Score Tests for exploring complex models:

Application to HIV dynamics models

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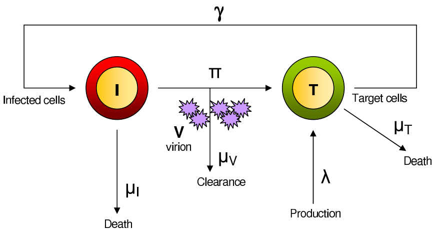
A basic model



For subject i:

$$\begin{cases} \frac{dT^i}{dt} = \lambda^i - \gamma V^i T^i - \mu_T^i T^i \\ \frac{dI^i}{dt} = \gamma V^i T^i - \mu_I^i I^i \\ \frac{dV^i}{dt} = \pi^i I^i - \mu_V V^i \end{cases}$$

T^i: non-infected susceptible CD4 (target cells)
I^i: infected CD4
V^i: virus
$\Longrightarrow$ **How can we quickly compare many models ?** Likelihood ratio test ? Wald test ? ...

The advantages of score tests

- Only the model under the null hypothesis need to be fitted
- The score test often takes a simple form

The score statistic typically is:

- A linear form of residuals for testing regression coefficients
- A quadratic form for homogeneity testing

Objective

To develop a score test for the analysis of fixed and/or random effects in complex models based on differential equations systems

The statistical model

We consider for subject i, $i = 1, ..., n$:

- The observed vector: $Y_i = (Y_{ijk}, j = 1, \ldots, n_i, k = 1, \ldots, M)$
- The individual parameters vector: $\boldsymbol{\xi}^i = (\xi^i_l, l = 1, \ldots, p)$

Y_i is modelled by:

$$Y_{ijk} = g(t_{ijk}, \xi^i) + \epsilon_{ijk}, \qquad j = 1, ..., n_i$$

In the previous model:

- $\boldsymbol{\xi}^i = (\lambda^i, \mu^i_I, \pi^i, \mu^i_T)$, γ and μ_V are supposed to be known.
- We observed: $Y_{ij1} = \log_{10}(V^i) + \epsilon_{ij1}$ and $Y_{ij2} = (T^i + I^i)^{0.25} + \epsilon_{ij2}$.

The statistical model

Individual parameters are modelled by:

$$\xi_l^i = \phi_l + \omega_l u_l^i + \beta_l z_l^i$$

with $u^i \sim \mathcal{N}(0, I_p)$, where $u^i = (u_l^i, l = 1, \ldots, p)$.

$\boldsymbol{\theta} = (\phi_l, \omega_l, \beta_l; l = 1, \ldots, p)$ is the set of parameters of the model

We test:

- $\beta_l = 0$ for explanatory variable
- $\omega_l = 0$ for random effect

Score test for explanatory variables

$$\xi_l^i = \phi_l + \omega_l \mathbf{u}_l^i + \beta_l \mathbf{z}_l^i$$

- We want to test a possible effect of an explanatory variable z_l^i on ξ_l^i
- The null hypothesis H_0 is "$\beta_l = 0$"
- The score for β_l:

$$U_{\beta_l}^{\bullet}(\theta) = \frac{\partial L}{\partial \beta_l}|_{\theta}$$

Because $U_{\beta_l}^{\bullet} = \sum_{i=1}^{n} U_{\beta_l}^{i}$ applying the central limit theorem, we have:

$$\frac{U_{\beta_l}^{\bullet}(\theta_*)}{\sqrt{\mathrm{var}\ U_{\beta_l}^{\bullet}(\theta_*)}} \sim \mathcal{N}(0,1)$$

Score test for explanatory variables

$$\xi_l^i = \phi_l + \omega_l u_l^i + \beta_l \mathbf{z}_l^i$$

$\hat{\boldsymbol{\theta}}_0$ denote the maximum likelihood estimator of $\boldsymbol{\theta}_*$
If H_0 is true then:

$$S = \frac{U_{\beta_l}^{\bullet}(\hat{\boldsymbol{\theta}}_0)}{\sqrt{\widehat{\mathrm{var}}\ U_{\beta_l}^{\bullet}(\hat{\boldsymbol{\theta}}_0)}} \sim \mathcal{N}(0,1)$$

where $\widehat{\mathrm{var}}\ U_{\beta_l}^{\bullet}(\hat{\boldsymbol{\theta}}_0)$ is a consistent estimator of $\mathrm{var}\ U_{\beta_l}^{\bullet}(\hat{\boldsymbol{\theta}}_0)$.
We take:

- $U_{\beta_l}^i(\hat{\boldsymbol{\theta}}_0) = \mathbf{z}_l^i U_{\phi_l}^i(\hat{\boldsymbol{\theta}}_0)$
- $\widehat{\mathrm{var}}\ U_{\beta_l}^{\bullet}(\hat{\boldsymbol{\theta}}_0) = \sum_{i=1}^{n} {U_{\beta_l}^i}^2(\hat{\boldsymbol{\theta}}_0)$

Score test for explanatory variables

A global test

We define a global score test:

