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About this presentation

A number of things happened since February 2014:

- Updated the code in `salamboR`.
- Re-computed the models for 2 studies (on-going publications).
- Initiated the data repositories on github.com/ugcd/

In this presentation we would like to share with you:

- the achieved results
- **our** rules on computing' and interpreting'em all
- focus on details when interpreting the models

Table of content

Link to access to the presentation: github.com/ugcd/

Results

Models for thrombosis

DISEASE	N	H2R	H2R.SE	H2R.P	AGE	AGE.SE	AGE.P
AT	1113	0.234	0.194	1.409e-01	-0.0352	0.0051	9.8881e-18
VT	1113	0.669	0.165	1.600e-06	-0.0234	0.0038	6.2843e-12
Throm	1113	0.456	0.134	9.430e-05	-0.0329	0.0036	5.4151e-27

Comments

- the heretability of `AT` is not significant.

Work 1: Platelets traits

TRAIT1	TRAIT 2	RHOG	RHOG.SE	RHOG.P	RHOE	RHOE.SE	RHOE.P
BA	VT	-0.104	0.158	0.511	0.367	0.238	0.169
EO	VT	-0.237	0.151	0.133	-0.436	0.225	0.045
LE	VT	0.030	0.194	0.876	0.225	0.268	0.361
LI	VT	0.117	0.160	0.472	0.073	0.277	0.786
MOt	VT	0.178	0.185	0.365	0.236	0.209	0.285
NE	VT						

Comments

- None of the genetic correlations are significant.
- Correlation between `NT` and `VT` is not computable.

Work 2: TEG traits

TRAIT1	TRAIT 2	RHOG	RHOG.SE	RHOG.P	RHOE	RHOE.SE	RHOE.P
VT	TGTlagtime	0.125	0.140	3.784e-01	0.186	0.235	4.515e-01
VT	TGTPeak	0.356	0.136	1.079e-02	0.257	0.234	2.907e-01
VT	TGTETP	0.314	0.121	2.079e-02	0.323	0.211	1.406e-01

Comments

- Two genetic correlations with `TGTPeak` and `TGTETP`, which of them does make more sense?

Work 2: TEG traits

TRAIT1	TRAIT2	RHOG	RHOG.SE	RHOG.P
VT	TGTETP	-0.25	0.32	
VT	TGTPeak	0.42	0.044	
TGTPeak	TGTETP	0.729	0.062	

Idea

- The genes affecting all traits `VT`, `TGTPeak` and `TGTETP` are considered **simultaneously**.

Decision making

Questions we had at the beginning

- What is `N` of the GAIT2 study?
- What disease to model in correlation with a trait: `VT`, `AT` or `Throm`?
- How to use covariates like `antiAgreg`?
- If ρ_p is not significant, should I panic?
- If ρ_g is estimated as 0.9 ± 0.001 with p-value 1.2×10^{-8}, should I make the boss happy by reporting this?

Modeling background

Model and its parameters

Think of a statistical model in terms of its parameters.

Univariate Model:

FIXED EFFECTS PARAMETERS	RANDOM EFFECTS PARAMETERS
$\mu, \beta_{AGE}, \beta_{SEX}$	σ_g^2, σ_e^2

A fixed effect controlling the mean of height

Idea: http://users.du.se/~lrn/DUweb/

A random effect controlling the variance of height

Image source: http://ludwig.design.ru/

Tests of model parameters

FIXED EFFECTS PARAMETERS	RANDOM EFFECTS PARAMETERS
$\mu, \beta_{AGE}, \beta_{SEX}$	σ_g^2, σ_e^2

Heritability: $h^2 = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_e^2}$.

