# Expanding polygenic risk scores to include automatic genotype encodings and gene-gene interactions

This manuscript (<u>permalink</u>) was automatically generated from <u>lelaboratoire/rethink-prs-ms@3cde4f1</u> on August 3, 2019.

#### **Authors**

- Trang T. Le
  - **©** 0000-0003-3737-6565  **○** trang1618  **●** trang1618

Department of Biostatistics, Epidemiology and Informatics, Institute for Biomedical Informatics, University of Pennsylvania, Philadelphia, PA 19104

- Hoyt Gong
  - **1** 0000-0001-9339-4763 · **1** hoytgong · **1** GongHoyt

Life Sciences and Management, Wharton School, University of Pennsylvania

- · Patryk Orzechowski
  - © <u>0000-0003-3578-9809</u>

Department of Biostatistics, Epidemiology and Informatics, Institute for Biomedical Informatics, University of Pennsylvania, Philadelphia, PA 19104

- · Elisabetta Manduchi
  - © 0000-0002-4110-3714

Department of Biostatistics, Epidemiology and Informatics, Institute for Biomedical Informatics, University of Pennsylvania, Philadelphia, PA 19104

- · Jason H. Moore<sup>†</sup>
  - © <u>0000-0002-5015-1099</u> · ♠ <u>EpistasisLab</u> · **୬** <u>moorejh</u>

Department of Biostatistics, Epidemiology and Informatics, Institute for Biomedical Informatics, University of Pennsylvania, Philadelphia, PA 19104 · Funded by National Institutes of Health Grant Nos. LM010098, LM012601, Al116794

- These authors contributed equally to this work.
- <sup>†</sup> Direct correspondence to jhmoore@upenn.edu.

#### **Abstract**

Polygenic Risk Scores (PRS) are aggregation of genetic risk factors of specific diseases and have been successfully used to identify subgroups of individuals who are more susceptible to those diseases. While several studies have focused on identifying the correct genetic variants to include in PRS, most existing statistical models focus on the marginal effect of the variants on the phenotypic outcome but do not account for the effect of gene-gene interactions. Here, we propose a novel calculation of the risk score that expands beyond marginal effect of individual variants on the phenotypic outcome. The Multilocus Risk Score (MRS) method effectively selects alternative genotype encodings and captures epistatic gene-gene interactions by utilizing an efficient implementation of the model-based Multifactor Dimensionality Reduction technique. On a diverse collection of datasets, MRS outperforms the standard PRS in the majority of the cases, especially when at least two-way interactions between

genes are present. Our findings suggest that more precise models that incorporate epistatic interactions are necessary and will yield greater utility for polygenic risk profiling.

#### Introduction

As the field of traditional genomics rapidly expands its sequencing technologies and translational abilities, novel applications of genomic data are starting to arise in addressing disease burden. Complementing the rapid growth in our understanding of human genetic variation was the emergence of genome-wide association studies (GWAS) in the early 2000s to identify gene variants associated with common human diseases. Non-candidate-driven in design, these observational studies carry out chip array genotyping across population subsamples to subsequently assay for phenotype signal association via statistical approaches in silico. Measuring averaged allelic effects across all genomics backgrounds and environmental exposures, GWAS have primarily sought to discern genetic association with phenotypes of interest by studying single nucleotide polymorphisms (SNPs) and other DNA variants across the human genome [1,2,3].

In tandem with the movement towards precision medicine, the post-GWAS era strives to bring relevant population-derived gene variants into individual level metrics actionable in health delivery settings. While GWAS indeed capture gene variants associated with a phenotype of interest on a population level, translating such results to personalized individual metrics of risk requires aggregating contributions of many gene variants in the form of polygenic risk scores (PRS). PRS provide an ability to explain inherited risk for disease in an individual by representing a weighted sum aggregate of risk alleles based on measured loci effect contributions derived from GWAS [4,5]. In quantifying the effect of particular combinations of genetic SNP variants towards risk prediction, PRS offers a probabilisitic susceptibility value of an individual to disease. Such genetic risk estimation scores are central to clinical decision-making, serving to reinforce individual health management in heritable disease detection and early prevention of various adult-onset conditions. The utility of PRS scores have been demonstrated in previous studies towards disease risk stratification across leading heritable causes of death in the developed world [6,7,8,9].

