

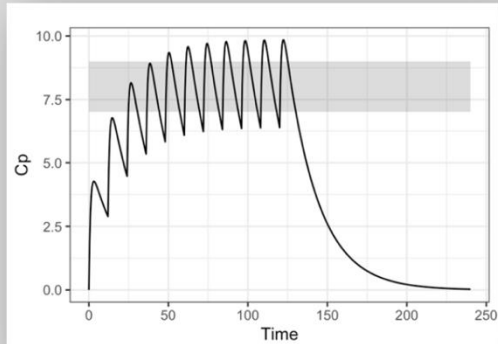
Virtual Patient Simulation

Curtis K. Johnston & Shen Cheng

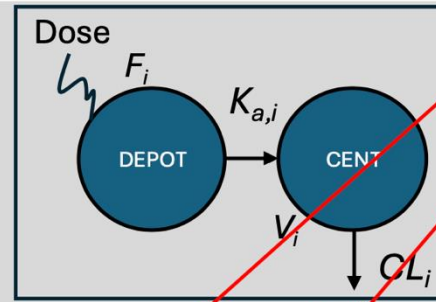
11/01/2024

Stochastic Simulation

Simulation design:
Treatment regimen
Study duration
Sampling schedule



WT	AGE	SEX	...
65	31	F	...
77	25	M	...
102	36	M	...
...



$$CL_i = \theta_1 \times \frac{WT_i}{70kg} \times e^{\eta_{1,i}}$$

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

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}} \right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

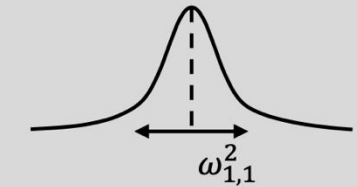
Population parameters (.ext)

1. Fixed-effect

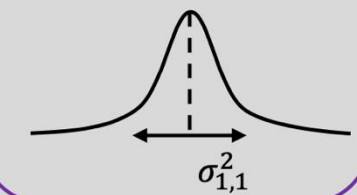
$\theta_1, \theta_2 \dots$

2. Random-effect

2.1 Ω matrix



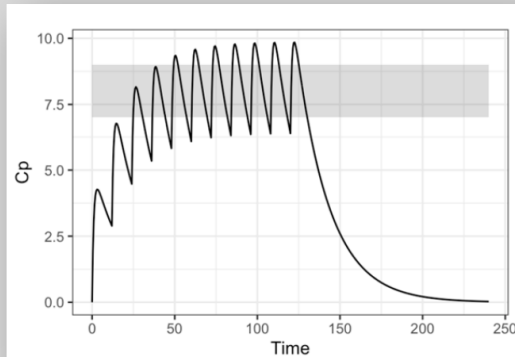
2.2 Σ matrix



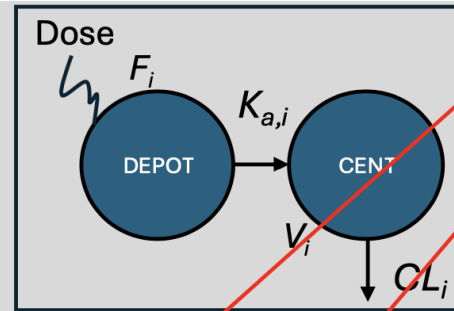
Covariate (Virtual Patient) Simulations

Simulation design:

Treatment regimen
Study duration
Sampling schedule



WT	AGE	SEX	...
45	12	M	...
57	15	F	...
33	6	F	...
...



$$CL_i = \theta_1 \times \frac{WT_i^{\theta_2}}{70kg} \times e^{\eta_{1,i}}$$

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

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}} \right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

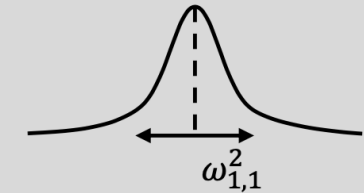
Population parameters (ext)

1. Fixed-effect

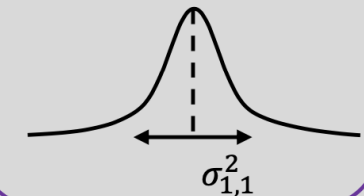
$\theta_1, \theta_2 \dots$

2. Random-effect

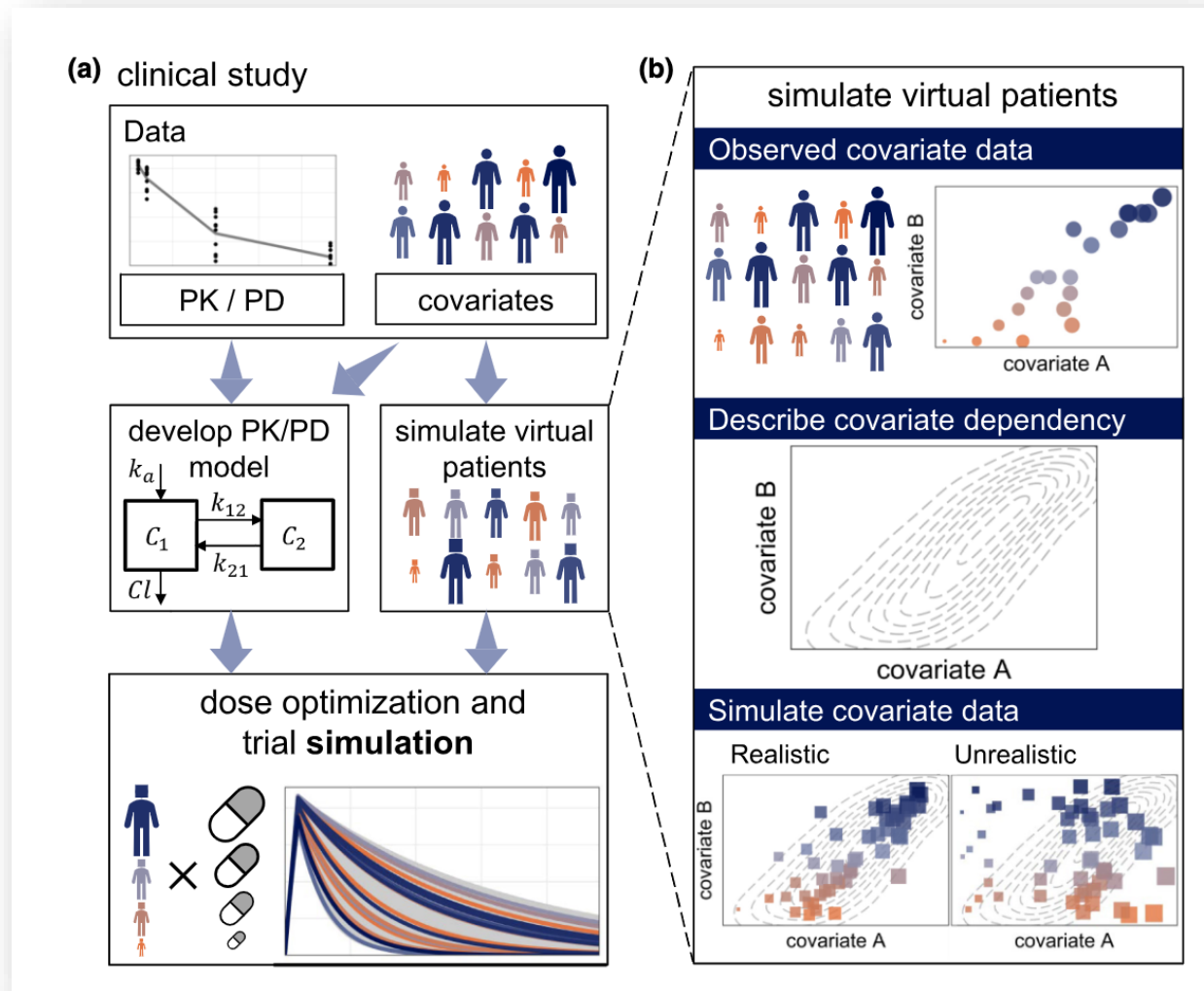
2.1 Ω matrix



2.2 Σ matrix



“Realistic” Virtual Population



Difficulties in simulating **realistic** virtual population:

