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Paper

`simmr`: An open-source tool to perform simulations in Mendelian Randomization

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Abstract

Mendelian Randomization (MR) has become a popular tool for inferring causality of risk factors on disease. There are currently over 50 different methods available to perform MR. The need for so many methods comes from the numerous challenges that real-world applications of MR can face. However, the literature currently lacks a standard simulation environment in which researchers can fairly evaluate the performance of competing methods. This has sometimes led to conflicting and misleading simulation results from independent researchers intending to simulate the same reality. We present `simmr`, an open-source software for performing simulations to evaluate the performance of different MR methods. other researchers can directly modify the `simmr` source code with the intended purpose of eventually arriving at a widely accepted protocol for researchers to evaluate the performance of MR methods in different real-world conditions.

Key words: Mendelian Randomization, bias, causal inference, instrumental variables, simulation, statistical genetics

Introduction

Mendelian Randomization is a genetic instrumental variable method that has become a popular statistical tool for identifying risk factors that may cause disease [46, 44]. The validity of inferences made using MR relies heavily on the satisfaction of three primary assumptions [16]: the genetic instruments are (i) strongly associated with the exposure(s) [14, 48], (i) not associated with the outcome conditional on the exposures [26], and (iii) not associated with any confounders of the exposure(s)-outcome relationship(s) [35]. Violation of any of these assumptions can lead to bias in causal estimation, false positive, and/or false negative findings [2]. Three additional challenges are present in MR analyses: (a) some individuals may have been present in both the exposure(s) and outcome GWAS [6], (b) applying strict IV selection criteria to satisfy assumption (i) above can introduce a 'winner's curse' bias [29], and (c)

strong LD between IVs [21], and its imprecise estimation using reference panels, can drastically inflate false positive rates [23].

Many MR methods have been introduced in the literature to address different subsets of assumptions (i)-(iii) and scenarios (a)-(c) in either the single-exposure (univariable) or multiple-exposure (multivariable) settings [1]. These methods include IVW [5], dIVW [59], pIVW [56], MR-Egger [3], MR-RAPS [62], MRAID [60], MRMix [40], MR-cML [57], MVMR-cML [32], MR-PRESSO [52], IMRP [63], MR-Median [3], MR-MaxLike [7], MR-Corr [11], MR-Robust [43], MR-Lasso [30], MR-Conmix [8], CAUSE [35], MR-CUE [13], MR-Horse [24], MR-BMA [64], MR-Robin [22], EMIC [28], MR-Mode [25], MRBEE [34], MR-Lap [36], the Wald test [38], JAM [37], MR using factor analysis [39], mixIE [31], MRMO [18], BMRMO [17], BWMR [61], moPMR-Egger [33], sisVIVE [30], MR-LDP [12], MR-CIP [55], MR-PATH [27], MR-Clust [20], BayesMR [4], BMRE [49], MR-link [51], OMR [54], CoJo [58], MR using PCA [10], and GRAPPLE [53]. Clearly, the literature is saturated with MR estimators. In each of these studies introducing the methods, simulation was performed to evaluate the performance of new and existing methods.

The range of simulation settings reported in the literature is vast. Some use 50 or fewer SNPs to explain all phenoptypic [52, 63] or genetic [32] variance while others have used hundreds [34] or even thousands [36] of SNPs. Additionally, some have used GWAS sample sizes no larger than 500 [18] while others have used GWAS sample sizes no less than 100k [55]. Nearly all multivariable MR simulations are inconsistent with the literature, namely because 50 or less IVs are used in simulation [32, 45, 47] but real data analyses with multiple exposures may contain hundreds or thousands of IVs [15, 34]. Since weak IV bias generally becomes more severe as more IVs are used [14, 34], MVMR simulations in which very few IVs are used may unrealistically reflect optimal performance of MVMR methods, which of course may break down in practice. The wide array of conditions in which different subsets of all available MR methods have been tested has produced a literature of results potentially sensitive to the unique simulation conditions that may or may not mirror reality. Indeed, some independent simulations intended to mimic the same reality have even produced conflicting results (e.g., [36] and [59], [32] and [50], [41] and [57]).

