Individualized Risk Prediction with Intermediate Events

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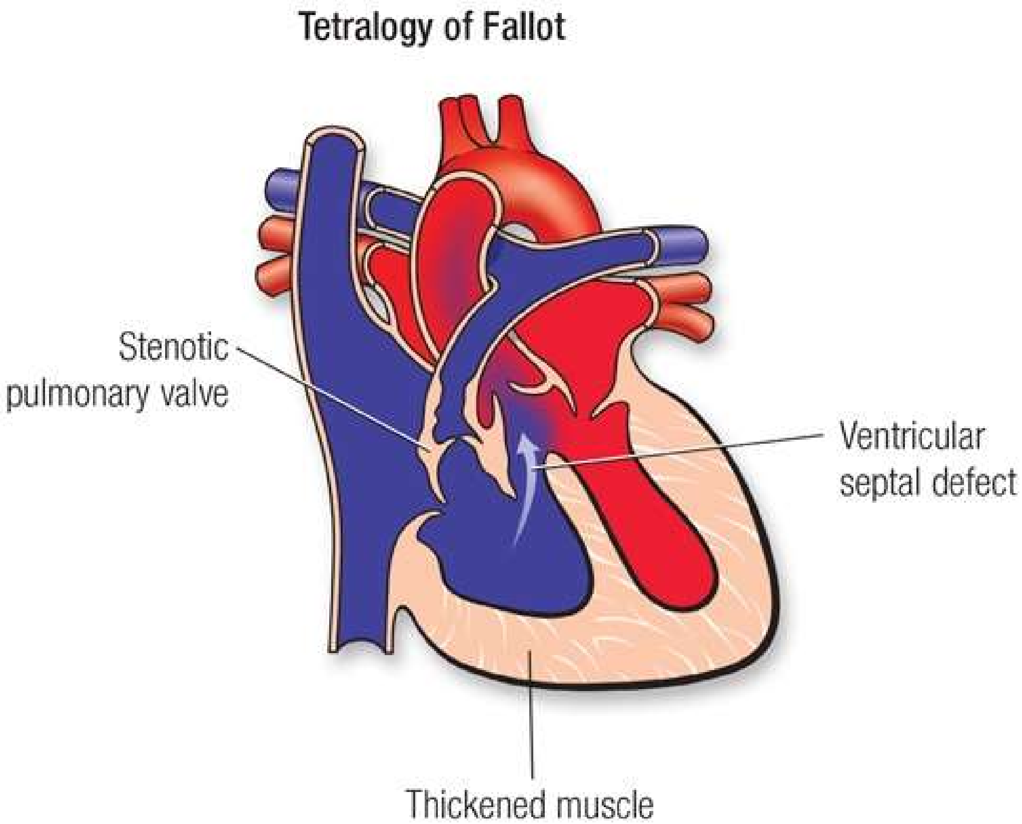
December 18, 2018

Individualized Risk Predictions

- Precision medicine and shared decision making
  - early disease diagnosis
  - optimal timing of intervention
  - detection of response to therapy
  - prognostic monitoring of patients

Pulmonary Gradient Study

- Motivating case study



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Pulmonary Gradient Study (cont'd)

- Valve transplants do not last forever

- Re-operation: very likely
  - Too early $\rightarrow$ Additional re-operation
  - Too late $\rightarrow$ Permanent damage

Pulmonary Gradient Study (cont'd)

