Non-linear Bayesian joint models to estimate direct and indirect treatment effects in oncology clinical trials

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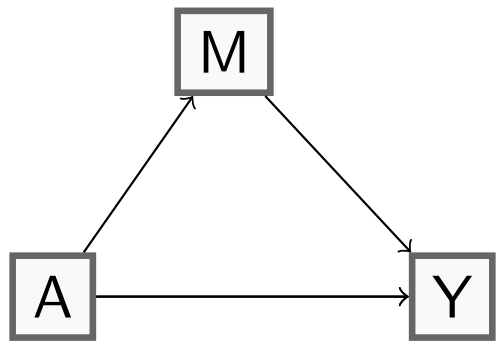
Introduction

- Aim: Estimation of the Proportion of Treatment effect mediated through longitudinal biomarker $\longrightarrow$ Surrogacy evaluation. [1]
- Joint models
  - 1st endpoint
    - **Longitudinal** (tumor size)
    - Time to event (time to progression)
    - Binary (Complete / partial response)
  - 2nd endpoint
    - **Survival**
    - Progression free survival
- Bayesian inference
  - Prior distributions
  - Markov chain Monte Carlo sampling $\longrightarrow$ complex numerical integration

[1] [Zhou et al., 2022, Alonso et al., 2016, Wang et al., 2020]

Introduction

- A: Treatment
- Y: Time to event endpoint: Overall survival
- M: Biomarker: Sum of the Longest Diameters



Introduction

Direct and Indirect effect

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- Y: Time to event endpoint: Overall survival
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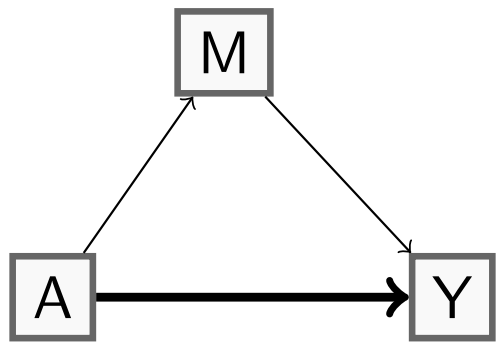

Introduction

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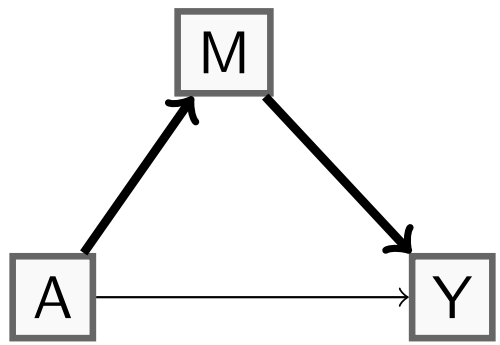


Methods. Joint model

Survival part

$$h_i(t) = h_0(t|\theta) exp\left(\gamma X_i + \beta f(t \mid \psi_i)\right)$$

$$S(t) = 1 - H(t)$$

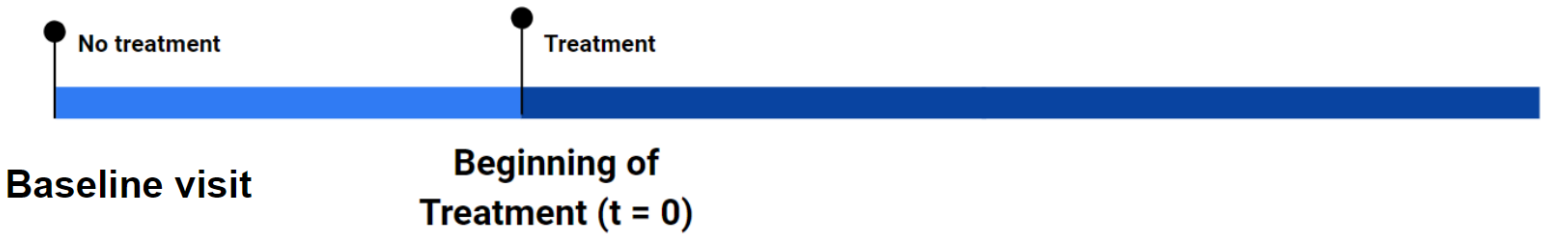
where:

