Dynamic Posterior Predictive Check for Joint Models

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1 Background & Motivation

Joint Models - A Popular Modeling Framework

- ▷ biomarker identification
- ▷ handling of missing data
- ▷ dynamic predictions
- ▷ ...

1 Background & Motivation (cont'd)

Despite their widespread adoption, there is a lack of tools for assessing goodness-of-fit

- ▷ often joint models are compared with information criteria
- ▷ these metrics will suggest which model is 'best'
- ▷ no reassurance that the model actually fits the data

1 Background & Motivation (cont'd)

Bio-SHiFT Data

- ▷ 263 patients with chronic heart failure
  - * aged 28 to 88 years
  - * 189 males

Hypothesis: Renal dysfunction is associated with adverse outcomes in patients with chronic heart failure

1 Background & Motivation (cont'd)

Bio-SHiFT Data

Endpoint: heart failure hospitalization, cardiac death, left ventricular assist device placement, and heart transplantation

▷ Follow-up

* creatinine-estimated glomerular filtration rate (eGFR)
* plasma neutrophil gelatinase-associated lipocalin (NGAL)

1 Background & Motivation (cont'd)

Bio-SHiFT Data

Are the eGFR and NGAL trajectories associated with the risk of the composite endpoint?

2 Bio-SHiFT Data Analysis

Four bivariate joint models

▷ eGFR & NGAL models

* *fixed effects*: linear time effect + baseline covariates
* *random effects*: intercepts and linear slopes

* *fixed effects*: nonlinear time effect + baseline covariates
* *random effects*: intercepts and nonlinear slopes

* baseline covariates: age, sex, NYHA class, diabetes, ischemic heart disease, and diuretics use

2 Bio-SHiFT Data Analysis (cont'd)

Four bivariate joint models

▷ Composite event model

  * current value of eGFR and NGAL
  * average of eGFR and NGAL from baseline

  * baseline covariates: the same as in the eGFR & NGAL models

2 Bio-SHiFT Data Analysis (cont'd)

	DIC	WAIC	LPML
nonlinear average	10703.00	11023.70	−5612.09
linear average	11120.25	11108.45	−5584.62
linear value	11167.66	11120.05	−5588.30
nonlinear value	10704.55	11135.23	−5796.62

No uniform ranking of the four models

3 PPC Framework

Posterior Predictive Checks: We compare simulated outcomes from the fitted model with the observed data

- ▷ $\mathbf{y}_i$ longitudinal responses
- ▷ T_i^* true event time
- ▷ T_i and δ_i observed event time and event indicator
- ▷ $\mathcal{X}_i$ baseline covariates
- ▷ $\mathcal{D}_n$ all observed data

3 PPC Framework (cont'd)

Posterior Predictive Distribution

$$p(\mathbf{O}_i^{\text{rep}} \mid T_i, \delta_i, \mathbf{y}_i, \mathcal{X}_i, \mathcal{D}_n) = \int \int p(\mathbf{O}_i^{\text{rep}} \mid \mathbf{b}_i, \mathcal{X}_i, \boldsymbol{\theta})\, p(\mathbf{b}_i \mid T_i, \delta_i, \mathbf{y}_i, \mathcal{X}_i, \boldsymbol{\theta})\, p(\boldsymbol{\theta} \mid \mathcal{D}_n)\, d\mathbf{b}_i d\boldsymbol{\theta}$$

▷ $\mathbf{O}_i^{\text{rep}}$ denotes either $\mathbf{y}_i^{\text{rep}}$ or $T_i^{*\text{rep}}$

3 PPC Framework (cont'd)

Sampling Scheme

▷ Step 1: Sample $\{\tilde{\boldsymbol{\theta}}, \tilde{\mathbf{b}}_i\}$ from the MCMC sample $[\boldsymbol{\theta}, \mathbf{b}_i \mid T_i, \delta_i, \mathbf{y}_i, \mathcal{X}_i, \mathcal{D}_n]$

▷ Step 2: Sample $\mathbf{y}_i^{\text{rep}}$ or $T_i^{*\text{rep}}$

* longitudinal outcome distribution – *standard form*
* event outcome distribution – *non-standard form*

Posterior-Posterior Predictive Checks

3 PPC Framework (cont'd)

- Generic subjects from the target population
  - ▷ no longitudinal or event time information
  - ▷ but we do have covariate information

$$p(\mathbf{O}_i^{\textsf{rep}} \mid \mathcal{X}_i, \mathcal{D}_n) = \int\int p(\mathbf{O}_i^{\textsf{rep}} \mid \mathbf{b}_i, \mathcal{X}_i, \boldsymbol{\theta})\, p(\mathbf{b}_i \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta} \mid \mathcal{D}_n)\, d\mathbf{b}_i d\boldsymbol{\theta}$$

Posterior-Prior Predictive Checks

3 PPC Framework (cont'd)

- Joint models often used for dynamic predictions
  - ▷ longitudinal measurements $\mathbf{y}_i(t_L)$ up to time t_L
  - ▷ $T_i = t_L$ and $\delta_i = 0$

$$p\{\widetilde{\mathbf{O}}_i^{\mathsf{rep}} \mid T_i = t_L, \delta_i = 0, \mathbf{y}_i(t_L), \mathcal{X}_i, \mathcal{D}_n\}$$

$$= \int\int p(\widetilde{\mathbf{O}}_i^{\mathsf{rep}} \mid \mathbf{b}_i, \mathcal{X}_i, \boldsymbol{\theta})\, p\{\mathbf{b}_i \mid T_i = t_L, \delta_i = 0, \mathbf{y}_i(t_L), \mathcal{X}_i, \boldsymbol{\theta}\}\, p(\boldsymbol{\theta} \mid \mathcal{D}_n)\, d\mathbf{b}_i d\boldsymbol{\theta}$$