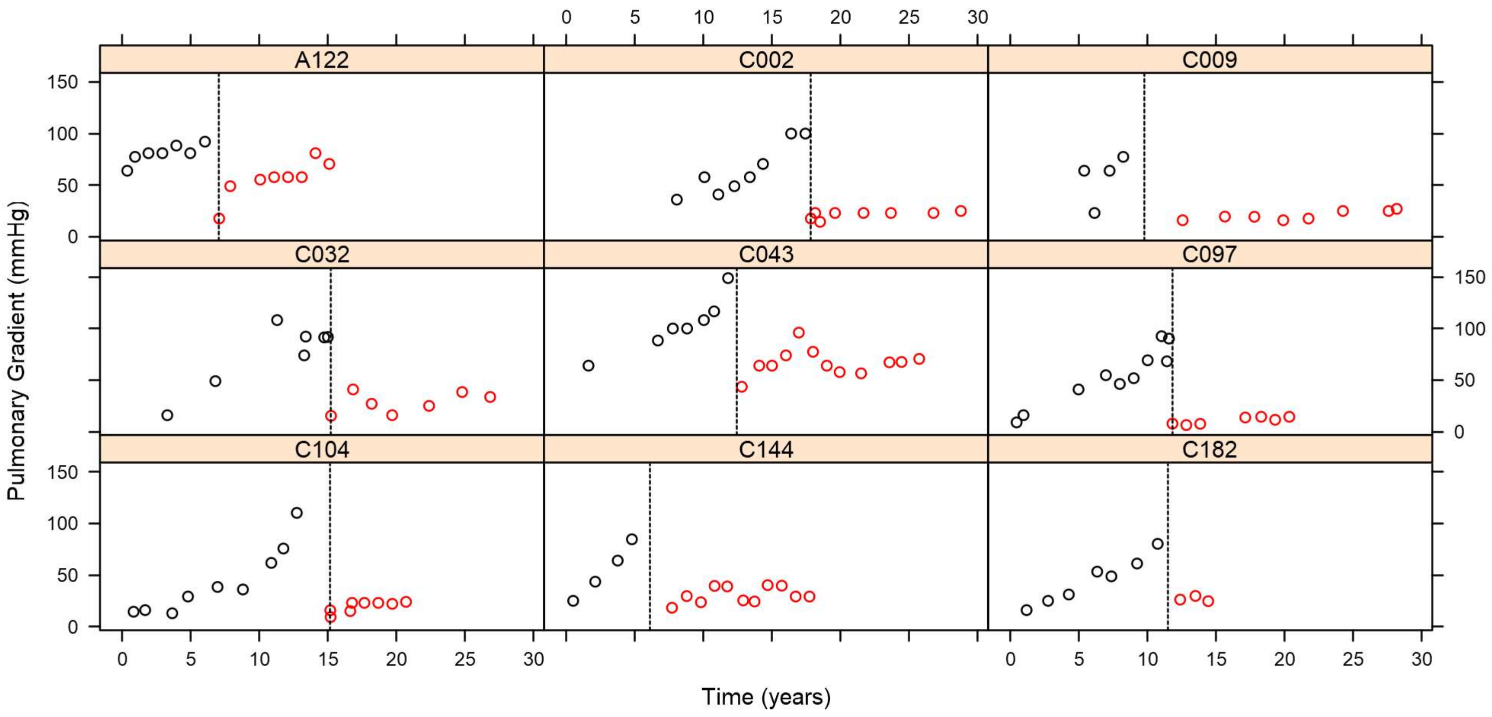
- Data from the dept. of Cardiothoracic Surgery of Erasmus MC
    - 467 patients
    - follow-up of 30 years

- Outcomes of interest:
    - 34 (7%) deaths
    - 65 (14%) re-operated patients
    - 3967 longitudinal Pulmonary Gradient measurements

Pulmonary Gradient Study (cont'd)

Outcome:

subject PG



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Pulmonary Gradient Study (cont'd)

How to better plan re-interventions?

- In steps:
  - *How the longitudinal Pulmonary Gradient is related to death & re-operation?*
  - *How to use the Pulmonary Gradient measurements predict death with & without re-operation?*

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Time-varying Covariates

- To answer these questions we need to link
  - the time to death (primary endpoint)
  - the time to re-intervention (intermediate event)
  - the Pulmonary Gradient measurements (longitudinal outcome)

- Biomarkers are *endogenous* time-varying covariates
  - their future path depends on previous events
  - standard time-varying Cox model not appropriate

Time-varying Covariates (cont'd)