- $h_i(t)$ Hazard over time for subject i
- $h_0(t)$ Baseline hazard function at time t conditioned on parameters θ
- X_i Treatment indicator for subject i
- $f(t \mid \psi_i)$ Link function at time t given parameters ψ_i for subject i
- β Link parameter
- γ Treatment effect

Methods. Joint model

Longitudinal part

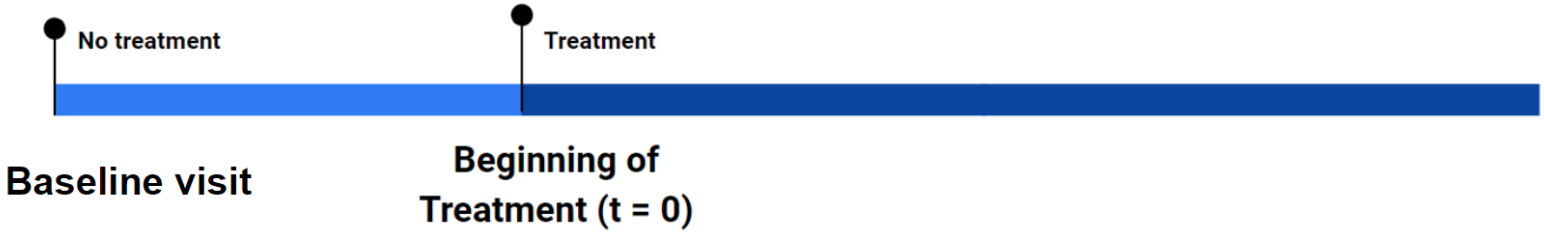
Sum of longest diameter measured every 6-8 weeks



$$g(t,\psi_i) = M_{0_i} exp(\mathbf{K_{g_i}} t) \quad g(t,\psi_i) = M_{0_i}(exp(\mathbf{K_{g_i}} t) + exp(-(\mathbf{K_{s_i}} + \gamma \mathbf{X_i})t) - 1)$$

Methods. Joint model

Longitudinal part



$$g(t,\psi_i) = M_{0_i} exp(\mathbf{K_{g_i}} t) \quad g(t,\psi_i) = M_{0_i}(exp(\mathbf{K_{g_i}} t) + exp(-(\mathbf{K_{s_i}} + \gamma \mathbf{X_i})t) - 1)$$

- K_g and K_s: constant, correlate with survival. [2]
- Biological interpretation. [3]
- Prior knowledge. [4]
- Time to Nadir and the current slope of the sum of longest diameter are good predictors of overall survival. [5]

[2] Wilkerson et al. [2017]
[3] Kerioui et al. [2022]
[4] Yin et al. [2019]
[5] Tardivon et al. [2019]