Dynamic Posterior-Posterior Predictive Checks

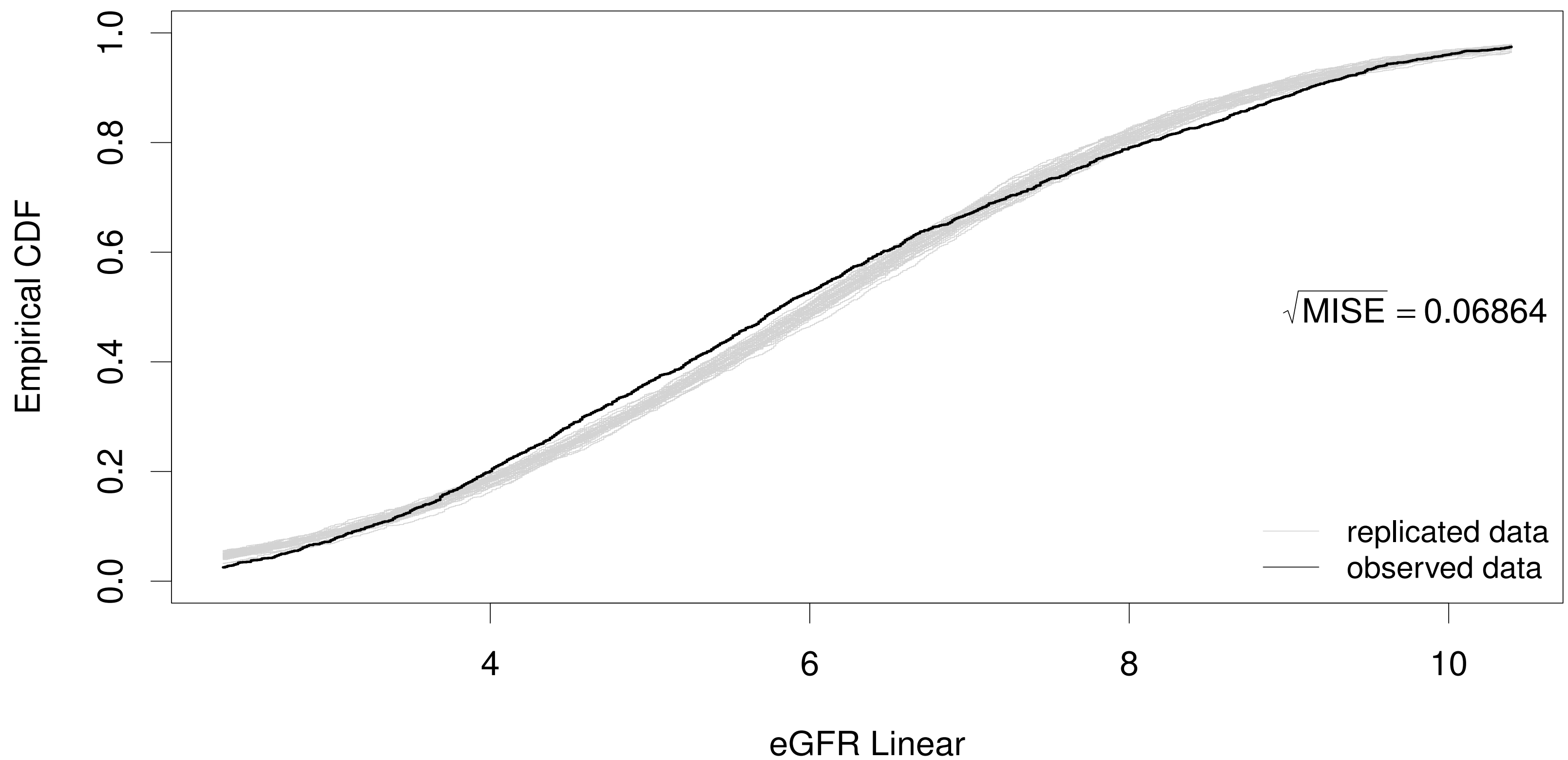
4 Goodness-of-Fit Measures

Longitudinal Outcome

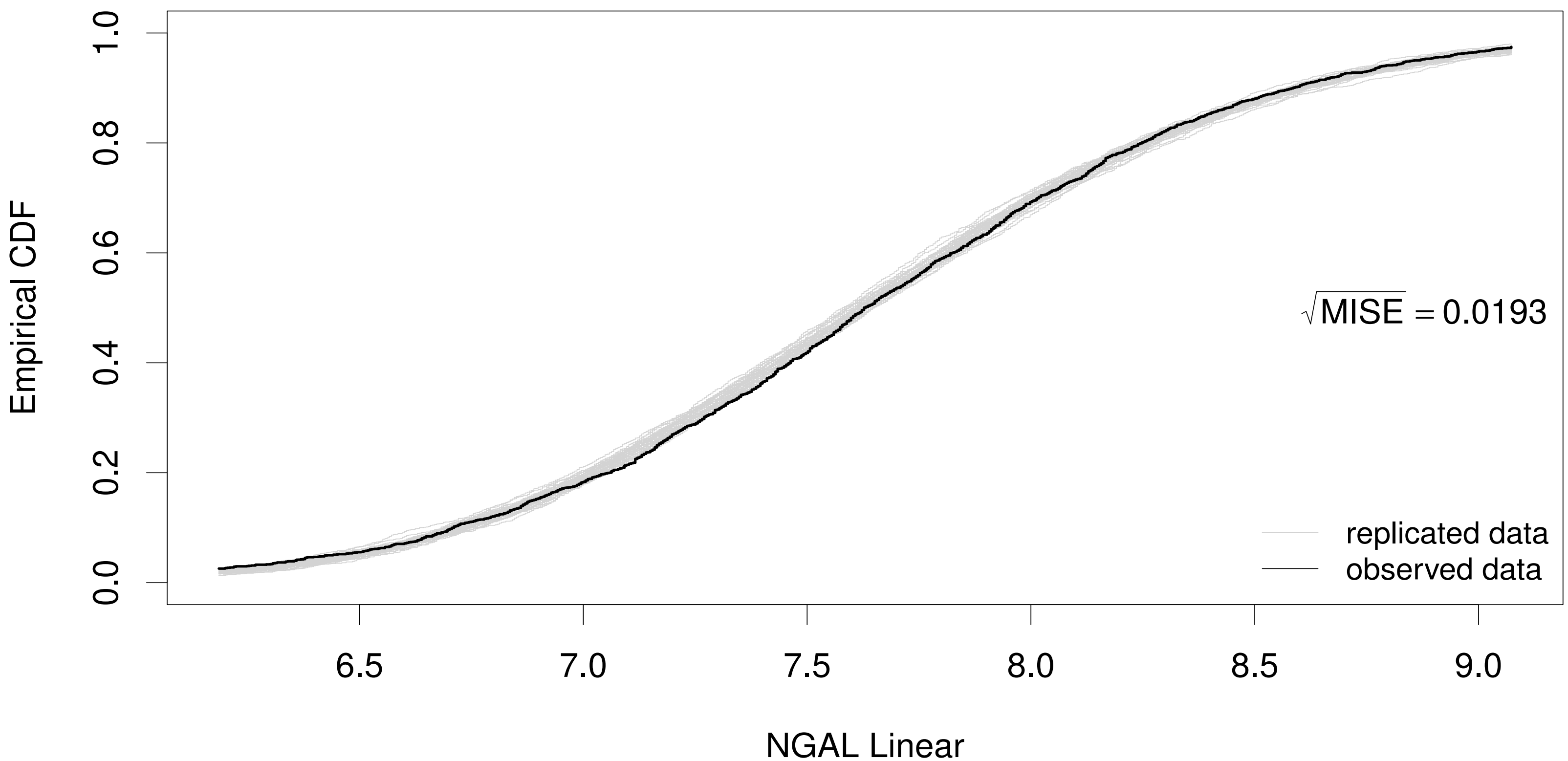
▷ *empirical Cumulative Distribution Function (eCDF)*

▷ overall comparison between the observed and simulated outcome distributions

4 Goodness-of-Fit Measures (cont'd)



4 Goodness-of-Fit Measures (cont'd)



4 Goodness-of-Fit Measures (cont'd)

Numerical summary measure

$$\mathsf{MISE} = \frac{1}{M} \sum_{m=1}^{M} \int \Big\{ \widehat{F}_{\mathbf{y}_m^{\mathsf{rep}}}(\mathbf{s}) - \widehat{F}_{\mathbf{y}}(\mathbf{s}) \Big\}^2 \, \mathsf{ds}$$

