

# Challenges and opportunities of combined analysis of multiple outcomes in longitudinal studies

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# Introduction

A lot of information is available

→ Electronic medical records

A lot of information is available

→ Electronic medical records

Different types of information

→ Baseline characteristics

→ Longitudinal outcomes

→ Time-to-event outcomes

## Applications

- Heart valve
- Stroke
- Cystic Fibrosis

## Applications

### → Heart valve

- ◇ Aortic gradient
- ◇ Aortic regurgitation
- ◇ Time-to death/reoperation

### → Stroke

### → Cystic Fibrosis

## Applications

- Heart valve
- Stroke
  - ◇ Extremity performance
  - ◇ Limb strength
- Cystic Fibrosis

## Applications

- Heart valve
- Stroke
- Cystic Fibrosis
  - ◇  $FEV_1$
  - ◇ BMI
  - ◇ Time-to death/exacerbation



## Separate analysis

- Each longitudinal outcome
- Survival outcomes

## Separate analysis - Stroke data

- ◇ 412 patients
- ◇ Outcome of interest:

Fugl-Meyer

*van der Vliet, R., Selles, R. W.,  
Andrinopoulou, etc (2020). Predicting upper  
limb motor impairment recovery after stroke:  
a mixture model. Annals of Neurology,  
87(3), 383-393.*

# Introduction: Extensions

## Combined analysis - Cystic Fibrosis data

- ◇ 17,100 patients
- ◇ Outcomes of interest:

$FEV_1$

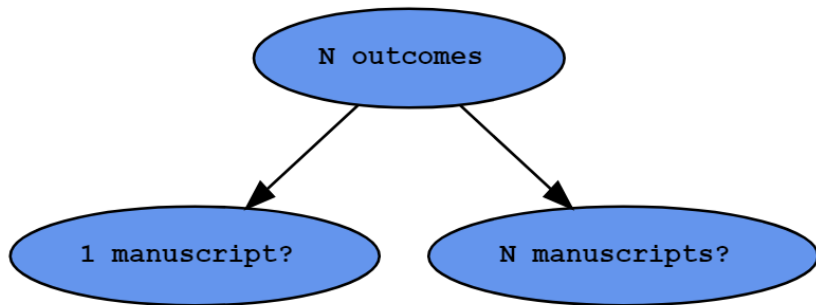
BMI

weight-for-age

height-for-age

time-to first exacerbation

*Andrinopoulou, E. R., Clancy, J. P., & Szczesniak, R. D. (2020). Multivariate joint modeling to identify markers of growth and lung function decline that predict cystic fibrosis pulmonary exacerbation onset. BMC pulmonary medicine, 20, 1-11.*



## Combined analysis - Heart valve data

- 296 patients
- Association of **Aortic Gradient** with **time-to-death/reoperation**
  - ◇ Aortic Gradient is measured with error

## Combined analysis - Heart valve data

- 296 patients
- Association of **Aortic Gradient** with **time-to-death/reoperation**
  - ◇ Aortic Gradient is measured with error
  - ◇ Different features of Aortic Gradient

# Statistical Models

# Statistical Models

Let's assume that we have a longitudinal outcome



$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^{\top}(t)\beta_1 + z_{1i}^{\top}(t)b_{1i} + \epsilon_{1i}(t)$$

where

- ◇  $b_{1i} \sim N(0, D)$
- ◇  $\epsilon_{1i}(t) \sim N(0, \Sigma_{1i})$

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- ◇  $b_{1i} \sim N(0, D)$
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Let's assume that we have two longitudinal outcomes

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

where

$$\diamond b_i^\top = (b_{1i}^\top, b_{2i}^\top) \sim N(0, D)$$

# Statistical Models: Multivariate Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

where

$$\diamond b_i^\top = (b_{1i}^\top, b_{2i}^\top) \sim N(0, D)$$

**Challenge:** Quantify the association between  $y_1$  and  $y_2$

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha m_{2i}(t) + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

where

◇  $\alpha$  denotes the association

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where

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**Challenge:** Is that our only option?



# Statistical Models: Multivariate Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$

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where

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**Challenge:** Is that our only option?