Methods. Link function

Expected sum of longest diameter value at time of event

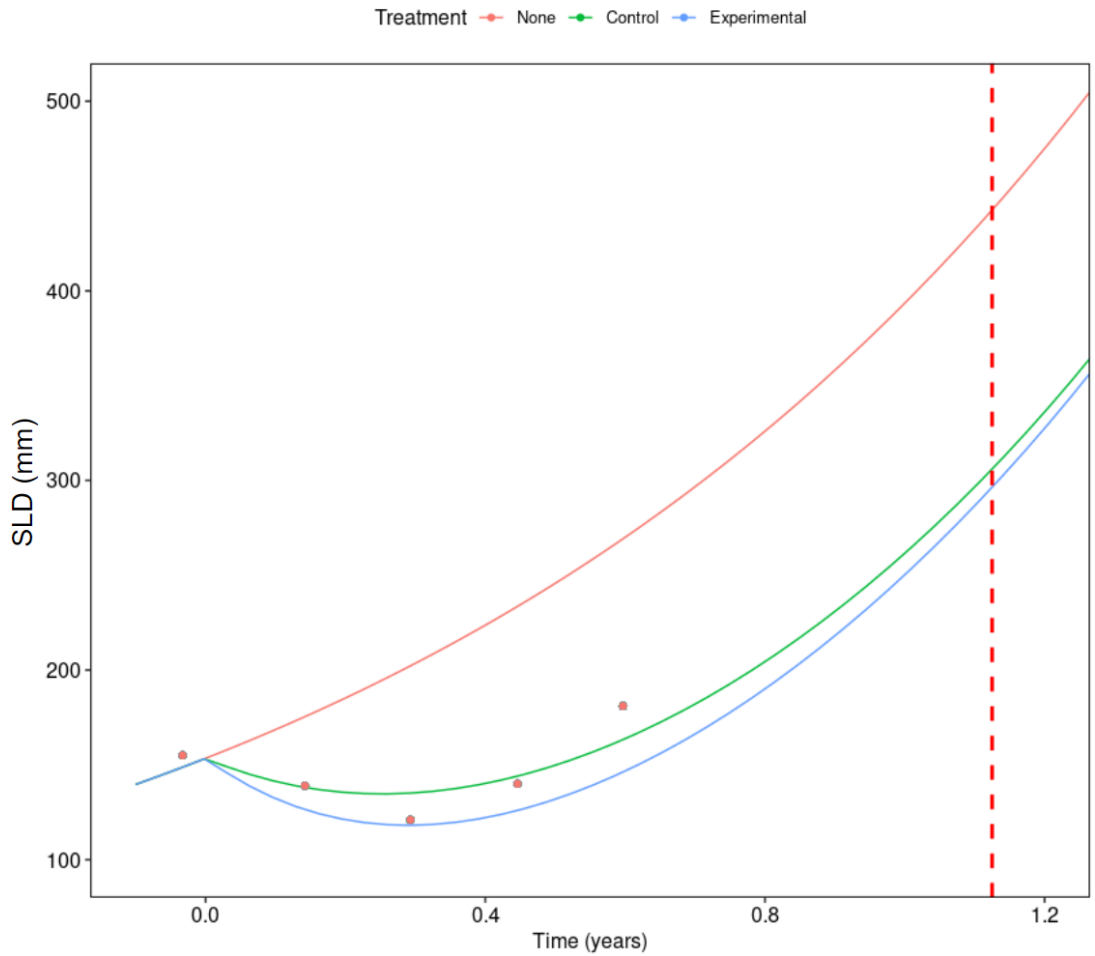
$$G_{sld_i}(t, M_{0_i}, K_{s_i}, K_{g_i}, \gamma, X_i) = M_{0_i}(e^{K_{g_i} t} + e^{-(K_{s_i} + \gamma X_i)t} - 1)$$

- G_{sld} Expected sum of longest diameter value for subject i
- M_{0_i} Estimated sum of longest diameter at time of baseline visit for subject i
- K_{s_i} Tumor shrinkage parameter for subject i
- K_{g_i} Tumor growth parameter for subject i
- X_i Treatment indicator for subject i
- γ Treatment effect
- t Time
- Random effects $\eta_i \sim N(0, \Omega)$ per subject level

