Copula Random Effect Estimation and Simulation in Pumas

Patrick Kofod Mogensen[1], Andreas Noack[1]

[1]PumasAI

Random Effects, Copulas, Estimation, Simulation

Introduction

Multivariate random effects are often multivariate Gaussian random effects in pharmacometrics but not all random effects are naturally represented as Gaussian. Recently, pharmacometricians have considered Copulas to sample from realistic covariate distributions; weight may be right skewed for example. The same framework can be used to combine non-Gaussian distributions into multivariate relationships for random effects in non-linear mixed effects models (NLME models).

In this poster we investigate how Copula Random effects models may be implemented in the Pumas [1] software and perform a simulation and re-estimation exercise to show that we can recover the data generating process using [2] and [3].

Data Generating Process

Number of subjects: $N = 50$

Sample times: $\{0, 0.5, 1, 2, 3, 5, 10\}$.

Structural model $\frac{\mathrm{d}\, A_i(t)}{\mathrm{d}\, t} = -\frac{\mathrm{CL}_i}{V_{c,i}}\, A_i(t), \quad A_i(0) = 10,$

Individual parameters $\mathrm{CL}_i = \exp\left(\eta_{i,1}\right), \quad V_{c,i} = \exp\left(\eta_{i,2}\right).$

Random effects via copula $\eta_i = \left(\eta_{i,1}, \eta_{i,2}\right)$ is drawn from a `SklarDist` combining a Gaussian copula with non-Gaussian marginals,

$$\eta_i \sim \mathrm{SklarDist}\Big(C_{\mathrm{Gauss}(\Omega_{\mathrm{Cop}})}, (\mathrm{Normal}(0, \Omega_1), F_2 = \mathrm{Gamma}(\nu, \mu/\nu))\Big),$$

Residual error: $\mathrm{conc}_{ij} \sim \mathrm{Normal}\left(1000 \cdot A_i\left(t_j\right)/V_{c,i}, 1.0\right).$

True values. $\mu = 0.4$, $\nu = 0.25$, $\Omega_1 = 0.3$, and $\Omega_{\mathrm{Cop}} = \begin{pmatrix} 1 & 0.7 \\ 0.7 & 1 \end{pmatrix}$.

Pumas Code

```
using Pumas, Copulas
pop = map(i -> Subject(id = i, events = DosageRegimen(10, time = 0,
cmt = 1), observations = (:conc,)), 1:50)

pk_01 = @model begin
    @param begin
        ν in RealDomain(init = 1.0)
        μ in RealDomain(init = 0.4)
        Ω1 ∈ RealDomain()
        ΩCop ∈ CorrDomain(2)
    end
    @random begin
        η ~ SklarDist(GaussianCopula(ΩCop), [Normal(0, Ω1), Gamma(ν,
μ / ν)])
    end
    @pre begin
        CL = exp(η[1])
        Vc = exp(η[2])
    end
    @dynamics Central1
    @derived begin
        cp := @. 1000 * (Central / Vc)
        conc ~ @. Normal(cp, 1.0)
    end
end
params = (μ = 0.4, ν = 0.25, Ω1 = 0.3, ΩCop = [1 0.7; 0.7 1])
sims = simobs(pk_01, pop, params; obstimes = [0.0, 0.5, 1.0, 2.0,
3.0, 5.0, 10.0])
ft = fit(pk_01, Subject.(sims), params, FOCE())
```

