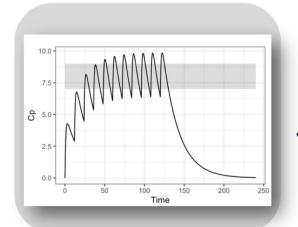
Virtual Patient Simulation

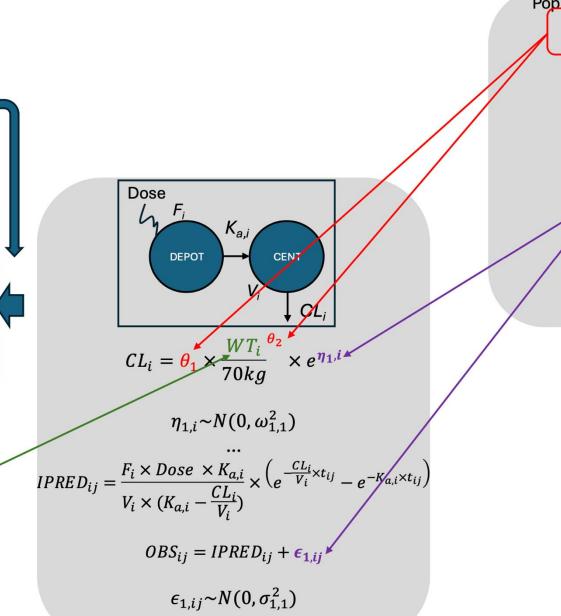
Curtis K. Johnston & Shen Cheng 11/01/2024

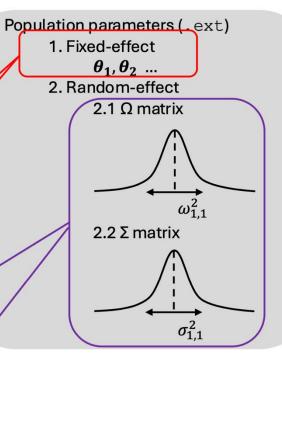
Stochastic Simulation

Simulation design: Treatment regimen Study duration Sampling schedule



	WT	AGE	SEX			
	65	31	F	•••		
	77	25	М	•••		
	102	36	М	•••		
	•••	•••	•••	•••		

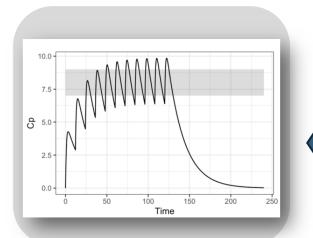




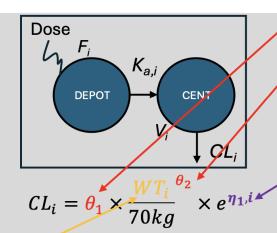
Covariate (Virtual Patient) Simulations

Simulation design:

Treatment regimen Study duration Sampling schedule

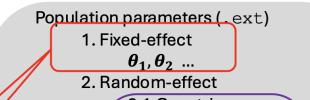


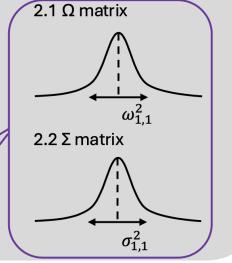
WT	AGE	SEX	•••
45	12	М	
57	15	F	•••
33	6	F	
	•••	•••	•••



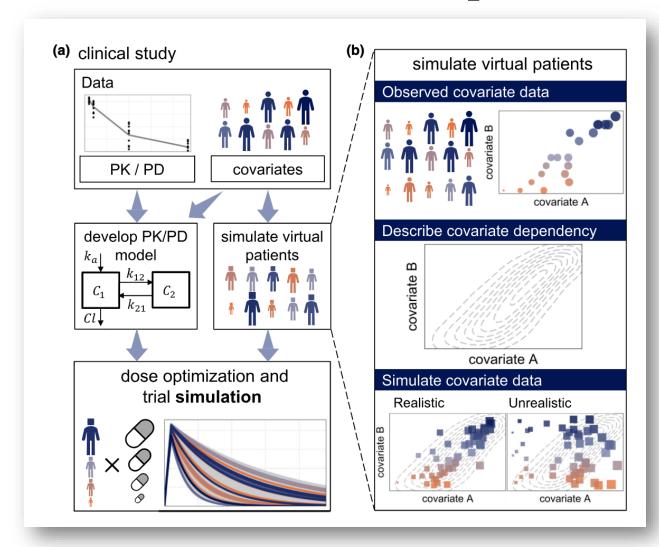
$$\eta_{1,i} \sim N(0, \omega_{1,1}^2)$$

