Joint modelling of PFS and OS in oncology trials using the gamma threshold model

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Motivation

In oncology trials, different clinical endpoints can be considered for the analysis of overall survival (OS). Time-to-progression (TTP) is defined as the time from study entry to recurrence of the disease (e.g. tumour growth). Progression-free survival (PFS) represents the time from study entry until cancer progression or death depending on what occurs first. OS is the most important endpoint but often TTP or PFS are strongly related to overall survival. Observing OS may require long follow-up after time-to progression; long and expensive trials might be the consequence. Progression-related endpoints are often used for the evaluation of treatment effects on OS in order to gain efficiency in terms of costs and time. PFS can also be used as a direct surrogate endpoint for OS for some cancers but is too stringent as an assumption for other type of cancers. Existing challenges of assessing the efficiency in the analysis of OS using information on progression are to adequately model the joint distribution of PFS and OS. It is of interest to investigate the extent to which existing modelling approaches can increase the efficiency in assessment of the treatment effects on survival using PFS.

The Gamma Threshold model

One framework for modelling PFS and OS is based on assuming a semi-competing risks model, where a patient can experience both a terminal event and nonterminal event. The terminal event such as death censors the nonterminal event such as progression but not vice versa. A new approach [1] of modelling semi-competing risks data considers the events to arise through the first passage times of an unobserved stochastic growth process. In other words, it can be considered as a threshold model with a fixed level for death and a random level for progression of cancer. If the process crosses the level for relapse first, the random growth continues until level for death has been crossed. If the process crosses the level for death first, it is stopped.

Notation and Definition

Gamma process

Consider a continuous-time stochastic process $\{D(t), t \geqslant 0\}$, which is a gamma process with a shape function $\alpha(t) > 0$ and scale parameter $\lambda > 0$. If

- $D(t) \sim \Gamma(\alpha(t), \lambda)$ for any $t \geqslant 0$,
- $\{D(t), t \geqslant 0\}$ has independent increments,
- $D(t_1) - D(t_0) \sim \Gamma(\alpha(t_1) - \alpha(t_0), \lambda)$ for any $t_1 > t_0$.

First passage time of a stochastic process

The first passage time T_d of the process $D(t)$ over a fixed threshold $d > 0$ is defined as the time until the process crosses the level : $T_d = \inf\{t : D(t) \geqslant d\}$

Threshold model with a fixed level for death and random level for progression of cancer

- T_S : first passage time to a random theshold for relapse
- T_c : first passage time to a fixed level $c > 0$ for death.
- If $S = s_1 < c$: After T_S is observed, the gamma process $D(t)$ continues until level c has been crossed
- If $S = s_2 > c$: The process is stopped when level c is crossed

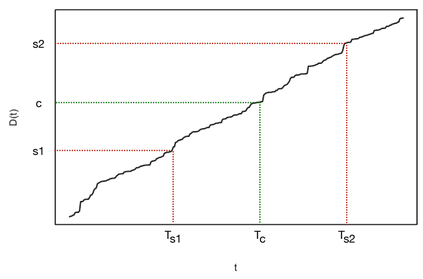


Illustration of modelling semi-competing risks with a fixed level c and a random level S

Evaluation of this modelling approach in terms of the implied transition intensities of the observable process

Our initial work in this project was to analyze this modelling approach in terms of the implied transition hazards between the states of the observable process. We have derived an expression of the general hazard function, hazard function given progression and hazard function without progression based on this new modelling approach.

- General hazard

$$F(t) = \mathbb{P}[T \leq t] = \mathbb{P}(D(t) > c) = \frac{\Gamma(\alpha(t), c\lambda)}{\Gamma(\alpha(t))} = F_{\gamma(\alpha(t),\lambda)}(c)$$

where $\Gamma(\alpha(t), c\lambda)$ is the upper incomplete gamma function.

$\rightarrow$ Hazard intensity $h(t) = \frac{f(t)}{1-F(t)} \approx \frac{\frac{1}{\delta}(F(t+\delta)-F(t))}{1-F(t)}$

- Hazard after progression

$$F(t|T_P = u < t) = \mathbb{P}(t|T_P = u < t) = \int_0^c F_{\gamma(\alpha(t)-\alpha(s))}(c-s) f_S(s) ds$$

$\rightarrow$ Hazard intensity: $h(t|T_P = u < t) \approx \frac{\frac{1}{\delta}(F(t+\delta|T_P=u<t+\delta)-F(t|T_P=u<t))}{1-F(t|T_P=u<t)}$

- Hazard without progression

$$F(t|T_P \geqslant t) = (1 - F_S(c)) \times \mathbb{P}(D(t) > c)$$

$$f(t|T_P \geqslant t) \approx (1 - F_S(c)) \times \frac{\frac{1}{\delta}(F(t+\delta|T_P \geqslant t+\delta) - F(t|T_P \geqslant t))}{\delta}$$

$$S(t|T_P \geqslant t) = \mathbb{P}(D(t) < c)(1 - F_S(c)) + \int_0^c \mathbb{P}(D(t) < s) f_S(s) ds$$

$\rightarrow$ Hazard intensity: $h(t|T_P \geqslant t) = \frac{f(t|T_P \geqslant t)}{S(t|T_P \geqslant t)}$

Extension of the model

As one of our aims is to see if the model implies any gain efficiency in estimating the treatment effect on OS, we have extended the model by including covariates such as treatment. We use an accelerated failure time model and replace the shape function $\alpha(t)$ by $\alpha(t \exp(X^T \rho))$. Other options for how to incorporate the treatment effect might be to let the scale parameter λ be a function of covariates, to put the covariates on threshold c for death or on threshold S for progression.