Is the heritability significant? Likelihood Ratio Test (LRT):

HYPOTHESIS	FREE PARAMETERS	RESTRICTED PARAMETERS
No polygenic effect	$\mu, \beta_{AGE}, \beta_{SEX}, \sigma_e^2$	σ_g^2 = 0

Is `AGE` covariate significant? Likelihood Ratio Test (LRT):

HYPOTHESIS	FREE PARAMETERS	RESTRICTED PARAMETERS
No effect of `AGE`	$\mu, \beta_{SEX}, \sigma_g^2, \sigma_e^2$	$\beta_{AGE} = 0$

Bivariate Model for correlations

Univariate Model

FIXED EFFECTS PARAMETERS	RANDOM EFFECTS PARAMETERS
$\mu, \beta_{AGE}, \beta_{SEX}$	σ_g^2, σ_e^2

Bivariate Model

FIXED EFFECTS PARAMETERS	RANDOM EFFECTS PARAMETERS
$\mu_1, \mu_2, (\beta_1, \beta_2)_{AGE}, (\beta_2)_{SEX}$	$(\sigma_1^2, \sigma_2^2, \rho)_g, (\sigma_1^2, \sigma_2^2, \rho)_e$

Is the genetic correlation significant? Likelihood Ratio Test (LRT):

HYPOTHESIS	FREE PARAMETERS	RESTRICTED PARAMETERS
No genetic correlation	$\ldots, (\sigma_1^2, \sigma_2^2)_g$, $(\sigma_1^2, \sigma_2^2, \rho)_e$	$\rho_g = 0$
No pleiotropy	$\ldots, (\sigma_1^2, \sigma_2^2)_g$, $(\sigma_1^2, \sigma_2^2, \rho)_e$	$\rho_g = 1$

Changes in code

Changes in code

Fixes

1) Trait-specific covariates in bivariate models

Example: bivariate model of `VT` and `TGTETP`

- Independent univariate models

TRAIT	COVARIATES
VT	AGE
TGTETP	AGE, AGE2, contraception, sedentaryD

- A bivariate model before February 2014

TRAIT	COVARIATES
VT	AGE, AGE2, contraception, sedentaryD
TGTETP	AGE, AGE2, contraception, sedentaryD

Changes in code

Fixes

2) P-values of all test covariates vs. final covariates (in reports)

Example: univariate model of `VT`.

- Testing model with `6` covariates

AGE	AGE.P	SEX.P	CONTRA.P	AINES.P	ANTIAGREG.P	SMOKE.P
-0.02	5.15e-10	1.36e-01	1.68e-01	7.85e-01	9.26e-01	8.92e-01

- Final model with `1` covariates

AGE	AGE.P
-0.02	6.2843e-12

Changes in code

New options

1. `Compute hard` options (see `solarPolyg` function).
2. Computing the phenotypic correlation can be skipped.
3. Trivariate models are available.

Rules

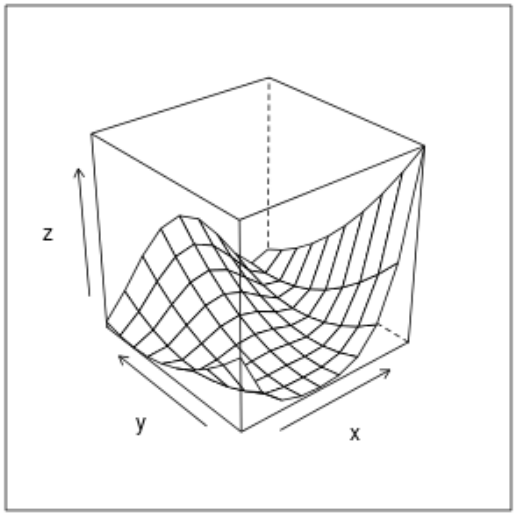
Rule: think twice when adding a covariate

Example: `antiAgreg` covariate in a model for `AT`

Rule: Filter out suspicious results

Problem:

- If the optimization algorithm does not converge, then the returned model is not OK.
- Consequently, SOLAR warnings and extreme estimations like $\rho_g = 1$.
- See `optim` R function and an example with Rosenbrock Banana function.
  - $z = f(x, y)$ has the global minimum at `(1, 1)` point, where the function is equal to `0`.



Rule: Filter out suspicious results

Example: bivariate correlation `NE` and `VT` (not OK)

TRAIT1	TRAIT 2	RHOG	RHOG.SE	RHOG.P	RHOE	RHOE.SE	RHOE.P
NE	VT	0.6748	NA	7.9140e-04	1.0000e+00	0.8246	NA

What is wrong?

- Estimation of standard errors are `NA`.
- Estimation of ρ_e is `1`.