 $\eta_{1,i} \sim N(0, \omega_{1,1}^{2})$... $IPRED_{ij} = \frac{F_{i} \times Dose \times K_{a,i}}{V_{i} \times (K_{a,i} - \frac{CL_{i}}{V_{i}})} \times \left(e^{\frac{-CL_{i}}{V_{i}} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$ OPS $OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$ $\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$





"Realistic" Virtual Population



Difficulties in simulating **realistic** virtual population:

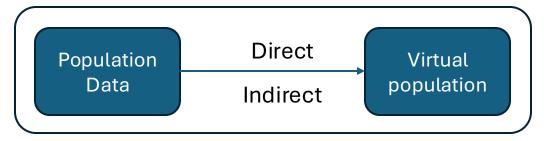
- Different covariates exhibit different distributions (i.e., marginal distributions)
- Intricate dependency structure (i.e., correlation)

Unrealistic virtual patient example: A patient of <u>95 years old</u>, with a <u>high body</u> weight and a <u>very good kidney</u>.

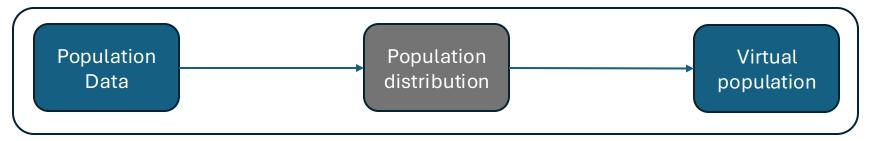
Failing to consider such correlations inflate the variability of covariates, in other words, unrealistic virtual patients.

Methods of Virtual Patient Simulations

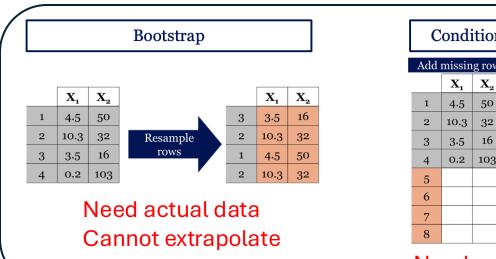
- Data (Resample)-based methods
 - Bootstrap
 - Conditional distributions
 - Also known as Multiple Imputation by Chained Equations (MICE)

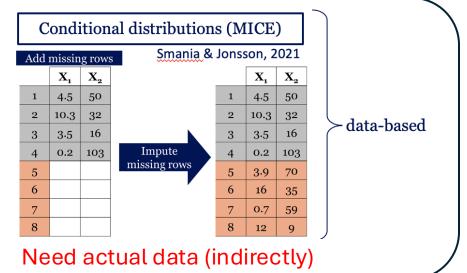


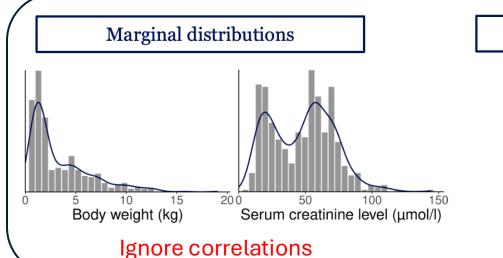
- Distribution-based methods
 - Marginal distributions
 - Multivariate normal distributions (MVND)
 - Copula modeling