# Statistical Models: Multivariate Mixed Models

# Statistical Models: Multivariate Mixed Models

Let's assume that we have a longitudinal and a survival outcome

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_i^\top(t)b_{1i} + \epsilon_i(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha m_i(t)]$$

where

◇  $\alpha$  denotes the association

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_{1i}^\top(t)b_i + \epsilon_i(t)$$

$$h_i(t) = h_0(t) \left[ \gamma^\top w_i + \sum_{j=1}^J \alpha_j f_j\{\mathcal{M}_i(t)\} \right]$$

where

- ◇  $\alpha_j$  denotes the association
- ◇ Shrinkage

*Andrinopoulou, E. R., & Rizopoulos, D. (2016). Bayesian shrinkage approach for a joint model of longitudinal and survival outcomes assuming different association structures. Statistics in medicine, 35(26), 4813-4823.*

Let's assume that we have two longitudinal and a survival outcome

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha_{S1} f\{\mathcal{M}_{1i}(t)\} + \alpha_{S2} f\{\mathcal{M}_{2i}(t)\}],$$

where

◇  $\alpha_{S1}$  and  $\alpha_{S2}$  denote the associations



What about the association between the longitudinal outcomes?

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha_L f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha_S f\{\mathcal{M}_{1i}(t)\}]$$

where

- ◇  $\alpha_S$  denotes the survival association
- ◇  $\alpha_L$  denotes the longitudinal association

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha_L f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$

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- ◇  $\alpha_S$  denotes the survival association
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# Simulations

# Simulations

## Multivariate Mixed Models

## Simulate

### → Outcome 1

Linear time

Treatment

Value of outcome 2

### → Outcome 2

Linear time

## Simulate

### → Outcome 1

Linear time

Treatment

Value of outcome 2

### → Outcome 2

Linear time

## Fit

### → Outcome 1

Linear time

Treatment

~~Value of outcome 2~~

### → Outcome 2

Linear time



## Simulate

### → Outcome 1

Linear time

Treatment

Value of outcome 2

### → Outcome 2

Linear time

## Fit

### → Outcome 1

Linear time

Treatment

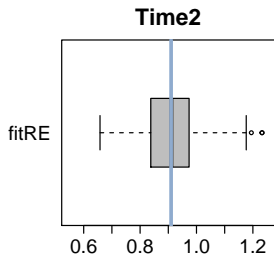
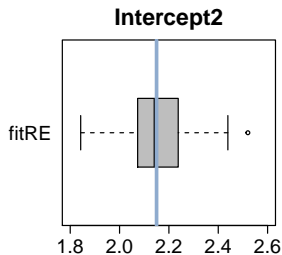
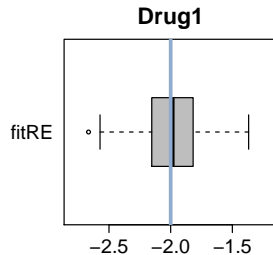
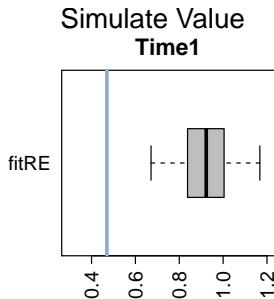
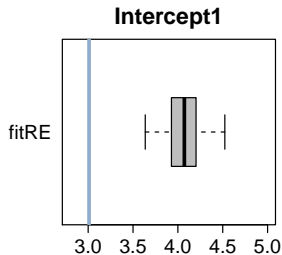
~~Value of outcome 2~~