We introduce `simmr`, an open-source and easily accessible tool for generating data to use in MR simulations. `simmr` can be used in both the univariable and multivariable MR settings and users can simultaneously specify different properties of uncorrelated horizontal pleiotropy, correlated horizontal pleitoropy, weak instrument bias, GWAS sample size and overlap, winner's curse, and linkage disequilibrium between instrumental variables. With no standard set in the literature, the purpose of the publicly modifiable `simmr` software is to begin the construction of a standard simulation environment in which fair comparisons can be made between competing MR estimators in different settings that are encountered in practice.

Implementation

Simulation models

The simulation data-generating process is based on the directed acyclic graph (DAG) in Figure 1. Simulation data are generated under the directed acyclic graph in Figure

2 and the following models:

$$U = \mathbf{g}^\top \boldsymbol{\gamma}^C + \epsilon_U, \tag{1}$$

$$\mathbf{x} = \mathbf{B}^\top \mathbf{g} + \pi_{\mathbf{x}} U + \boldsymbol{\epsilon}_{\mathbf{x}}, \tag{2}$$

$$Y = \mathbf{x}^\top \boldsymbol{\theta} + \pi_Y U + \mathbf{g}^\top \boldsymbol{\gamma}^U + \epsilon_Y \tag{3}$$

$$= \boldsymbol{\alpha}^\top \mathbf{g} + \widetilde{\epsilon}_Y \tag{4}$$

where U is a confounder of the relationship between exposure(s) $\mathbf{x}$ and outcome Y, $\boldsymbol{\theta}$ represents the corresponding causal effect(s), $\mathbf{B}$ represents true associations between $\mathbf{g}$ and $\mathbf{x}$, and $\boldsymbol{\gamma}^C$ and $\boldsymbol{\gamma}^U$ are respectively CHP and UHP effects. Users of `simmr` can fix the variance explained in each phenotype by the others and partition the variance in $\mathbf{x}$ explained by $\mathbf{g}$ into effects from UHP, CHP, valid, and weak SNPs using the procedure in Algorithm 1:

Figure 3 shows an example of data generated under the above models alongside computation times for different combinations of GWAS sample overlap, GWAS sample sizes, and numbers of causal exposure SNPs. This set of SNPs can then be reduced by the user-specified significance and LD pruning thresholds [19], both of which are implemented in the `simmr` software. Users also have the option to perform IV pruning such that a specific F-statistic for instrument strength [9] is achieved for each exposure. Some MR methods use the matrix $\boldsymbol{\Omega}$ of correlations between GWAS estimation errors across cohorts to correct for weak instrument bias (e.g., [32], [34], [12], [36]). These methods calculate $\boldsymbol{\Omega}$ using non-significant GWAS summary statistics [34, 36] or LD score regression [32, 12]. `simmr` will directly calculate $\boldsymbol{\Omega}$ from realized values of $(\mathbf{x}, Y)$ without any estimation error and return it to the user.

Software

`simmr` uses the popular R software v4.0.0 or later [42] and only requires downloading 3 files: `basicfunctions.R`, `set_params.R`, and `generate_data.R`. Users of `simmr` change the parameters in the `set_params.R` file to their desired quantities. These parameters are displayed in blue text in Figure 2. Next, another file named `generate_data.R` is sourced and the simulation data is automatically loaded into the user's R environment where simulations can be performed. The `simmr` software is available at `https://github.com/noahlorinczcomi/simmr`, where a tutorial is present and researchers can directly change any of the source code to improve it. Changes are tracked automatically and earlier versions can be restored at any time.

Conclusion

There is currently no standard simulation framework for performing simulations in Mendelian Randomization research. Different researchers have independently performed simulations designed to reflect the same real world conditions, but the performance of the same methods can vary greatly. The MR literature is replete with MR estimators, with each at some point having a demonstrated advantage over others in simulation. The transferability of their performance to real world settings may be in question if their performance in independent simulations cannot be replicated. We

Algorithm 1 Pseudo-code of simulated data generation using `simmr`

Require: $\text{Var}(Y|\mathbf{x}, U)$, $\text{Cov}(\mathbf{x}|U)$, $\text{Cov}(\mathbf{x}|\mathbf{g})$, phenotypic and genetic correlation between exposures $\mathbf{S}_P$ and $\mathbf{S}_G$, exposures and outcome GWAS sample size n_1 and n_0 and proportion of overlap p_{01}, number of causal exposure SNPs M and their LD structure $\mathbf{R}$, number of UHP and CHP causal exposure SNPs m^U and m^C, respective variance in Y and U explained by UHP and CHP causal exposure SNPs $\sigma^2_{\gamma^U}$ and $\sigma^2_{\gamma^C}$, LD pruning threshold for IV selection κ^2, simulation type (either winner's curse or weak IVs), P-value threshold for IV selection if performing winner's curse simulations τ, F-statistic for IV strength of association with exposures (F) if performing a weak instrument simulation.