Because common PRS method assumes a simplified genetic architecture consisting of independent weights, understanding interactive relationships among genes and SNPs that associate with disease outcome remain a challenge. Existing standard multivariate categorical data analysis approaches fall short in handling such enormous possible genetic interaction combinations with both linear and nonlinear effects. In this context, more robust and efficient methods towards a polygeneic risk calculation are necessary in capturing the overlap between context-dependent effects of both rare and common alleles on human genetic disorder. Herein, we use the terminology gene-gene (GxG) interactions to indicate any genetic interaction including ones among SNPs that may fall outside of coding regions.

With respect to better understanding the epistasis across an individual's genome, various statistical models have been designed with the intent of capturing high dimensional GxG interactions. The Multifactor Dimensionality Reduction (MDR) method is one such nonparametric framework that addresses these challenges and has been extensively applied to detect nonlinear complex GxG interactions associated with individual disease [10,11]. By isolating a specific pool of genetic factors from all polymorphism and cross-valiating prediction scores averaged across identified high risk multi-locus genotypes, the original MDR approach is able to categorize multilocus genotypes into two groups of risk based on a threshold value. While created with the primary intention towards GxG interaction detection by reducing dimensionality interactively in inferring genotype encodings, the MDR model has additionally demonstrated applicability as a risk score calculation model in constructing PRS scores [12].

Modifications built on top of the MDR framework have been proposed in order to better capture multiple significant epistasis models and potential missed interactions owning to limitations of the original model in the higher dimensions. Model-Based Multifactor Dimensionality Reduction (MB-MDR) was formulated as a flexible GxG detection framework for both dichotomous and continuous traits [13,14]. Rather than a direct comparison against a threshold level in the original MDR method, MB-MDR merges multilocus genotypes exhibiting significant High or Low risk levels through association testing and adds an additional 'No evidence of risk' categorization. In comparison to the standard MDR framework which reveals at most one optimal epistasis model, the MB-MDR method flexibly weighs multiple models by producing a model list ranked with respect to their statistical parameters.

In the present work, we aim to reformulate the PRS leveraging the MB-MDR approach to better capture alternative encodings and epistatic interactions of individual disease risk in a novel Multilocus Risk Score (MRS). Through the following sections, we briefly review the features of the MDR and MB-MDR software, describe how our new MRS method evaluates polygenic risk, and compare MRS profiling performance to the standard PRS method on evidence-based simulated dataset collections. In observing prediction accuracy results, we demonstrate the improved performance of our multi-model weighted epistasis framework with inferred genotype encodings over existing PRS methods, showing great potential for more accurate identification of high risk individuals for a specific complex disease.

#### **Methods**

### Multifactor Dimensionality Reduction (MDR) and model-based MDR (MB-MDR)

MDR is a nonparametric method that detects multiple genetic loci associated with a clinical outcome by reducing the dimension of a genotype dataset through pooling multilocus genotypes into high-risk and low-risk groups [10]. Extended from the original MDR algorithm, MB-MDR was first introduced in 2009, and its current implementation efficiently and effectively detects multiple sets of significant gene-gene interactions in relation to a trait of interest while efficiently controlling type I error rates.

In addition to the test statistic and P values associated with each genotype combination, another important output of MB-MDR is the HLO matrices. Briefly, in the case of a binary trait, for each genotype combination, an HLO matrix is a 3 x 3 matrix with each cell containing H (high), L (low) or O (no evidence), indicating risk of an individual whose genotype pairs fall into that cell [ $\underline{15}$ ]. For an example binary outcome problem, a genotype combination  $SNP_1$  and  $SNP_2$  will have an HLO matrix that looks like

$$SNP_1 = 0$$
  $SNP_1 = 1$   $SNP_1 = 2$   $SNP_2 = 0$   $O$   $O$   $O$   $SNP_2 = 1$   $O$   $H$   $L$   $SNP_2 = 2$   $O$   $L$ 

We discuss in the following subsection how these values were utilized in the formulation of the Multilocus Risk Score (MRS).