- The null hypothesis is H_0: "$\boldsymbol{\beta}_{\mathbf{l}} = 0, l = 1, \ldots, p$"
- The test statistic is $S_G = \mathbf{U}^{\bullet T} [\widehat{\text{var}}\, \mathbf{U}^{\bullet}]^{-1} \mathbf{U}^{\bullet}$
- This statistic has an asymptotic χ^2_p distribution under H_0

Score test of homogeneity

$$\xi_l^i = \phi_l + \omega_l \mathbf{u}_l^i + \beta_l \mathbf{z}_l^i$$

- We want to test if there is a random effect on ξ_l^i
- The null hypothesis H_0 is "$\omega_l = 0$"

The general score statistic is (Commenges and Jacqmin-Gadda, 1997):

$$T_{WPC} = \mathbf{U}^T W^* \mathbf{U} - \text{Tr}(\hat{I}_\epsilon W^*)$$

where

- $\mathbf{U}$ is the vector of dimension $N = \sum_{i=1}^{n} n_i$ of $U_l^{ij} = \frac{\partial \log \mathcal{L}^\theta_{\mathcal{Y}_{ij}|u_l^i}}{\partial \varepsilon_{ijl}}|_{\hat{\theta}_0}$
- $\hat{I}_\varepsilon$ is the matrix whose entries are $-\frac{\partial^2 \log \mathcal{L}^\theta_{\mathcal{Y}_{ij}|u_l^i}}{\partial \varepsilon_{ijl} \partial \varepsilon_{i'j'l}}|_{\hat{\theta}_0}$
- W^* is the correlation matrix of $\mathbf{u}_l^i$ minus the identity matrix

Score test of homogeneity

$$T_{WPC} = \mathbf{U}^T W^* \mathbf{U} - \mathrm{Tr}(\hat{I}_\epsilon W^*)$$

In the complex situation (random(s) effect(s) under H_0):

- $\hat{I}_\epsilon$ involves the second derivative of a complex likelihood
- The informative term is still $\mathbf{U}^T W^* \mathbf{U}$
- BUT we do not have $\mathrm{E}[\mathbf{U}^T W^* \mathbf{U}] = 0$ under H_0: the second term is needed to ensure $\mathrm{E}[T_{WPC}] = 0$

Score test of homogeneity

The proposed test statistic is:

$$S_H = \frac{T - \widehat{\mathrm{E}}_{H_0}[T]}{\sqrt{\widehat{\mathrm{var}}_{H_0} \; T}}$$

where $\widehat{\mathrm{E}}_{H_0}[T]$ and $\widehat{\mathrm{var}}_{H_0} \; T$ are estimators of the expectation and the variance of T under H_0. It has an asymptotic $\mathcal{N}(0, 1)$ distribution under H_0.

Score test of homogeneity

$$\xi_l^i = \phi_l + \omega_l \mathbf{u}_l^i + \beta_l \mathbf{z}_l^i$$

To obtain $\widehat{\mathrm{E}}_{H_0}[T]$ and $\widehat{\mathrm{var}}_{H_0}\ T$, we use a parametric bootstrap:

- We simulate K datasets of n patients under H_0
- For each replication we compute the statistics $T_{(k)}$

Our estimates are the empirical mean and variance of these values.

Simulation study

- 100 simulated datasets of 100 patients
- For binary explanatory variables: a Bernoulli distribution
- For continuous variables: a normal distribution
- The expectation and the variance under H_0 for the test on random effects are calculated using 100 datasets simulated under H_0

Score test for explanatory variables

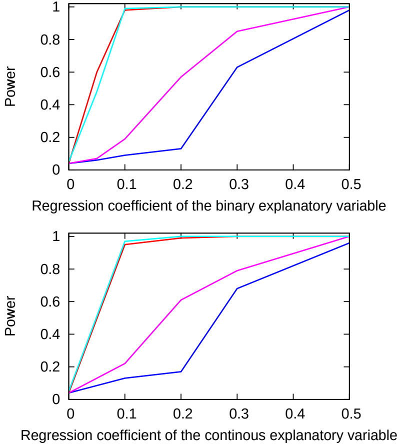


Figure 1: Power of the score test for binary and continuous explanatory variables for λ (_), μ_I (_), π (_) and μ_T (_)

Score test of homogeneity

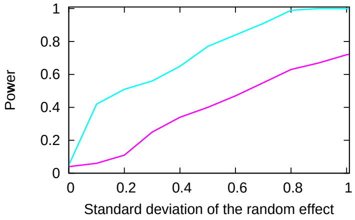


Figure 2: Power of the homogeneity score test for π (_) and μ_T (_)

Application to the CASCADE study

Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) dataset

Selection of patients:

- The delay between last negative and first positive HIV test $\leq$ 3 years
- Naive of antiretroviral treatment
- At least 3 measurements during the first year of follow-up

$\Longrightarrow$ **761 selected patients**

We tested the variable *gender* and *age* at first positive HIV test

- Median age: 34 years (IQR=21-40)
- 84% were men

Explanatory variables

$\Longrightarrow$ Global test (degree of freedom = 4):

