

# Package ‘GEint’

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**Type** Package

**Title** Misspecified Models for Gene-Environment Interaction

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## Description

The first major functionality is to compute the bias in misspecified linear gene-environment interaction models. The most generalized function for this objective is `GE_bias()`. However `GE_bias()` requires specification of many higher order moments of covariates in the model. If users are unsure about how to calculate/estimate these higher order moments, it may be easier to use `GE_bias_normal_squaredmis()`. This function places many more assumptions on the covariates (most notably that they are all jointly generated from a multivariate normal distribution) and is thus able to automatically calculate many of the higher order moments automatically, necessitating only that the user specify some covariances. There are also functions to solve for the bias through simulation and non-linear equation solvers, these can be used to check your work. Second major functionality is to implement the Bootstrap Inference with Correct Sandwich (BICS) testing procedure, which we have found to provide better finite-sample performance than other inference procedures for testing GxE interaction. More details on these functions are available in Sun, Carroll, Christiani, and Lin (2018) <[doi:10.1111/biom.12813](https://doi.org/10.1111/biom.12813)>.

**Imports** mvtnorm, bindata, nleqslv, pracma, speedglm, rje, geepack, stats

**License** GPL-3

**RoxygenNote** 6.1.1

**Suggests** knitr, rmarkdown, testthat

**VignetteBuilder** knitr

**NeedsCompilation** no

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GE_bias	<i>GE_bias.R</i>
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### Description

A function to calculate the bias in testing for GxE interaction.

### Usage

```
GE_bias(beta_list, cov_list, cov_mat_list, mu_list, HOM_list)
```

### Arguments

beta_list	A list of the effect sizes in the true model. Use the order beta_0, beta_G, beta_E, beta_I, beta_Z, beta_M. If G or Z or M is a vector, then beta_G/beta_Z/beta_M should be vectors. If Z and/or M/W do not exist in your model, then set beta_Z and/or beta_M = 0.
cov_list	A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE_enumerate_inputs(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, if Z doesn't exist and W includes 2 covariates, then set cov(EZ) = 0 and cov(ZW) = (0,0). If describing expectations relating two vectors, i.e. Z includes two covariates and W includes three covariates, sort by the first term and then the second. Thus in the example, the first three terms of cov(ZW) are cov(Z_1,W_1),cov(Z_1,W_2), cov(Z_1,W_3), and the last three terms are cov(Z_3,W_1), cov(Z_3,W_2), cov(Z_3,W_3).
cov_mat_list	A list of matrices of expectations as specified by GE_enumerate_inputs().
mu_list	A list of means as specified by GE_enumerate_inputs().
HOM_list	A list of higher order moments as specified by GE_enumerate_inputs().

**Value**

A list of the fitted coefficients alpha

**Examples**

```
solutions <- GE_bias_normal_squaredmis( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3, cov_Z=1, cov_W=1)
GE_bias(beta_list=solutions$beta_list, solutions$cov_list, solutions$cov_mat_list,
solutions$mu_list, solutions$HOM_list)
```

---

GE\_bias\_normal\_squaredmis

*GE\_bias\_normal\_squaredmis.R*

---

**Description**

A function to calculate the bias in testing for GxE interaction, making many more assumptions than GE\_bias(). The additional assumptions are added to simplify the process of calculating/estimating many higher order moments which the user may not be familiar with.

The following assumptions are made:

- (1) All fitted covariates besides G (that is, E, all Z, and all W) have a marginal standard normal distribution with mean 0 and variance 1. This corresponds to the case of the researcher standardizing all of their fitted covariates.
- (2) All G are generated by means of thresholding two independent normal RVs and are centered to have mean 0.
- (3) The joint distributions of E, Z, W, and the thresholded variables underlying G can be described by a multivariate normal distribution.
- (4) The misspecification is of the form  $f(E)=h(E)=E^2$ , and  $M_j=W_j^2$  for all j. In particular, W always has the same length as M here.