#### From Polygenic Risk Scores (PRS) to Multilocus Risk Scores (MRS)

In this subsection, we quickly review the standard PRS formula then present our modification to this popular risk score calculation. For both methods, we consider a dataset of n individuals with genomes of m possible SNPs.

In PRS, for each SNP j of an individual i, the PRS score is calculated via a summation across k selected SNPs as

$$PRS(i) = \sum_{j=1}^{k} \beta_j \times SNP_{ij}$$

where  $\beta_j$  is the weighted risk contribution of the  $j^{\text{th}}$  SNP derived from the association test parameters and  $SNP_{ij}$  represents the number of minor alleles (0, 1, or 2) at the  $j^{\text{th}}$  locus of individual i. Various approaches towards predicting risk of the same disease exist across PRS studies based on the above equation; models may vary according to the specific statistical model used to produce the weights  $\beta_j$  for individual genetic variations, the number of genetic variants considered k, and the ability of the PRS to generalize to the entire population [4].

In the MRS framework, we let  $k_d$  denote the number of significant combinations for a specific model dimension d (e.g. d=2 results in pairs of SNPs). In this study, no significance threshold is imposed at the SNP combination level and, thus,  $k_d$  reaches its maximum value of  $C_m^d$  (m choose d). For each subject i ( $i=1,2,\cdots,n$ ), the d-way multilocus risk score is calculated as

$$MRS_d(i) = \sum_{j=1}^{k_d} \gamma_j \times \text{HLO}_j(X_{ij})$$

where  $\gamma_j$  is the test statistic of the  $j^{\rm th}$  genotype combination output from MB-MDR,  $X_{ij}$  is the  $j^{\rm th}$  genotype combinations of subject i and  ${\rm HLO}_j$  represents the  $j^{\rm th}$  recoded HLO matrix (1 = High, -1 = Low, 0 = No evidence). As an example, consider a pair  $X_{*j} = (SNP_{j_1}, SNP_{j_2})$  with  $\gamma_j = 8.3$  and corresponding HLO matrix of all O's except an L in the first cell. Then, all subjects' current risks would remain the same except the ones with  $SNP_{j_1} = SNP_{j_2} = 0$  where their risks are subtracted by 8.3.

In this study, we consider 1-way and 2-way interactions. We denote by MRS the combined risk score MRS1 + MRS2. The significance level of each combination of SNPs on a given dataset is obtained by applying on that dataset the MB-MDR software [14,15] v.4.4.1. We will compare the performance of the standard PRS method to the combined risk MRS and also its components, MRS1 and MRS2, separately.

#### Mutual information and information gain

For a given simulated data set, we apply entropy-based methods to measure how much information about the phenotype is due to either marginal effects or the synergistic effects of the variants after subtracting the marginal effects. A dataset's amount of main effect ME can be measured as the total of mutual information between each genotype  $SNP_j$  and the phenotypic class Y based on Shannon's entropy H [16]:

Shannon's entropy 
$$H$$
 [16]: 
$$ME = \sum_{j}^{k} I(SNP_{j};Y) = \sum_{j}^{k} H(Y) - H(Y|SNP_{j}).$$

We measure the 2-way interaction information (i.e. degree of synergistic effects of genotypes on the phenotype) of each dataset by summing the pairwise information gain between all pairs of genetic attributes. Specifically, if we let  $X_j$  denote the  $j^{\rm th}$  genotype combination  $(SNP_{j_1},SNP_{j_2})$ , the total 2-way interaction gain (i.e. synergistic effects SE) is calculated as

$$SE = \sum_{j=1}^{k} IG(X_j; Y) = \sum_{j=1}^{k} (I(SNP_{j_1}, SNP_{j_2}; Y) - I(SNP_{j_1}; Y) - I(SNP_{j_2}; Y)$$

where IG measures how much of the phenotypic class Y can be explained by the 2-way epistatic

interaction within the genotype combination  $X_j$ . We refer the reader to Ref. [17] for more details on the calculation of the entropy-based terms.