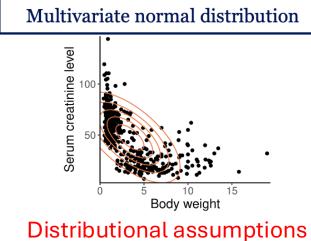


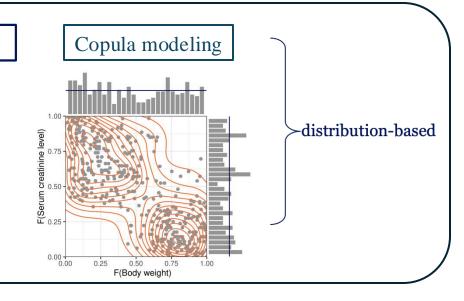
Methods of Virtual Patient Simulations





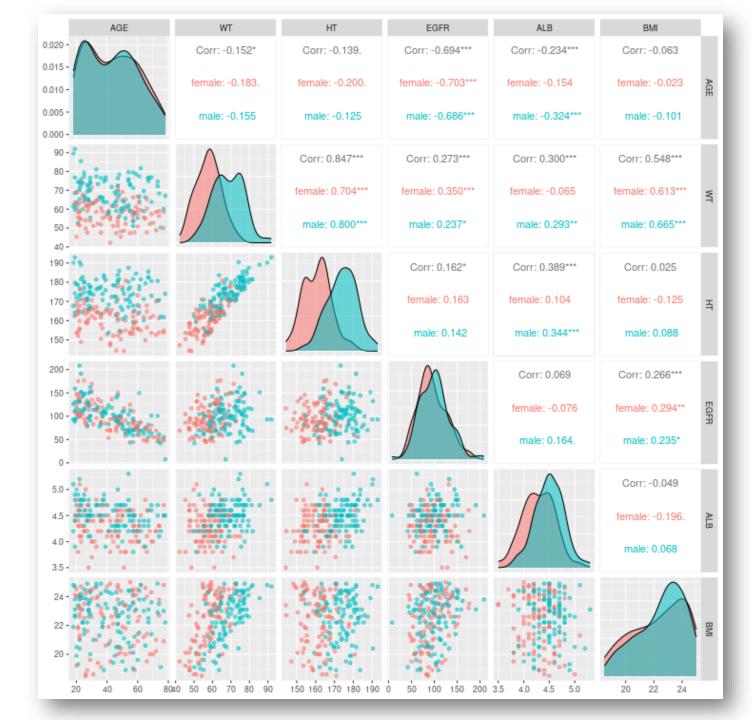






Distribution-Based Methods

- Marginal distributions
- Multivariate normal distributions (MVND)
- Copula modeling



Population Data

./wk9/data/pop.csv

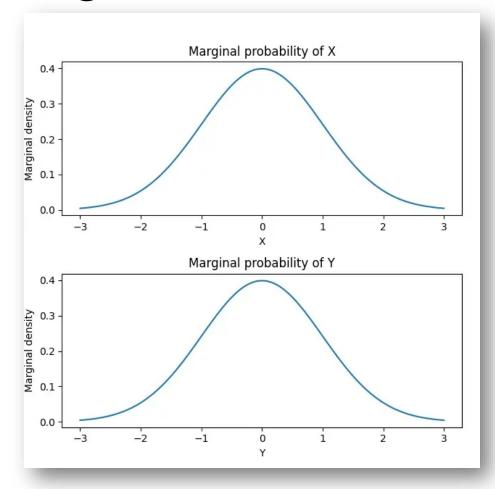
Seven covariates:

- Continuous:
 - AGE: age in years
 - WT: body weight in kg
 - HT: height in cm
 - EGFR: estimated glomerular filtration rate in mL/min
 - ALB: albumin concentration in g/dL
 - BMI: body mass index in kg/m²
- Categorical:
 - SEX: gender (male vs female)

