Virtual Patient Simulation

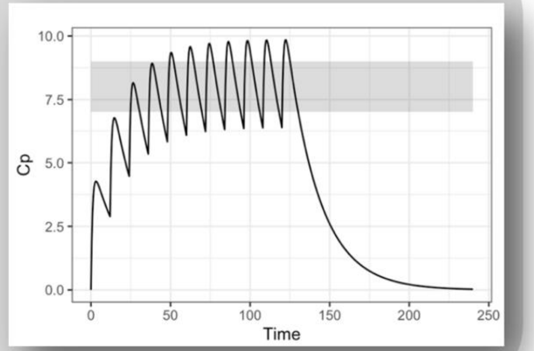
Shen Cheng

11/01/2024

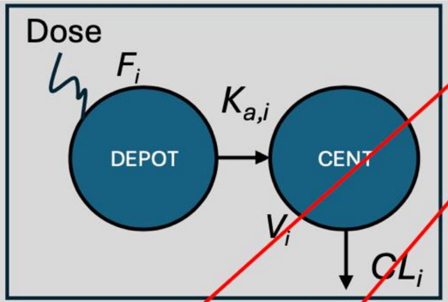
Stochastic Simulation

Simulation design:

- Treatment regimen
- Study duration
- Sampling schedule



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



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

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

...

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

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

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

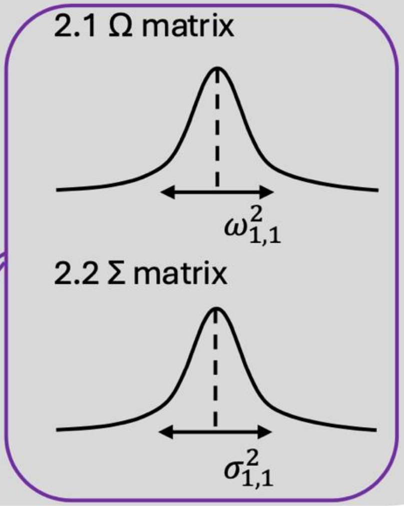
...

Population parameters (`.ext`)

1. Fixed-effect

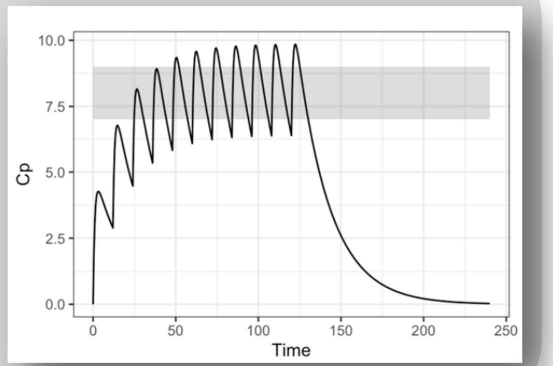
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

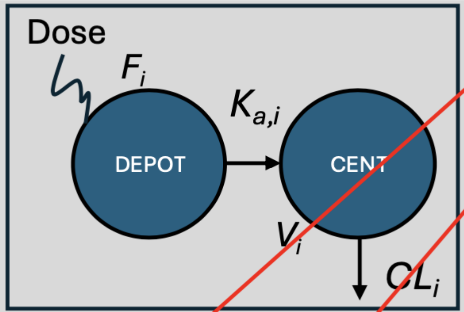


Covariate (Virtual Patient) Simulations

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule



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



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

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

...

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

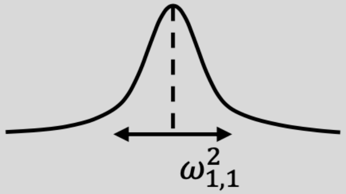
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

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

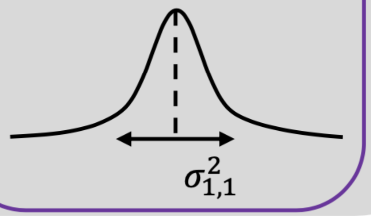
...

Population parameters (`.ext`)

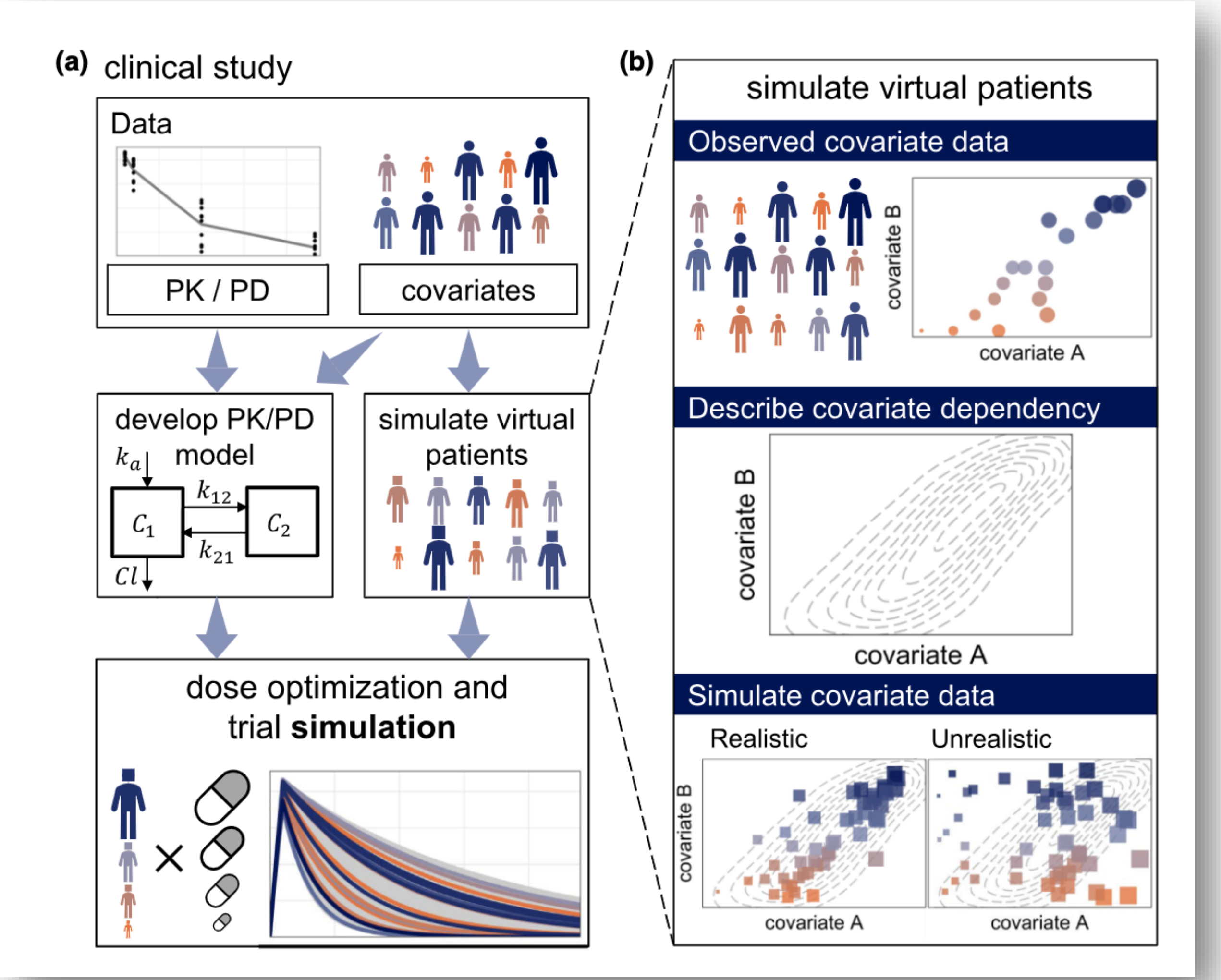
1. Fixed-effect
   θ_1, θ_2 ...
2. Random-effect
   - 2.1 Ω matrix