### → Outcome 2

Linear time

**All models were fitted under the Bayesian framework**

# Simulations: Results



## Simulate

### → Outcome 1

Linear time

Treatment

Value of outcome 2

### → Outcome 2

Linear time

## Fit

### → Outcome 1

Linear time

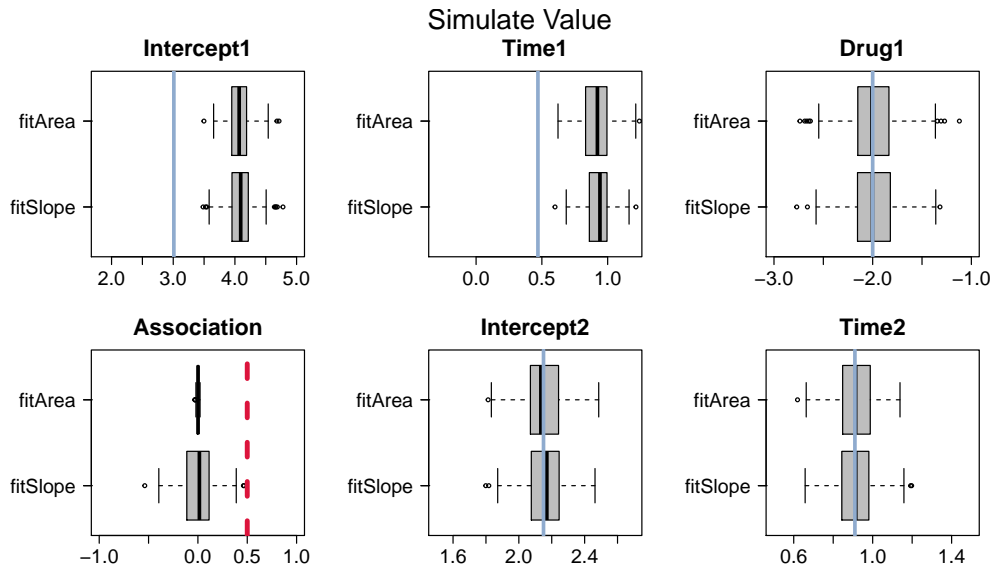
Treatment

Slope/Area of outcome 2

### → Outcome 2

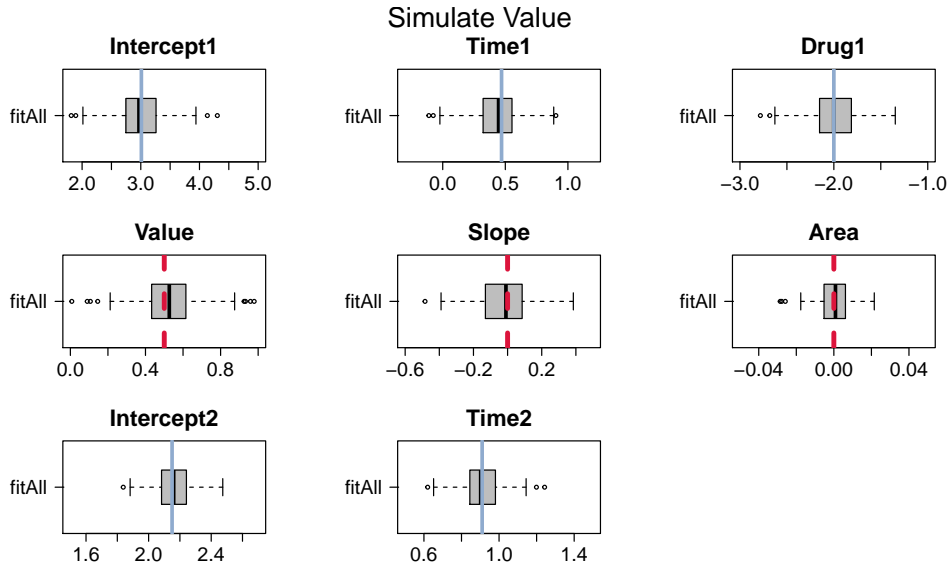
Linear time

# Simulations: Results



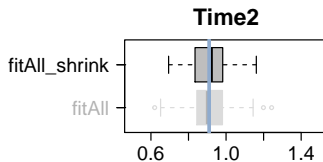
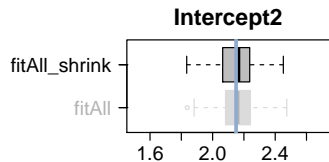
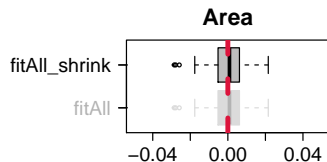
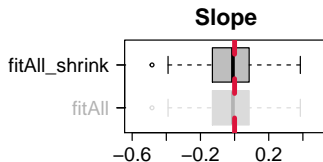
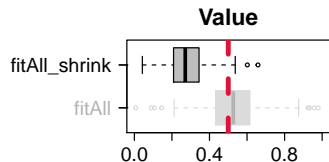
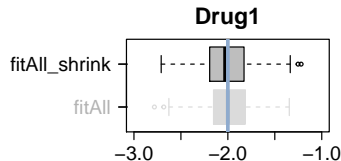
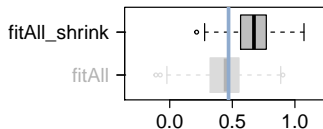
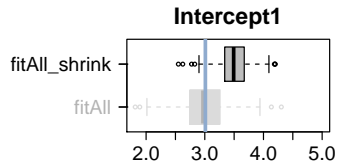
What if we fit all functional forms