Experiments

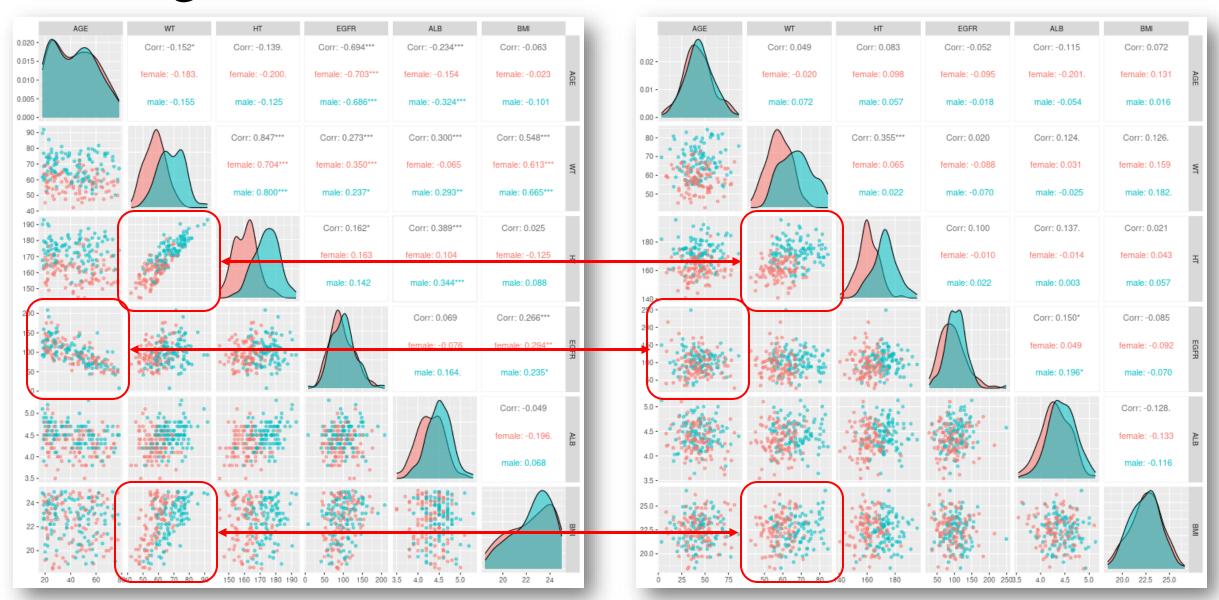
- Separate the population data based on SEX (male vs female)
- Derive two distributions, one for male, one for female, using different method:
 - Marginal distributions
 - Multivariate normal distributions
 - Copula modeling
- Simulate from the derived distributions
- Compare the simulated data with the population data, determine which method simulate the most "**realistic**" data (i.e., most similar to population data).

Marginal Distributions



- Derive the means and standard
 deviations (SDs) of each variable in the
 population dataset.
- Sample from a (truncated) normal distribution (or other distributions) with the same mean and SD of each variable.

Marginal Distributions



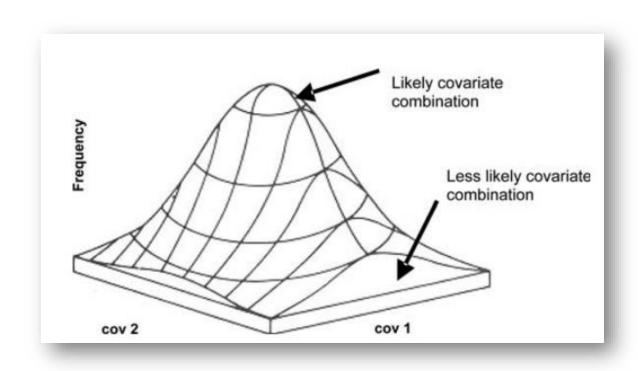
simulatedobserved type simulatedobserved AGE type simulatedobserved AGE WT type simulatedobserved AGE HT type 50 60 70 80 150160170180190 50 100 150 simulatedobserved EGFR type 150160170180190 50 100 150 200 3.6 4.0 4.4 4.8 5.2 simulatedbbserved 50 60 70 80 90 WT HT EGFR ALB type