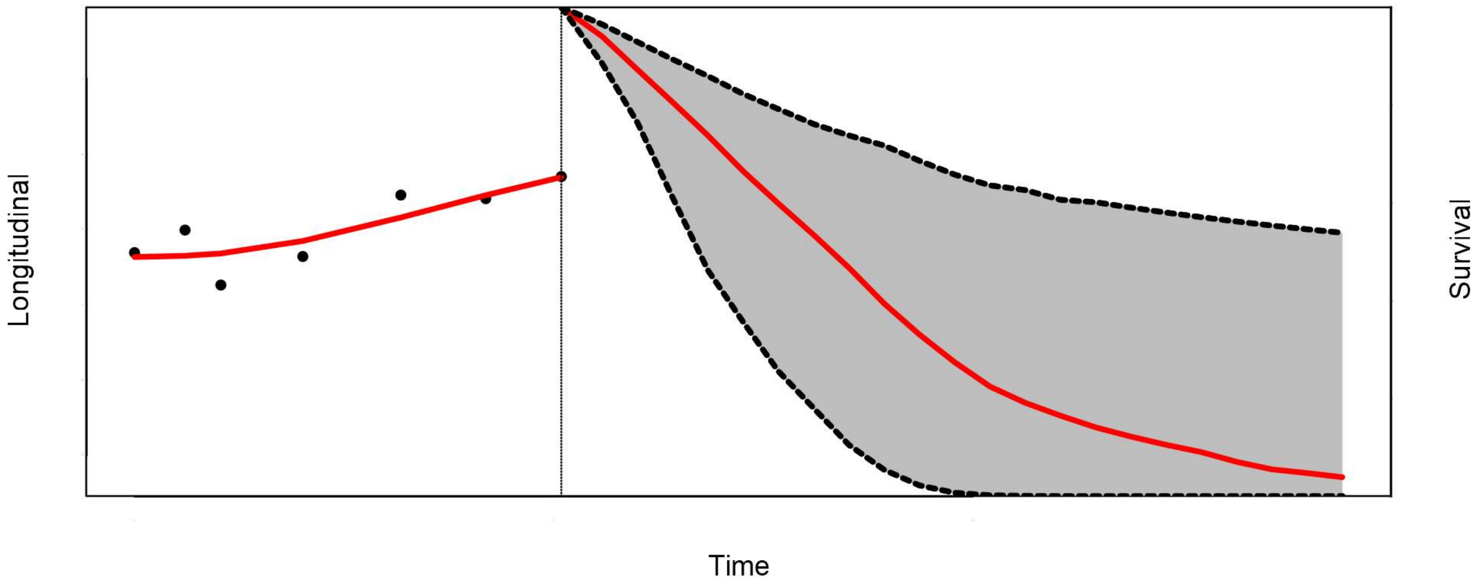
To account for endogeneity we use the framework of

Joint Models for Longitudinal & Survival Data

The Basic Joint Model

Measurements:

1 7 10



The Basic Joint Model (cont'd)

- We need some notation
  - T_i^* the true time-to-death
  - $\{T_i, \delta_i\}$ observed time-to-death & event indicator
  - $\mathbf{y}_i$ vector of longitudinal Pulmonary Gradient measurements
  - $\mathcal{Y}_i(t) = \{y_i(s), 0 \leq s < t\}$

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The Basic Joint Model (cont'd)

- Formally, we have

$$\left\{\begin{array}{lcl} h_i(t) & = & h_0(t) \exp\{\gamma^\top \mathbf{w}_i + \alpha \eta_i(t)\} \\ & & \\ y_i(t) & = & \eta_i(t) + \varepsilon_i(t) \\ & = & \mathbf{x}_i^\top(t)\beta + \mathbf{z}_i^\top(t)\mathbf{b}_i + \varepsilon_i(t) \\ & & \\ & & \mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{D}), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2) \end{array}\right.$$

The Basic Joint Model (cont'd)

- The longitudinal and survival outcomes are jointly modeled

$$p(y_i, T_i, \delta_i) = \int p(y_i \mid b_i) \times \left\{ h(T_i \mid b_i)^{\delta_i} \, S(T_i \mid b_i) \right\} \times p(b_i) \; db_i$$

  - the random effects b_i explain the interdependencies

Intermediate Events

- Re-operation ρ_i as a binary time-varying covariate:

$$\mathcal{R}_i(t) = I(t_i \geq \rho_i) = \begin{cases} 1 & = & \text{if re-operation time after } t_i \\ \\ 0 & = & \text{otherwise} \end{cases}$$

Intermediate Events (cont'd)