Rule: Filter out suspicious results

Example: bivariate correlation `EO` and `VT` executed with `compute hard` options (not OK)

TRAIT1	TRAIT 2	RHOG	RHOG.SE	RHOG.P	RHOE	RHOE.SE	RHOE.P
EO	VT	-0.7623	0.0977	1.3693e-11	-0.9000	0.0723	7.6188e-18

What is wrong?

- Estimation of ρ_e is `-0.9` (it is on the boundary).
  - Estimations of standard errors are suspiciously small.
  - P-values are suspiciously small.

Rule: `Throm` is preferred to `VT`

Problem

- Small `N` → instability, low statistical power

Solution

- Try correlation with `VT`
- Change the order of traits to test the consistence of the results
- Confirm results by comparing with correlation with `Throm`

Rule: `Throm` is preferred to `VT`

Example: trivariate correlation `VT`, `TGTPeak` and `TGTETP`

- Order `VT`, `TGTlagtime`, `TGTETP`

Not computable.

- Order `VT`, `TGTPeak`, `TGTETP` (not OK)

TRAIT1	TRAIT2	RHOG	RHOG.SE
VT	TGTETP	0.008	0.005
VT	TGTPeak	0.506	0.004
TGTPeak	TGTETP	0.796	NA

Rule: Throm is preferred to VT

Example: trivariate correlation VT, TGTPeak and TGTETP

- Order VT, TGTETP, TGTPeak (OK)

TRAIT1	TRAIT2	RHOG	RHOG.SE
VT	TGTETP	-0.25	0.32
VT	TGTPeak	0.42	0.044
TGTPeak	TGTETP	0.729	0.062

- Model with Throm, order Throm, TGTPeak, TGTETP (OK?)

TRAIT1	TRAIT2	RHOG	RHOG.SE
Throm	TGTETP	-0.117	0.007
Throm	TGTPeak	0.438	0.006
TGTPeak	TGTETP	0.755	0.007

Rule: only ρ_g matters

Explanation:

- The genetic correlation ρ_g has a co-variance matrix **structured** (kinship), while the residual environmental ρ_e has the identity matrix (i.i.d.)
- Indeed, the environmental correlation ρ_e is a part of not explained residual (error).
- Phenotipic correlation ρ_p
  - is not a model parameter
  - it has a large error
  - it computationally complicated to test (remember its formula)

Rule: only ρ_g matters

Why ρ_e and ρ_p are out?

- Have you ever tried to response to such a Reviewer's comment of a submitted manuscript?

Page 9, lines 36-38. It is stated that there is no environmental correlation between BMI and thrombosis risk. This is in contrary to conventional perception about these two phenotypes. For example, diet is a risk factor for both obesity and thrombosis, especially arterial thrombosis. Other risk factors, such as physical inactivity, could also influence both phenotypes.

Rule: only ρ_g matters

Example: bivariate correlation between `EO` and `VT`

TRAIT1	TRAIT 2	RHOG	RHOG.SE	RHOG.P	RHOE	RHOE.SE	RHOE.P
EO	VT	-0.237	0.151	0.133	-0.436	0.225	0.045

Comments:

- The environmental correlation ρ_e is significant, but the genetic correlation ρ_g is not.
  - That means the model must be recomputed with restriction $\rho_g = 0$, that will give the correct estimation of ρ_e.

Alessandra's Rule: p-value 1e-22

Example: bivariate correlation between `EO` and `VT`

- The current results

TRAIT1	TRAIT 2	RHOG	RHOG.P	RHOE	RHOE.P
EO	VT	-0.237	0.133	-0.436	0.045

- Computed before Feb 2014

TRAIT1	TRAIT 2	RHOG	RHOG.P	RHOE	RHOE.P
EO	VT	-0.81	6.2e-12	-0.9	3.6e-22

What was wrong?

- All the issues commented above
  - `bmi` as covariate
  - covariates not trait-specific
- ~~Bad luck~~ Lack of our rules for interpretation the results

Summary

Our experience (our feeling)

~~All models are wrong, but some are useful.~~

Most of correlations are insignificant, but some are ... incomputable.

Our proposal

Work hard / Keep learning / Share **all** at https://github.com/ugcd/

Credits

- slidify, io2012
- knitr
- knitcitations

Thank you