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Virtual Population Generation using Gaussian Copulas

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INTRODUCTION

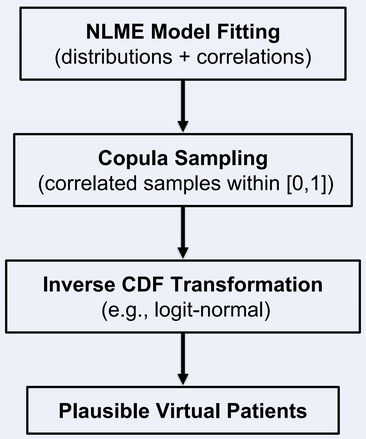
- In silico clinical trials (ISCTs) use virtual populations to represent inter-patient variability in drug response.
- NLME models estimate not only parameter distributions, but also inter-parameter correlations.
- Independent parameter sampling breaks these correlations, producing unrealistic virtual patients.
- Copula-based sampling preserves multivariate structure, enabling biologically plausible ISCT simulations.
- This work adopts the ISCT workflow of Cortés-Ríos et al. [1] to demonstrate copula-based virtual population generation

OBJECTIVES

- Illustrate why independent parameter sampling fails to represent NLME-derived heterogeneity.
- Implement Gaussian copula sampling within a Pumas (Julia) framework.
- Demonstrate preservation of Spearman correlations after nonlinear transformations.
- Validate the approach using a tumor burden ISCT example from published literature.

METHODS

Copula-based Sampling Algorithm



Example: The Tumor Burden Model

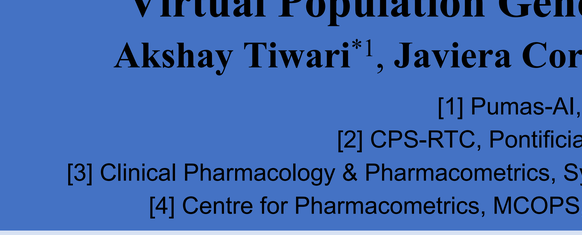
- Used a model describing tumor dynamics during cancer chemotherapy [2].
- The baseline-normalized tumor size (N_t) over time (t) was given as:

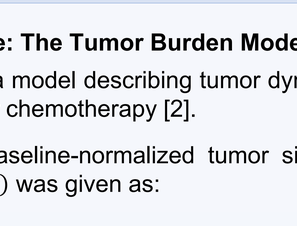
$$N_t = N_0 f e^{-k*t} + N_0(1-f)e^{g*t}$$

- The model included three NLME-estimated parameters:
  - f − treatment-sensitive fraction
  - g − tumor growth rate
  - k − cell death rate

Step 1: Distributions and correlations

- Define marginal parameter distributions on a transformed scale (logit-normal) and specify NLME-estimated Spearman correlation matrix.





- Critical correlation: $r(f, g)$ = **-0.64**

Step 2: Copula sampling

- Construct a Gaussian copula capturing parameter dependence and generate correlated uniform samples within [0, 1].

Step 3: Transform uniform samples to target marginals

If $\boldsymbol{U} \sim Uniform(0,1)$ and $\boldsymbol{\mathcal{F}}$ is the CDF of a random variable, then,

$$\boldsymbol{X} = \boldsymbol{\mathcal{F}}^{-1}(\boldsymbol{U})$$

follows the distribution with CDF $\boldsymbol{\mathcal{F}}$

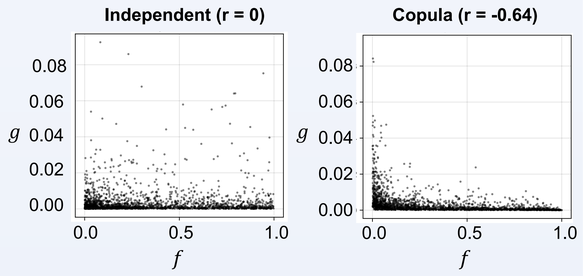
Step 4: Transform to original parameter scale (bounded scale)

$$\boldsymbol{P} = a + (b-a) * logistic(\boldsymbol{X})$$

RESULTS

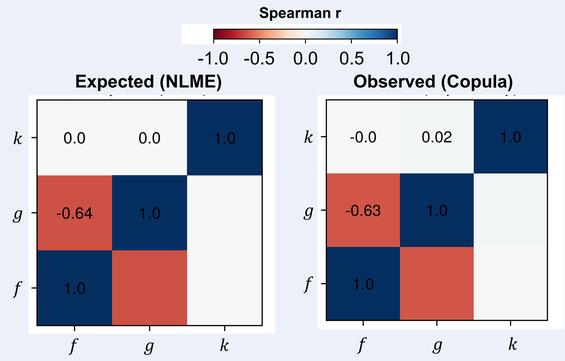
Independent Sampling Breaks NLME Correlations

- Independent sampling from marginal distributions produced near-zero correlation between parameters f and g.



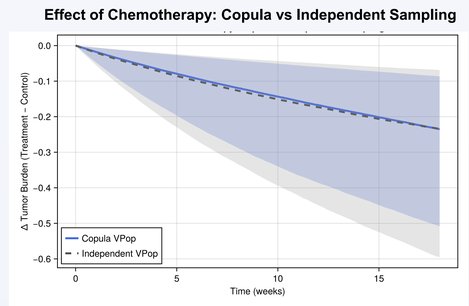
Correlation Validation

- Copula-based virtual population sampling preserves NLME-estimated rank correlations between parameters.



Effect of Copula-Preserved Correlations on Treatment–Control Tumor Burden

- Median and interquartile range across 10,000 virtual patients.
- Independent sampling inflates uncertainty by allowing biologically implausible parameter combinations.
- Copula sampling yields more coherent and interpretable treatment responses.



CONCLUSION

- Independent parameter sampling distorts NLME-derived patient heterogeneity.
- Gaussian copulas preserve rank correlations through nonlinear parameter transformations.
- This framework enables credible virtual population generation for ISCTs in Pumas.

REFERENCES

[1] Cortés-Ríos J, et al., *CPT Pharmacometrics Syst Pharmacol.*, 2025.

[2] Qi T, Cao Y., *CPT Pharmacometrics Syst Pharmacol.*, 2023

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