Marginal Distributions

Summary-Marginal Distributions

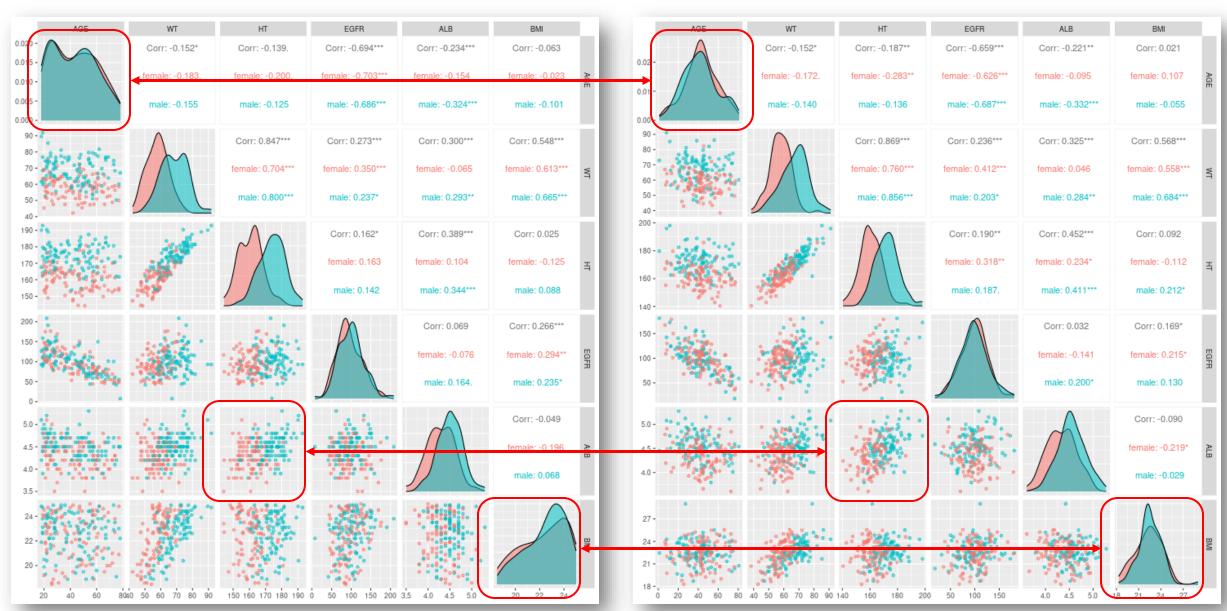
- Simulation ignoring correlations (i.e., joint distribution)
- Unrealistic simulation
 - Unrealistic combination of covariates
 - Low weight + high BMI/height
 - High age + high eGFR
- Easy to implement
- Not appropriate to use when high-dimensional covariates were simulated

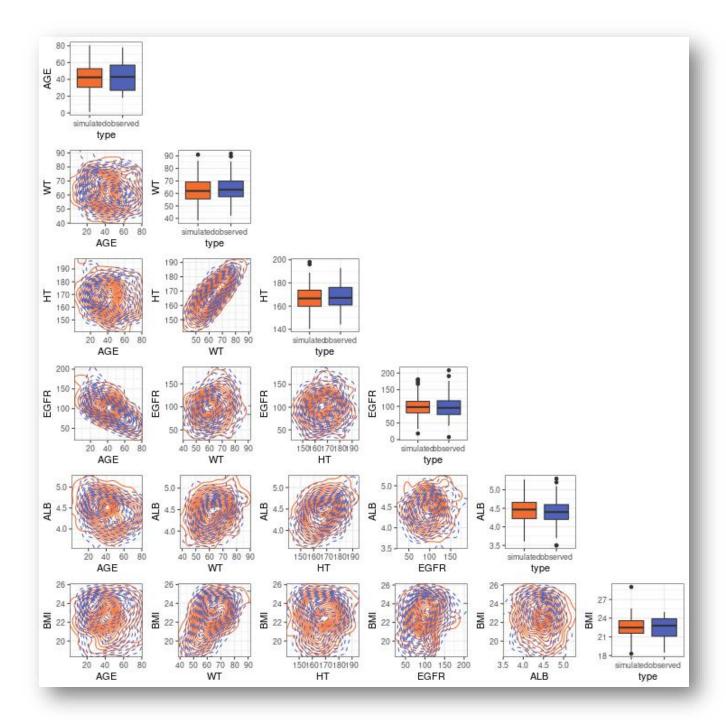
Multivariate Normal Distributions



- Derive the means and the covariance matrix of the population dataset.
- Sample from the multivariate normal distribution defined by the means and the covariance matrix.

Multivariate Normal Distributions





Multivariate Normal Distributions

Summary-Multivariate Normal Distributions

- Simulation considering both marginal and joint distribution
- More realistic simulation
 - Realistic combination of covariates
- Strong distributional assumptions
 - Normal marginal distribution
 - Linear correlation

Copula Modeling



ARTICLE

Virtual Patient Simulation Using Copula Modeling

Laura B. Zwep¹, Tingjie Guo¹, Thomas Nagler², Catherijne A.J. Knibbe^{1,3}, Jacqueline J. Meulman^{4,5} and J. G. Coen van Hasselt^{1,*}

Journal of Pharmacokinetics and Pharmacodynamics https://doi.org/10.1007/s10928-024-09929-4