#### Simulated data

The primary objective of this data simulation process was to provide a comprehensive set of reproducible and diverse datasets for the current study. Each dataset was generated in the following manner. For an individual, each genotype was randomly assigned with 1/2 probability of being heterozygous (*Aa*, coded as 1), 1/4 probability of being homozygous major (*AA*, coded as 0) and 1/4 probability of being homozygous minor (*aa*, coded as 2). The binary endpoint for the data was determined using a recently proposed evolutionary-based method for dataset generation called Heuristic Identification of Biological Architectures for simulating Complex Hierarchical Interactions (HIBACHI) [18]. Details on data simulation are provided in the README of the study's analysis repository <a href="https://github.com/lelaboratoire/rethink-prs/">https://github.com/lelaboratoire/rethink-prs/</a>.

The final collection has 450 datasets containing 1000 individuals and 10 SNPs with various amount of epistatic effect on the binary phenotypic outcome. For each simulated dataset, after randomly splitting the entire data in two smaller sets (80% training and 20% holdout), we built the MRS model on training data to obtain the  $\gamma$  coefficients and the HLO matrix, and then we calculated risk score for each individual in the holdout set. We assess the performance of the MRS by comparing the area under the Receiving Operator Characteristic curve (auROC) with that of the standard PRS method on the holdout set.

#### **Manuscript drafting**

This manuscript is collaboratively written using the Manubot software which supports open paper writing via GitHub with Markdown [19]. Manubot uses continuous integration to monitor changes and automatically update the manuscript. As a result, the latest version of this manuscript is always available at <a href="https://lelaboratoire.github.io/rethink-prs-ms/">https://lelaboratoire.github.io/rethink-prs-ms/</a>.

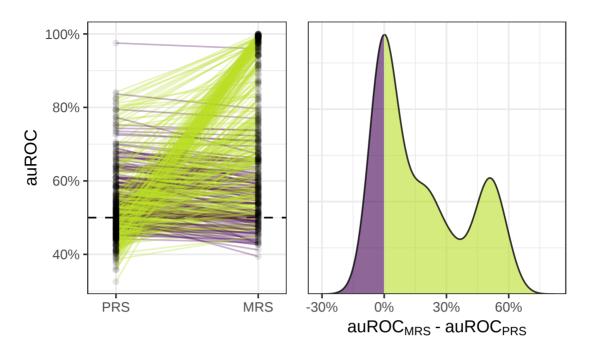
#### **Availability**

Detailed simulation and analysis code needed to reproduce the results in this study is available at <a href="https://github.com/lelaboratoire/rethink-prs/">https://github.com/lelaboratoire/rethink-prs/</a>.

#### Results

### MRS outperforms standard PRS in the majority of simulated datasets

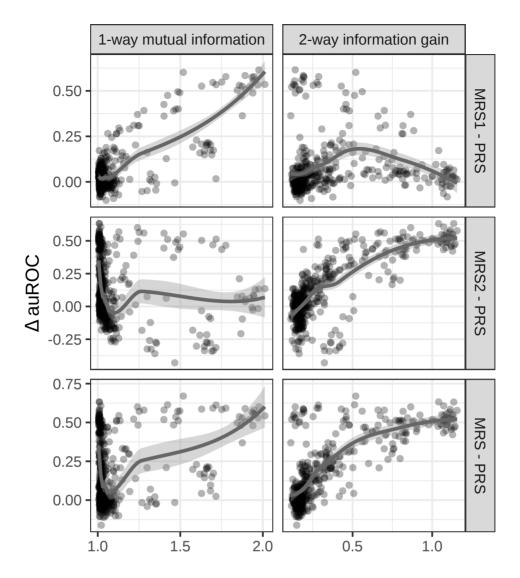
In 335 out of 450 simulated datasets, MRS produces higher auROC compared to PRS (green lines, Fig. 1). In 363 datasets where the standard PRS method performs poorly (auROC < 60%), MRS performs particularly well (auROC > 90%) in 102 datasets. When MRS yields smaller auROC, the difference is small (3.3%  $\pm$  2.8%, purple lines/areas). Across all datasets, the improvement of MRS over PRS is significant (P <  $10^{-15}$ ) according to a Wilcoxon signed rank test. To assess whether this improvement in performance correlates with the amount of interaction effects contained in each dataset, in the following section, we untangled the two components of MRS and test for the correlation between the difference in auROC and two entropy-based measures, main and interaction effect, of each dataset.