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

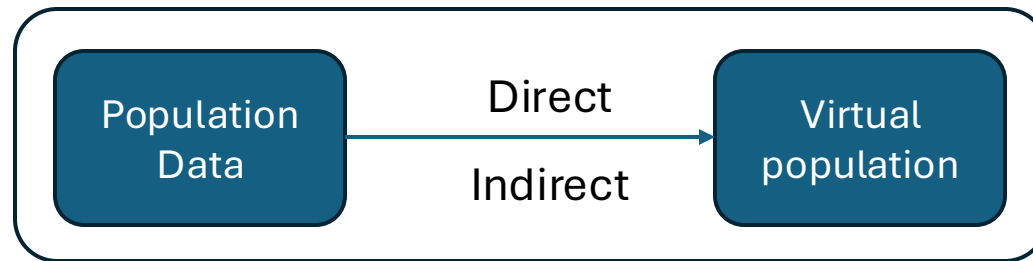
Unrealistic virtual patient example:

A patient of 95 years old, with a high body weight and a very good kidney.

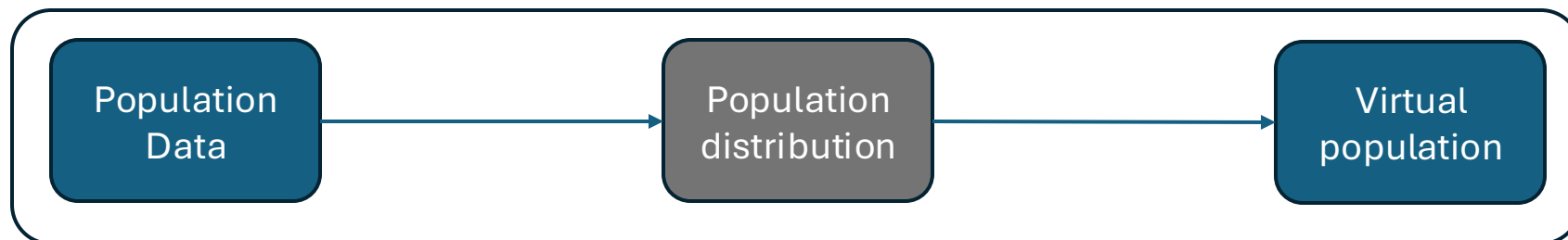
Failing to consider such correlations inflate the variability of covariates, in other words, unrealistic virtual patients.

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

Bootstrap

	X_1	X_2
1	4.5	50
2	10.3	32
3	3.5	16
4	0.2	103

Resample rows

	X_1	X_2
3	3.5	16
2	10.3	32
1	4.5	50
2	10.3	32

Need actual data
Cannot extrapolate

Conditional distributions (MICE)

Add missing rows

	X_1	X_2
1	4.5	50
2	10.3	32
3	3.5	16
4	0.2	103
5		
6		
7		
8		

Smania & Jonsson, 2021

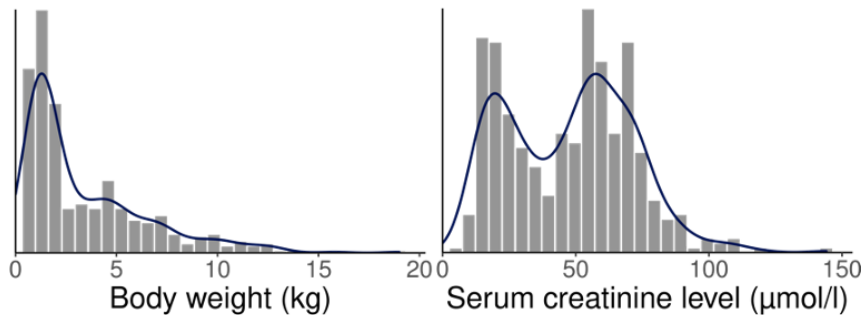
Impute missing rows

	X_1	X_2
1	4.5	50
2	10.3	32
3	3.5	16
4	0.2	103
5	3.9	70
6	16	35
7	0.7	59
8	12	9

data-based

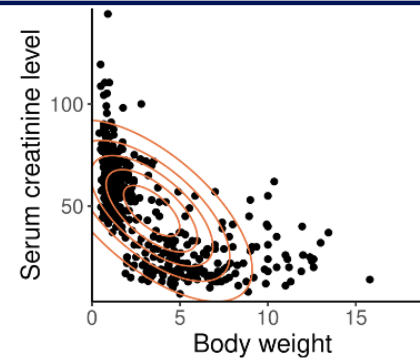
Need actual data (indirectly)

Marginal distributions



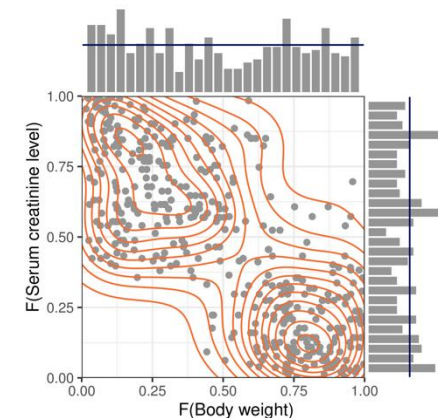
Ignore correlations

Multivariate normal distribution



Distributional assumptions

Copula modeling



distribution-based

Distribution-Based Methods

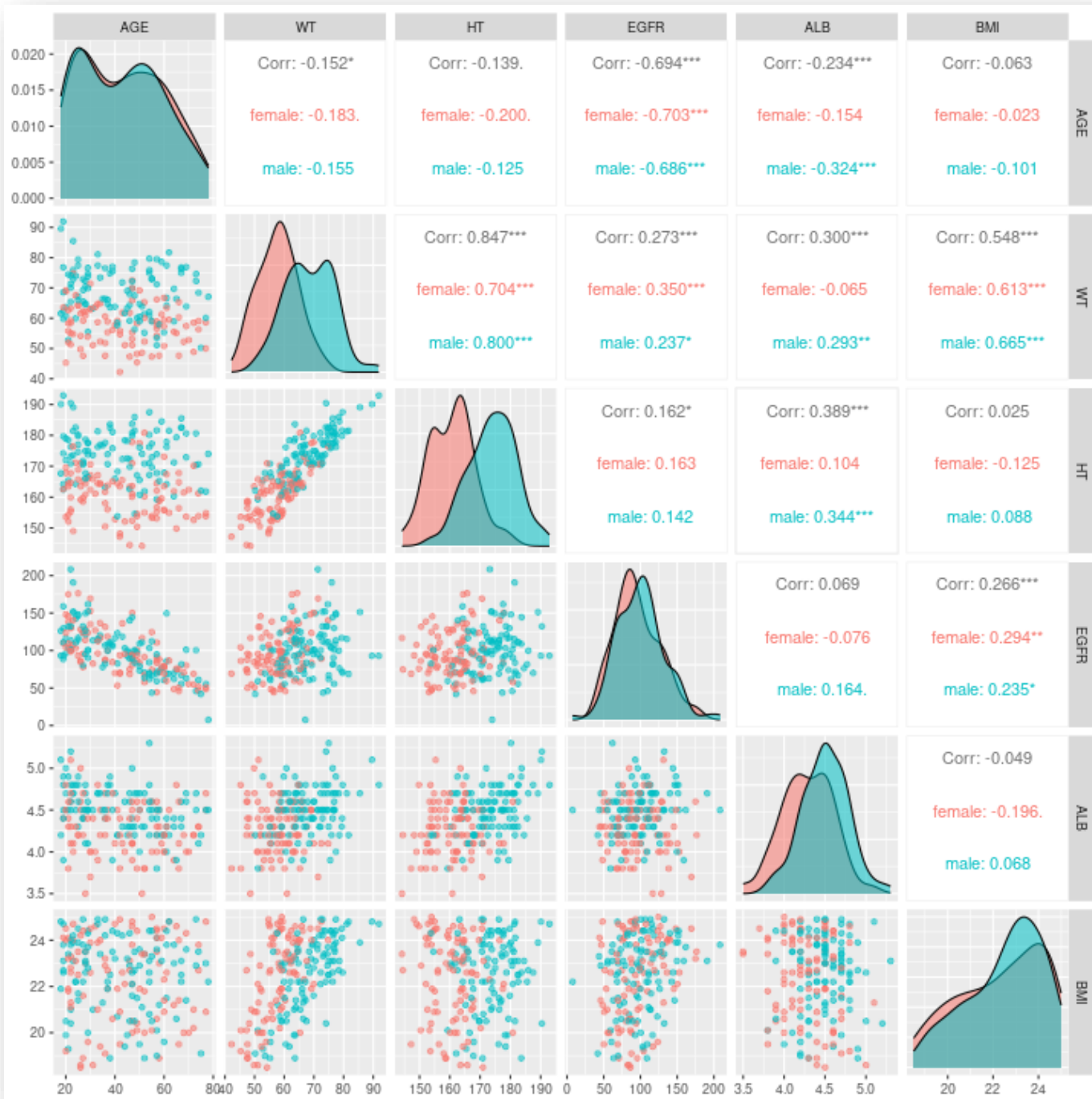
- Marginal distributions
- Multivariate normal distributions (MVND)
- Copula modeling