▷ $\mathbf{y}_m^{\mathsf{rep}}$ m-th realization of the replicated data $(m = 1, \ldots, M)$

▷ $\widehat{F}_{\mathbf{y}_m^{\mathsf{rep}}}$ eCDF simulated data

▷ $\widehat{F}_{\mathbf{y}}$ eCDF observed data

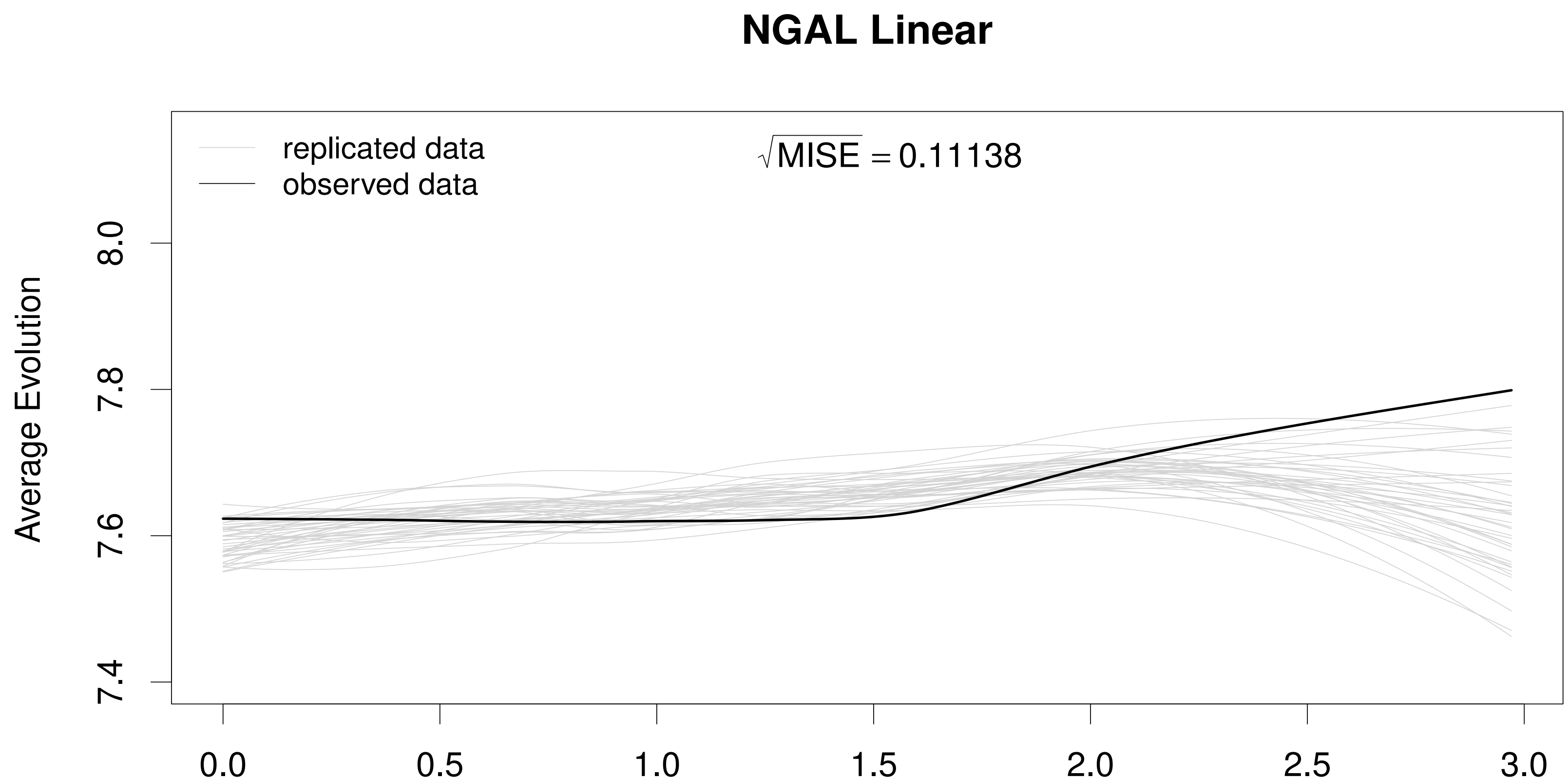
Longitudinal Outcome

▷ *Mean Function:* average longitudinal evolution

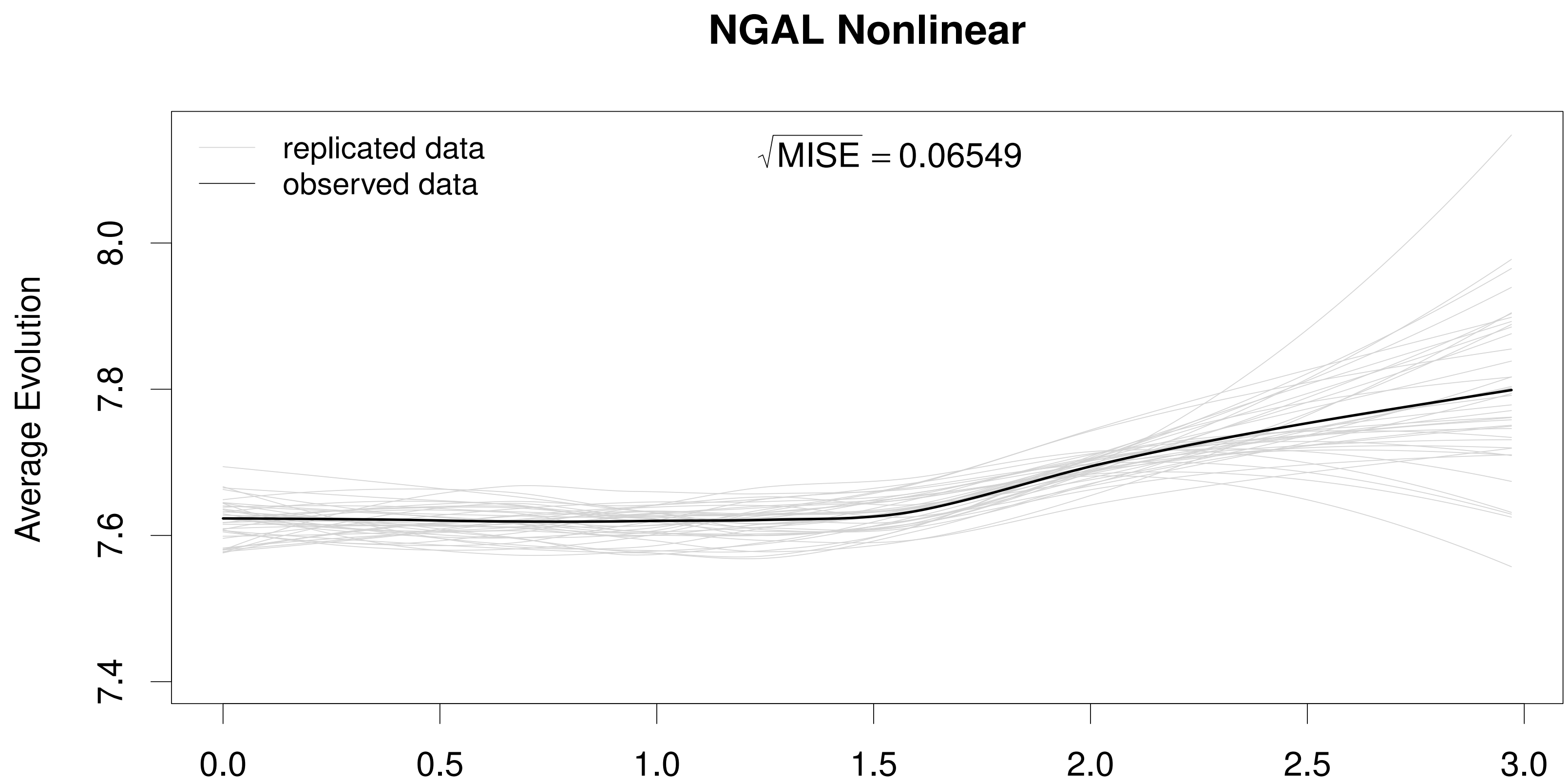
▷ non-parametrically estimated using local polynomial regression (LOESS)