Methods. Link function

Expected sum of longest diameter value at time of event

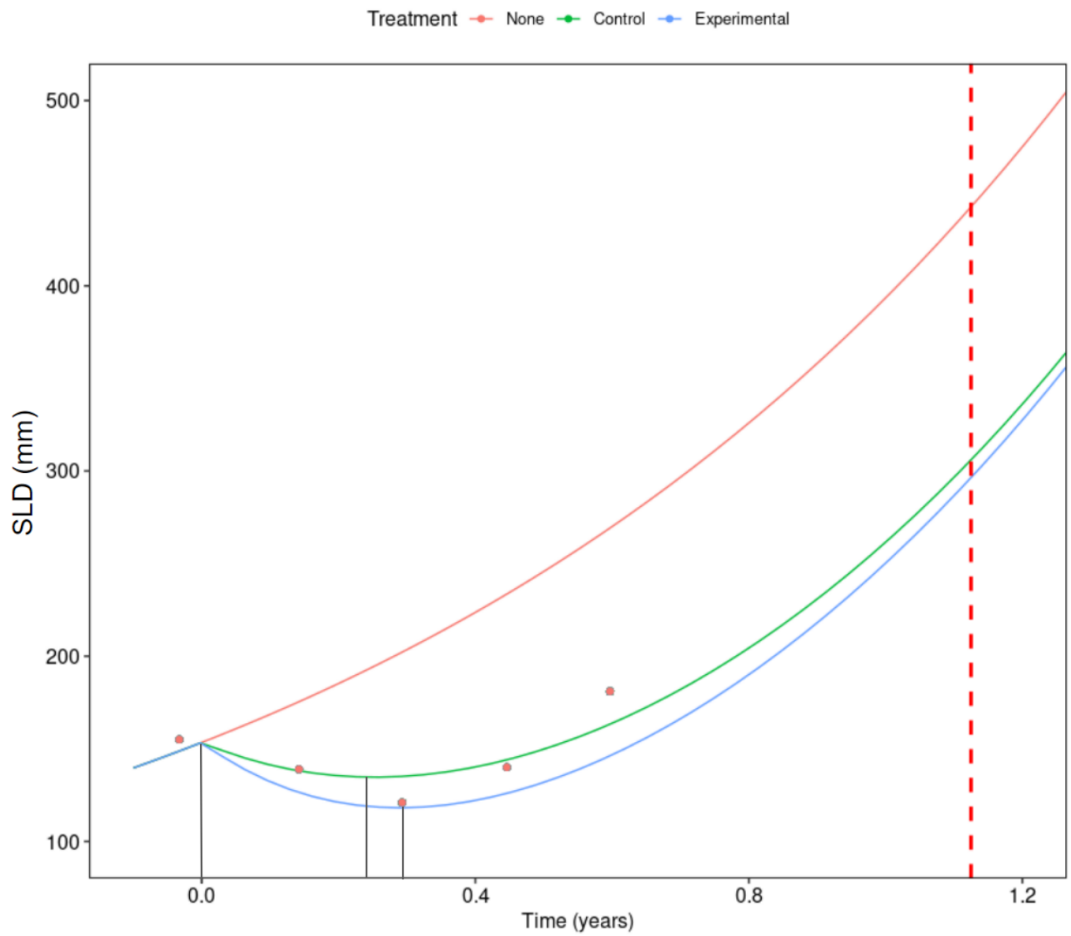
$$G_{sld_i}(t, M_{0_i}, K_{s_i}, K_{g_i}, \gamma, X_i) = M_{0_i}(e^{K_{g_i} t} + e^{-(K_{s_i} + \gamma X_i)t} - 1)$$



Methods. Link function

Time to Nadir (estimated)

$$G_{ttn_i} = \frac{log((K_{s_i} + \gamma X_i)K_{g_i}^{-1})}{(K_{s_i} + \gamma X_i) + K_{g_i}}$$



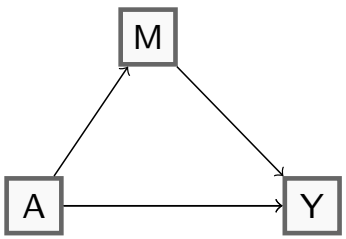
Methods. Natural Direct and Indirect effect

Link: Expected sum of longest diameter at time of event

- Natural indirect effects
  $\text{NIE} = S(X_{long} = 1, X_{surv} = 1) - S(X_{long} = 0, X_{surv} = 1)$