**Figure 1:** MRS produces improved auROC in the majority (335 green lines) of the 450 simulated datasets (each line represents a dataset). In many datasets, the standard PRS method performs poorly (auROC < 60%) while the new method yields auROC over 90%. This improvement in performance can be seen at the second peak (~50% auROC increase) in the density of the difference between the auROCs from the two methods (right).

#### Assess improvement in performance

Individually, MRS1 and MRS2 both significantly outperformed the standard PRS method (both P values  $< 10^{-15}$ ) according to a Wilcoxon signed rank test. As the amount of main effects increases (Fig. 2 left column), MRS1 increasingly performs better than PRS, which is likely because encodings are inferred (top left). Meanwhile, MRS2's accuracy remain mostly similar to that of PRS (middle left). On the other hand, when the amount of interaction effects increases (Fig. 2 right column), MRS1 performs mostly on par to PRS while MRS2 increasingly performs better than PRS. Combining the gain from both MRS1 and MRS2, MRS's performance progressively increases compared to the standard PRS.



**Figure 2:** Combining 1-way (MRS1) and 2-way (MRS2) risk scores, MRS shows increasing outperformance to standard PRS as dataset contains more main and interaction effects.

#### **Discussion**

We introduce a Multilocus Risk Score (MRS) method to improve the performance of the standard PRS in disease risk stratification of patient populations. While PRS holds much promise for development of new precision medicine approaches by identifying high risk individuals who may benefit from prioritized interventions, one of its current limitations is the model simplicity [5]. As a first step towards addressing this issue and increasing comprehensiveness of risk profiling models, in this study, we developed a new applied MRS method from the MB-MDR framework that enables automatic genotype encodings and takes into account multiple models for detecting GxG interactions. Utilizing the efficient implementation of MB-MDR, MRS automatically infers the genotype encodings and simultaneously computes the risk of variant combinations. Through comparing method performance on a diverse collection of simulated data, we demonstrate the robust polygenic risk profiling ability of MRS and suggest the importance of flexible, precise methods in better capturing epistasis behind individual patient risk.

We showed that the MRS method outperformed standard PRS in many of the simulated datasets, highlighting the importance of genotype encodings and consideration of epistasis. We further examined the association between this improvement and the amount of two-way epistatic effect induced in the binary phenotypic outcome. Appropriate phenotype encodings are important for

improving the accuracy when there is a large amount of main effects of the variants on the phenotypic outcome. Meanwhile, inclusion of epistatic terms significantly increases the accuracy from PRS, especially when two-way interactions are present in the data. Although we only considered up to two-way GxG interactions, it is straightforward to incorporate higher order interactions (e.g. three-way, four-way) into MRS. However, preliminary analyses on the simulated datasets for such higher order interactions did not show significant improvement from the current MRS (results not shown). We also recommend estimating the computational expense prior to implementing high order interactions, especially for larger datasets encountered in practice.

Although MRS captures the improvements of MB-MDR in reporting polygenic risk profiles, there are three primary limitations. First, MRS has not been applied to real-world data. Although we compensated the lack of real data with a diverse set of simulated datasets, a future study analyzing real-world data will prove beneficial to quantify the new MRS model's utility in practice. Second, accounting for epistasis, in principle, is largely more computationally expensive compared to investigating solely main effects. Therefore, even with fast and efficient software, pre-selecting the variants (e.g. based on specific pathways or prior knowledge) will prove beneficial for accurate MRS computing when analyzing datasets containing a larger number of variants. Nevertheless, we hope the promising preliminary results from this study will open the door to future approaches that encompass both main and interaction effects while improving scalability.