Population Data

[./wk9/data/pop.csv](#)

Seven covariates:

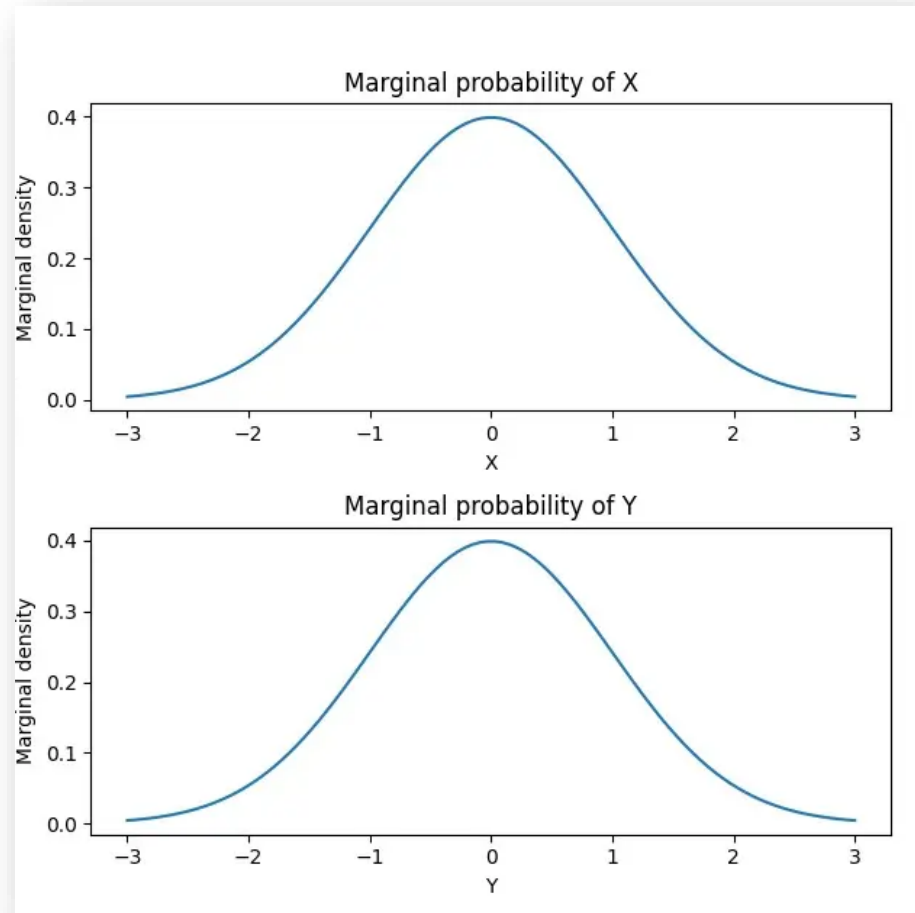
- Continuous:
 - AGE: age in years
 - WT: body weight in kg
 - HT: height in cm
 - EGFR: estimated glomerular filtration rate in mL/min
 - ALB: albumin concentration in g/dL
 - BMI: body mass index in kg/m²
- Categorical:
 - SEX: gender (male vs female)



Experiments

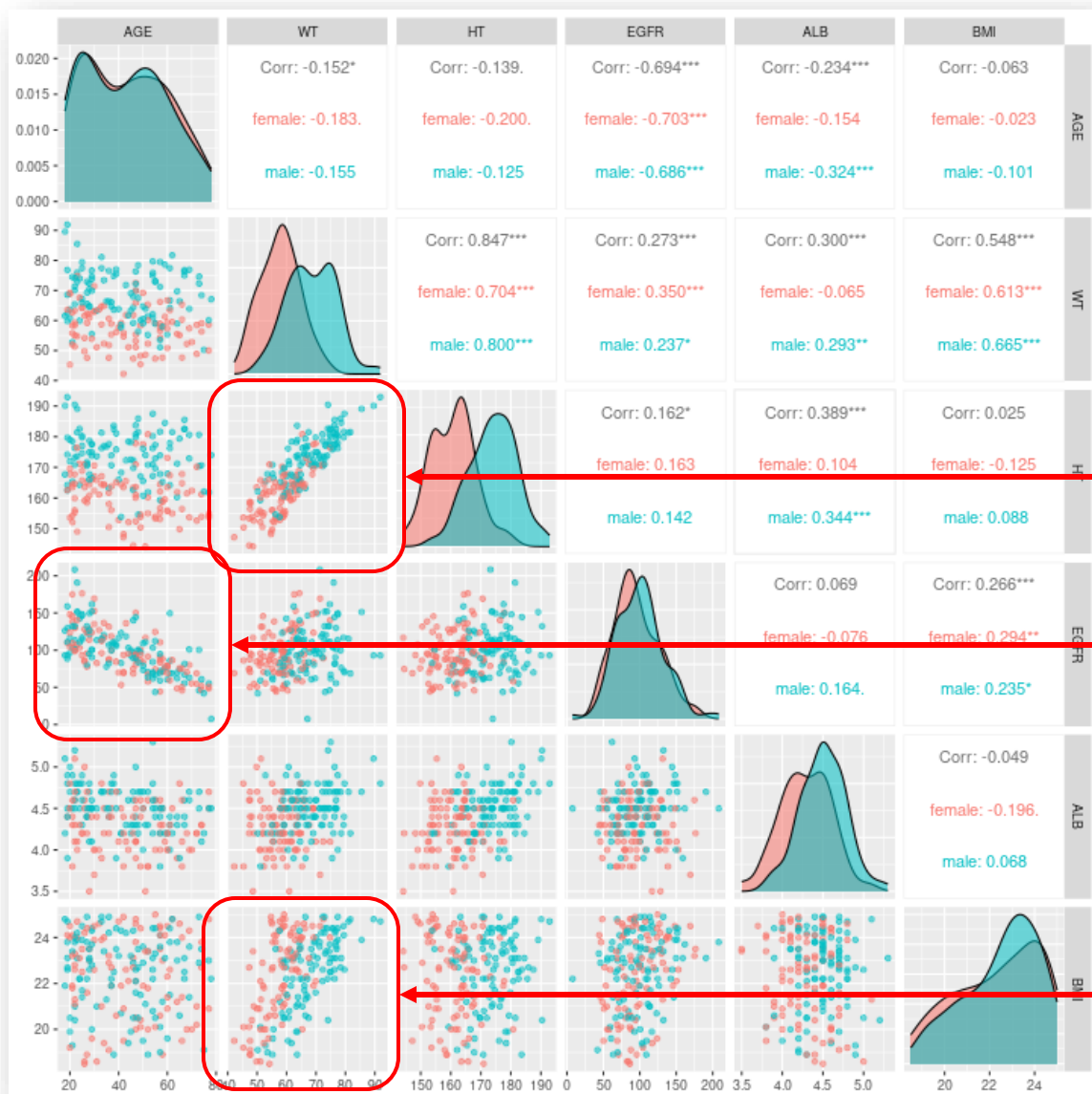
- Separate the population data based on SEX (**male** vs **female**)
- Derive two distributions, one for male, one for female, using different method:
 - Marginal distributions
 - Multivariate normal distributions
 - Copula modeling
- Simulate from the derived distributions
- Compare the simulated data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