$$\mathcal{L}(\mathbf{y}, \mathbf{t})$$

4 Goodness-of-Fit Measures (cont'd)



4 Goodness-of-Fit Measures (cont'd)



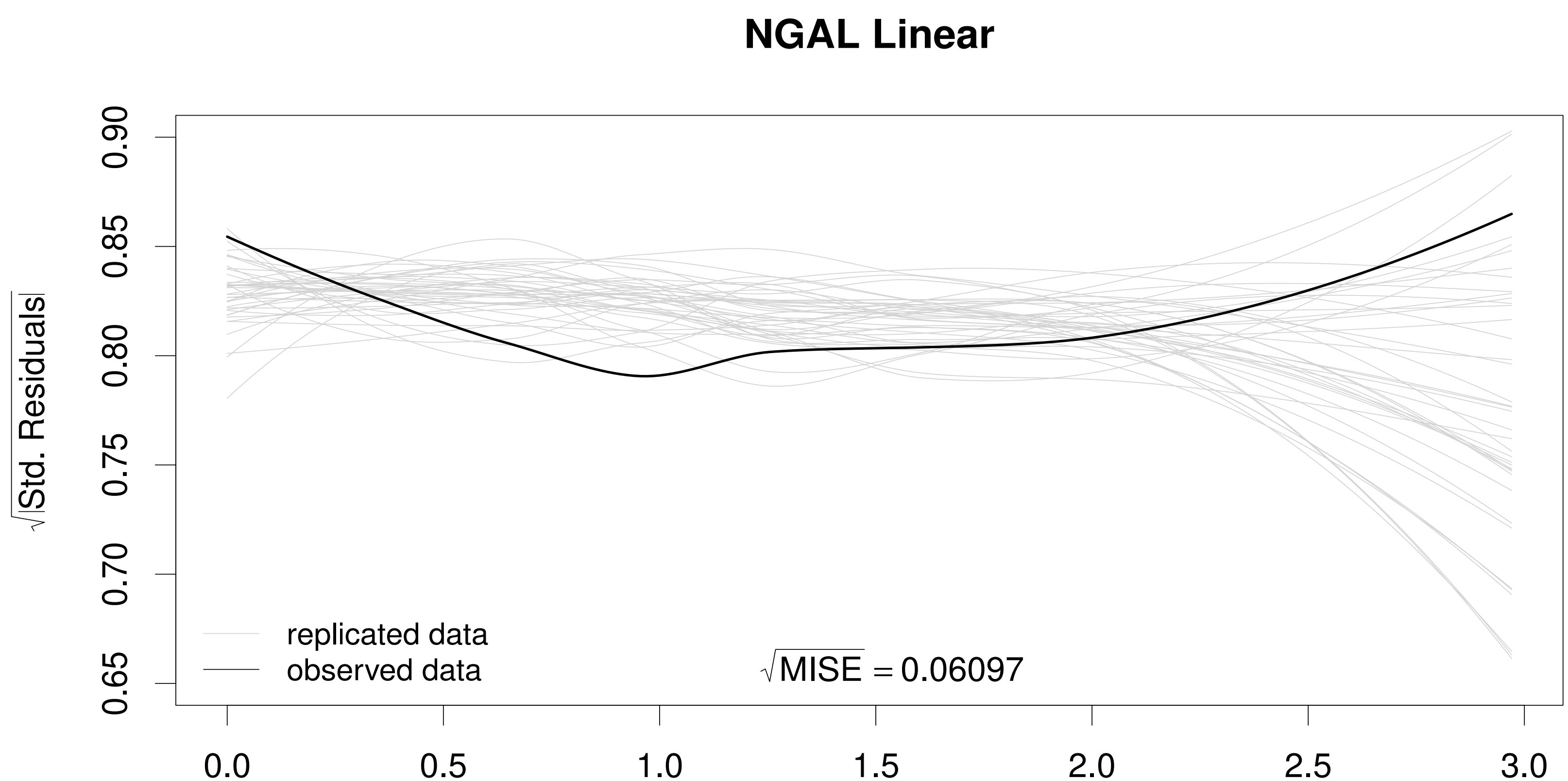
4 Goodness-of-Fit Measures (cont'd)

Longitudinal Outcome

- ▷ *Variance Function:* variance over time
- ▷ standardized non-parametric loess residuals
- ▷ square root, absolute value transformation (*Scale-Location*)