**Usage**

```
GE_bias_normal_squaredmis(beta_list, rho_list, prob_G, cov_Z = NULL,
cov_W = NULL, corr_G = NULL)
```

**Arguments**

- |           |                                                                                                                                                                                                                                                                                                                |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| beta_list | A list of the effect sizes in the true model. Use the order beta_0, beta_G, beta_E, beta_I, beta_Z, beta_M. If G or Z or M is a vector, then beta_G/beta_Z/beta_M should be vectors. If Z and/or M/W do not exist in your model, then set beta_Z and/or beta_M = 0.                                            |
| rho_list  | A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE_enumerate_inputs(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, if Z doesn't exist and W includes 2 covariates, then set cov(EZ) = 0 and |

cov(ZW) = (0,0). If describing expectations relating two vectors, i.e. Z includes two covariates and W includes three covariates, sort by the first term and then the second. Thus in the example, the first three terms of cov(ZW) are cov(Z\_1,W\_1),cov(Z\_1,W\_2), cov(Z\_1,W\_3), and the last three terms are cov(Z\_3,W\_1), cov(Z\_3,W\_2), cov(Z\_3,W\_3).

prob_G	Probability that each allele is equal to 1. Since each SNP has two alleles, the expectation of G is 2*prob_G. Should be a d*1 vector.
cov_Z	Should be a matrix equal to cov(Z) or NULL if no Z.
cov_W	Should be a matrix equal to cov(W) or NULL if no W.
corr_G	Should be a matrix giving the *pairwise correlations* between each SNP in the set, or NULL. Must be specified if G is a vector. For example, the [2,3] element of the matrix would be the pairwise correlation between SNP2 and SNP3.

### Value

A list with the elements:

alpha_list	The asymptotic values of the fitted coefficients alpha.
beta_list	The same beta_list that was given as input.
cov_list	The list of all covariances (both input and calculated) for use with GE_nleqslv() and GE_bias().
mu_list	List of calculated means for f(E), h(E), Z, M, and W for use with GE_nleqslv() and GE_bias().
HOM_list	List of calculated Higher Order Moments for use with GE_nleqslv() and GE_bias().

### Examples

```
GE_bias_normal_squaredmis( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), cov_Z=1, cov_W=1, prob_G=0.3)
```

---

```
GE_bias_normal_squaredmis_old
      GE_bias_normal_squaredmis_old.R
```

---

### Description

A function to calculate the bias in testing for GxE interaction, making many more assumptions than GE\_bias\_old(). The additional assumptions are added to simplify the process of calculating/estimating many higher order moments which the user may not be familiar with.

The following assumptions are made:

- (1) All fitted covariates besides G (that is, E, all Z, and all W) have a marginal standard normal distribution with mean 0 and variance 1. This corresponds to the case of the researcher standardizing all of their fitted covariates.
- (2) G is generated by means of thresholding two independent normal RVs and is centered to have mean 0.
- (3) The joint distributions of E, Z, W, and the thresholded variables underlying G can be

described by a multivariate normal distribution.

(4) The misspecification is of the form  $f(E)=h(E)=E^2$ , and  $M_j=W_j^2$  for all  $j$ . In particular,  $W$  always has the same length as  $M$  here.

### Usage

```
GE_bias_normal_squaredmis_old(beta_list, rho_list, prob_G, cov_Z = NULL,
                               cov_W = NULL)
```