Marginal Distributions

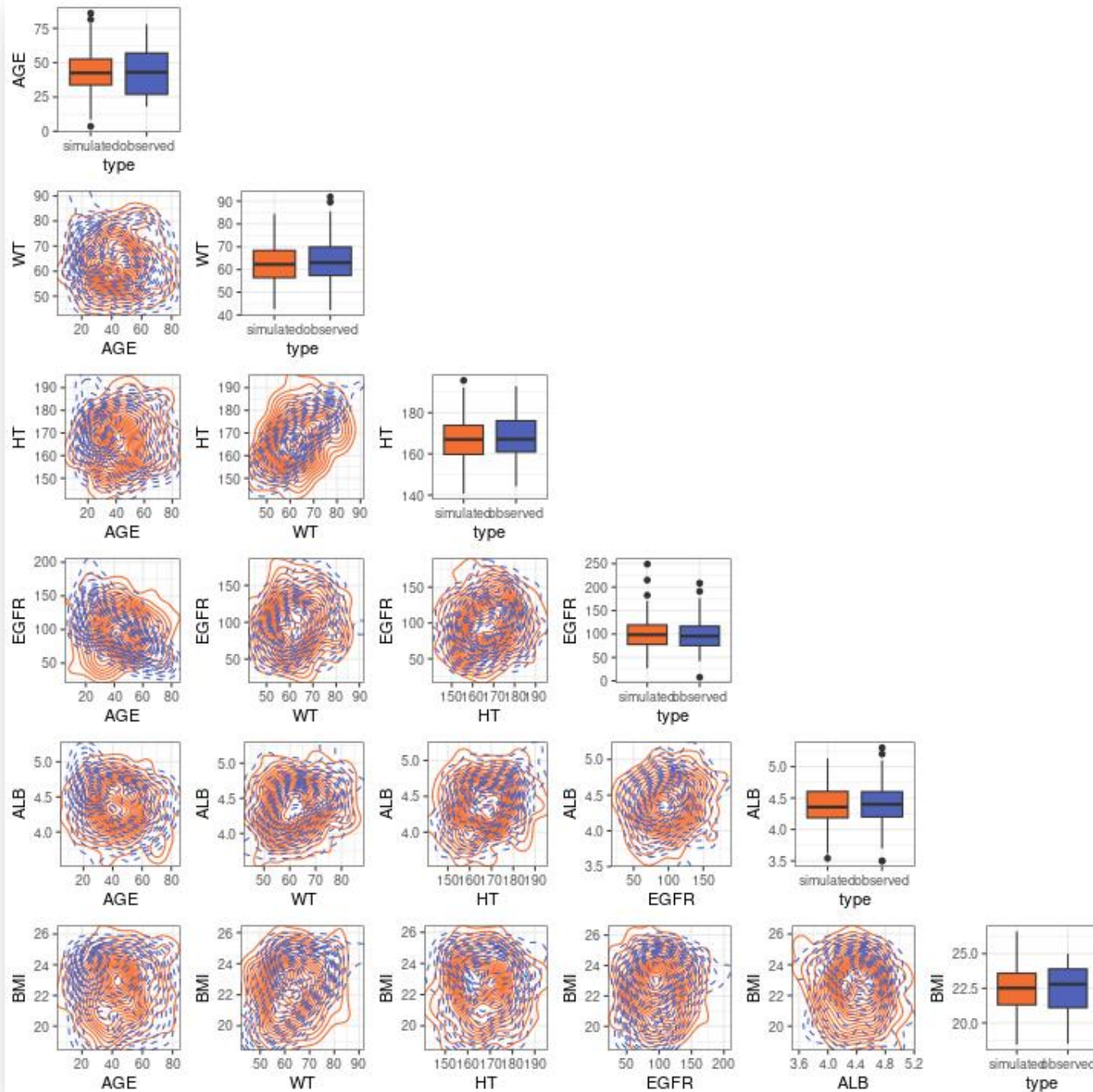


- Derive the means and standard deviations (SDs) of each variable in the population dataset.
- Sample from a (truncated) normal distribution (or other distributions) with the same mean and SD of each variable.