$$\mathcal{L}(\sqrt{|\mathbf{r}/\sigma_r|}, \mathbf{t})$$

4 Goodness-of-Fit Measures (cont'd)



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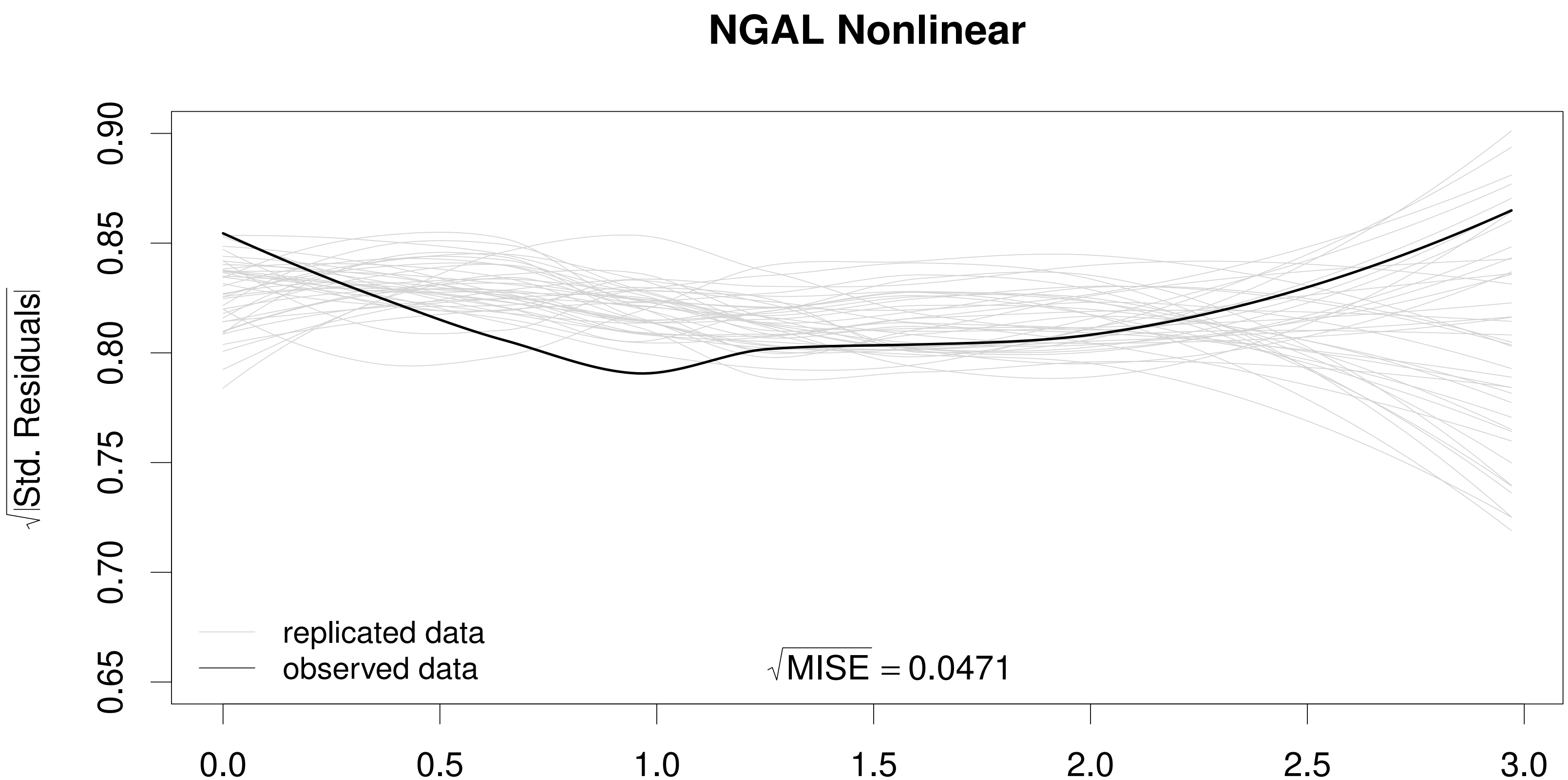


4 Goodness-of-Fit Measures (cont'd)

Longitudinal Outcome

▷ *Correlation Structure:* correlations between pairs of measurements

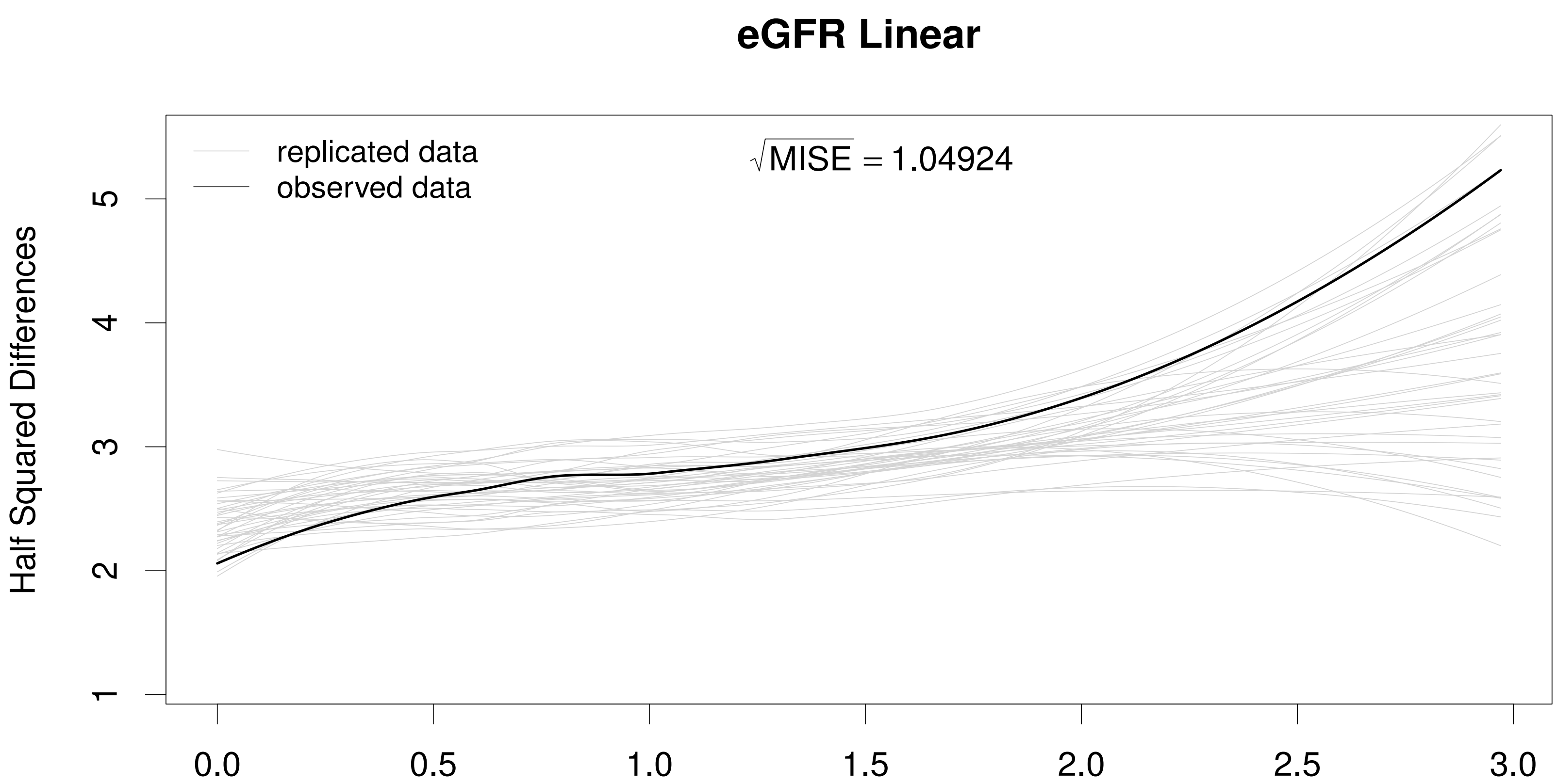
▷ non-parametric loess residuals r_{ij}

▷ we calculate the half-squared differences and the time lags (*Variogram*)