- The joint model becomes:

$$\left\{\begin{array}{lcl} h_i(t) & = & h_0(t)\exp\{\gamma^\top \mathbf{w}_i + \zeta \mathcal{R}_i(t) + \alpha \eta_i(t)\} \\ \\ y_i(t) & = & \eta_i(t) + \varepsilon_i(t) \\ \\ \eta_i(t) & = & \mathbf{x}_i^\top(t)\beta + \mathbf{z}_i^\top(t)\mathbf{b}_i \\ & & + \tilde{\mathbf{x}}_i^\top(t_+)\tilde{\beta} + \tilde{\mathbf{z}}_i^\top(t_+)\tilde{\mathbf{b}}_i \end{array}\right.$$

where $t_+ = \max(t - \rho_i, 0)$

Pulmonary Gradient Analysis

- Longitudinal model

$$PG_i\left(t\right) = \begin{cases} \left(\beta_0 + b_{i0}\right) + \left(\beta_1 + b_{i1}\right) \times t \\ \quad +\beta_4 Age + \beta_5 sex + \varepsilon_i\left(t\right), \quad 0 < t < \rho_i \\ \\ \left(\beta_0 + b_{i0}\right) + \left(\beta_1 + b_{i1}\right) \times t + \left(\tilde{\beta}_2 + \tilde{b}_{i2}\right) \times \mathcal{R}_i\left(t\right) \\ \quad + \left(\tilde{\beta}_3 + \tilde{b}_{i3}\right) \times t_+ + \beta_4 Age + \beta_5 sex + \varepsilon_i\left(t\right), \quad t \geq \rho_i \end{cases}$$

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Pulmonary Gradient Analysis (cont'd)

- Risk of death

$$h_i\left(t\right) = h_0\left(t\right)\exp\{\gamma_1 \mathrm{Age}_i + \gamma_2 \mathrm{sex}_i + \zeta \mathcal{R}_i\left(t\right) + \alpha \eta_i\left(t\right)\}$$

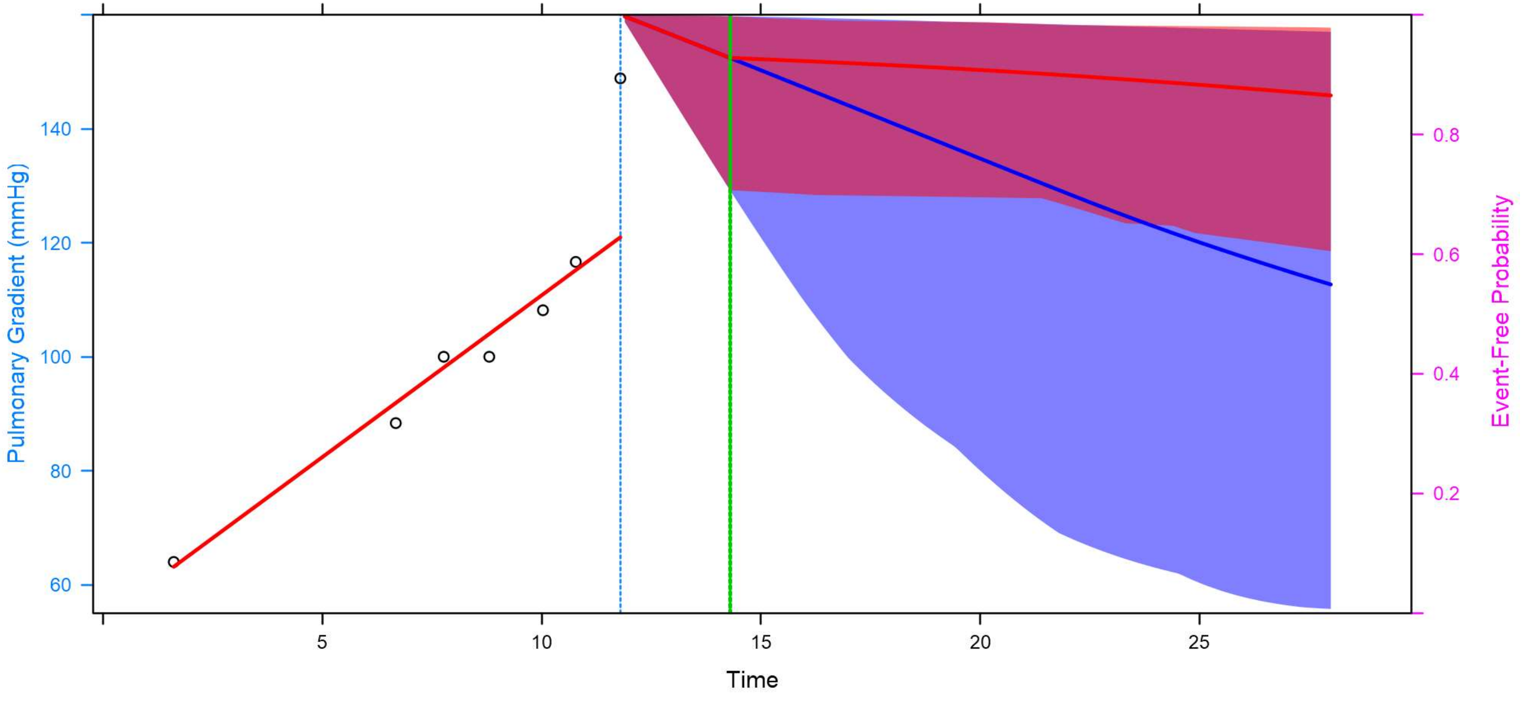
Pulmonary Gradient Analysis (cont'd)

