail, so that the results can be interpreted by resorting to the specialised literature. The selected polymorphism is the one with at position 103188709 of chromosome 4 (version GRCh37 of the Human Reference Genome), named rs13107325 (NCBI, 2020). The link between this SNP and schizophrenia was discovered by Carrera et al. (2012) and confirmed by Ripke et al. (2014). What is more, it is the missense SNP of the whole human genome that is more clearly linked to schizophrenia (Costas, 2018).

Using distance “0=1”, three interactions stand out (Table 8). These results will be interpreted next.

| SNP         | p-value (controls) | p-value (cases) |
|-------------|--------------------|-----------------|
| rs1014286   | <0.001             | 0.591           |
| rs398607    | <0.001             | 0.409           |
| rs2075756   | <0.001             | 0.409           |

Table 8. The three top significant (putative) interactions of rs13107325 with other SNPs

5.3. Discussion of the SNP analysis

The most useful distance in practice turned out to be “0=1”—it is the most suitable metric to detect the effect of those SNPs that follow a recessive inheritance pattern, that is, those for which what matters phenotypically is the presence or absence of 2 copies of the minor allele (whether there is 0 or 1 is irrelevant). This suggests that the existence of just one copy of the major allele is enough to avoid phenotypic consequences, which is indicative of the robustness of the system to perturbations.

The particular study of a SNP yielded the detection of 3 remarkable SNP pairs, one of which consists of rs13107325 and rs2075756. This putative interaction is very plausible from the biological point of view. On the one hand, rs2075756 lays on the TRIP6 gene, which acts (Willier et al., 2011) as an activator in the NF-κB signalling pathway, in turn related to immunity. On the other hand, rs13107325 lays on SLC39A8, which is an inhibitor in that same pathway (Liu et al., 2013). It is highly unlikely that this is a casual occurrence, given the high number of pathways that exist. Furthermore, this point is reinforced by several evidences that support the notion that an abnormal immune response is linked to schizophrenia (Costas, 2018).

This way, it has been discussed how plausible one of the 3 discoveries is. However, that is not the case of the other two. What is more, the literature queries that have been made have not found any tentative molecular explanation of the putative relation of rs13107325 with rs398607 or rs1014286. Consequently, the most reasonable conclusion is to consider them false positives.

At this point, it is reasonable to wonder which was the prior probability that, for a randomly (equiprobably) chosen gene, arguments to support its putative relation to
SLC39A8 can be found. Although not much is known about this gene, it is clear that it is involved in the NF-κB pathway and in the homeostasis of metal ions. A 2011 comprehensive review (White et al., 2011) documented 235 genes linked to NF-κB, so it can be estimated that roughly 300 are currently known. As far as metal ion homeostasis is concerned, the number of genes that have been proven to be related to it is much lower: about 50. All things considered, the prior probability of, given 3 of the initial 1000 SNPs, (at least) one presents a plausible interaction with rs13107325 is approximately 0.04.

In conclusion, albeit only having 1 plausible discovery out of 3 might seem slightly disappointing at first glance, the low prior probability shows that it is not unsatisfactory at all. Moreover, it should be noted that very few interactions of order 2 have been documented for complex diseases (even less using SNP data) and, in particular, no such interaction is known for schizophrenia. This, again, conveys the difficulty of the task.

As a final remark, the fact that biologically sound results have been obtained show that the deficiencies of the method by Cai and Liu (2016) (as displayed in Fig. 1) have been solved, at least to some extent. It would be interesting to check if further studies, with independently sampled data, can replicate these results.

6. Conclusion

Finally, it is possible to respond to the questions that motivated the article:

(a) Distance correlation has been shown to characterise independence in certain metric spaces, establishing how this theory is valid for the case of 3-point marginal spaces.

(b) The independence test that has been devised generalises LCTs as a technique to find pairs of random variables in which the nature of dependence (not only linear) differs between two groups of observations (e.g., cases and controls).

(c) Since any distance is valid, the procedure that has been introduced is extremely flexible: it allows to decide, a priori, which kind of interaction is going to be looked for. For example, among the metrics that were considered in this article, only one performed in satisfactorily for the database that was used.

(d) In light of the results of the simulation studies, it is apparent that the calibration of significance is adequate and that power is considerably high against manifold alternatives.

(e) The most significant interactions for the schizophrenia database have been studied, obtaining a biologically sound interaction, something that would be highly unlikely if the method was not functioning correctly.

Thus, a hypothesis test based on the general characterisation of independence that distance correlation offers has been designed, extending the idea of LCTs (Cai and Liu, 2016) to ternary data. In addition, HPC strategies have made it possible to overcome important computational hurdles. The test here presented performs satisfactorily in practice, as shown by the simulation studies. In addition, one of the metrics proved to be suitable for the target database, as it enabled the detection of a significantly high proportion of SNPs within the same co-expression module, leading to the discovery of an interaction within the same signalling pathway.

Nonetheless, there are several open problems. Future work on the topic may include investigating other distances, trying to design a procedure to infer from the sample which
metric is the optimal one in some sense. Another interesting point would be to adapt the techniques to the search for interactions between mitochondrial (haploid) and nuclear (diploid) genome, i.e., to the study of independence between binary and ternary variables. Delving into the mathematical properties of the test in 3-point spaces, attempting to derive an exact null distribution, would also be an exciting new challenge.

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