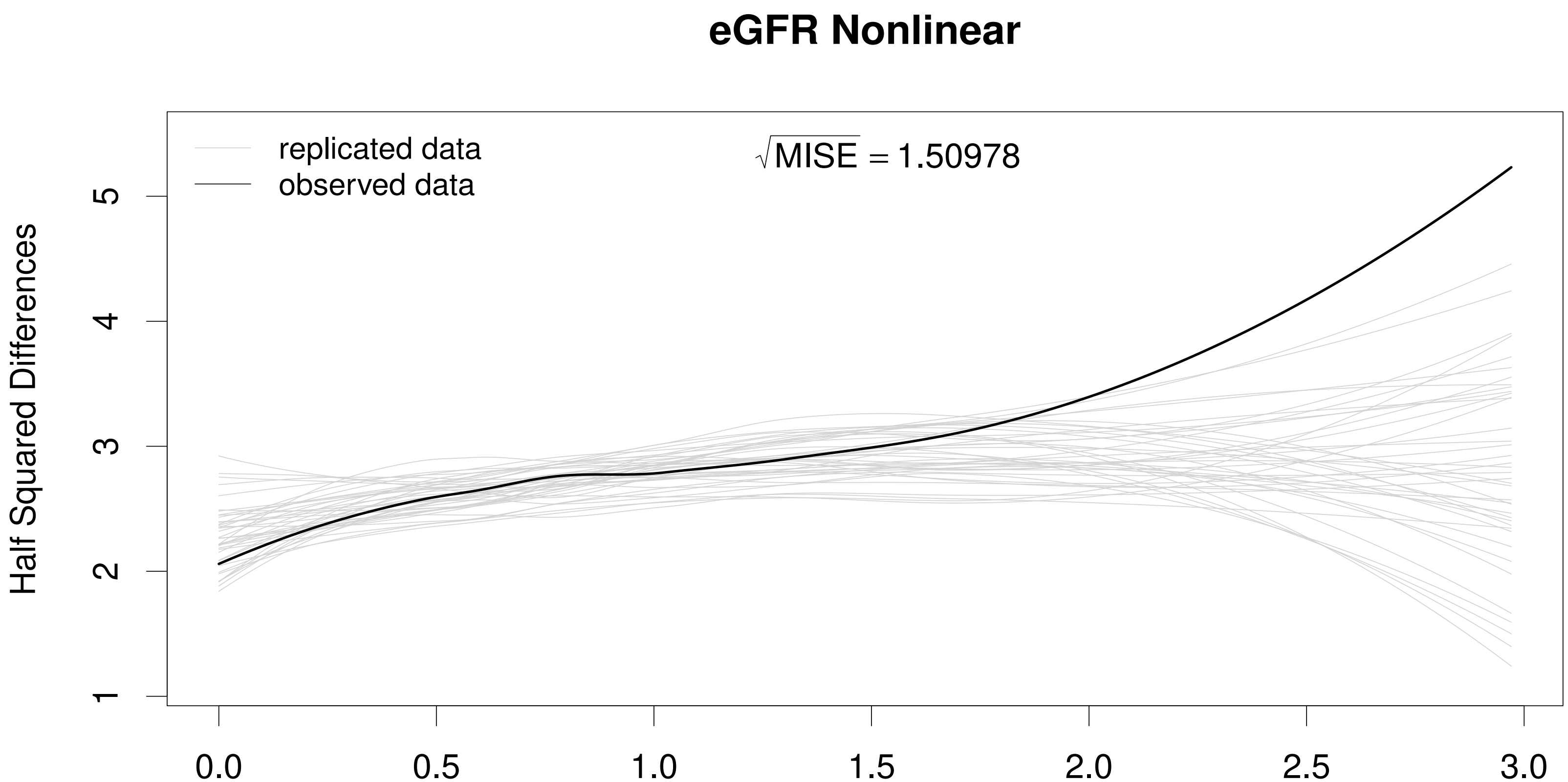
$$\Delta_{i,jk} = 0.5(r_{ij} - r_{ik})^2 \quad \text{and} \quad u_{i,jk} = |t_{ij} - t_{ik}|, \ \text{ with } \{j, k = 1, \ldots, n_i; j \neq k\}$$

$$\mathcal{L}(\boldsymbol{\Delta}, \mathbf{u})$$

4 Goodness-of-Fit Measures (cont'd)



4 Goodness-of-Fit Measures (cont'd)

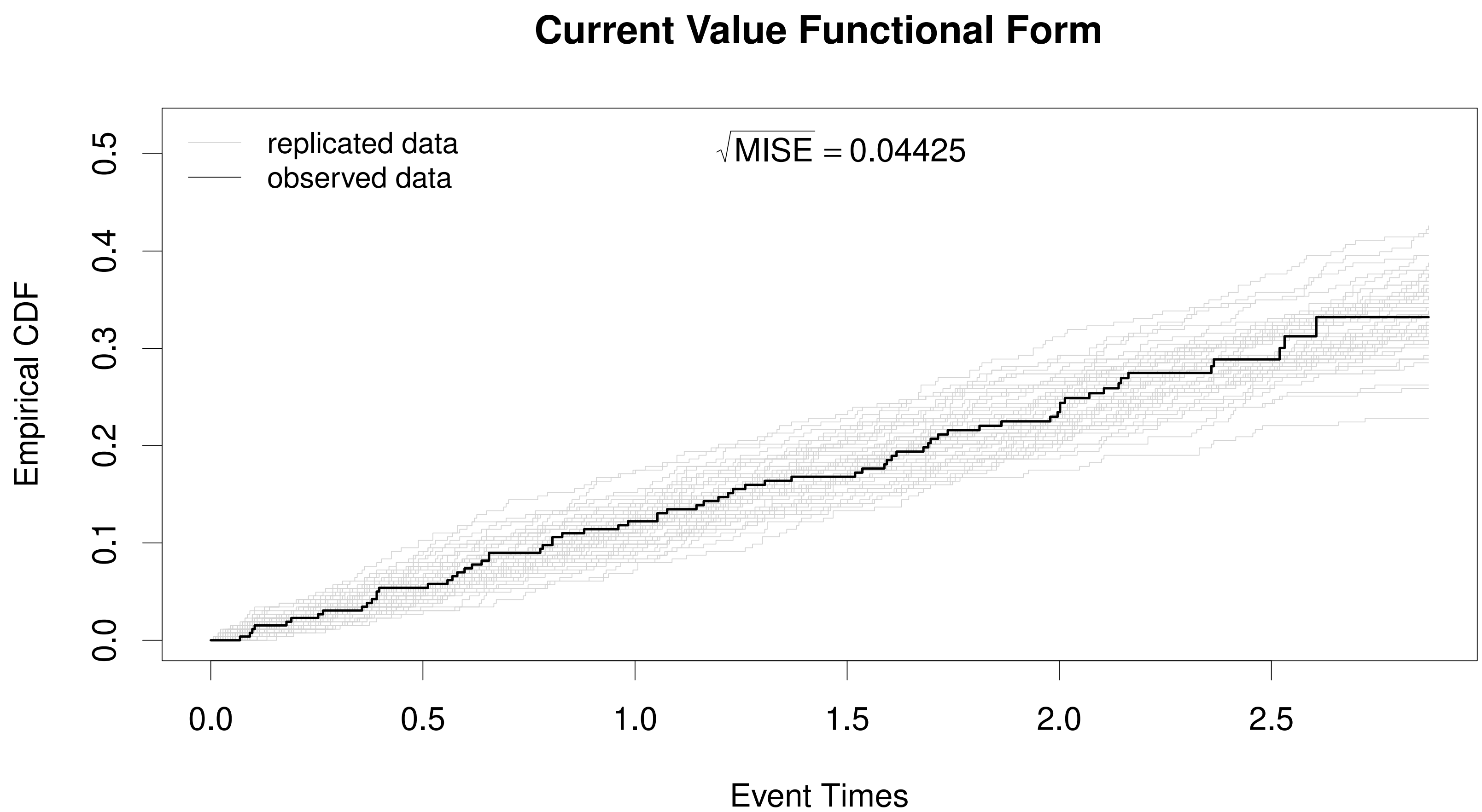


4 Goodness-of-Fit Measures (cont'd)

Event Time Outcome

- *empirical Cumulative Distribution Function (eCDF)*
- overall comparison between the observed and simulated outcome distributions