   - 2.2 Σ matrix



“Realistic” Virtual Population



Zwep LB et al., Clin Pharmacol Ther. 2023

Difficulties in simulating **realistic** virtual population:

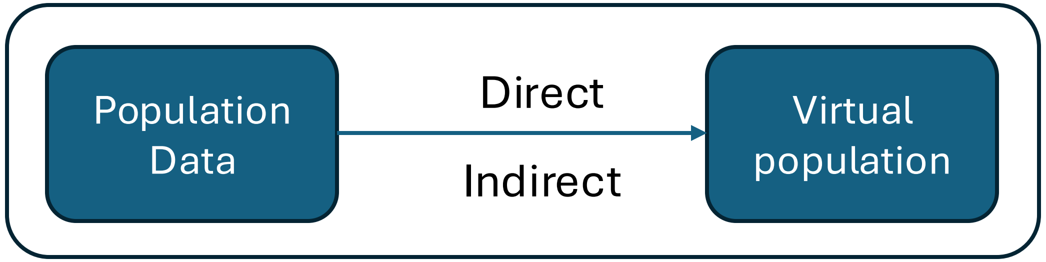
- Different covariates exhibit different distributions (i.e., marginal distributions)
- Intricate dependency structure (i.e., correlation)

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

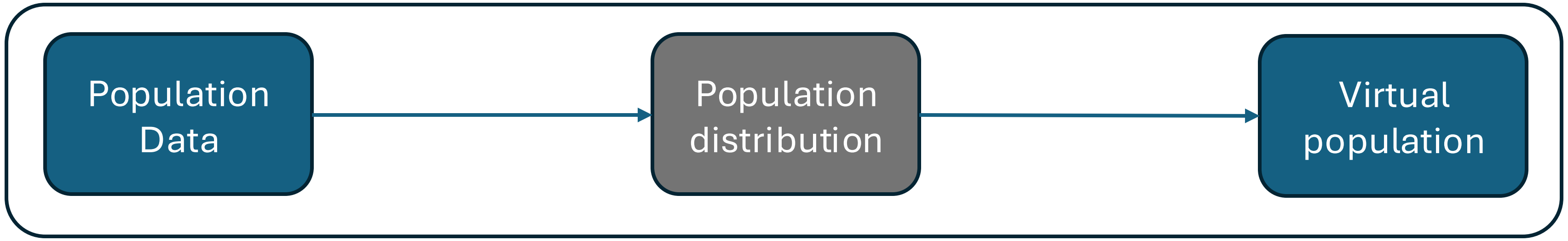
Failing to consider such correlations inflate the variability of covariates, in other words, unrealistic virtual patients.

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

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)

Smania & Jonsson, 2021

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		

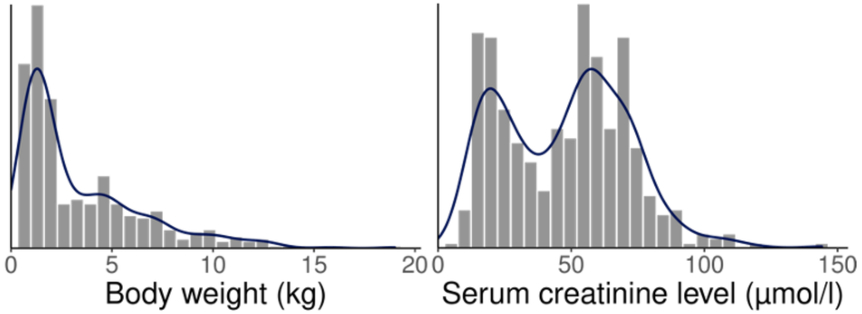
Impute missing rows

	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

Need actual data (indirectly)