### Arguments

- |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| beta_list | A list of the effect sizes in the true model. Use the order beta_0, beta_G, beta_E, beta_I, beta_Z, beta_M. If Z or M is a vector, then beta_Z and beta_M should be vectors. If Z or M is not in the model (i.e. all covariates other than G+E have been specified incorrectly, or all covariates other than G+E have been specified correctly, or the only covariates are G+E), then set beta_Z=0 and/or beta_M=0.                                                                                                                                                                                                                                                                                                                 |
| rho_list  | A list of the 6 pairwise covariances between the covariates. These should be in the order (1) cov_GE (2) cov_GZ (3) cov_EZ (4) cov_GW (5) cov_EW (6) cov_ZW. Again if Z or W are vectors then terms like cov_GZ should be vectors (in the order cov(G,Z_1),...,cov(G,Z_p)) where Z is of dimension p, and similarly for W. If Z or M are vectors, then cov_ZW should be a vector in the order (cov(Z_1,W_1),...,cov(Z_1,W_q), cov(Z_2,W_1),.....,cov(Z_p,W_q) where Z is a vector of length p and W is a vector of length q. If Z or M are not in the model then treat them as the constant 0. So for example if Z is not in the model and M (and therefore W) is a vector of length 2, we would have cov_EZ=0 and cov(ZW) = (0,0). |
| prob_G    | Probability that each allele is equal to 1. Since each SNP has two alleles, the expectation of G is 2*prob_G.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| cov_Z     | Only specify this if Z is a vector, gives the covariance matrix of Z (remember by assumption Z has mean 0 and variance 1). The (i,j) element of the matrix should be the (i-1)(i-2)/2+j element of the vector.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| cov_W     | Only specify this if W is a vector, gives the covariance matrix of W (remember by assumption W has mean 0 and variance 1). The (i,j) element of the matrix should be the (i-1)(i-2)/2+j element of the vector.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

### Value

A list with the elements:

- |              |                                                                                                  |
|--------------|--------------------------------------------------------------------------------------------------|
| alpha_list   | The asymptotic values of the fitted coefficients alpha.                                          |
| beta_list    | The same beta_list that was given as input.                                                      |
| cov_list     | The list of all covariances (both input and calculated) for use with GE_nleqslv() and GE_bias(). |
| cov_mat_list | List of additionally calculated covariance matrices for use with GE_nleqslv() and GE_bias().     |

- mu\_list            List of calculated means for f(E), h(E), Z, M, and W for use with GE\_nleqslv() and GE\_bias().
- HOM\_list           List of calculated Higher Order Moments for use with GE\_nleqslv() and GE\_bias().

### Examples

```
GE_bias_normal_squaredmis_old( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3)
```

---

GE_bias_old	<i>GE_bias_old.R</i>
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---

### Description

A function to calculate the bias in testing for GxE interaction.

### Usage

```
GE_bias_old(beta_list, cov_list, cov_mat_list, mu_list, HOM_list)
```

### Arguments

- beta\_list            A list of the effect sizes in the true model. Use the order beta\_0, beta\_G, beta\_E, beta\_I, beta\_Z, beta\_M. If Z or M is a vector, then beta\_Z and beta\_M should be vectors. If Z and/or M/W do not exist in your model, then set beta\_Z and/or beta\_M = 0.
- cov\_list             A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE\_enumerate\_inputs\_old(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, if Z doesn't exist and W includes 2 covariates, then set cov(EZ) = 0 and cov(ZW) = (0,0).
- cov\_mat\_list        A list of matrices of expectations as specified by GE\_enumerate\_inputs\_old().
- mu\_list             A list of means as specified by GE\_enumerate\_inputs\_old().
- HOM\_list            A list of higher order moments as specified by GE\_enumerate\_inputs\_old().

### Value

A list of the fitted coefficients alpha

### Examples

```
solutions <- GE_bias_normal_squaredmis_old( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3)
GE_bias_old(beta_list=solutions$beta_list, solutions$cov_list, solutions$cov_mat_list,
solutions$mu_list, solutions$HOM_list)
```

---

 GE\_BICS

*GE\_BICS.R*


---

**Description**

A function to perform inference on the GxE interaction regression coefficient. Shows better small sample performance than comparable methods.