PG Measurements:

1 7

Re-operation time:

1 7 13



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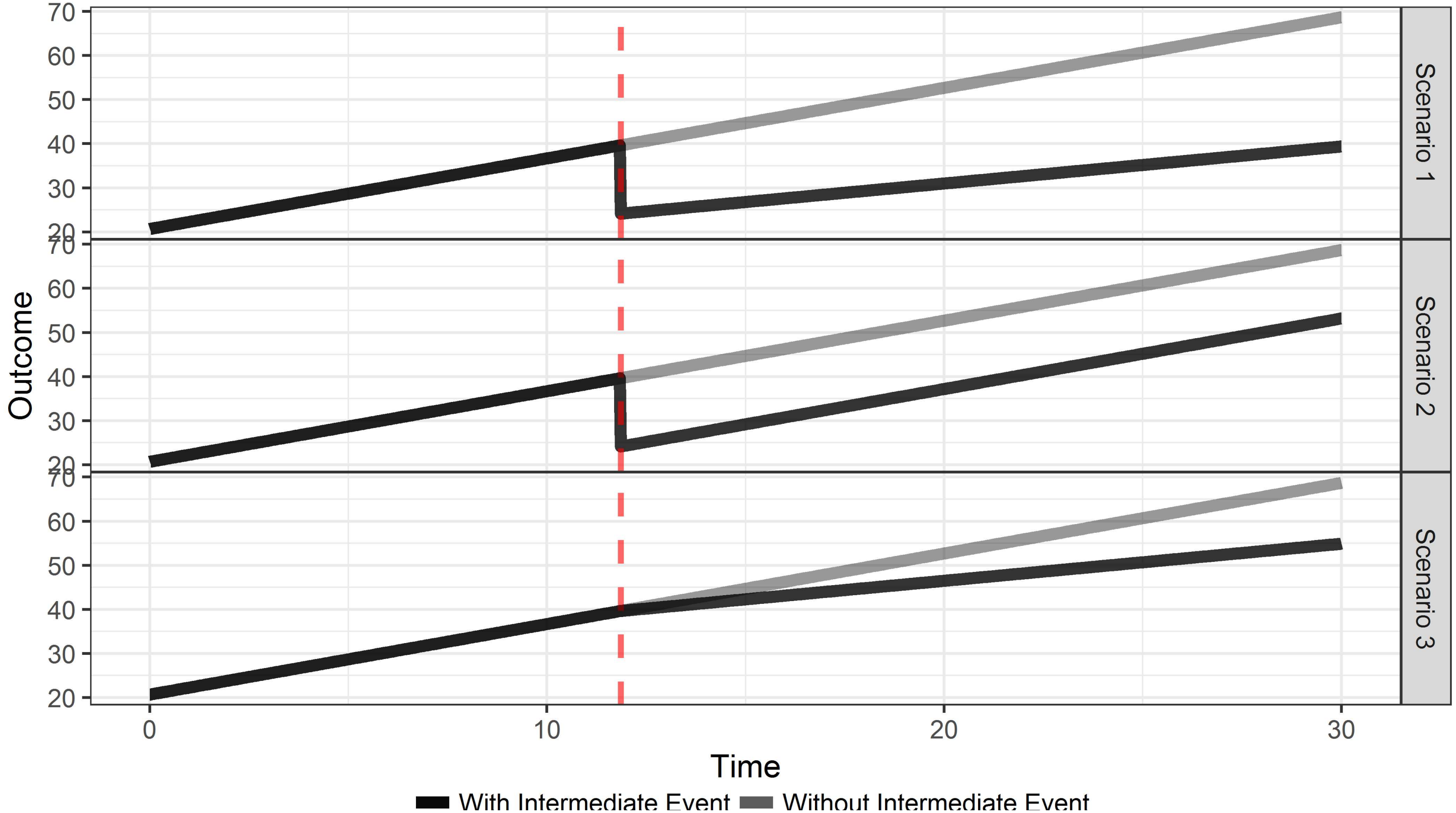
Simulation