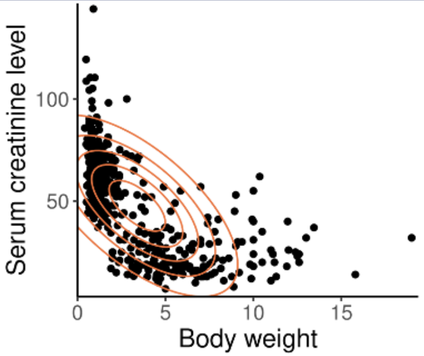
data-based

Marginal distributions



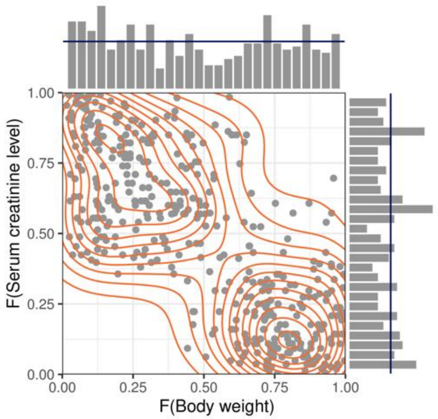
Ignore correlations

Multivariate normal distribution



Distributional assumptions

Copula modeling



distribution-based

Zwep LB et al., PAGE. 2022

Distribution-Based Methods

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

Population Data

./wk9/data/pop.csv

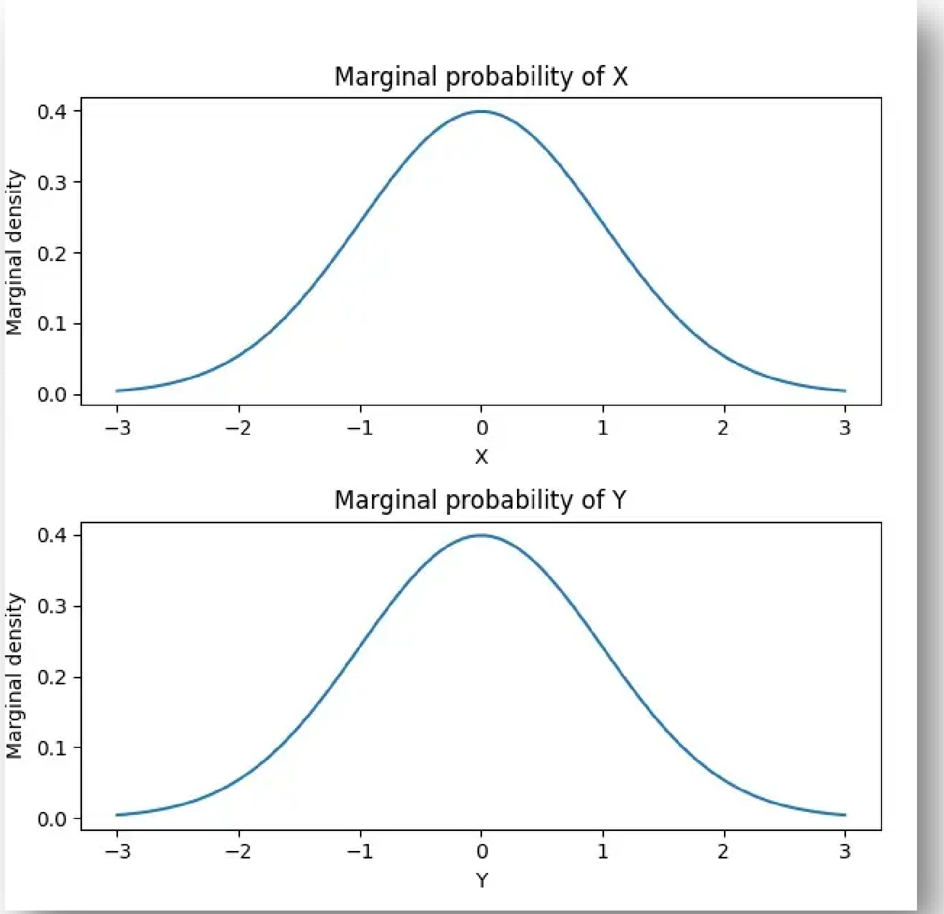
Seven covariates:

- 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/m^2
- 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).

