Multi-state models and joint models: a comparison using AIDS data

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Longitudinal data on AIDS patients

Multi-state survival models

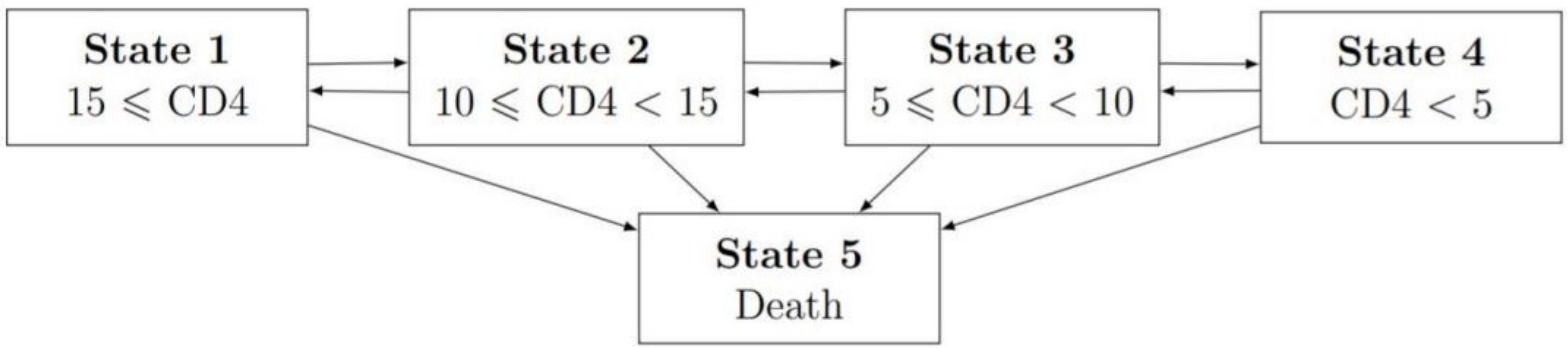
- Maximum Likelihood Estimation
- Intensity model
- Model Validation

Comparison with Joint Models

Conclusion

AIDS data

- 467 HIV patients treated with either didanosine or zalcitabine over a period of 18 months
- CD4 cell count measured at baseline, 6, 12 and 18 months
- Research question: How strong is the association between the administered drug and the risk of death?



- Interval censored data for living states

Fixed effect multi-state survival model

- Framework to model the transition intensity, q_{rs}, between states $r \to s$ using regression model
- Continuous time Markov assumption:

$$P(Y(t+u) = s | Y(t) = r, \mathcal{H}_{t-}) = P(Y(t+u) = s | Y(t) = r),$$
$$\text{where } u > 0$$

- Likelihood constructed using transition probabilities for time intervals
- Piecewise constant approximation used to extend to models with a parametric time dependency

Maximum Likelihood Estimation

- Interval-censored transition times between living states 1-4
- Time of death known (entry into state 5)
- Patient i will have a series of observed states $y_1, , ..., y_K$ at observation times $t_1, ..., t_K$, where the state at t_K can be right-censored
- Likelihood contribution of i:

$$\begin{aligned} L_i(\boldsymbol{\theta}|\boldsymbol{y}, \boldsymbol{x}) &= P(Y_K = y_K, Y_{K-1} = y_{K-1}, ..., Y_2 = y_2 | Y_1 = y_1, \boldsymbol{\theta}, \boldsymbol{x}) \\ &= \prod_{k=2}^{K-1} P(Y_k = y_k | Y_{k-1} = y_{k-1}, \boldsymbol{\theta}, \boldsymbol{x}) \times P_c(Y_K | Y_{K-1}, \boldsymbol{\theta}, \boldsymbol{x}) \end{aligned}$$

- If patient i died at t_K, the summation of the alive states are multiplied by the hazard intensity from each state s to death D:

$$\begin{aligned} P_c(Y_K = y_K | Y_{K-1} = y_{K-1}, \boldsymbol{x}) = \sum_{s=1}^{4} P(Y_K = s | Y_{K-1} = y_{K-1}, \boldsymbol{\theta}, \boldsymbol{x}) \\ \times q_{s5}(t_{K-1} | \boldsymbol{\theta}, \boldsymbol{x}) \end{aligned}$$