**Usage**

```
GE_BICS(outcome, design_mat, num_boots = 1000, desired_coef,
        outcome_type, check_singular = FALSE)
```

**Arguments**

outcome	The outcome vector
design_mat	The design matrix of covariates
num_boots	The number of bootstrap resamples to perform - we suggest 1000
desired_coef	The column in the design matrix holding the interaction covariate
outcome_type	Either 'D' for dichotomous outcome or 'C' for continuous outcome
check_singular	Make sure the design matrix can be inverted for variance estimation

**Value**

The p-value for the interaction effect

**Examples**

```
E <- rnorm(n=500)
G <- rbinom(n=500, size=2, prob=0.3)
design_mat <- cbind(1, G, E, G*E)
outcome <- rnorm(500)
GE_BICS(outcome=outcome, design_mat=design_mat, desired_coef=4, outcome_type='C')
```

---

 GE\_BICS\_old

*GE\_BICS\_old.R*


---

**Description**

A function to perform inference on the GxE interaction regression coefficient. Shows better small sample performance than comparable methods.

**Usage**

```
GE_BICS_old(outcome, design_mat, num_boots = 1000, desired_coef,
            outcome_type)
```

**Arguments**

outcome	The outcome vector
design_mat	The design matrix of covariates
num_boots	The number of bootstrap resamples to perform - we suggest 1000
desired_coef	The column in the design matrix holding the interaction covariate
outcome_type	Either 'D' for dichotomous outcome or 'C' for continuous outcome

**Value**

The p-value for the interaction effect

**Examples**

```
E <- rnorm(n=500)
G <- rbinom(n=500, size=2, prob=0.3)
design_mat <- cbind(1, G, E, G*E)
outcome <- rnorm(500)
GE_BICS_old(outcome=outcome, design_mat=design_mat, desired_coef=4, outcome_type='C')
```

---

GE\_enumerate\_inputs    *GE\_enumerate\_inputs.R*

---

**Description**

Call this function to display the necessary inputs for GE\_bias\_set. For terms in cov\_mat\_list like E[ZZ], these should be matrices where the (i,j) element is E[Z<sub>i</sub>\*Z<sub>j</sub>].

**Usage**

```
GE_enumerate_inputs()
```

**Value**

Nothing

**Examples**

```
GE_enumerate_inputs()
```



---

GE\_enumerate\_inputs\_old  
*GE\_enumerate\_inputs\_old.R*

---

### Description

Call this function to display the necessary inputs for GE\_bias. If you see a term like mu\_Gf, that means it is the scalar  $E[G*f(E)]$ . If you see a term like MU\_GM, that means it is the vector  $c(E[G*M_1], E[G*M_2], \dots, E[G*M_q])$  where M is of dimension q. For terms in cov\_mat\_list like E[ZZ], these should be matrices where the (i,j) element is  $E[Z_i*Z_j]$ .

### Usage

```
GE_enumerate_inputs_old()
```

### Value

Nothing

### Examples

```
GE_enumerate_inputs_old()
```

---

GE\_nleqslv                    *GE\_nleqslv.R #' Uses package nleqslv to get a numerical solution to the score equations, which we can use to check our direct solution from GE\_bias().*

---

### Description

GE\_nleqslv.R #' Uses package nleqslv to get a numerical solution to the score equations, which we can use to check our direct solution from GE\_bias().

### Usage

```
GE_nleqslv(beta_list, cov_list, cov_mat_list, mu_list, HOM_list)
```

### Arguments

beta\_list                    A list of the effect sizes in the true model. Use the order beta\_0, beta\_G, beta\_E, beta\_I, beta\_Z, beta\_M. If G or Z or M is a vector, then beta\_G/beta\_Z/beta\_M should be vectors. If Z and/or M/W do not exist in your model, then set beta\_Z and/or beta\_M = 0.