Finally, we caution that a risk score model should be evaluated based on not only sensitivity and specificity but also with respect to potential clinical efficacy, and any genetic risk should be interpreted in aggregate with other risk factors. Future works focusing on gene-environment interactions with time-dependent risk factors will be crucial in order to communicate risk properly for preventive interventions.

In conclusion, MRS enhances the predictive capacity of current risk profiling model for complex diseases with polygenic architectures. While there is much work left to do to improve the personal and clinical utility of general risk profiling framework, we highlight that more comprehensive models that infer proper genotype encodings and account for epistatic effects greatly improve the prediction efficiency and affords new opportunities for more accurate clinical prevention.

### Acknowledgement

We thank Dr. Kristel Van Steen and Aldo Camargo for their helpful responses to our inquires about the MB-MDR software.

#### References

#### 1. Chapter 11: Genome-Wide Association Studies

William S. Bush, Jason H. Moore

PLoS Computational Biology (2012-12-27) https://doi.org/gfr9pz

DOI: <u>10.1371/journal.pcbi.1002822</u> · PMID: <u>23300413</u> · PMCID: <u>PMC3531285</u>

#### 2. Genome-wide association studies for common diseases and complex traits

Joel N. Hirschhorn, Mark J. Daly

Nature Reviews Genetics (2005-02) <a href="https://doi.org/bhcc36">https://doi.org/bhcc36</a>

DOI: <u>10.1038/nrg1521</u> · PMID: <u>15716906</u>

#### 3. Genome-wide association studies: theoretical and practical concerns

William Y. S. Wang, Bryan J. Barratt, David G. Clayton, John A. Todd

Nature Reviews Genetics (2005-02) https://doi.org/fcqz33

DOI: 10.1038/nrg1522 · PMID: 15716907

#### 4. What Are Polygenic Scores and Why Are They Important?

Leo P. Sugrue, Rahul S. Desikan

JAMA (2019-05-14) https://doi.org/gfx8wg

DOI: 10.1001/jama.2019.3893 · PMID: 30958510

#### 5. The personal and clinical utility of polygenic risk scores

Ali Torkamani, Nathan E. Wineinger, Eric J. Topol

Nature Reviews Genetics (2018-05-22) https://doi.org/gd46bh

DOI: <u>10.1038/s41576-018-0018-x</u> · PMID: <u>29789686</u>

### ${\bf 6. \ Common\ polygenic\ variation\ contributes\ to\ risk\ of\ schizophrenia\ and\ bipolar\ disorder \it Nature}$

(2009-07-01) https://doi.org/cb5f2j

DOI: 10.1038/nature08185 · PMID: 19571811 · PMCID: PMC3912837

# 7. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting

Pradeep Natarajan, Robin Young, Nathan O. Stitziel, Sandosh Padmanabhan, Usman Baber, Roxana Mehran, Samantha Sartori, Valentin Fuster, Dermot F. Reilly, Adam Butterworth, ... Sekar Kathiresan *Circulation* (2017-05-30) <a href="https://doi.org/gbgqhb">https://doi.org/gbgqhb</a>

DOI: 10.1161/circulationaha.116.024436 · PMID: 28223407 · PMCID: PMC5484076

### 8. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States

Paige Maas, Myrto Barrdahl, Amit D. Joshi, Paul L. Auer, Mia M. Gaudet, Roger L. Milne, Fredrick R. Schumacher, William F. Anderson, David Check, Subham Chattopadhyay, ... Nilanjan Chatterjee *JAMA Oncology* (2016-10-01) https://doi.org/gf4w2z

DOI: <u>10.1001/jamaoncol.2016.1025</u> · PMID: <u>27228256</u> · PMCID: <u>PMC5719876</u>

# 9. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts

Tyler M Seibert, Chun Chieh Fan, Yunpeng Wang, Verena Zuber, Roshan Karunamuni, J Kellogg Parsons, Rosalind A Eeles, Douglas F Easton, ZSofia Kote-Jarai, Ali Amin Al Olama, ...