- Likelihood function formed by combining contributions for all patients and maximise over $\boldsymbol{\theta}$: $L = \prod_{i=1}^{437} L_i(\boldsymbol{\theta}|y, x)$
- The general optimiser package `ucminf` in `R` was used to maximise over $\boldsymbol{\theta}$
- Starting values of -3 were given for each transition intensity that was modelled
- Depending on the number of covariates used, the elapsed time for the `ucminf` function to maximise the likelihood function ranged from 20 to 30 minutes

Intensity model

- Regression model using time since the start of the trial as the time scale:
  - Patient i at time t_i since start of the trial
  - Intensity model for transition from state r to s:

$$q_{rs}(t|\boldsymbol{x}) = q_{rs}(t)\exp(\boldsymbol{\beta}_{rs}^{\top}\boldsymbol{x}(t))$$

  - Can choose from different parametric baseline intensities, eg;

$$\text{Gompertz}: \quad q_{rs}(t) = \lambda_{rs}\exp(\zeta_{rs}t) \qquad \lambda_{rs} > 0$$

- Approximate shape by piecewise-constant intensities
  - Intensities assumed constant within time intervals
  - Transition probabilities derived from the equation $P(t) = \exp(tQ)$ for use in maximum likelihood estimation

- Consider the model:

$$q_{rs}(t) = \exp(\beta_{rs} + \alpha_{rs} t + \gamma_{rs} drug + \xi_{rs} prevOI)$$
$$\text{for } (r,s) \in \{(1,2),(2,3),(3,4)\}$$
$$\gamma_{23} = \gamma_{34}, \quad \xi_{23} = \xi_{34}$$

$$q_{rs}(t) = \exp(\beta_{rs} + \alpha_D t + \gamma_D drug + \xi_D prevOI)$$
$$\text{for } (r,s) \in \{(1,5),(2,5),(3,5),(4,5)\}$$
$$\gamma_D = \gamma_{15} = \gamma_{25} = \gamma_{35} = \gamma_{45}$$

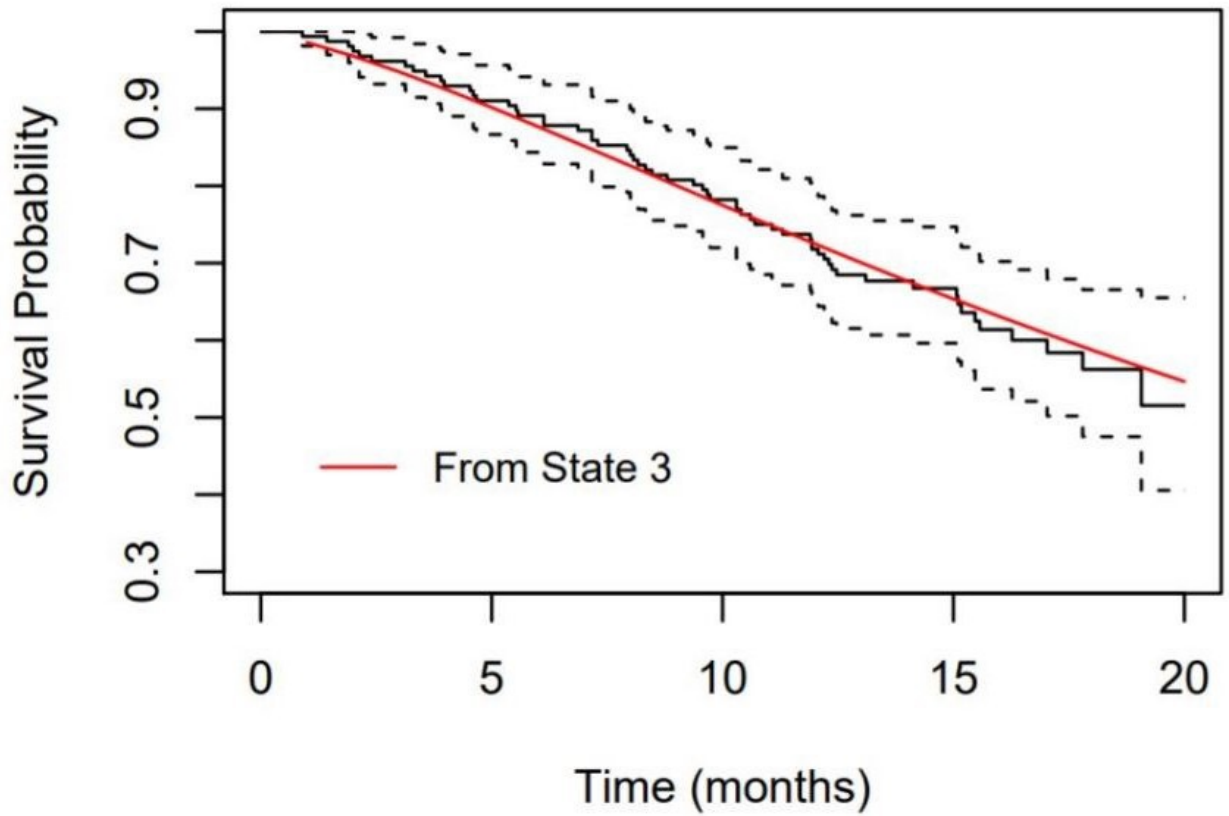
$$q_{rs}(t) = \exp(\beta_{rs} + \alpha_B t)$$
$$\text{for } (r,s) \in \{(2,1),(3,2),(4,3)\}$$
$$\alpha_B = \alpha_{21} = \alpha_{34} = \alpha_{43}$$