4 Goodness-of-Fit Measures (cont'd)



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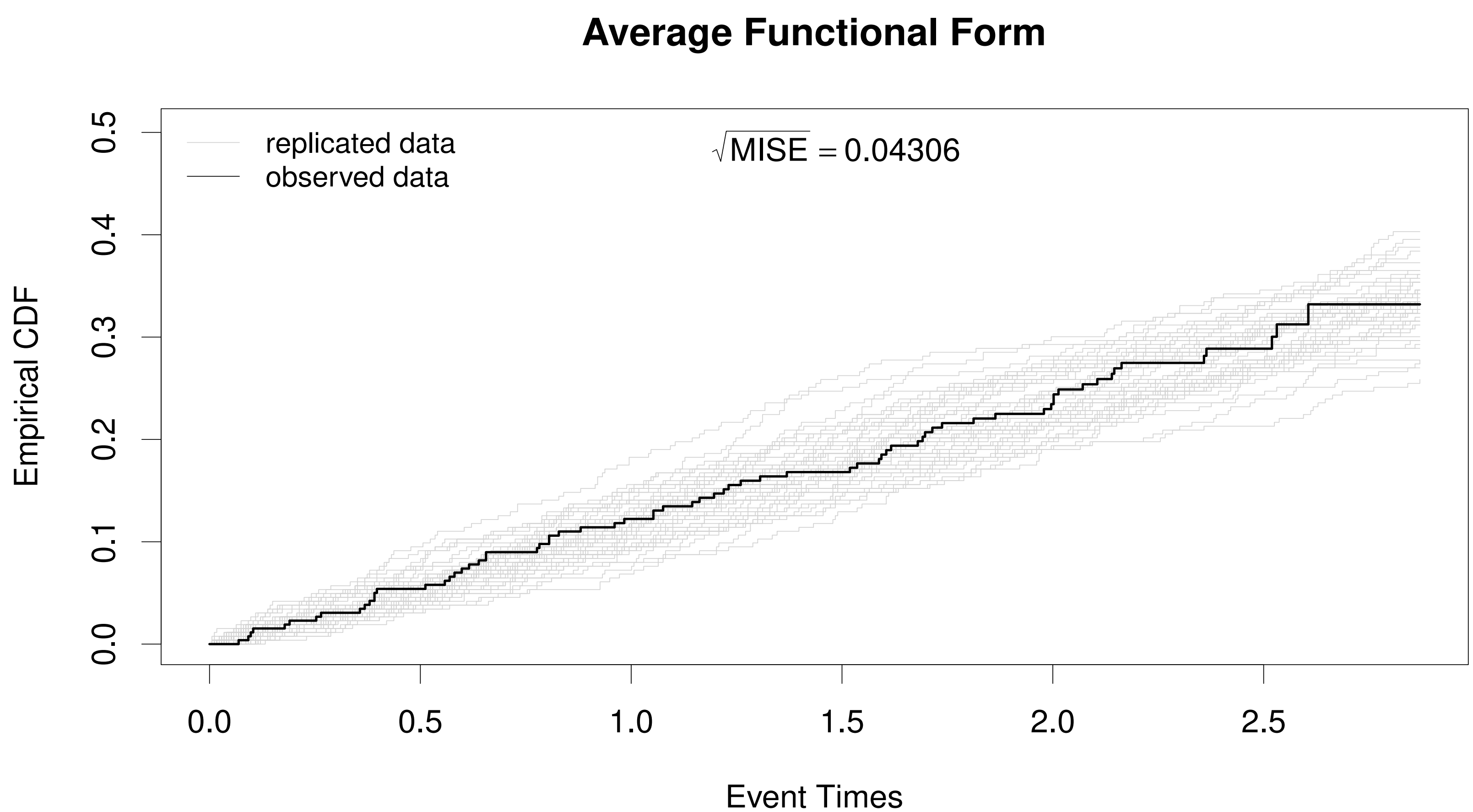


Joint Process

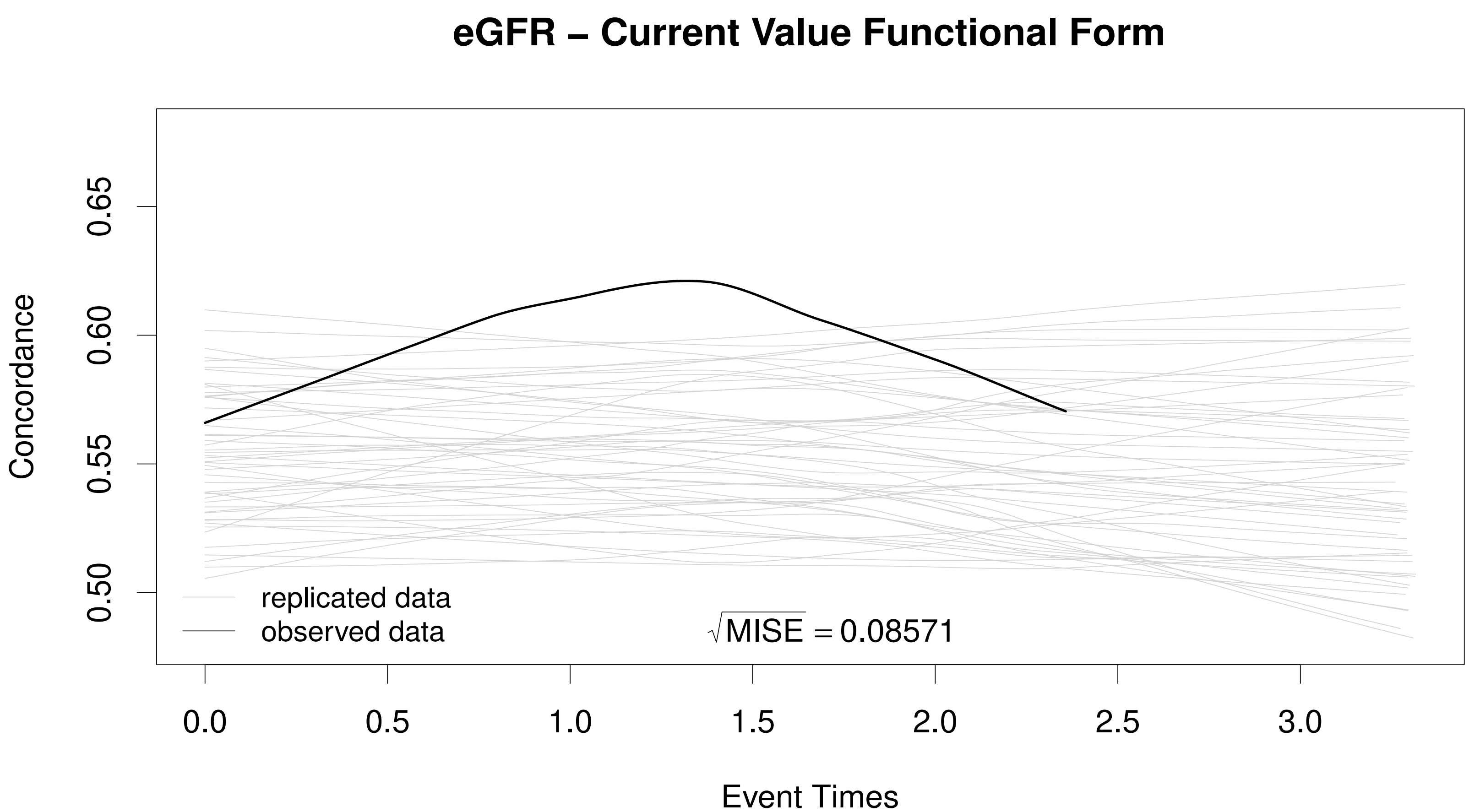
▷ *association structure* between the longitudinal and event time processes