- Aim: To compare Segmented Trajectory vs Extrapolation

- Scenarios
  - I: drop & same slope
  - II: drop & different slope
  - III: no-drop & different slope

- Metrics
  - AUC & Prediction error
  - at 3 follow-up times

Simulation (cont'd)



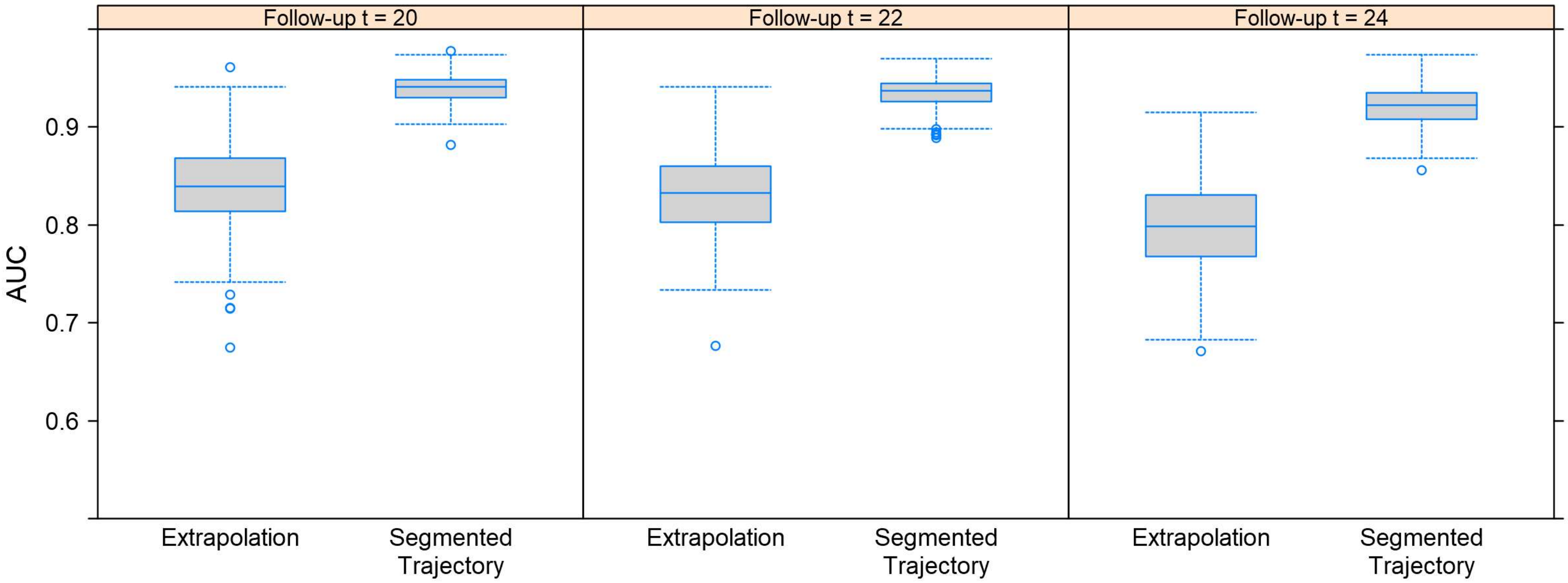
Simulation (cont'd)

Scenario:

1

Metric:

AUC



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Discussion

- Extensions
  - function forms (easy)
  - optimal timing of re-intervention (difficult)

- Preprint available at: https://arxiv.org/abs/1804.02334 (https://arxiv.org/abs/1804.02334)

- Software: available in **JMbayes** on CRAN & GitHub
  - https://cran.r-project.org/package=JMbayes (https://cran.r-project.org/package=JMbayes)
  - https://github.com/drizopoulos/JMbayes (https://github.com/drizopoulos/JMbayes)

Thank you for your attention!

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