Contact

Simulation of Prior

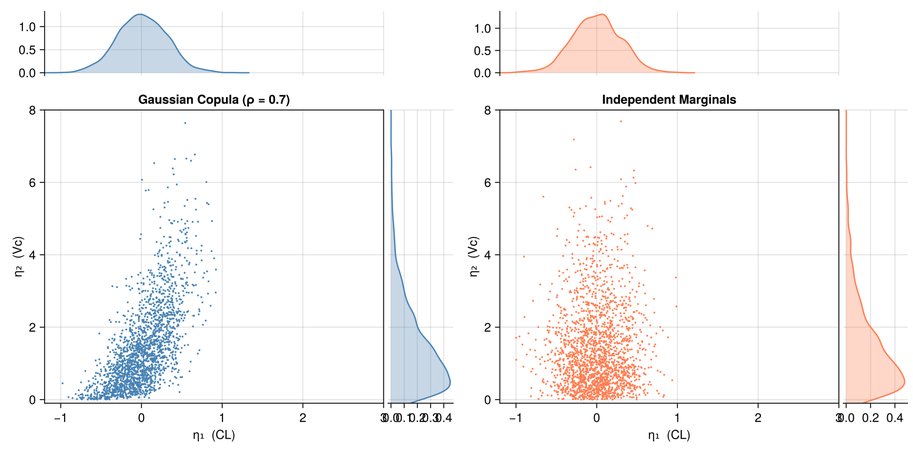


Figure 2: Simulated Random Effects and Estimated Empirical Bayes Estimates

Estimated EBEs

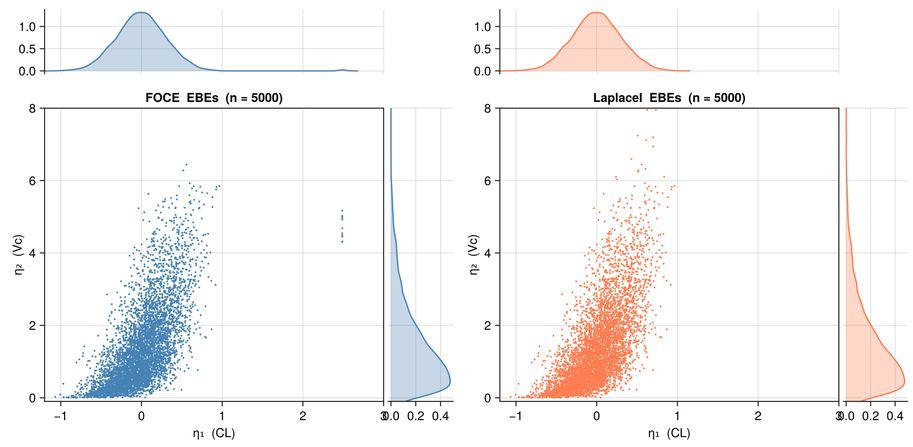
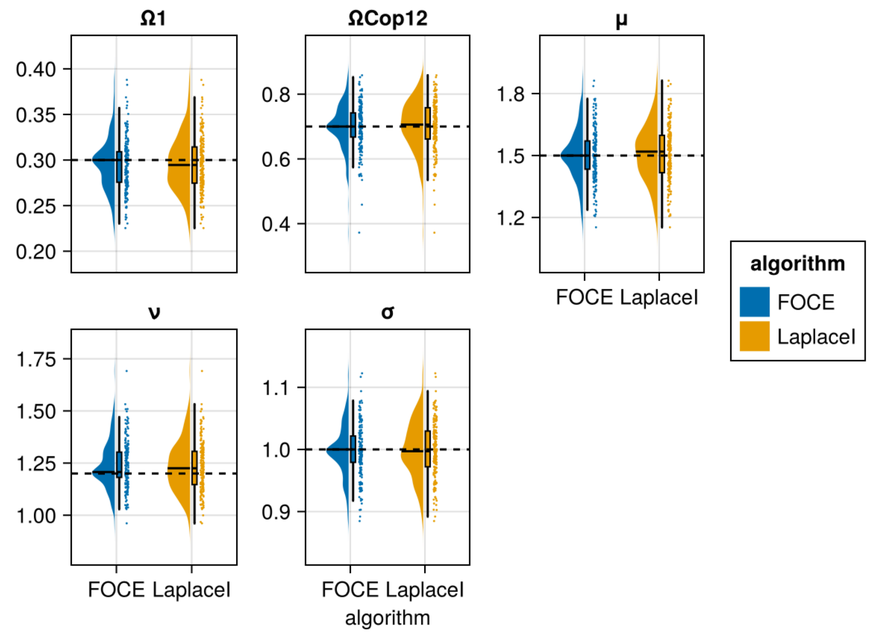


Figure 3: Simulated Random Effects and Estimated Empirical Bayes Estimates

Bias



Conclusion

We find that the Pumas framework that is oriented towards usage of distribution types from Distributions.jl and Copulas.jl makes it very easy to incorporate Copulas into the simulation and estimation framework. The existing support for non-Gaussian univariate distributions naturally extends to Copula-based multivariate relationships for unobserved heterogeneity between subjects.

Bibliography

[1] P. K. Mogensen *et al.*, "Pumas: A Unified Platform for Pharmaceutical Modeling and Simulation," *Quantitative Medicine (Forthcoming)*, 2026.

[2] M. Besançon *et al.*, "Distributions.jl: Definition and Modeling of Probability Distributions in the JuliaStats Ecosystem," *Journal of Statistical Software*, vol. 98, no. 16, pp. 1–30, 2021, doi: 10.18637/jss.v098.i16.

[3] O. Laverny and S. Jimenez, "Copulas.jl: A fully Distributions.jl-compliant copula package," *Journal of Open Source Software*, vol. 9, no. 94, p. 6189, 2024, doi: 10.21105/joss.06189.