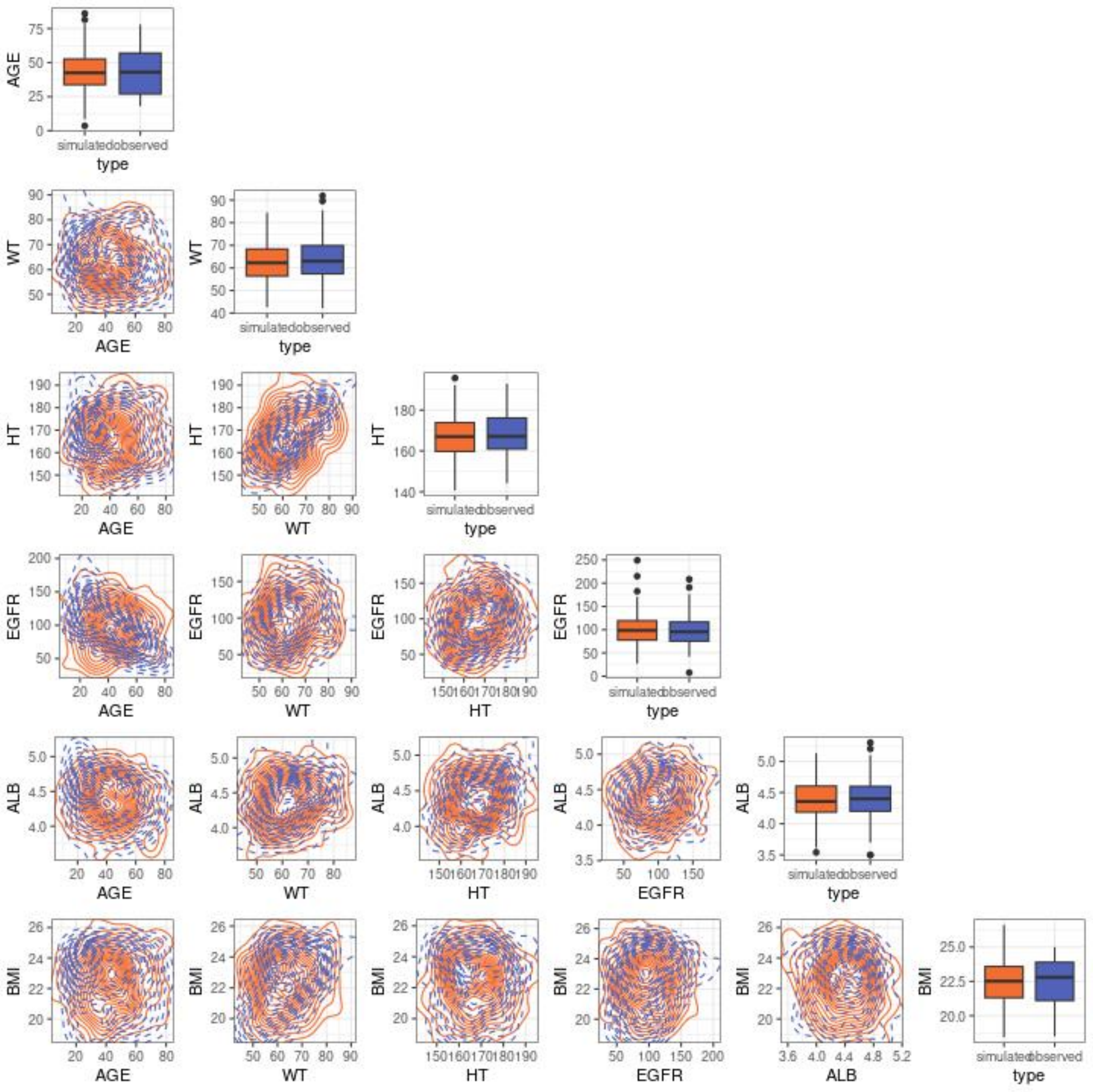
Marginal Distributions



Meccanismo Complesso. Marginal probability. 12/11/2023

- 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

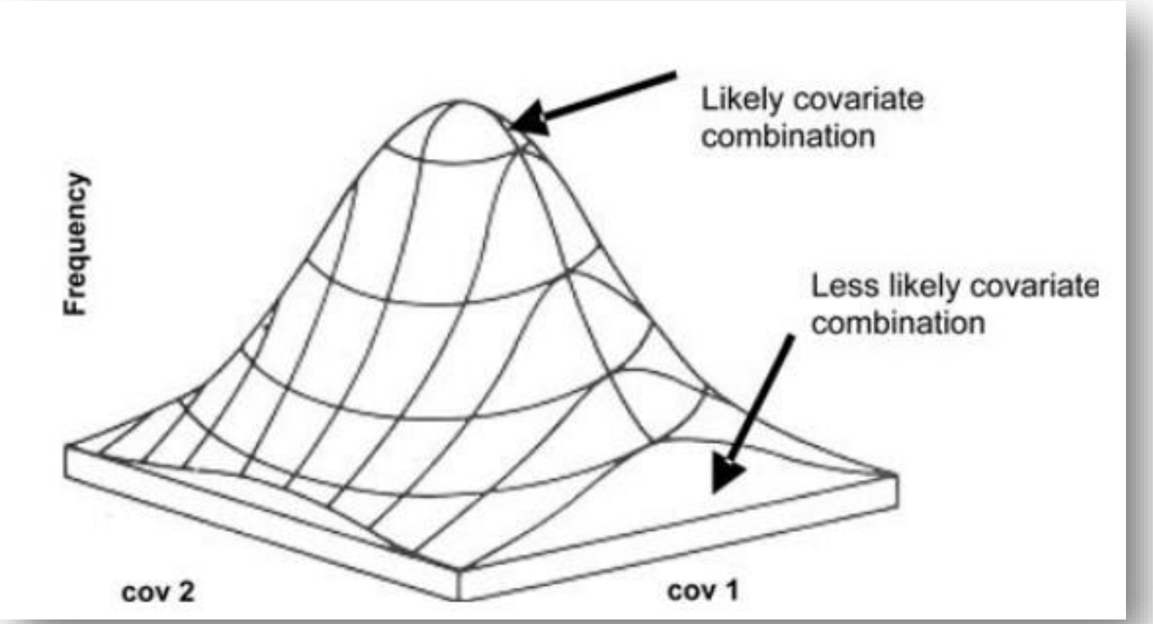


Marginal Distributions

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

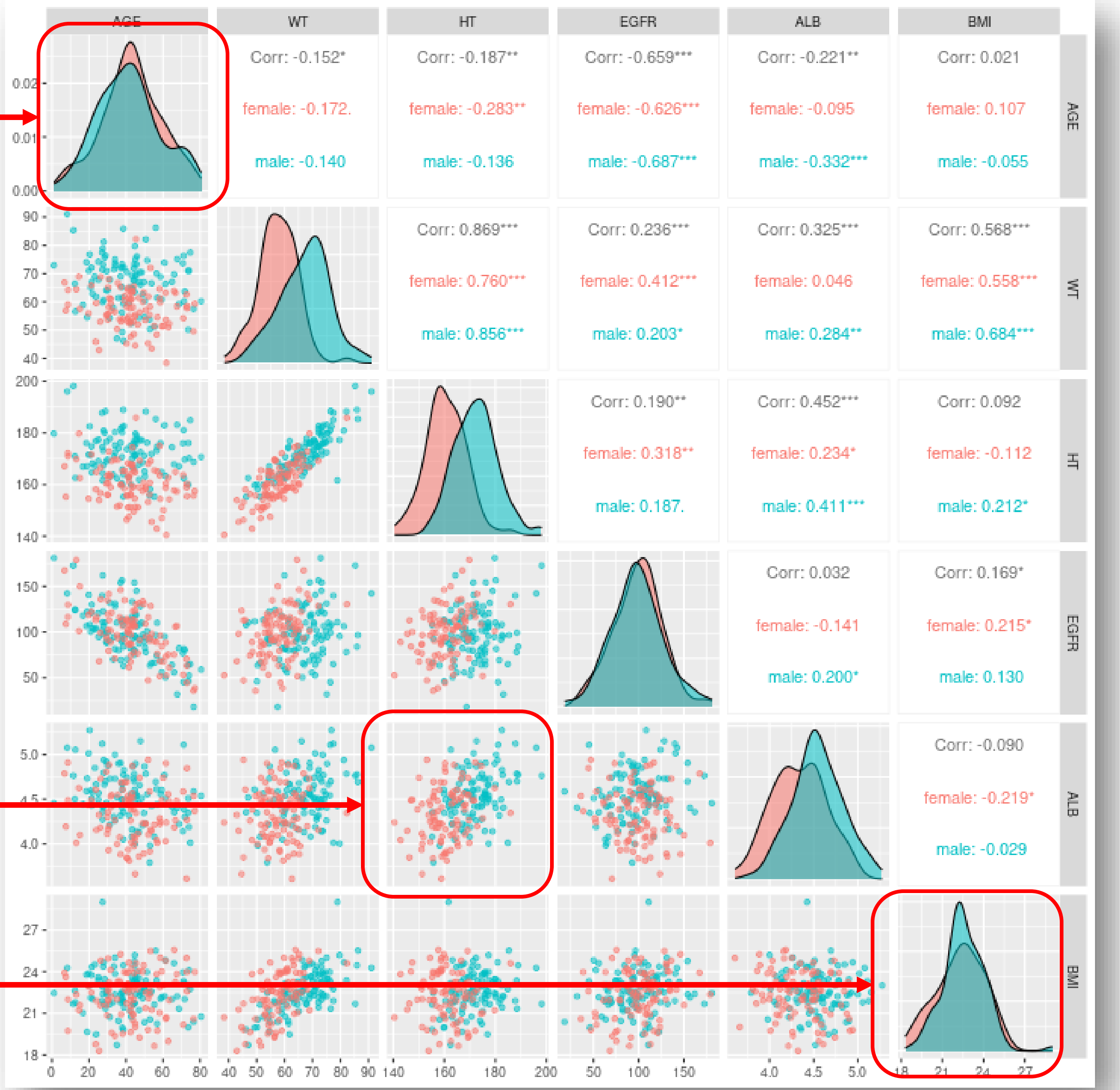
Multivariate Normal Distributions

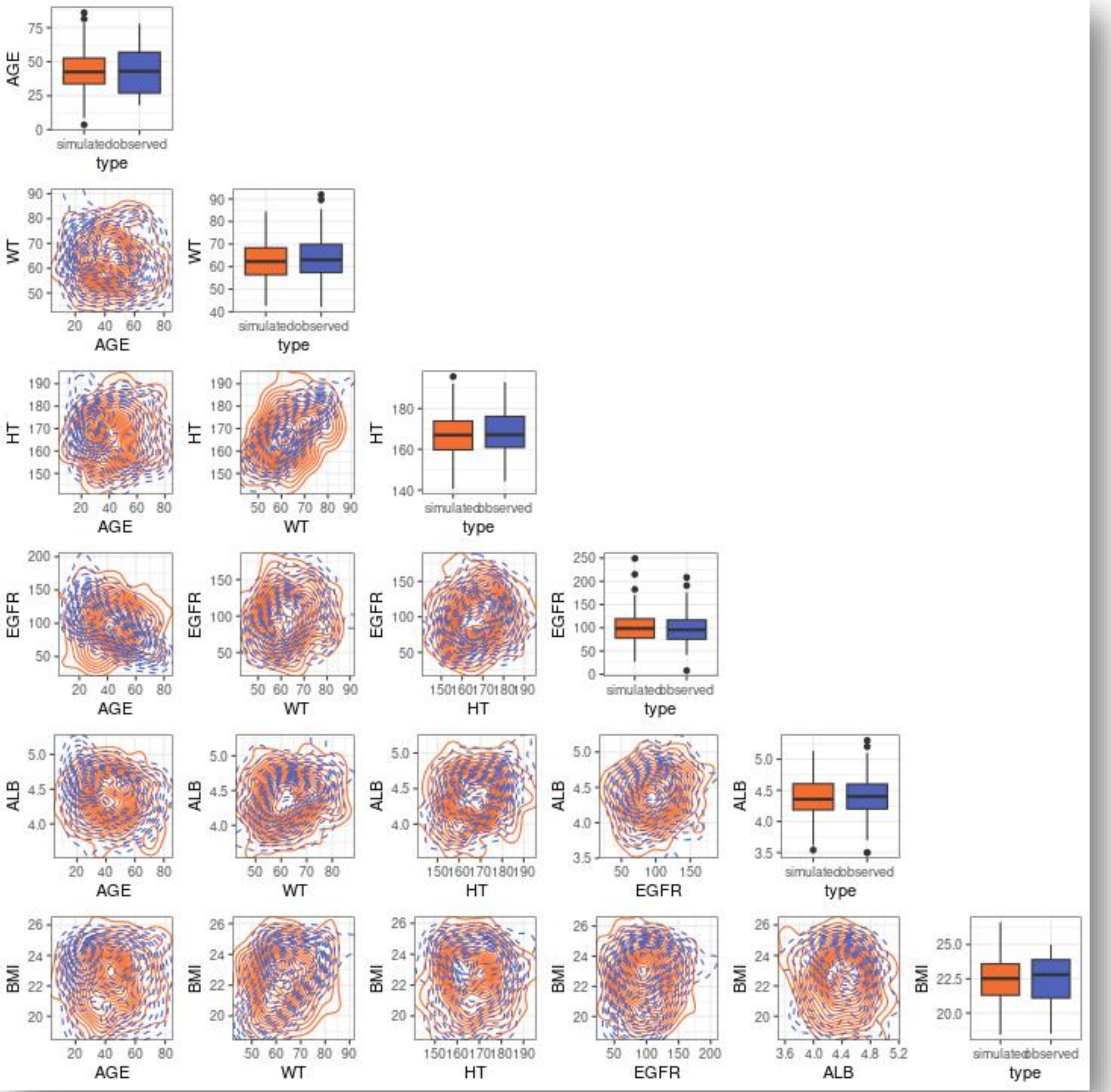


- Derive the means and the covariance matrix of the population dataset.
- Sample from the multivariate normal distribution defined by the means and the covariance matrix .

Tannenbaum et al. 2006. Journal of Pharmacokinetics and Pharmacodynamics

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 PAGEmeeting
Ljubljana • Slovenia
28 June – 1 July 2022
PAGE
Population Approach Group Europe

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. Zwep[1], Tingjie Guo[1], Thomas Nagler[2], 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

Check for updates

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

Yuchen Guo[1] · Tingjie Guo[1] · Catherijne A. J. Knibbe[1,2] · Laura B. Zwep[1] · J. G. Coen van Hasselt[1]