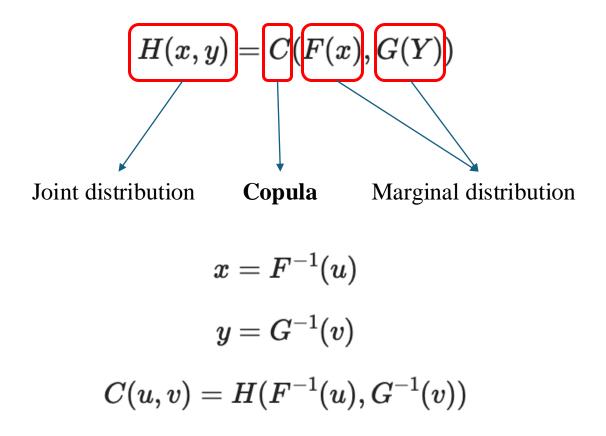
ORIGINAL PAPER



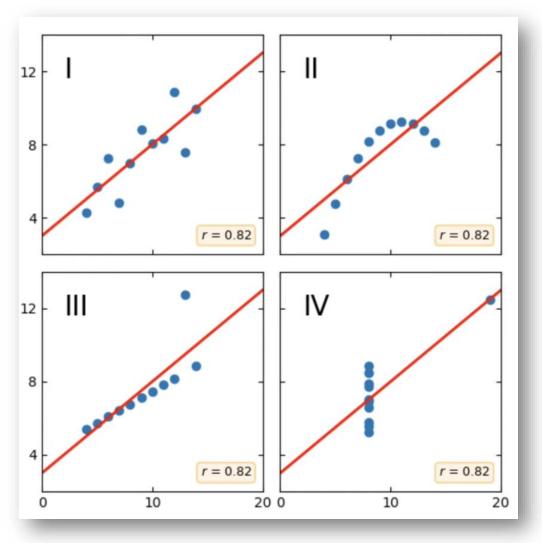
Generation of realistic virtual adult populations using a model-based copula approach

Yuchen Guo¹ · Tingjie Guo¹ · Catherijne A. J. Knibbe^{1,2} · Laura B. Zwep¹ · J. G. Coen van Hasselt¹

Sklar's Theorem

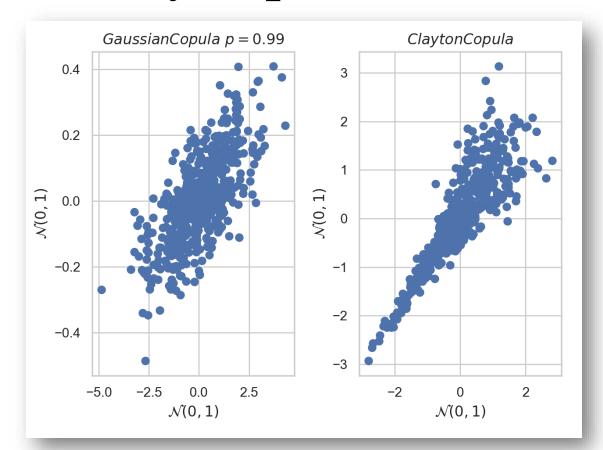


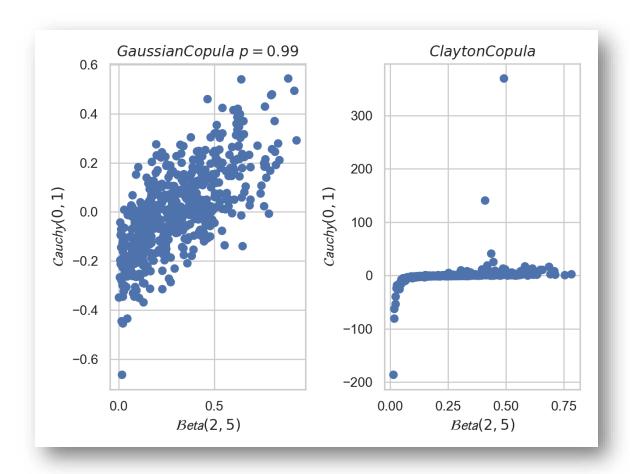
Why copula?