Marginal Distributions



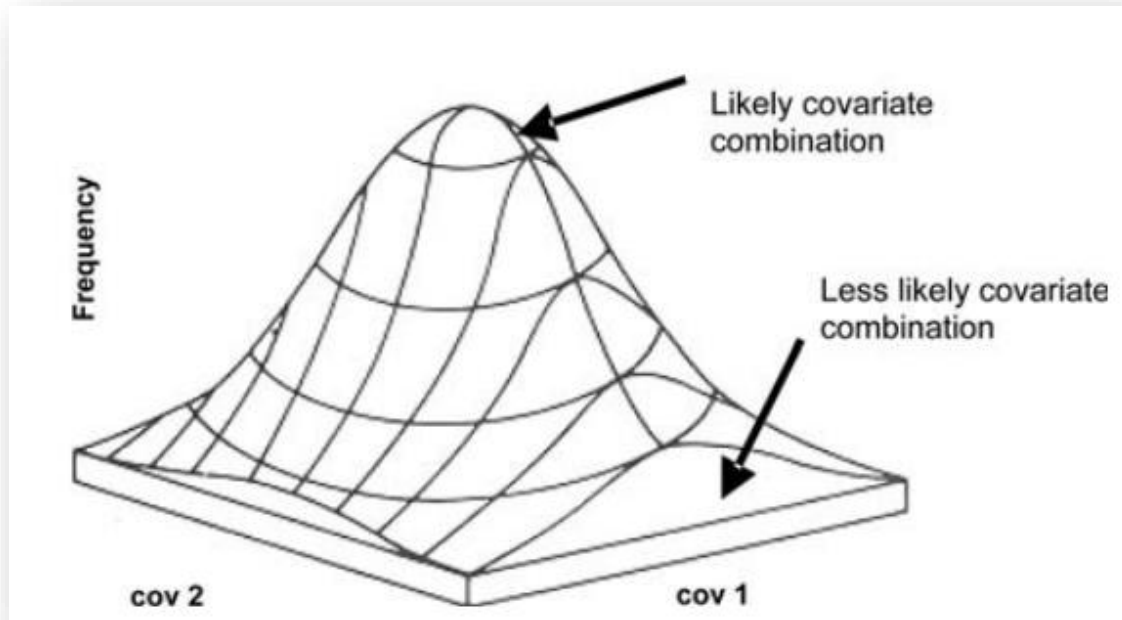
Marginal Distributions



Summary-Marginal Distributions

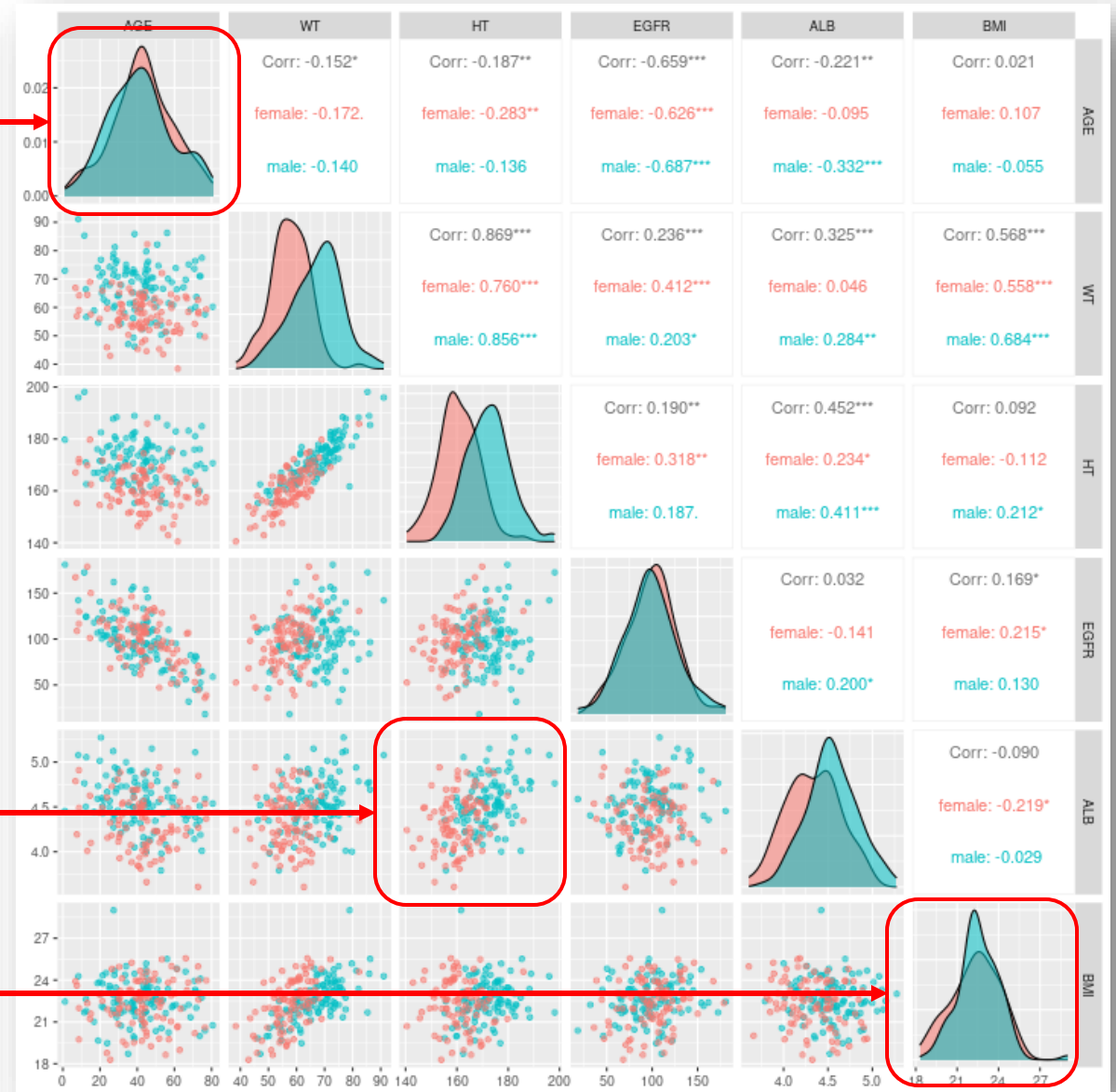
- Simulation ignoring correlations (i.e., joint distribution)
- Unrealistic simulation
 - Unrealistic combination of covariates
 - Low weight + high BMI/height
 - High age + high eGFR
- Easy to implement
- Not appropriate to use when high-dimensional covariates were simulated

Multivariate Normal Distributions

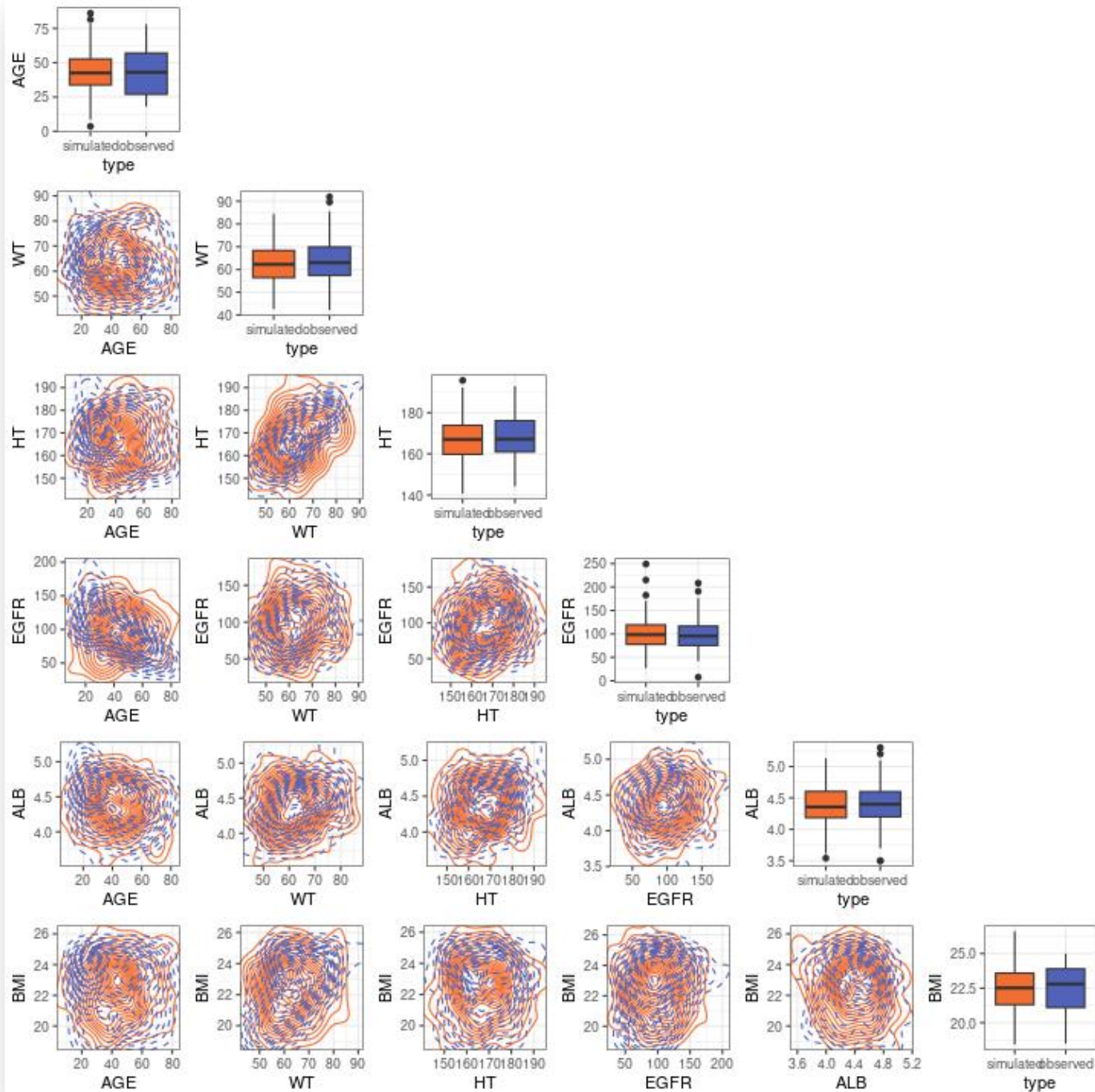


- Derive the means and the covariance matrix of the population dataset.
- Sample from the multivariate normal distribution defined by the means and the covariance matrix .