# Simulations: Results



# Simulations: Results

## Simulate Value



## Joint Models



## Simulate

### → Longitudinal outcome

Non linear time

Treatment

### → Survival outcome

Treatment

Value of longitudinal  
outcome

## Simulate

### → Longitudinal outcome

Non linear time  
Treatment

### → Survival outcome

Treatment  
Value of longitudinal  
outcome

## Fit

### → Longitudinal outcome

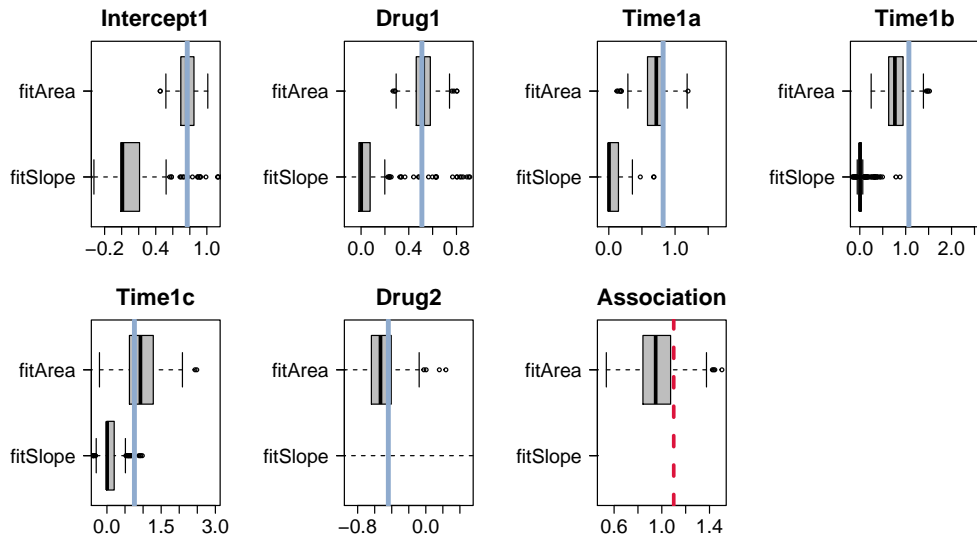
Non linear time  
Treatment

### → Survival outcome

Treatment  
Slope/Area of longitudinal  
outcome

# Simulations: Results

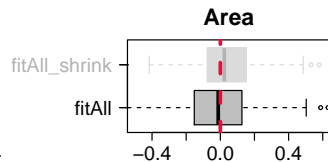
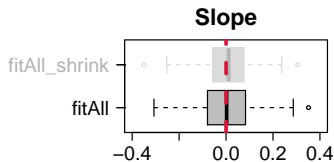
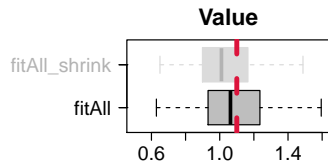
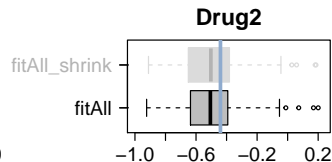
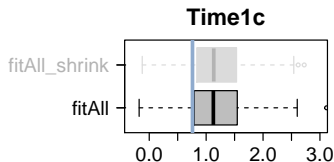
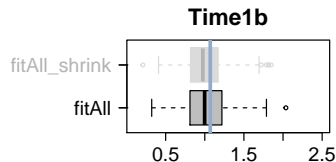
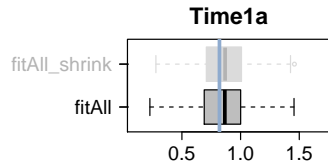
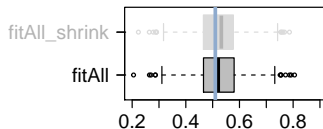
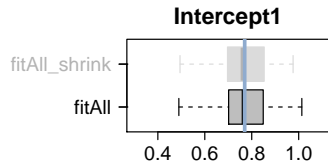
## Simulate Value