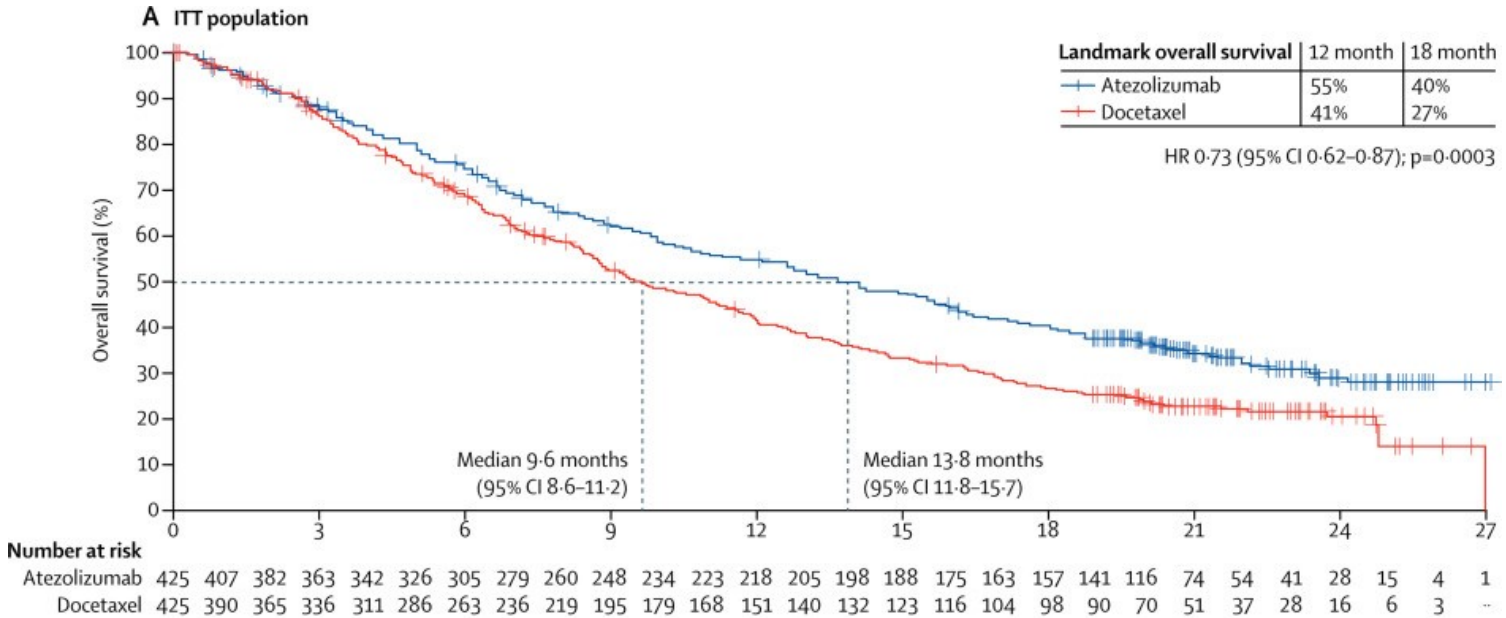
- Natural direct effects
  $\text{NDE} = S(X_{long} = 0, X_{surv} = 1) - S(X_{long} = 0, X_{surv} = 0)$