cov_list	A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE_enumerate_inputs(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, if Z doesn't exist and W includes 2 covariates, then set $\text{cov}(EZ) = 0$ and $\text{cov}(ZW) = (0,0)$ . If describing expectations relating two vectors, i.e. Z includes two covariates and W includes three covariates, sort by the first term and then the second. Thus in the example, the first three terms of $\text{cov}(ZW)$ are $\text{cov}(Z_1, W_1), \text{cov}(Z_1, W_2), \text{cov}(Z_1, W_3)$ , and the last three terms are $\text{cov}(Z_3, W_1), \text{cov}(Z_3, W_2), \text{cov}(Z_3, W_3)$ .
cov_mat_list	A list of matrices of expectations as specified by GE_enumerate_inputs().
mu_list	A list of means as specified by GE_enumerate_inputs().
HOM_list	A list of higher order moments as specified by GE_enumerate_inputs().

**Value**

A list of the fitted coefficients alpha

**Examples**

```
solutions <- GE_bias_normal_squaredmis( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3, cov_Z=1, cov_W=1)
GE_nleqslv(beta_list=solutions$beta_list, solutions$cov_list, solutions$cov_mat_list,
solutions$mu_list, solutions$HOM_list)
```

---

GE_nleqslv_old	<i>GE_nleqslv_old.R #</i> Uses package nleqslv to get a numerical solution to the score equations, which we can use to check our direct solution from GE_bias_old().
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---

**Description**

GE\_nleqslv\_old.R # Uses package nleqslv to get a numerical solution to the score equations, which we can use to check our direct solution from GE\_bias\_old().

**Usage**

```
GE_nleqslv_old(beta_list, cov_list, cov_mat_list, mu_list, HOM_list)
```

**Arguments**

beta_list	A list of the effect sizes in the true model. Use the order beta_0, beta_G, beta_E, beta_I, beta_Z, beta_M. If Z or M is a vector, then beta_Z and beta_M should be vectors. If Z and/or M/W do not exist in your model, then set beta_Z and/or beta_M = 0.
cov_list	A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE_enumerate_inputs_old(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, set $\text{cov}(EZ) = 0$ and $\text{cov}(ZW) = 0$ .

cov\_mat\_list A list of matrices of expectations as specified by GE\_enumerate\_inputs\_old().  
 mu\_list A list of means as specified by GE\_enumerate\_inputs\_old().  
 HOM\_list A list of higher order moments as specified by GE\_enumerate\_inputs\_old().

**Value**

A list of the fitted coefficients alpha

**Examples**

```
solutions <- GE_bias_normal_squaredmis_old( beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3)
GE_nleqslv_old(beta_list=solutions$beta_list, solutions$cov_list, solutions$cov_mat_list,
solutions$mu_list, solutions$HOM_list)
```

---

GE\_scoreeq\_sim                      *GE\_scoreeq\_sim.R*

---

**Description**

Here we perform simulation to verify that we have solved for the correct alpha values in GE\_bias\_norm\_squaredmis(). Make the same assumptions as in GE\_bias\_norm\_squaredmis().

**Usage**

```
GE_scoreeq_sim(num_sims = 5000, num_sub = 2000, beta_list, rho_list,
  prob_G, cov_Z = NULL, cov_W = NULL, corr_G = NULL)
```

**Arguments**

num\_sims The number of simulations to run, we suggest 5000.  
 num\_sub The number of subjects to generate in every simulation, we suggest 2000.  
 beta\_list A list of the effect sizes in the true model. Use the order beta\_0, beta\_G, beta\_E, beta\_I, beta\_Z, beta\_M. If G or Z or M is a vector, then beta\_G/beta\_Z/beta\_M should be vectors. If Z and/or M/W do not exist in your model, then set beta\_Z and/or beta\_M = 0.  
 rho\_list A list of expectations (which happen to be covariances if all covariates are centered at 0) in the order specified by GE\_enumerate\_inputs(). If Z and/or M/W do not exist in your model, then treat them as constants 0. For example, if Z doesn't exist and W includes 2 covariates, then set cov(EZ) = 0 and cov(ZW) = (0,0). If describing expectations relating two vectors, i.e. Z includes two covariates and W includes three covariates, sort by the first term and then the second. Thus in the example, the first three terms of cov(ZW) are cov(Z\_1,W\_1),cov(Z\_1,W\_2), cov(Z\_1,W\_3), and the last three terms are cov(Z\_3,W\_1), cov(Z\_3,W\_2), cov(Z\_3,W\_3).