Sklar’s Theorem

$$\boxed{H(x,y)} = \boxed{C}(\boxed{F(x)}, \boxed{G(Y)})$$

Joint distribution **Copula** Marginal distribution

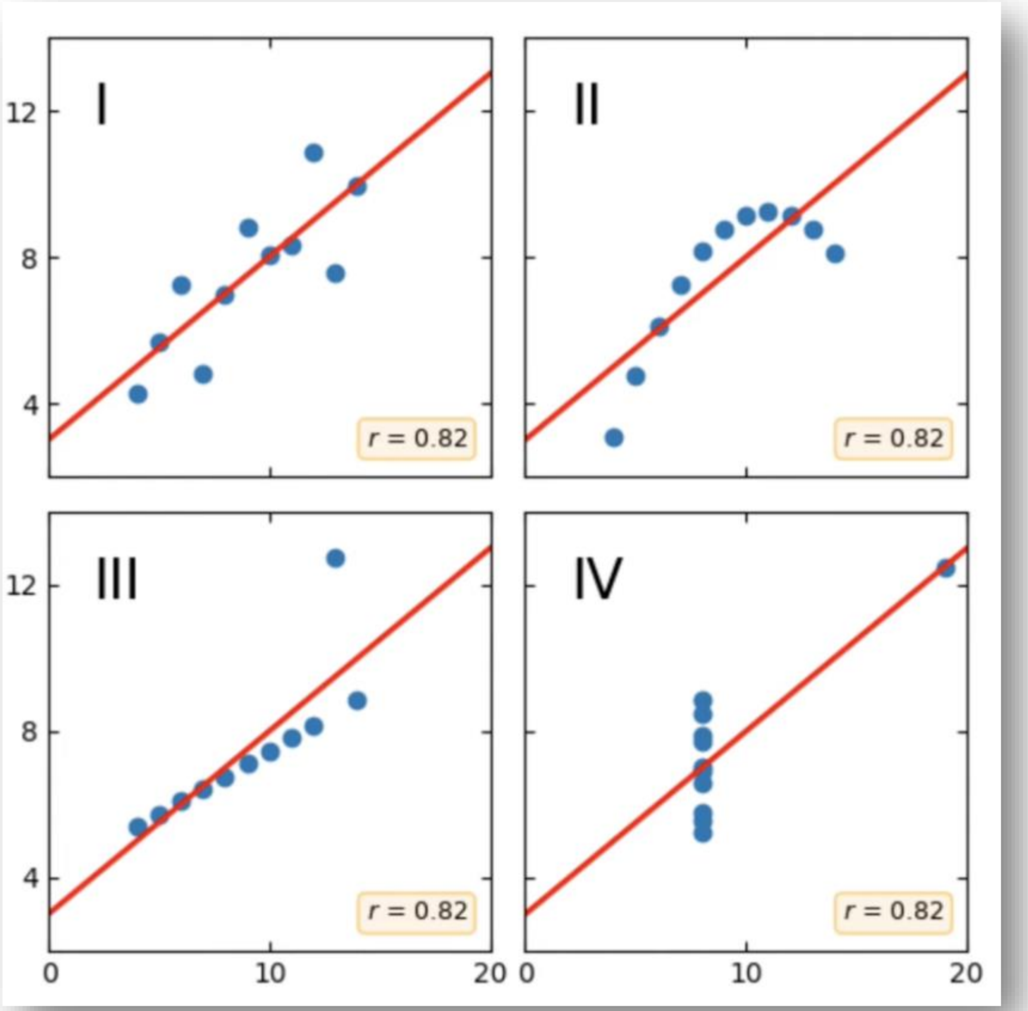
$$x = F^{-1}(u)$$

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

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

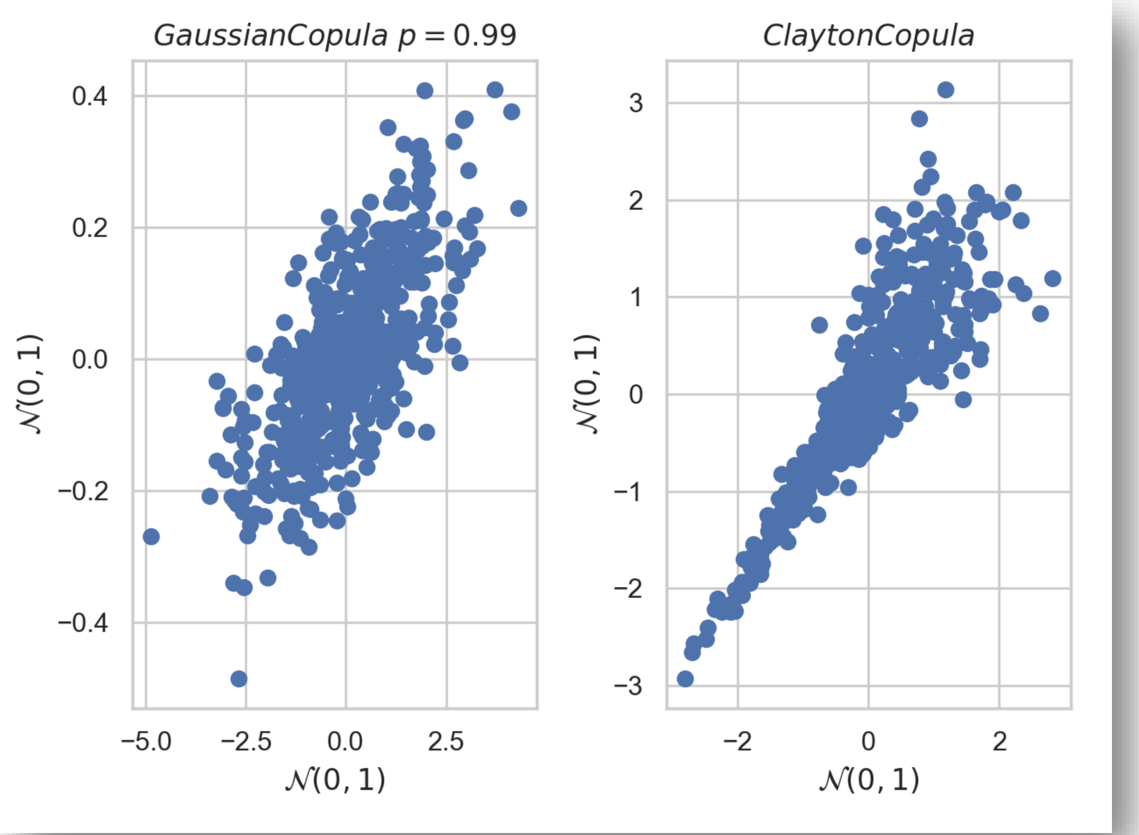
Kiran Karra. Copula Short Course. Youtube

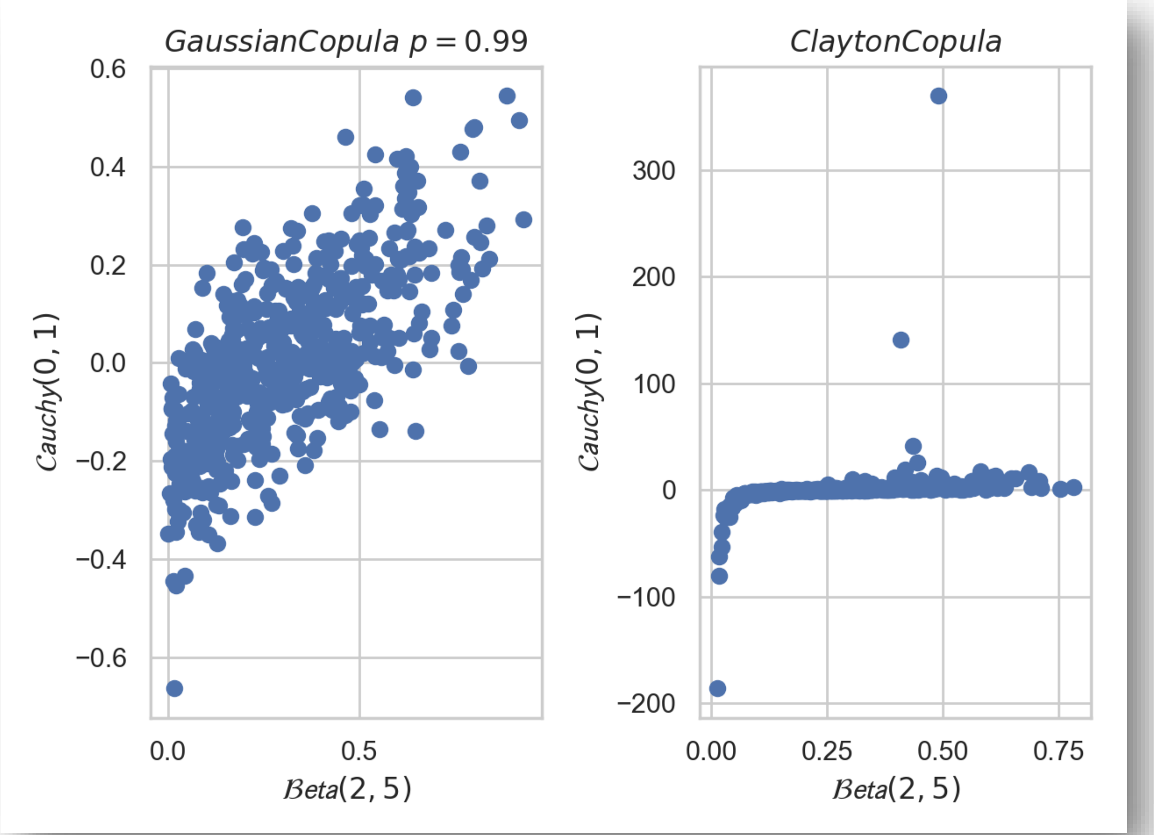
Why copula?