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

30th **PAGE**meeting Ljubljana • Slovenia
28 June – 1 July 2022

**Virtual patient simulation:
a copula approach**

Laura B. Zwep – Stuart Beal Methodology Session

 Universiteit
Leiden
The Netherlands

LACDR

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

$$H(x, y) = C(F(x), G(Y))$$

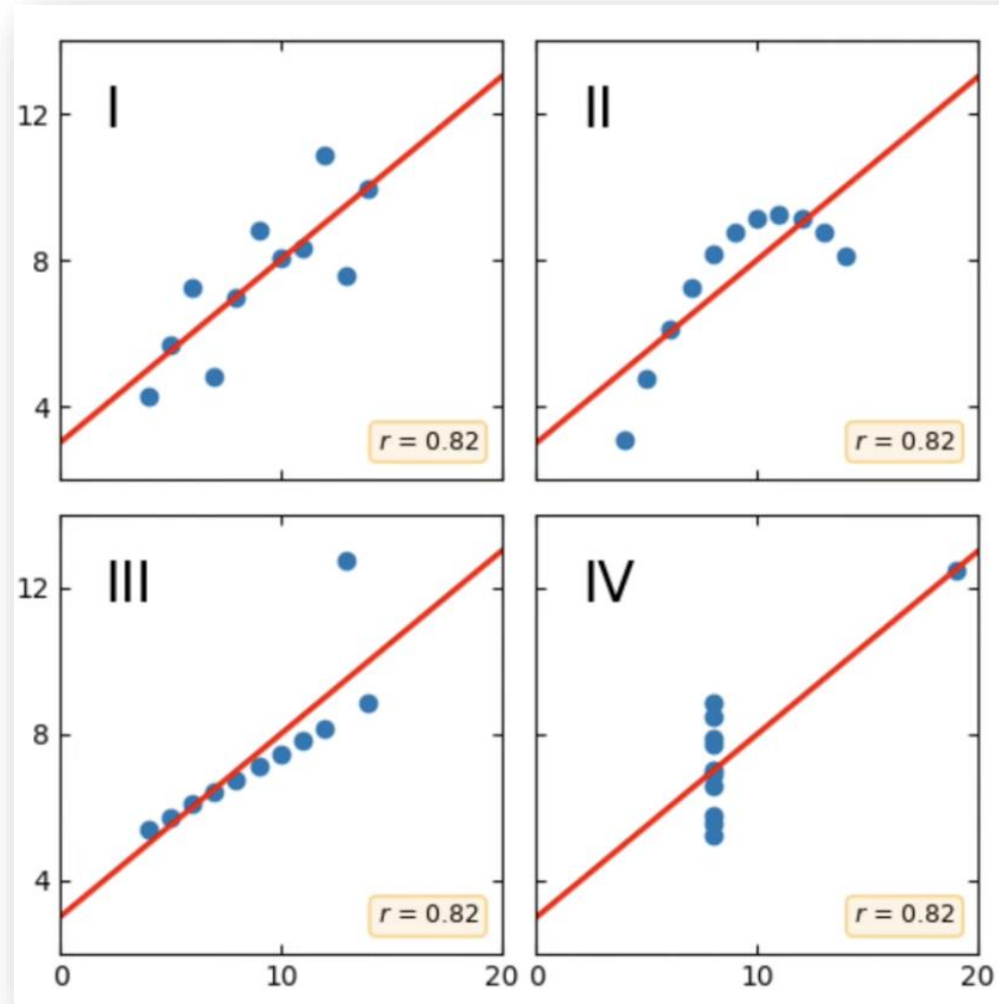
Joint distribution **Copula** Marginal distribution

$$x = F^{-1}(u)$$

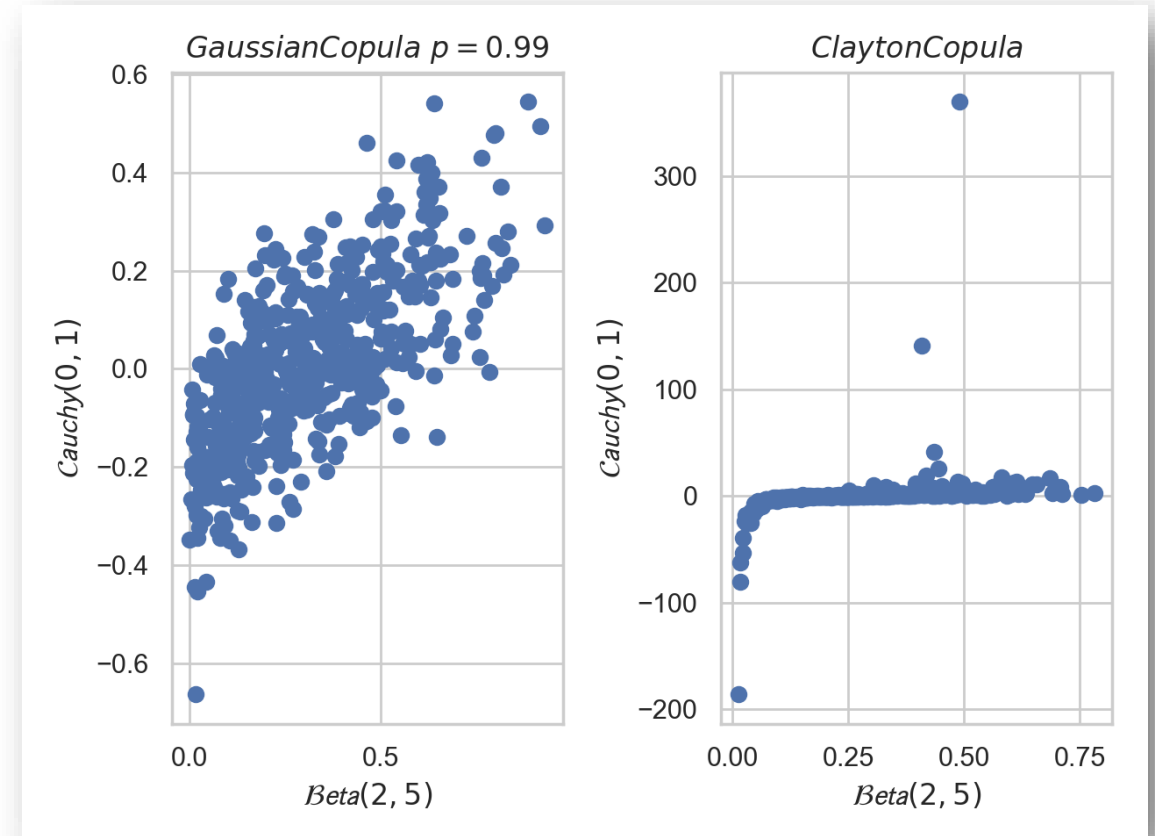
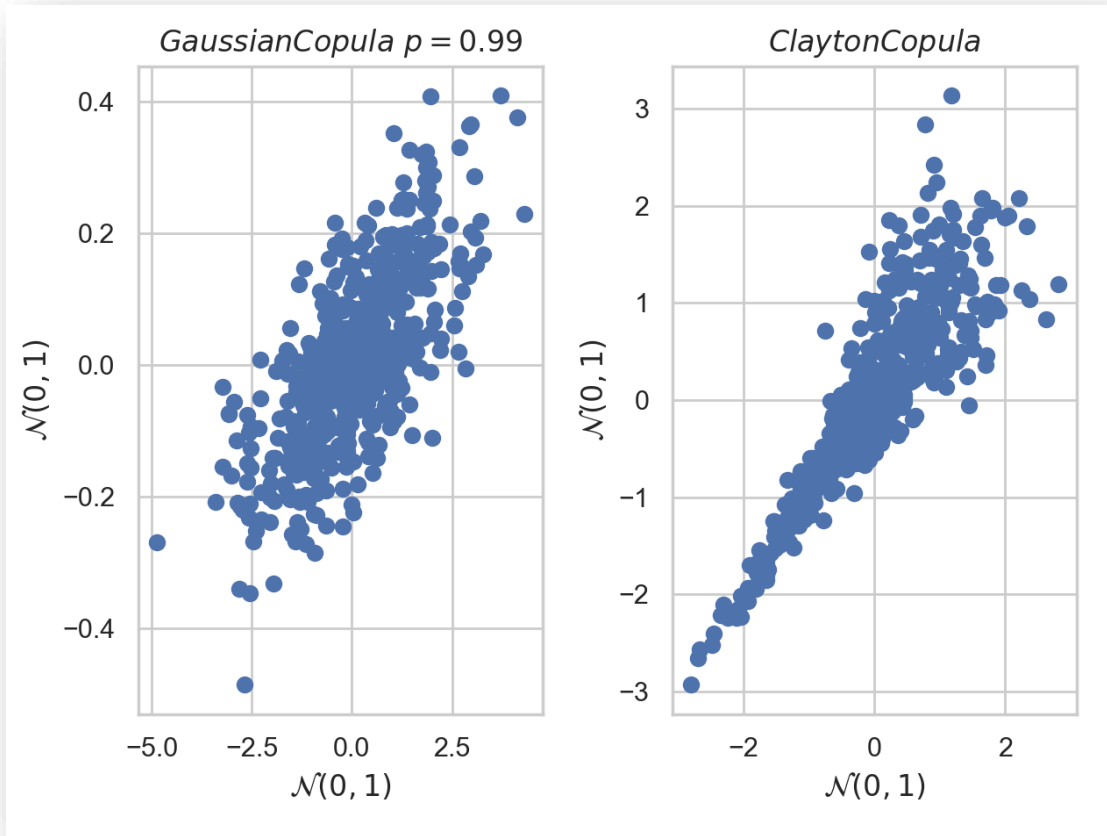
$$y = G^{-1}(v)$$