prob_G	Probability that each allele is equal to 1. Since each SNP has two alleles, the expectation of G is $2 \times \text{prob\_G}$ . Should be a $d \times 1$ vector.
cov_Z	Should be a matrix equal to $\text{cov}(Z)$ or NULL if no Z.
cov_W	Should be a matrix equal to $\text{cov}(W)$ or NULL if no W.
corr_G	Should be a matrix giving the <i>*pairwise correlations*</i> between each SNP in the set, or NULL. Must be specified if G is a vector. For example, the [2,3] element of the matrix would be the pairwise correlation between SNP2 and SNP3.

**Value**

A list of the fitted values alpha

**Examples**

```
GE_scoreeq_sim( num_sims=10, num_sub=1000, beta_list=as.list(runif(n=6, min=0, max=1)),
rho_list=as.list(rep(0.3,6)), prob_G=0.3, cov_Z=1, cov_W=1)
```

---

GE\_scoreeq\_sim\_old      *GE\_scoreeq\_sim\_old.R*

---

**Description**

Here we perform simulation to verify that we have solved for the correct alpha values in `GE_bias_norm_squaredmis_old()`. Make the same assumptions as in `GE_bias_norm_squaredmis_old()`.

**Usage**

```
GE_scoreeq_sim_old(num_sims = 5000, num_sub = 2000, beta_list, prob_G,
rho_list, cov_Z = NULL, cov_W = NULL)
```

**Arguments**

num_sims	The number of simulations to run, we suggest 5000.
num_sub	The number of subjects to generate in every simulation, we suggest 2000.
beta_list	A list of the effect sizes in the true model. Use the order beta_0, beta_G, beta_E, beta_I, beta_Z, beta_M. If Z or M is a vector, then beta_Z and beta_M should be vectors.
prob_G	Probability that each allele is equal to 1. Since each SNP has two alleles, the expectation of G is $2 \times \text{prob\_G}$ .
rho_list	A list of the 6 pairwise covariances between the covariates. These should be in the order (1) cov_GE (2) cov_GZ (3) cov_EZ (4) cov_GW (5) cov_EW (6) cov_ZW. Again if Z or W are vectors then terms like cov_GZ should be vectors (in the order $\text{cov}(G, Z_1), \dots, \text{cov}(G, Z_p)$ ) where Z is of dimension p, and similarly for W. If Z or M are vectors, then cov_ZW should be a vector in the order $(\text{cov}(Z_1, W_1), \dots, \text{cov}(Z_1, W_q), \text{cov}(Z_2, W_1), \dots, \text{cov}(Z_p, W_q)$ where Z is a vector of length p and W is a vector of length q.

<code>cov_Z</code>	Only used if <i>Z</i> is a vector, gives the covariance matrix of <i>Z</i> (remember by assumption <i>Z</i> has mean 0 and variance 1). The (i,j) element of the matrix should be the (i-1)(i-2)/2+j element of the vector.
<code>cov_W</code>	Only used if <i>W</i> is a vector, gives the covariance matrix of <i>W</i> (remember by assumption <i>W</i> has mean 0 and variance 1). The (i,j) element of the matrix should be the (i-1)(i-2)/2+j element of the vector.

**Value**

A list of the fitted values alpha

**Examples**

```
GE_scoreeq_sim_old( num_sims=10, beta_list=as.list(runif(n=6, min=0, max=1)),  
rho_list=as.list(rep(0.3,6)), prob_G=0.3)
```

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