Kiran Karra. Copula Short Course. Youtube

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

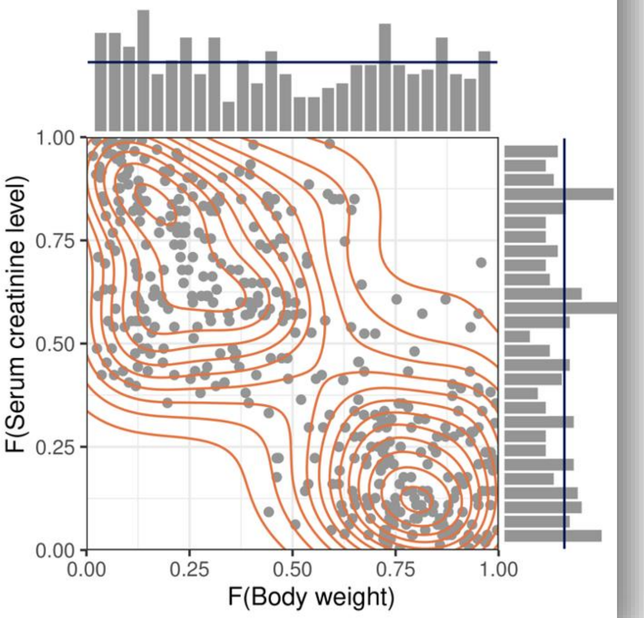
Inverse density:

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

- Joint density:

$$f(x_1, x_2) = f_1(x_1) \cdot f_2(x_2) \cdot \boxed{c\left(\boldsymbol{F_1}(x_1), \boldsymbol{F_2}(x_2)\right)}$$