$$C(u, v) = H(F^{-1}(u), G^{-1}(v))$$

Why copula?



Why copula?



Kiran Karra. Copula Short Course. Youtube

Copula: general process

- Density of the **dependence structure** between two **uniformly distributed** covariates

- Transform marginals to uniform

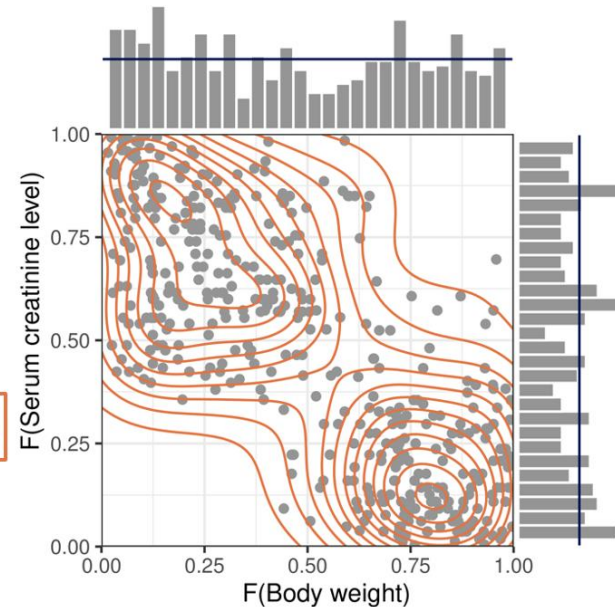
Inverse density:

$$F_1(X_1) \sim U(0,1) \text{ and } F_2(X_2) \sim U(0,1)$$

- Joint density:

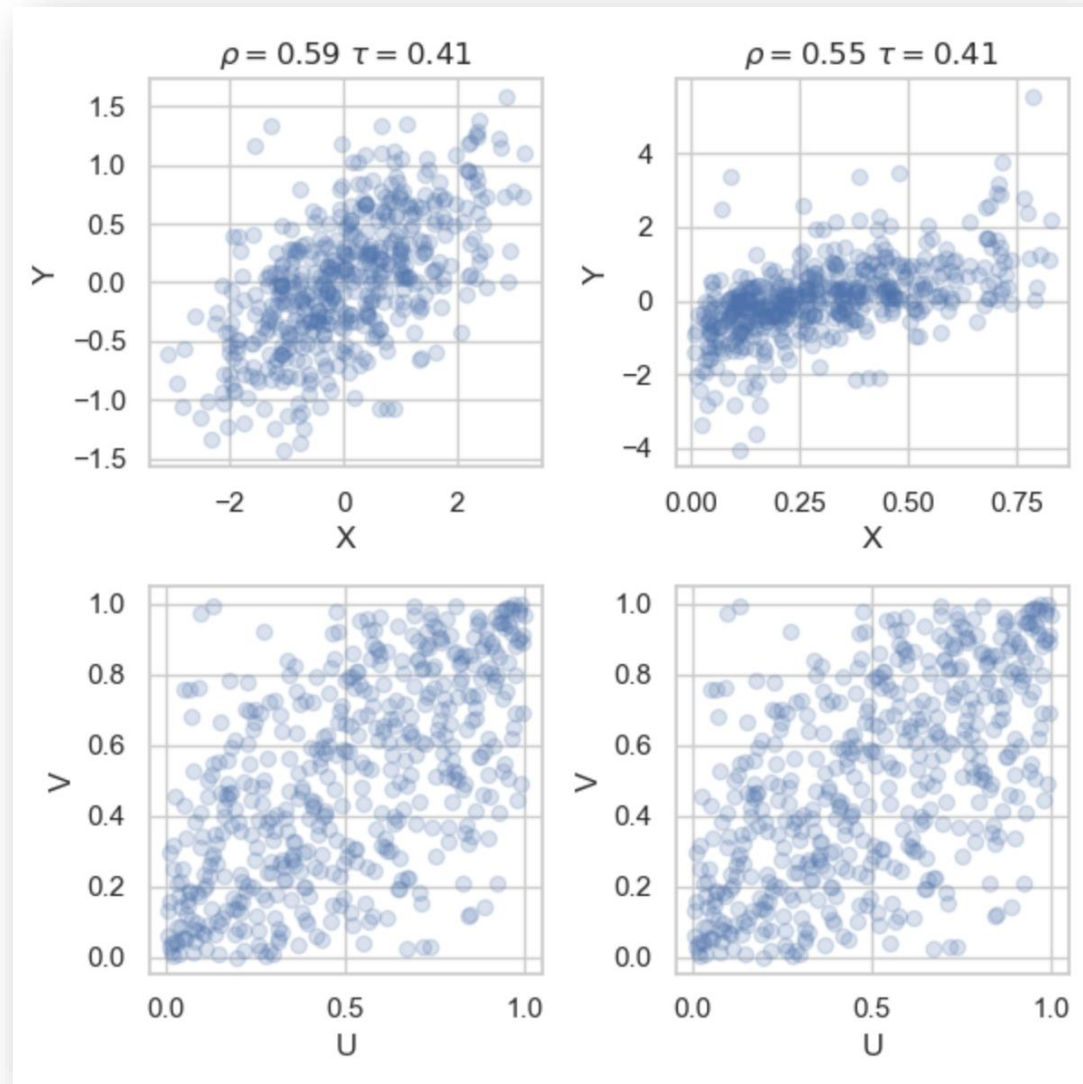
$$f(x_1, x_2) = f_1(x_1) \cdot f_2(x_2) \cdot c(F_1(x_1), F_2(x_2))$$

↑
copula density



- 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 a joint distribution into marginal distributions and the dependence structure

- 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)