▷ agreement between the time-to-event outcome and the longitudinal outcome
Concordance statistic

* unique event times $\{t_0 = 0, t_1, \ldots, t_K\}$
* we select the subjects at risk at t_k
* $\ddot{y}_i(t_k)$ their last available longitudinal measurement
* $C(t_k)$ concordance statistic

$$\mathcal{L}(\mathbf{C}, \mathbf{t})$$

4 Goodness-of-Fit Measures (cont'd)



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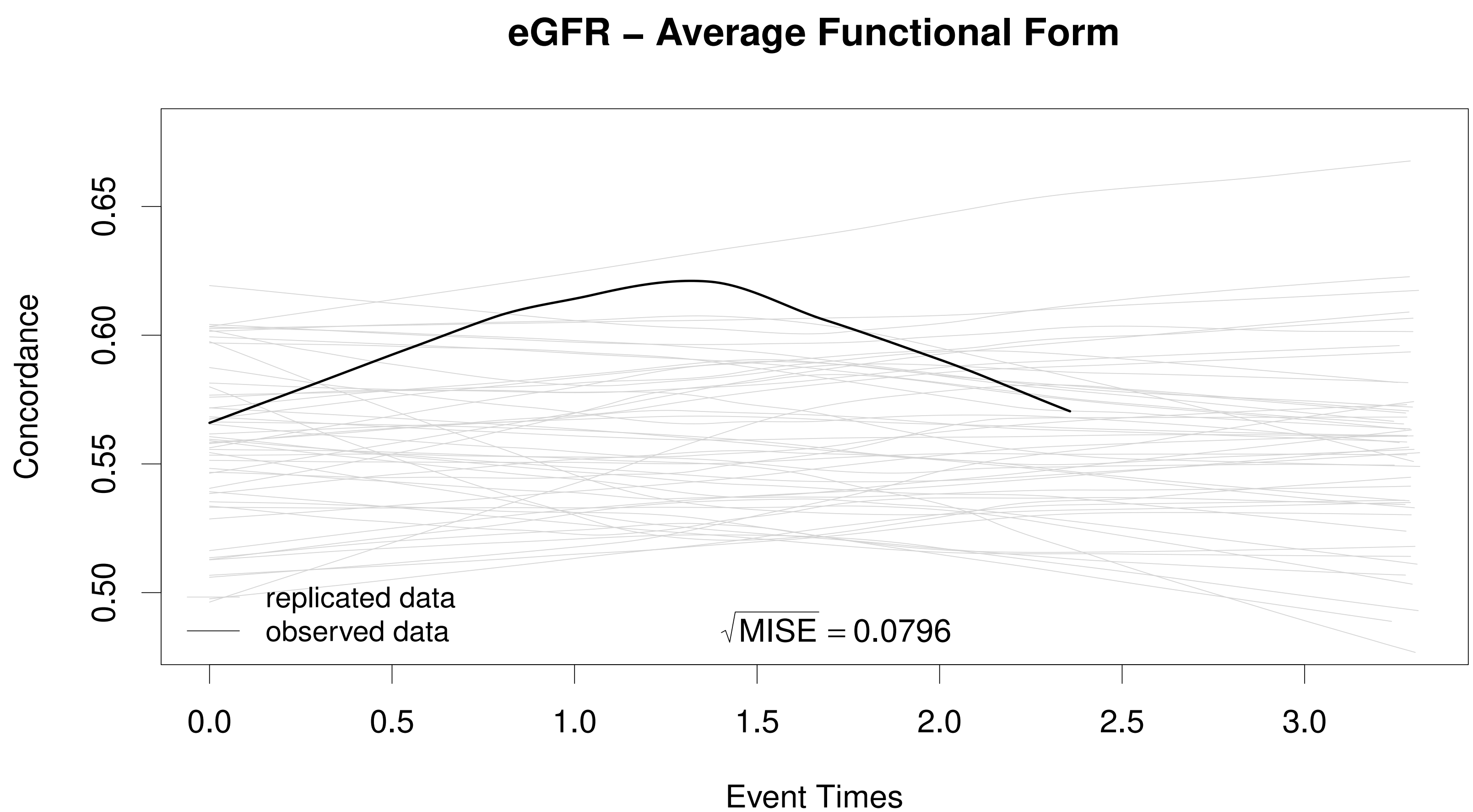

4 Goodness-of-Fit Measures (cont'd)

Summary

▷ The NGAL model shows a better overall fit than the eGFR model

▷ Using nonlinear trajectories improves the fit of the NGAL model in the mean, variance and correlation functions

▷ Linear trajectories seem better for eGFR

▷ No differences between the models in the eCDF plots for the composite event

▷ The average/area function form better for eGFR; for NGAL both functional forms OK

5 Software

Available in JMbayes2

- ▷ posterior-posterior
- ▷ posterior-prior
- ▷ dynamic posterior-posterior

For more info see
`https://drizopoulos.github.io/JMbayes2/`
→ `Articles` → `Posterior Predictive Checks`

Thank for your attention!

https://www.drizopoulos.com/

6 Visiting Process

At which time points should we simulate longitudinal responses?

- The joint model provides valid inferences when the visit times depend on previously observed data
  - ▷ baseline covariates
  - ▷ longitudinal history

- **However,** the statistics we considered are affected by an random visit process
  - ▷ *we simulate at the observed visit times*

7 Censoring Process

How to account for censoring?

- The joint model provides valid inferences when the censoring mechanism depends on previously observed data
  - ▷ baseline covariates
  - ▷ longitudinal history

- We simulate true event times $T_i^{*\mathsf{rep}}$ without censoring
  - ▷ we compared the eCDF of $T_i^{*\mathsf{rep}}$ with the Kaplan-Meier based on $\{T_i, \delta_i\}$
  - ▷ Kaplan-Meier assumes independent censoring
  - ▷ Breslow estimator from a Cox model for covariate-dependent censoring