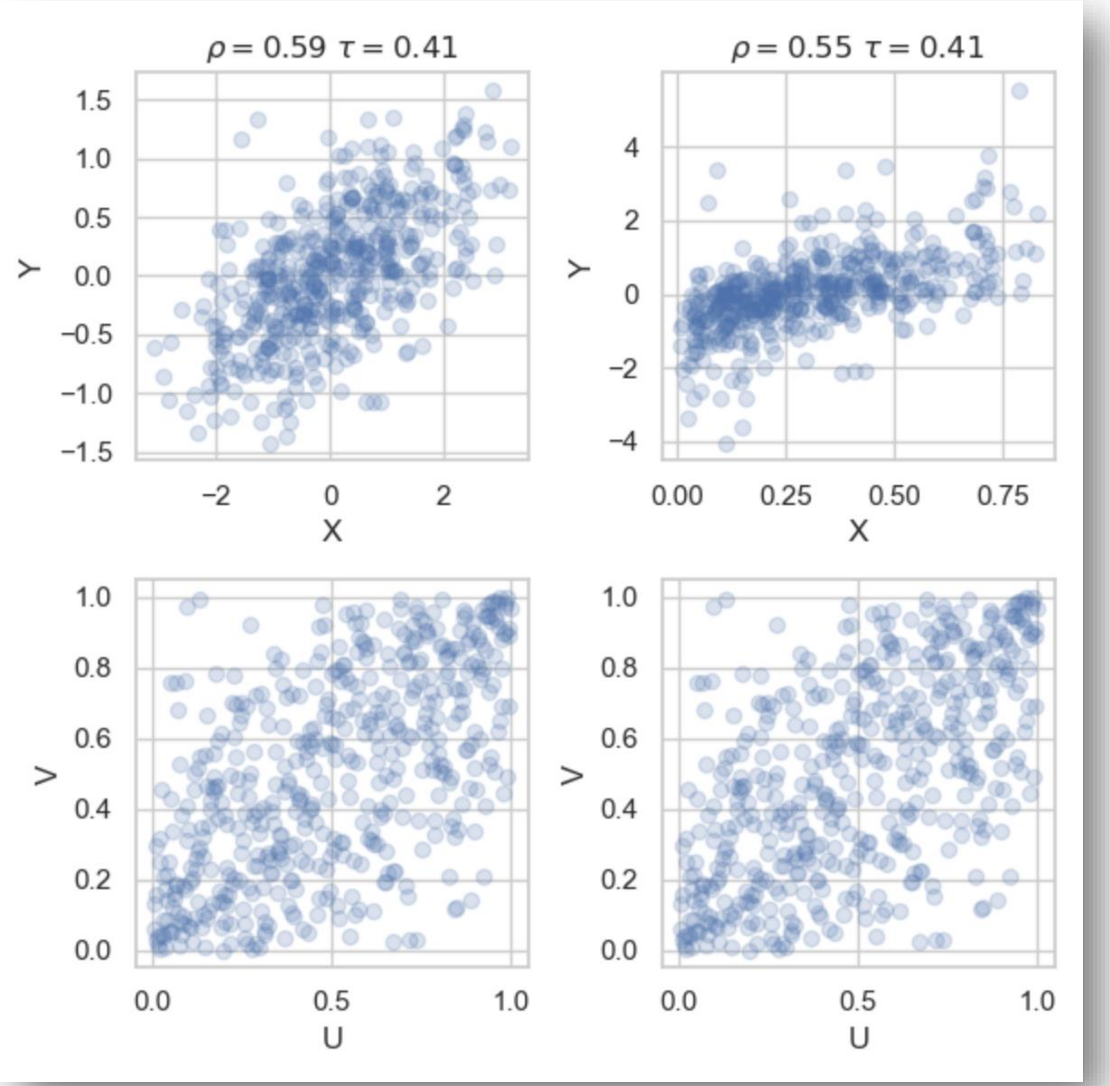
copula density



- 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

Zwep LB et al., PAGE. 2022

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

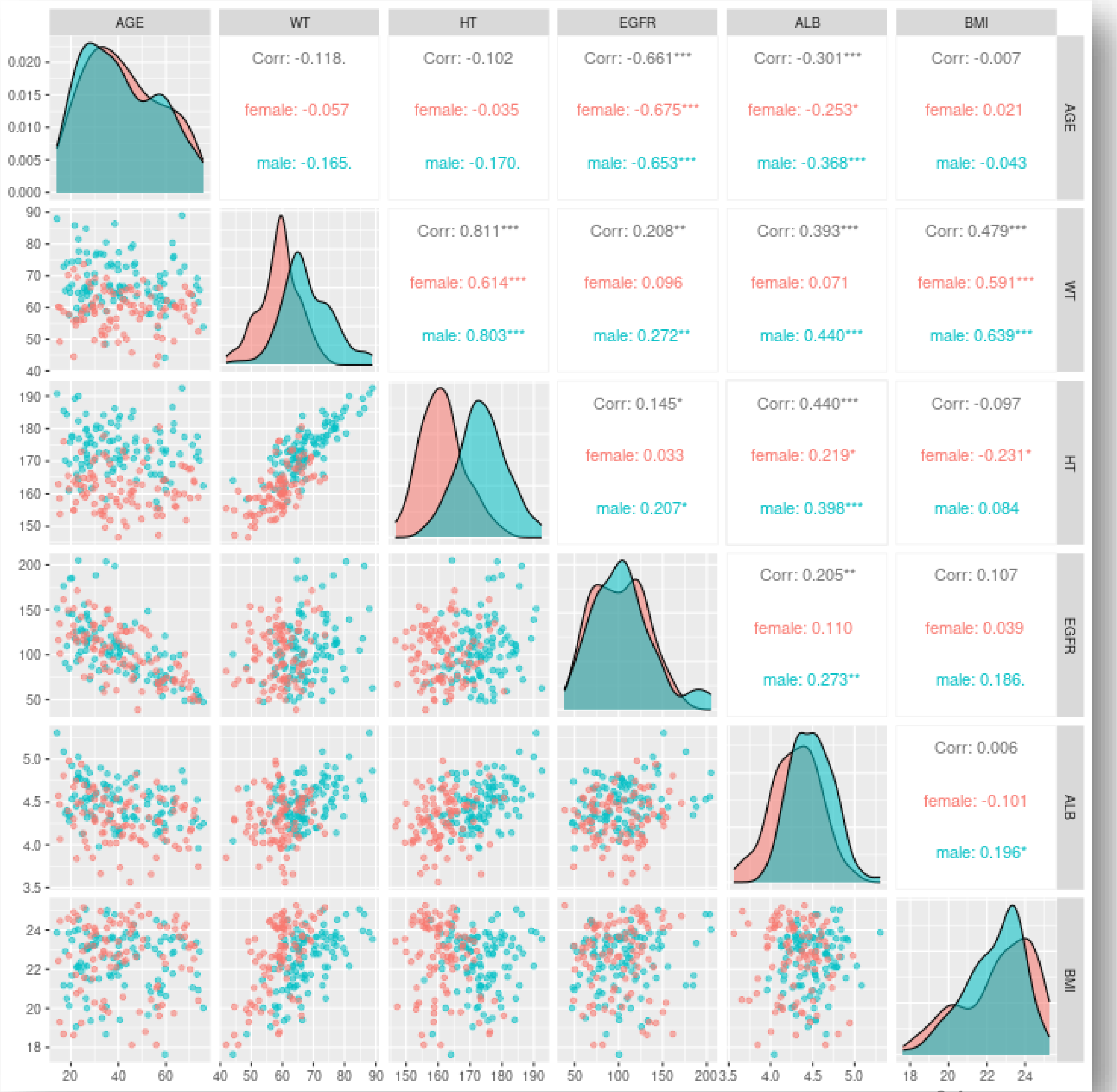
x	y
0.6	0.8
0.2	0.4
1.2	0.5
0.1	0.2

Rank observations

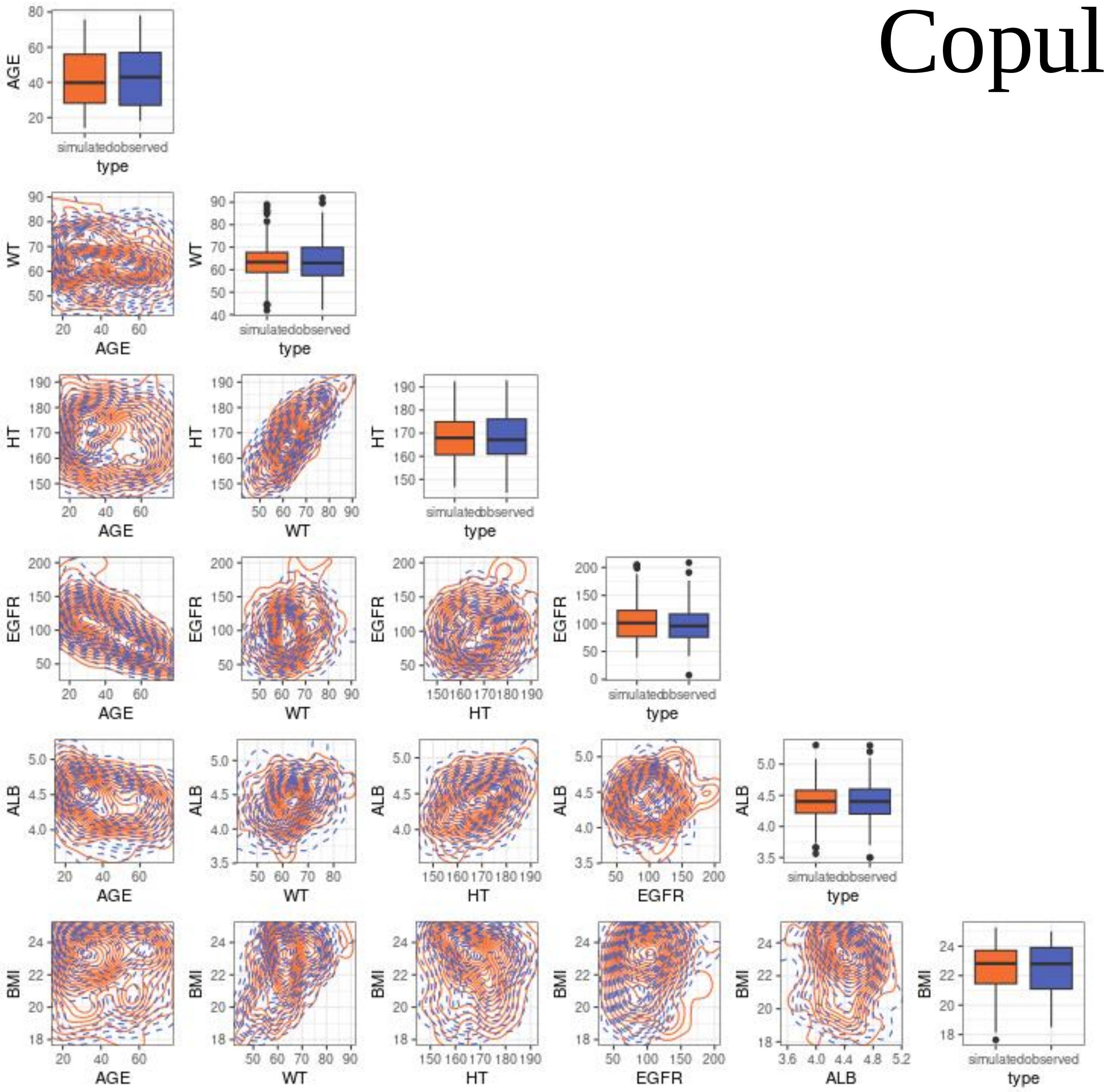
x	y
3	4
2	2
4	3
1	1

Kiran Karra. Copula Short Course. Youtube

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