Kiran Karra. Copula Short Course. Youtube

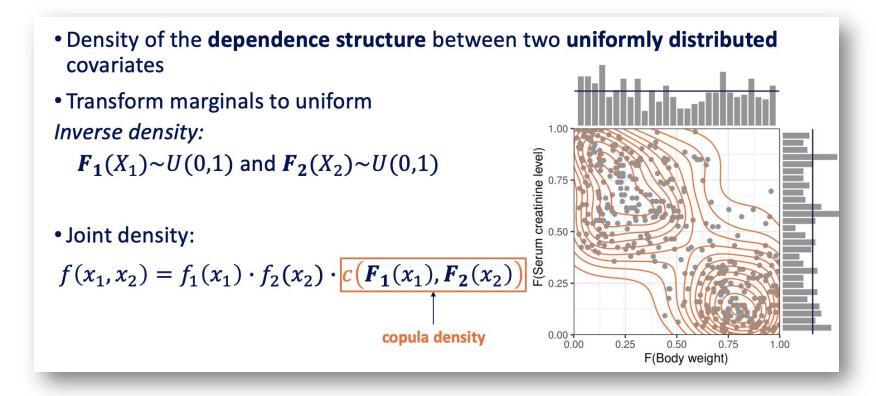
Why copula?





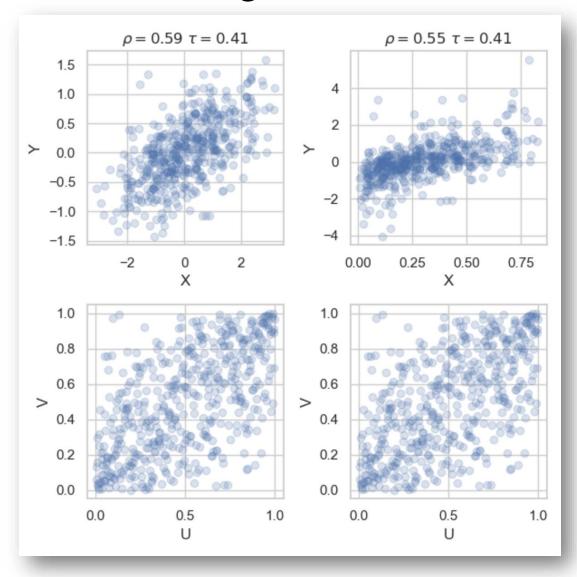
Kiran Karra. Copula Short Course. Youtube

Copula: general process



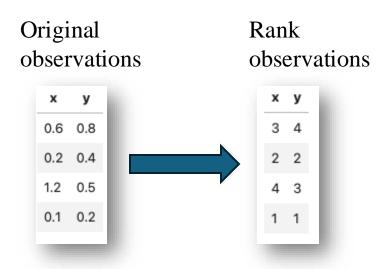
- Transform marginal distributions into uniform distributions
- Develop copula model
 - Vine copula: rvinecopulib
 - Copula selection using AIC
- Simulations
- Transform the simulated uniform distributions into the original marginal distributions