Original
observations

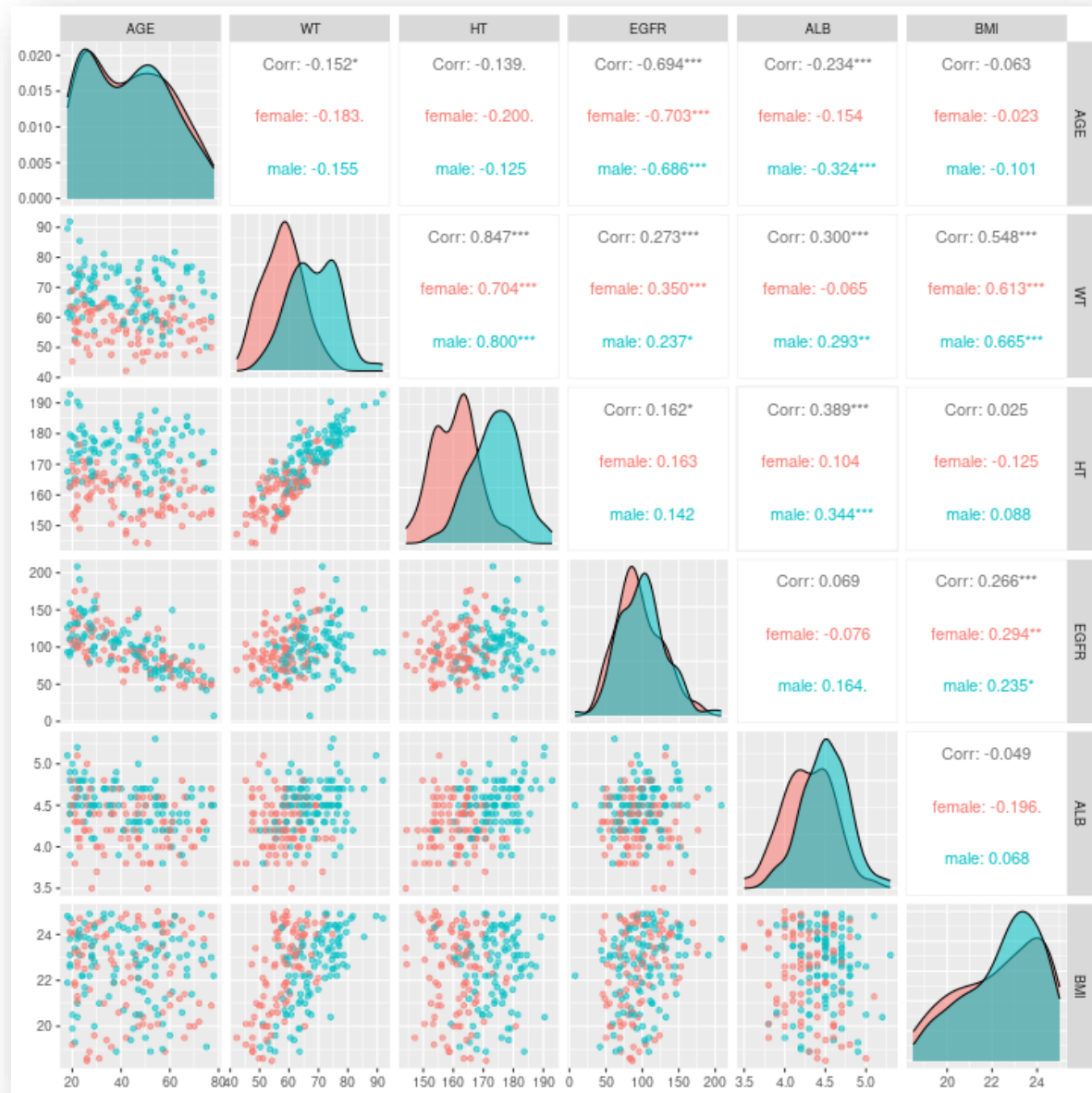
x	y
0.6	0.8
0.2	0.4
1.2	0.5
0.1	0.2



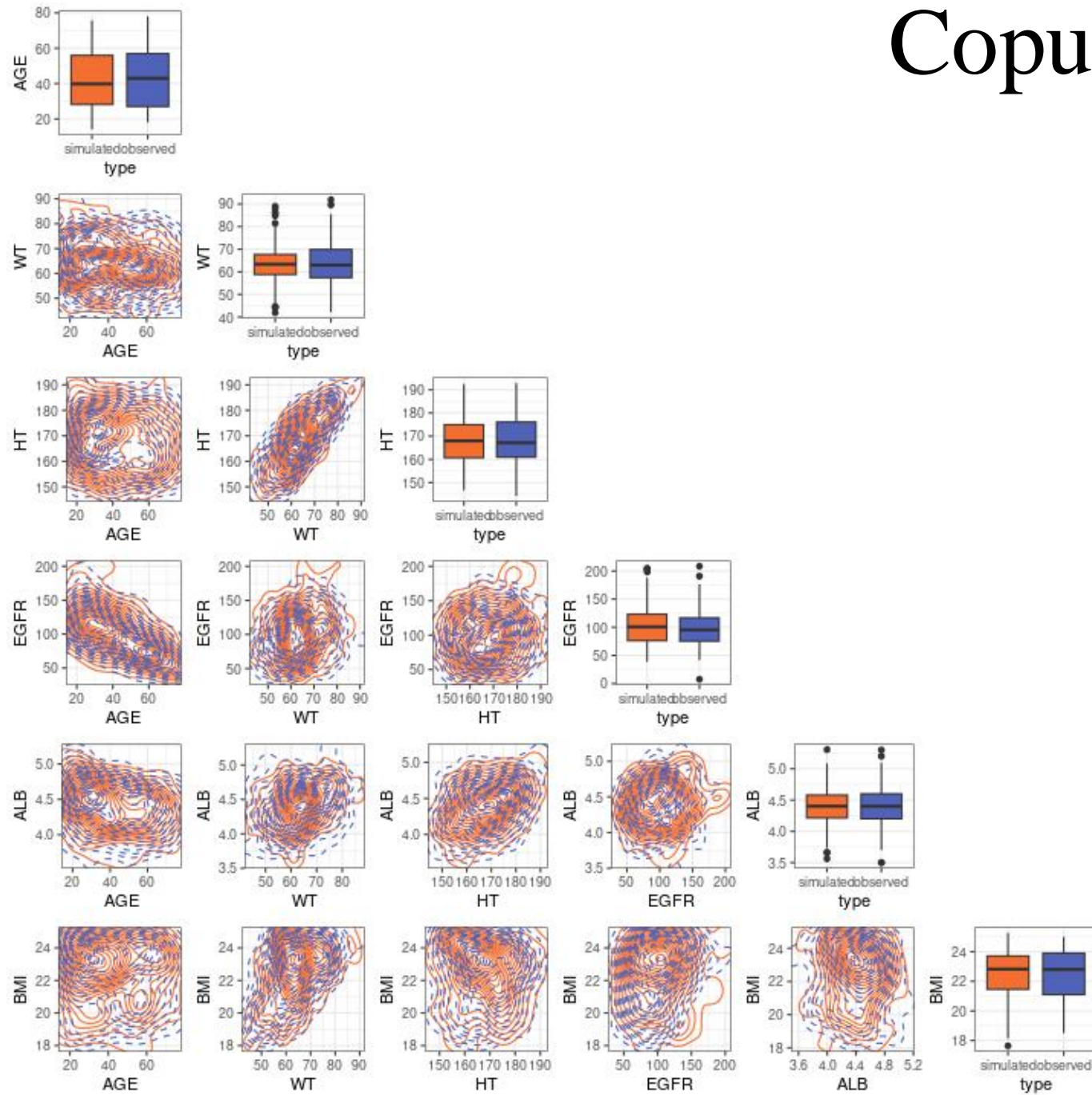
Rank
observations

x	y
3	4
2	2
4	3
1	1

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/vanhasseltnlab/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/vanhasseltnlab/NHANES_copula
 - ShinyAPP: <https://cocosim.lacdr.leidenuniv.nl/>
- Kiran Karra. Copula Short Course. Youtube

The End