Preliminaries: All phenotypes will have mean 0 and variance 1. UHP, CHP, and SNPs that are otherwise valid IV candidates are put into mutually exclusive groups (see Figure 2).

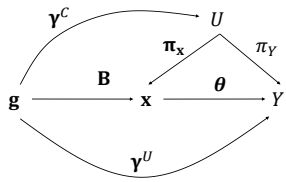
1. Draw $n_0 + n_1$ genotypes from $g_j \sim \text{Binomial}(2, 0.3)$ and standardize to $\text{E}(g_j) = 0, \text{Var}(g_j) = 1$; $j = 1, ..., M$
2. Draw m^C CHP effects from $\gamma^C_j \sim \text{Uniform}(-1, 1)$ and re-scale to explain $\sigma^2_{\gamma^C}$ variance in U
3. Draw m^U CHP effects from $\gamma^U_j \sim \text{Uniform}(-1, 1)$ and re-scale to explain $\sigma^2_{\gamma^U}$ variance in Y
4. Draw un-transformed true SNP associations with the exposures ($\widetilde{\mathbf{B}}$) from a matrix normal distribution with row-wise covariance $\mathbf{R}$ and column-wise covariance $\mathbf{S}_G$ and re-scale the columns such that $\left[\text{diag}(\widetilde{\mathbf{B}})\right]_k = 1 - \left[\text{diag}(\text{Cov}\{\mathbf{x}|\mathbf{g}\})\right]_k$
5. Transform $\widetilde{\mathbf{B}}$ using the copula method to convert to a multivariate uniform distribution: $\left[\mathbf{B}\right]_{jk} = \Phi\Big(\left[\tilde{B}\mathbf{S}_G^{-1/2}\right]_{jk}\Big)$
6. Set $\pi_Y = -1$ and $\boldsymbol{\theta} = (1, ..., 1)$ and re-scale each to achieve $\text{Var}(Y|\mathbf{x}, U)$
7. Define sets $\mathcal{P}_\mathbf{x}$ and $\mathcal{P}_Y$ of simulated individuals to respectively use in the exposure and outcome GWAS, of which $p_{01} \times \min(n_0, n_1)$ elements will overlap
8. Perform GWAS using OLS on phenotypes $Y_{\mathcal{P}_Y}$ and $\mathbf{x}_{\mathcal{P}_\mathbf{x}}$ using OLS
9. Perform IV selection according to κ^2, τ, and F to obtain IV set $\mathcal{S}$

Ensure: GWAS estimates for the set of IVs: $\widehat{\mathbf{B}}_\mathcal{S}$, $\widehat{\text{SE}}(\widehat{\mathbf{B}}_\mathcal{S})$, $\widehat{\boldsymbol{\alpha}}_\mathcal{S}$, and $\widehat{\text{SE}}(\widehat{\boldsymbol{\alpha}}_\mathcal{S})$ as the corresponding R objects `bx`, `bxse`, `by`, and `byse`; $\boldsymbol{\theta}$ as `theta`; $\boldsymbol{\Omega}$ as `RhoME`; $\mathbf{R}_\mathcal{S}$ as `LDMatrix`.

present `simmr`, an open-source software for performing simulations to evaluate the performance of Mendelian Randomization methods. Researchers can directly modify the `simmr` software. It is our intention that the community will use this opportunity to establish an accepted procedure for perfoming simulations using MR. As `simmr` is refined and expanded, the performance of new and existing MR methods should become more transferable to real-world conditions.