- Proportion of treatment effect
  $\text{PTE} = \frac{NIE}{NIE+NDE}$



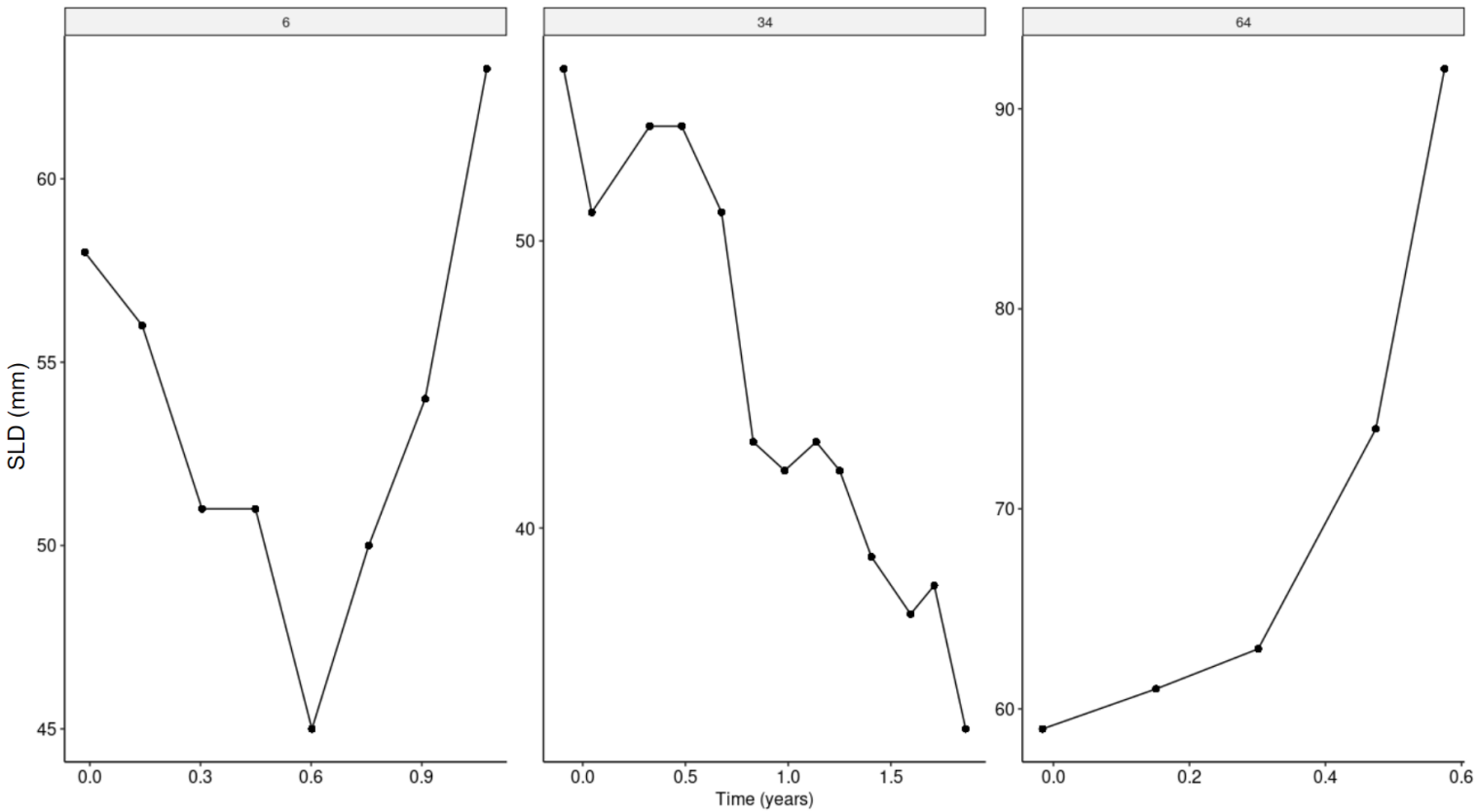
Application

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.[Rittmeyer et al., 2017]



Application

Tumor size profiles



Results. Natural Direct and Indirect effect

Link: Expected sum of longest diameter at time of event

Densities of Natural Direct and Indirect effects at fixed time.