What if we fit all functional forms

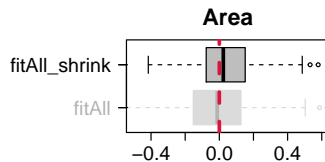
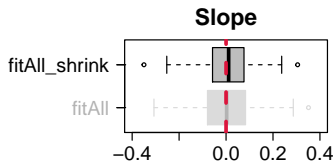
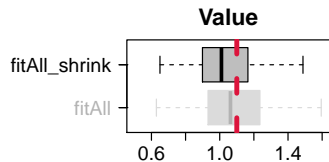
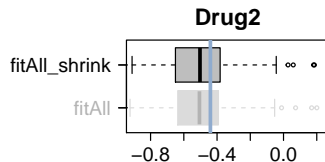
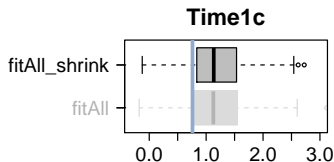
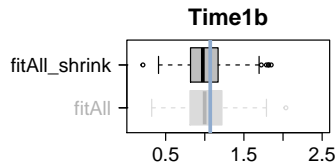
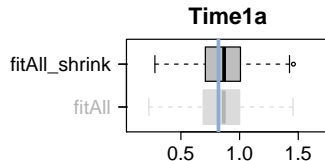
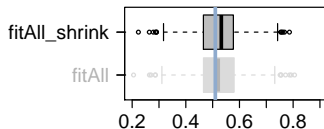
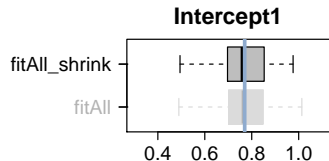
# Simulations: Results

## Simulate Value Drug1



# Simulations: Results

## Simulate Value



Let's combine everything

## Simulate

### → Longitudinal outcome 1

Non linear time

Treatment

Value of longitudinal  
outcome 2

### → Longitudinal outcome 2

Linear time

### → Survival outcome

Treatment

Value of longitudinal  
outcome 1



## Simulate

### → Longitudinal outcome 1

Non linear time

Treatment

Value of longitudinal  
outcome 2

### → Longitudinal outcome 2

Linear time

### → Survival outcome

Treatment

Value of longitudinal  
outcome 1

## Fit

### → Longitudinal outcome 1

Non linear time

Treatment

~~Value of longitudinal outcome 2~~

### → Longitudinal outcome 2

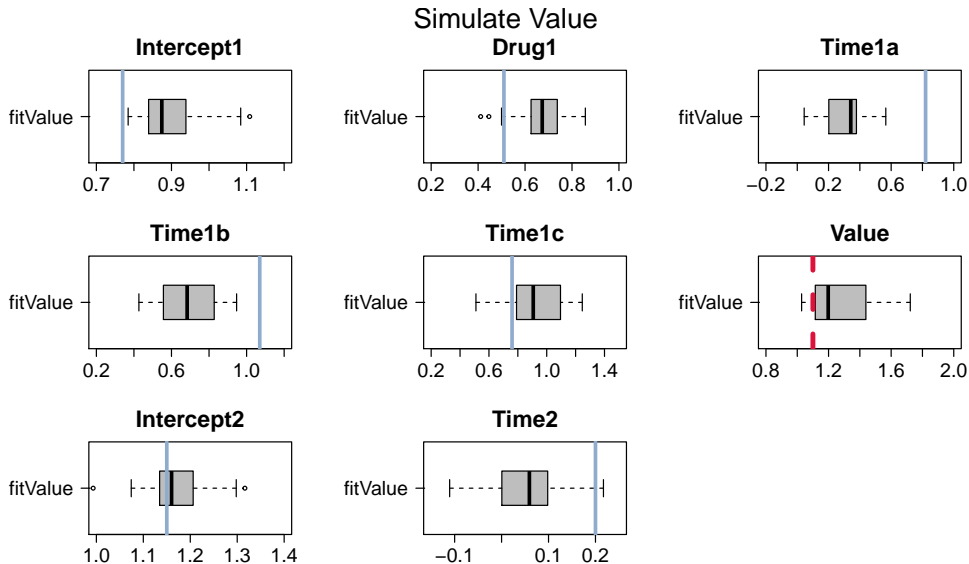
Linear time

### → Survival outcome

Treatment

Value of longitudinal outcome 1

# Simulations: Results



# Software

## → Joint models

- ◇ JMbayes, JM
- ◇ joiner, joinerML
- ◇ frailtypack
- ◇ stan\_jm
- ◇ lcmm
- ◇ bamlss
- ◇ jointAI

## → Multivariate mixed models

- ◇ lcmm
- ◇ brms
- ◇ MCMCglmm
- ◇ jointAI

# Summary and Discussion

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- A lot of information is available
- Correlation between outcomes

- A lot of information is available
- Correlation between outcomes
- Challenges and opportunities
  - ◇ Functional forms

# Thank you for your attention!

The slides are available at: <https://www.erandrinopoulou.com>