- No effect of *gender*: $S_G = 1.06$ (p=0.90)
- No effect of *age* taken as a continuous variable: $S_G = 0.84$ (p=0.93)
- Effect of *age* taken as a binary variable (≥ 50 years vs. younger): $S_G = 13.03$ (p=0.01)

$\Longrightarrow$ Effect of *age* as binary variable on each parameter. We found a significant effect of *age* on μ_I: $S = -1.99$ (p=0.04)

Random effects

We tested the random effects on π and μ_T.
To determine the expectation and the variance under the null hypothesis:

- We simulated 10 datasets of 761 patients under H_0
- With the same design of measurement as the real dataset

We did not find any additional random effect: $S_H = 1.42$ (p=0.08) and $S_H = 1.55$ (p=0.06), for π and μ_T respectively.

Conclusion

- We have developed score tests in non-standard situations
- The simulation study shows that these tests work well and are robust to misspecification of random effects
- These tests can be used in an ascendant strategy for exploring a family of complex models

CASCADE Collaboration

Steering Committee: Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner Bucher, Geneviève Chêne, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi
Co-ordinating Centre: Kholoud Porter (Project Leader), Sara Lodi, Sarah Walker, Abdel Babiker, Janet Darbyshire
Clinical Advisory Board: Heiner Bucher, Andrea de Luca, Martin Fisher, Roberto Muga

Collaborators: Australia Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, Tony Kelleher, Tim Ramacciotti, Linda Gelgor, David Cooper, Don Smith); Canada South Alberta clinic (John Gill); Denmark Copehhagen HIV Seroconverter Cohort (Louise Bruun Jorgensen, Claus Nielsen, Court Pedersen); Estonia Tartu likool (Irja Lutsar); France Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiébaut, Bernard Masquelier), French Hospital Database (Dominique Costagliola, Marguerite Guiguet), Lyon Primary Infection cohort (Philippe Vanhems), SEROCO cohort (Laurence Meyer, Faroudy Boufassa); Germany German cohort (Osamah Hamouda, Claudia Kucherer); Greece Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Angelos Hatzakis, Dimitrios Paraskevis, Anastasia Karafoulidou); Italy Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci, Benedetta Longo, Claudia Balotta); Netherlands Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Liselotte van Asten, Akke van der Bij, Ronald Geskus, Roel Coutinho); Norway Oslo and Ulleval Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne Eskild, Johan N Bruun); Poland National Institute of Hygiene (Magdalena Rosinska); Portugal Universidade Nova de Lisboa (Ricardo Camacho); Russia Pasteur Institute (Tatyana Smolskaya); Spain Badalona IDU hospital cohort (Roberto Muga), Barcelona IDU Cohort (Patricia Garcia de Olalla), Madrid cohort (Julia Del Amo, Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos, Ildefonso Hernandez Aguado); Switzerland Swiss HIV cohort (Heiner Bucher, Martin Rickenbach, Patrick Francioli); Ukraine Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); United Kingdom Edinburgh Hospital cohort (Ray Brettle), Health Protection Agency (Valerie Delpech, Sam Lattimore, Gary Murphy, John Parry, Noel Gill), Royal Free haemophilia cohort (Caroline Sabin, Christine Lee), UK Register of HIV Seroconverters (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker, Janet Darbyshire, Valerie Delpech), University College London (Deenan Pillay), University of Oxford (Harold Jaffe).

Competition between explanatory variable and random effect

We simulated a dataset of 100 patients with a binary explanatory variable on μ_T:

$$\tilde{\mu}_T = \phi_{\mu_T} + z^i_{\mu_T}\beta_{\mu_T}$$

with $\beta_{\mu_T} = 0.3$ with a Bernoulli distribution

- The score test of homogeneity for $H_0 : \omega_{\mu_T} = 0$ was significant: $S_H = 2.17$ (p=0.015)
- The score test for explanatory variable for $H_0 : \beta_{\mu_T} = 0$ was also significant: $S = 4.25$ (p=2.10^{-5})
- We included the explanatory variable in the model and the score test of homogeneity was no more significant: $S_H = 0.72$ (p=0.24)

The robustness of score tests to misspecification

- The robustness of the score tests to misspecification of the random effects in terms of type I error.
- We simulated 100 datasets with three random effects.
- We included only the first two under the null hypothesis: H_0 was incorrectly specified.

Table 1: Type 1 errors of score tests for explanatory variables and random effects for well-specified and misspecified models

	Parameter	Well-specified	Misspecified
Explanatory Variables	λ	0.04	0.05
	μ_I	0.04	0.05
	π	0.04	0.04
	μ_T	0.04	0.05
Random effects	π	0.04	0.03
	μ_T	0.05	0.04

Computation of the expectation and the variance under H_0

The duration of computation for simulating 100 datasets increases with:

- The number of patients
- The number of measurements times
- The number of random effects under H_0

We studied the power of the score test statistic simulating only 1 and 10 datasets under H_0.

- For a variance of 0.01, the difference of power was 15% and 2%
- For a variance of 0.1, the difference of power was 7% and 1%