The advantage of the uniform marginal distributions

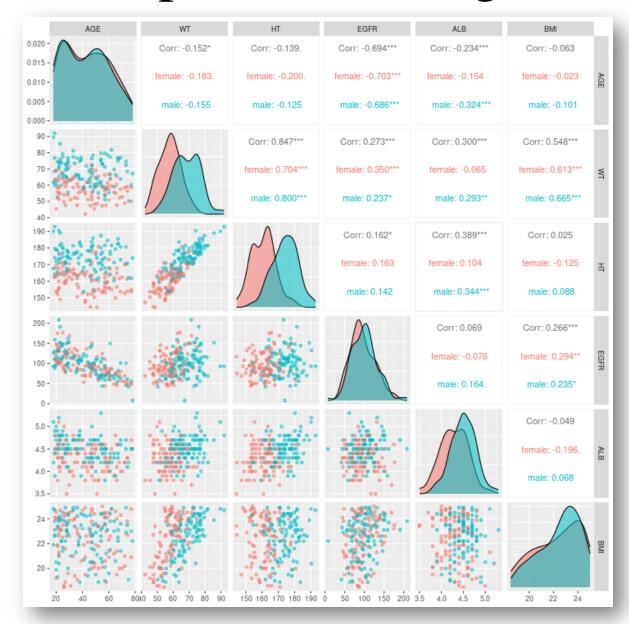


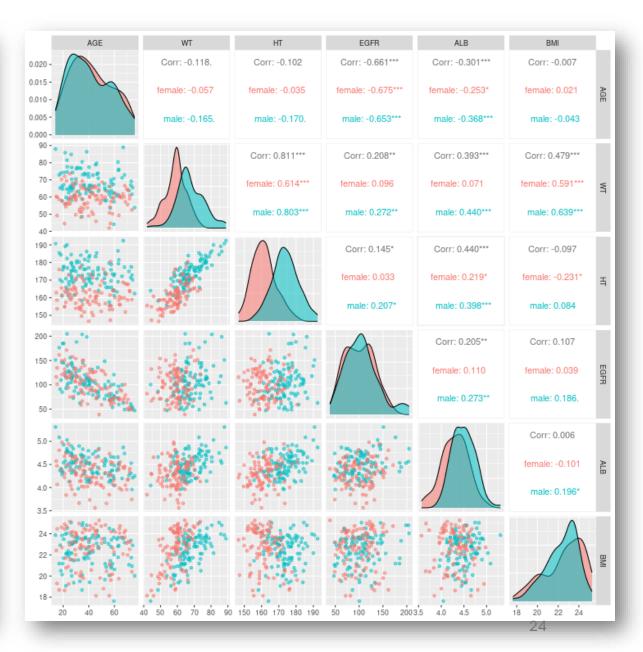
Separate <u>a joint distribution</u> into <u>marginal</u> <u>distributions</u> and <u>the dependence structure</u>

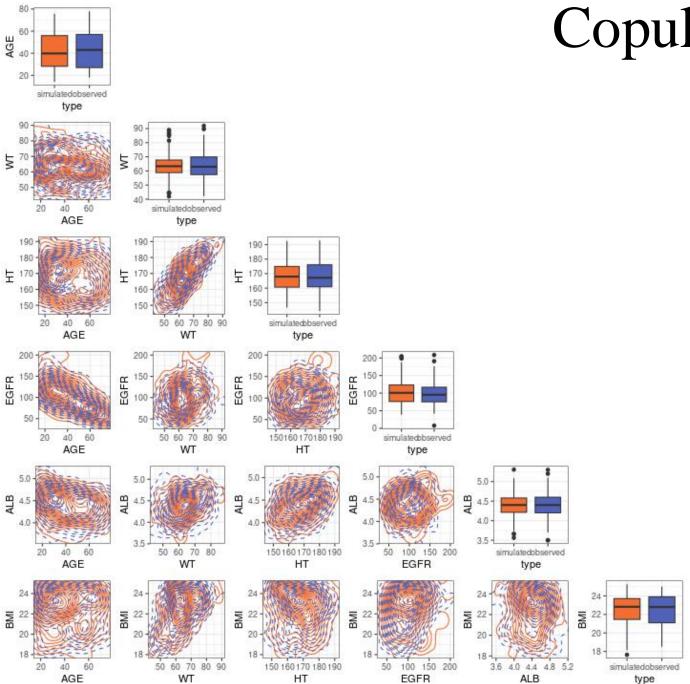
- Standardize copula modeling, more flexible and efficient to model the complex joint distribution
- Rank correlation (Kendell's tau) is independent of marginal distributions (simplicity and robustness)



Copula Modeling







Copula Modeling

Copula resources

- Laura B. Zwep, Tingjie Guo, Jacqueline J. Meulman, J.G. Coen van Hasselt. Copula modeling for realistic virtual patient covariate simulation. PAGE 2022
- Zwep, L.B., Guo, T., Nagler, T., Knibbe, C.A.J., Meulman, J.J. and van Hasselt, J.G.C. (2024), Virtual Patient Simulation Using Copula Modeling. Clin Pharmacol Ther, 115: 795-804. https://doi.org/10.1002/cpt.3099
 - Github: https://github.com/vanhasseltlab/copula_vps
- Guo, Y., Guo, T., Knibbe, C.A.J. et al. Generation of realistic virtual adult populations using a model-based copula approach. J Pharmacokinet Pharmacodyn (2024). https://doi.org/10.1007/s10928-024-09929-4
 - Github: https://github.com/vanhasseltlab/NHANES_copula
 - ShinyAPP: https://cocosim.lacdr.leidenuniv.nl/
- Kiran Karra. Copula Short Course. Youtube

The End