*BMJ* (2018-01-10) <a href="https://doi.org/gcsrzs">https://doi.org/gcsrzs</a>

DOI: <u>10.1136/bmj.j5757</u> · PMID: <u>29321194</u> · PMCID: <u>PMC5759091</u>

#### 10. Multifactor-Dimensionality Reduction Reveals High-Order Interactions among Estrogen-Metabolism Genes in Sporadic Breast Cancer

Marylyn D. Ritchie, Lance W. Hahn, Nady Roodi, L. Renee Bailey, William D. Dupont, Fritz F. Parl, Jason H. Moore

The American Journal of Human Genetics (2001-07) https://doi.org/bh3x75

DOI: 10.1086/321276 · PMID: 11404819 · PMCID: PMC1226028

#### 11. Epistasis Analysis Using Multifactor Dimensionality Reduction

Jason H. Moore, Peter C. Andrews

Methods in Molecular Biology (2014-11-04) https://doi.org/gf5ptc

DOI: 10.1007/978-1-4939-2155-3 16 · PMID: 25403539

### 12. Risk score modeling of multiple gene to gene interactions using aggregated-multifactor dimensionality reduction

Hongying Dai, Richard J Charnigo, Mara L Becker, J Steven Leeder, Alison A Motsinger-Reif *BioData Mining* (2013-01-08) https://doi.org/gb5fmn

DOI: <u>10.1186/1756-0381-6-1</u> · PMID: <u>23294634</u> · PMCID: <u>PMC3560267</u>

# 13. Model-Based Multifactor Dimensionality Reduction to detect epistasis for quantitative traits in the presence of error-free and noisy data

Jestinah M Mahachie John, François Van Lishout, Kristel Van Steen European Journal of Human Genetics (2011-03-16) https://doi.org/bndfnk

DOI: 10.1038/ejhg.2011.17 · PMID: 21407267 · PMCID: PMC3110049

# 14. Model-Based Multifactor Dimensionality Reduction for detecting epistasis in case-control data in the presence of noise

Tom Cattaert, M. Luz Calle, Scott M. Dudek, Jestinah M. Mahachie John, François Van Lishout, Victor Urrea, Marylyn D. Ritchie, Kristel Van Steen

Annals of Human Genetics (2010-09-08) https://doi.org/bgg3n2

DOI: 10.1111/j.1469-1809.2010.00604.x · PMID: 21158747 · PMCID: PMC3059142

#### 15. An efficient algorithm to perform multiple testing in epistasis screening

François Van Lishout, Jestinah M Mahachie John, Elena S Gusareva, Victor Urrea, Isabelle Cleynen, Emilie Théâtre, Benoît Charloteaux, Malu Luz Calle, Louis Wehenkel, Kristel Van Steen *BMC Bioinformatics* (2013-04-24) https://doi.org/f4v3n7

DOI: <u>10.1186/1471-2105-14-138</u> · PMID: <u>23617239</u> · PMCID: <u>PMC3648350</u>

#### 16. A Mathematical Theory of Communication

C. E. Shannon

Bell System Technical Journal (1948-07) https://doi.org/b39t

DOI: <u>10.1002/j.1538-7305.1948.tb01338.x</u>

#### 17. Epistasis Analysis Using Information Theory

Jason H. Moore, Ting Hu

Methods in Molecular Biology (2014-11-03) <a href="https://doi.org/gf484q">https://doi.org/gf484q</a>

DOI: 10.1007/978-1-4939-2155-3 13 · PMID: 25403536

# 18. A heuristic method for simulating open-data of arbitrary complexity that can be used to compare and evaluate machine learning methods

Jason H. Moore, Maksim Shestov, Peter Schmitt, Randal S. Olson

Biocomputing 2018 (2017-11-17) <a href="https://doi.org/gf5b6s">https://doi.org/gf5b6s</a>

DOI: 10.1142/9789813235533\_0024

### 19. Open collaborative writing with Manubot

Daniel S. Himmelstein, Vincent Rubinetti, David R. Slochower, Dongbo Hu, Venkat S. Malladi, Casey S. Greene, Anthony Gitter

PLOS Computational Biology (2019-06-24) https://doi.org/c7np

DOI: <u>10.1371/journal.pcbi.1007128</u> · PMID: <u>31233491</u> · PMCID: <u>PMC6611653</u>