- 21 parameters, ten β's, five α's, three γ's , three ξ's

- Effect of time
  - $\hat{\alpha}$ parameters all negative - increase in CD4 count and moving backwards through the states
- Effect of previous opportunistic infection - no previous AIDS diagnosis/previous AIDS diagnosis (0/1)
  - $\hat{\xi}$ parameters all positive - patients with a previous AIDS diagnosis have a higher risk of moving into higher states
- Effect of drug - zalcitabine/didanosine (0/1)
  - $\hat{\gamma_{23}} = \hat{\gamma}_{34} = -0.178$ (0.143)
  - $\hat{\gamma}_D = 0.272$ (0.148)
  - Different drug have different effect on transitions

Kaplan-Meir Curves

- Important to validate the models
- Can be done by comparing Kaplan Meir survival curve with survival curve from multi-state model



- Curves also fit from other baseline states

Joint Models

- Different way of modelling
- Combines two sub models
  - Linear mixed-effect model to model longitudinal biomarker
  - Proportional hazards model to model survival
- Let $m_i(t)$ be the true and unobserved value of the biomarker as modelled by the linear mixed-effect model
- Survival modelled by

$$q_i(t) = q_0(t) \exp(\gamma \text{drug}_i + \alpha m_i(t))$$

  using $m_i(t)$ as a covariate
- $\gamma = 0.335 \ \ (0.157)$ with zalcitabine/didanosine (0/1)
- $\alpha = -0.288 \ \ (0.036)$

- Research question: How strong is the association between the administered drug and the risk of death?
- Can compare effect of drug, $\hat{\gamma}$ as estimated from multi-state model and compare to joint model

	Multi-state model	Joint model
Parameter estimate	$\hat{\gamma} = 0.335 \ (0.157)$	$\hat{\gamma}_D = 0.272 \ (0.148)$
Relative risk	$\exp(0.335) = 1.4$	$\exp(0.272) = 1.3$

Table: Comparing the effect of drug on survival. Standard error given in brackets

- Simlar relative risk for both models
- Didanose is associated with a 1.3-1.4 – fold increase in risk of death
- Zalcitabine more protective against death

Conclusion

- Considered two types of modelling in the case of HIV patients
- Modelling disease trajectory provides an opportunity to gain a deeper understanding of the disease process
- Scope of modelling: planning the future of patients healthcare

Thank you for listening!