Availability and requirements

Project name: `simmr`
Project home page: `https:github.com/noahlorinczcomi/simmr`
Operating system(s): Platform independent



$$\mathbf{g} = (g_1, g_2, \ldots, g_M)^\top$$
$$\mathbf{x} = (x_1, x_2, \ldots, x_p)^\top$$
$$\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_p)^\top$$

Fig. 1: This DAG is used to produce the simulation models described in the main text. Users of `simmr` can modify all parameters that are present in this DAG.

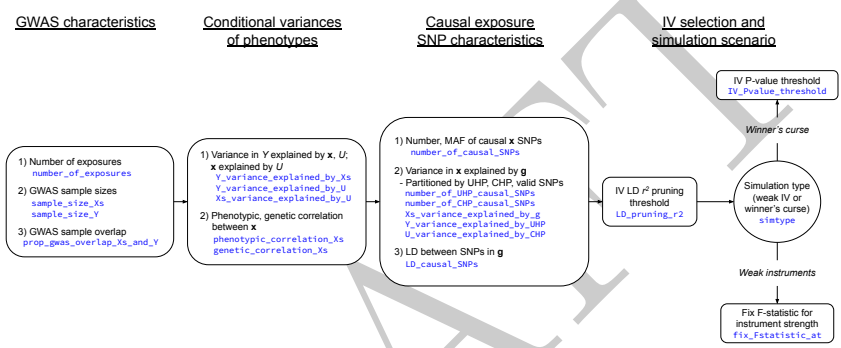


Fig. 2: This figure provides a conceptual overview of the `simmr` data-generating process. First, users specify the sizes of exposure and outcome GWAS sample sizes and their degree of overlap. Next, users specify the true causal model by changing variances in each phenotype explained by each other and by the SNPs that are causally related to the exposures. Next, the user specifies the particular characteristics of the causal SNPs, inputting the degree of UHP, CHP, and LD between them. Finally, the user can perform IV selection to evaluate winner's curse or weak instrument bias. `simmr` commands are presented in blue text underneath the description for each parameter.

Programming language: R
Other requirements: R 4.1.1 or higher
License: MIT
Any restrictions to use by non-academics: License needed

Competing interests

No competing interest is declared.

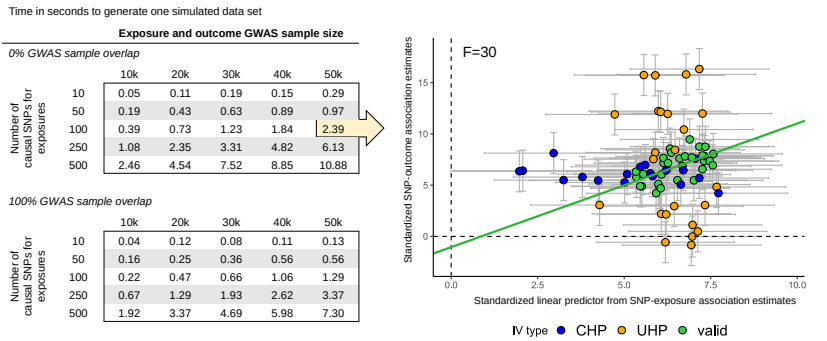


Fig. 3: This figure shows computation times to generate one simulated data set using `simmr` (left) and an example of the generated summary data for evaluation of MR methods (right). The data in the right panel is only of the final selected and pruned set of instruments. The original number of causal SNPs was 100, but the selected number of IVs to achieve an F-statistic of 30 was 91. The full code used to produce this figure is available at `https://github.com/noahlorinczcomi/simmr`. The x-axis in the right panel is the standardized linear predictor used in multivariable MR ($\hat{\mathbf{B}}\boldsymbol{\theta}$) and the y-axis is the estimated association of the IVs with the outcome in standardized scale. The green line is the linear fit to the green points representing valid instrumental variables. The yellow arrow in the left panel indicates that the time it took to generate the data in the right panel was 2.4 seconds when there is no GWAS sample overlap and GWAS sample sizes are 50k. When the exposure and outcome GWAS sample overlap is 100%, computation time was reduced to 1.39 seconds.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The `simmr` software is available at `https://github.com/noahlorinczcomi/simmr`, where you can also find all R code to reproduce the results in Figure 3.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NLC conceived of the idea, wrote the manuscript, and created the software. YY and XZ edited the manuscript and software.

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