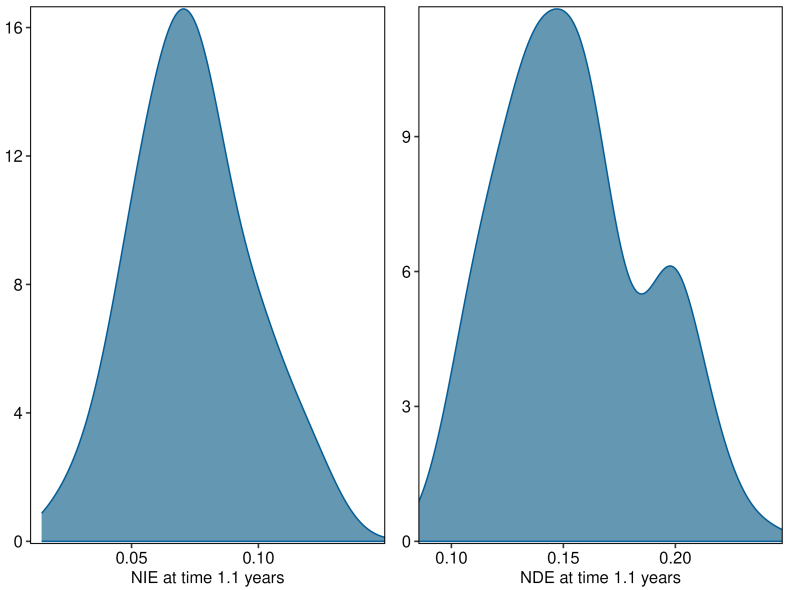


Figure: For individuals

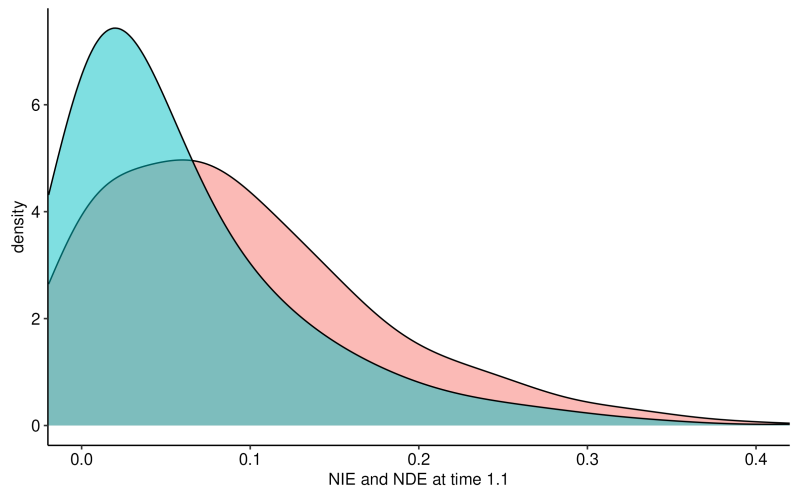
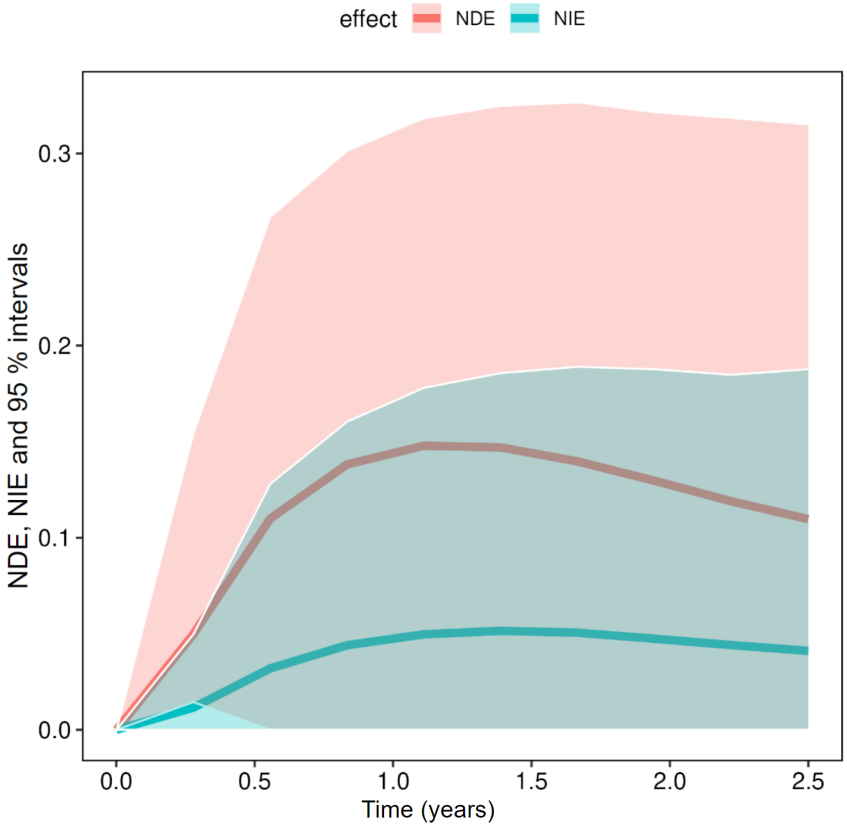
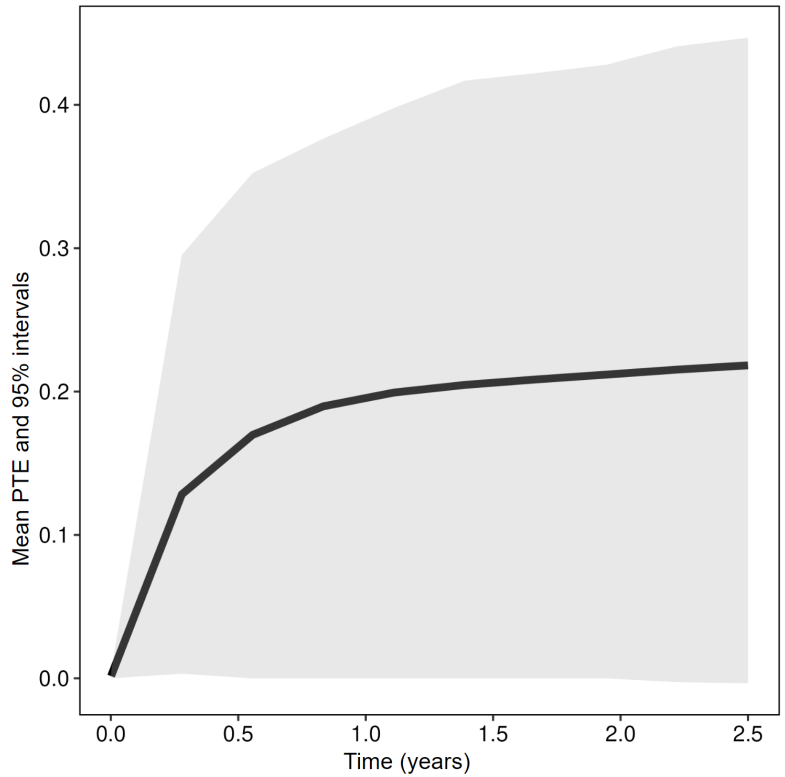


Figure: For population

Results. "Proportion of Treatment effect"

Link: Expected sum of longest diameter at time of event





Conclusions

- Non linear Bayesian Joint models provide a framework to assess surrogacy

Nest steps:

- Baseline characteristics
- Alternative models
- Model assumptions

End of Presentation

Link function

Time to Nadir

$$G_{ttn_i} = \frac{log((K_{s_i} + \gamma X_i)K_{g_i}^{-1})}{(K_{s_i} + \gamma X_i) + K_{g_i}}$$

- G_{ttn_i} Time to nadir for subject i
- K_{s_i} Tumor shrinkage parameter for subject i
- K_{g_i} Tumor growth parameter for subject i
- γ Treatment effect
- X_i Treatment indicator for subject i

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