Simulation

In order to illustrate and analyze the gamma threshold model with treatment effects, we simulated a dataset using the threshold model with shape function of the gamma process. We consider the shape function as $\nu(t) = \alpha t^\beta$, where $\alpha = 5$ and $\beta = 1$. Let threshold c for death be 7 and S be log-normally distributed. We simulated 1000 realizations of the model. The distribution of the censoring time was based on a gamma distribution with parameter values, such that T_c is censored in 10% of observations. We also assume a treatment effect of $\rho = -0.3$.

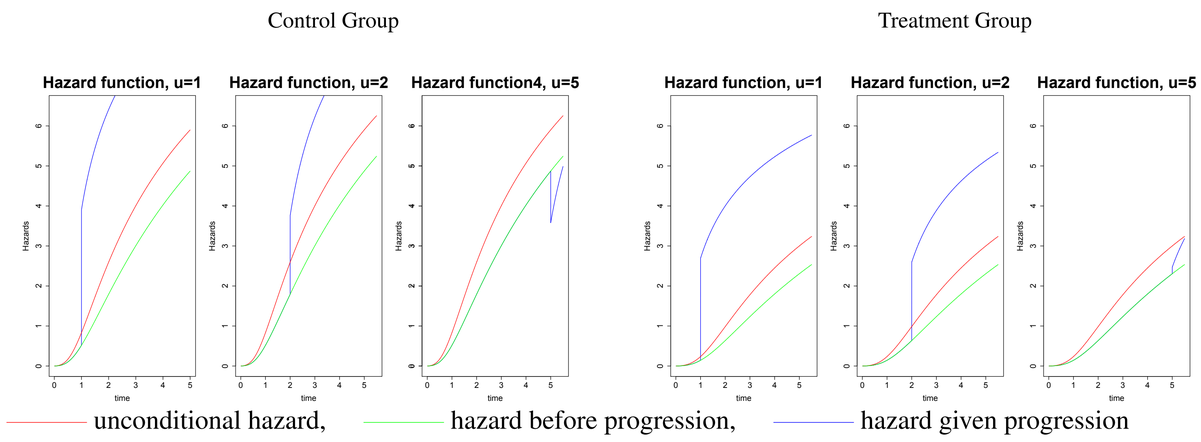
Model estimation In order to estimate the parameters of the gamma threshold model, we use the MLE's. The likelihood function compromises of contributions from the four possible cases of observed data: patients who progress and then are censored without death; patients who progress and then die; patients who die before progression; and patients who are censored without progression or death.

Results

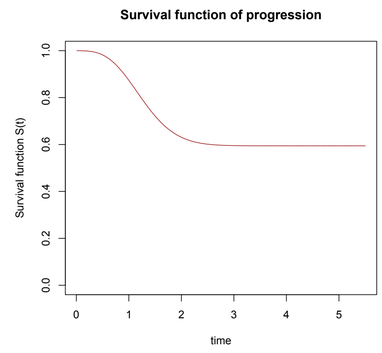
The table below shows the true values of the gamma threshold model and the maximum likelihood estimates of those parameters. Further, the standard errors calculated from the Hessian matrix and the 95% confidence interval are included.

Parameters	True values	Estimates	St.err.	CI
a	5	5.235	0.264	(4.743, 5.779)
b	1	0.946	0.030	(0.888, 1.007)
c	7	6.739	0.302	(6.172, 7.357)
μ_s	2	1.942	0.045	(1.855, 2.033)
σ_s	0.25	0.143	0.013	(0.120, 0.170)
ρ	-0.3	-0.392	0.025	(-0.444, -0.347)

Based on the estimates, we have an illustration of the gamma threshold model in terms of the implied transition intensities of the observable process. The general hazard function, the hazard function given progression and the hazard without progression are shown for both the treatment group and the control group. The curve of the hazard function given progression depends on the time when progression occurs. For each treatment group, the hazard function given progression is shown for specific times to progression ($u = 1$, $u = 2$ or $u = 5$).



The curves of the derived transition hazards from the gamma threshold model seem to be plausible. As expected, the implied transition intensities show higher hazards in the control group than in the treatment group. The hazard function given progression makes a jump up after progression occurs. However, the performance of the model seems to depend on the scenario regarding the progression of the data. According to the values of the distribution of S in our simulation scenario, quick progression is expected. However, if the progression occurs very late, the hazard of death given progression is lower than hazard of death before progression. That is quite unusual, as the risk of death is usually expected to be higher after progression occurs.



Conclusions

Our aim is to investigate approaches to joint modelling of PFS and OS and their efficiency in estimating the treatment effect on OS using information on progression. We have investigated the new recently published approach of modelling semi-competing risks data since it seems to be a promising approach for that purpose. In particular, incorporating the treatment to the gamma threshold model effect seems to be more convenient than in a multi-state model, where treatment effects need to be estimated for every transition intensity. However, it seems difficult to apply the model to real datasets, as it isn't very flexible and robust in terms of modelling the time to death and time to progression. A possible reason for this situation might be that two endpoints don't provide enough information to model the stochastic process based on the threshold model.

References

[1] Sildnes, B. , Lindqvist, B. H. (2017). Modeling of semi-competing risks by means of first passage times of a stochastic process. Lifetime Data Analysis, 1-32

Acknowledgements

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