

Covariate effects on competing events:

A simulation study comparing approaches

Blesson Chacko, Jon Moss, Joachim Grevel and Rupert Austin

BAST Inc Ltd., Loughborough, UK

Oncology setup and simulations:

- This simulation work is based on our experiences estimating exposure-response relationships in oncology projects, where often both clinical response and dropout are influenced by drug exposure.
- We repeatedly simulated 200 studies (of 100 to 1000 patients), where satisfactory exposure and inadequate exposure were represented with a covariate (COV) assuming the values 1 and 0, respectively. The patients’ time of interest ended either with a response or with dropout due to adverse events. All individual observation periods not ended with an event were right-censored at the end of study which was assumed to at 600 days (arbitrary time unit).
- The primary interest of the developer (drug company) was to show that COV=1 increased the rate of responses. The primary interest of the patient (also payer and treating physician) was to know the chance of enjoying a response within a reasonable time frame and to know the risk of dropping out without response, having thus wasted what little life time was left to him/her.

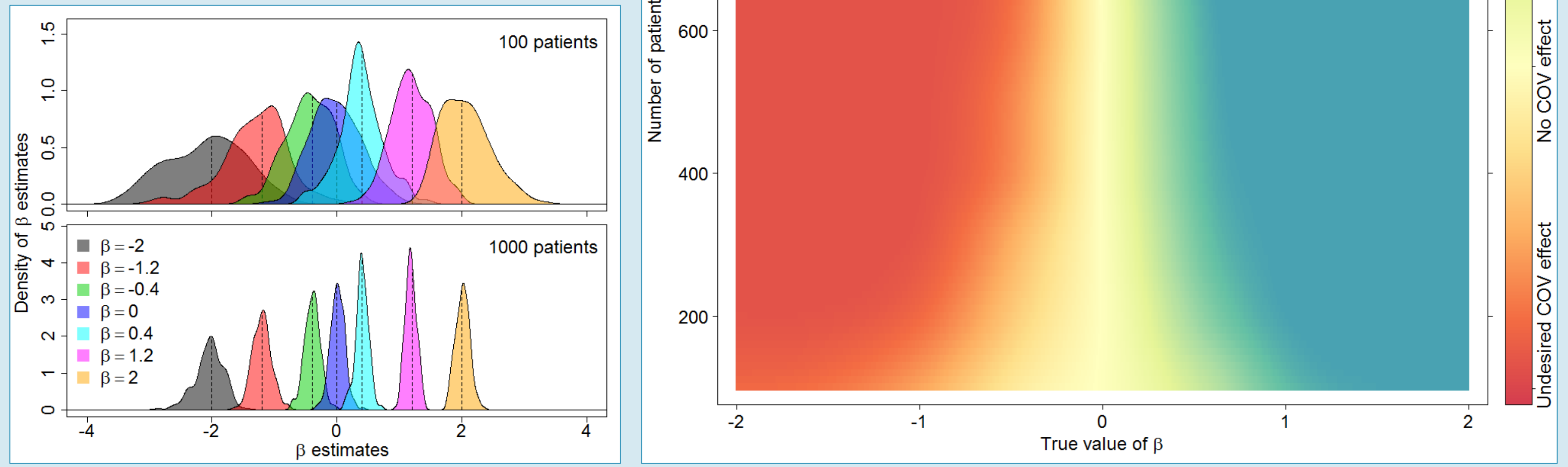
In the simulations, response and dropout followed the same exponential hazard function ($\lambda=0.0025$). The influence of COV on the hazards was introduced as follows:

- Response hazard: $h(t)=\lambda\cdot\exp(\beta\cdot\text{COV})$ [varying $\beta = -2, -1.8, \dots, 1.8, 2$]
- Dropout hazard: $h(t)=\lambda\cdot\exp(\gamma\cdot\text{COV})$ [fixed $\gamma=1$]

Note: In the special case of $\beta = 1$ and $\gamma = 1$, COV=1 equally increases the hazard of a response and of a dropout.

CS approach serving the drug developer’s interest

- Cox PH model was used.
- The heat map on right shows where the desired effects can be found and at what cost.
- Finding the true covariate effect, β , is illustrated below.



Different approaches for different interests:

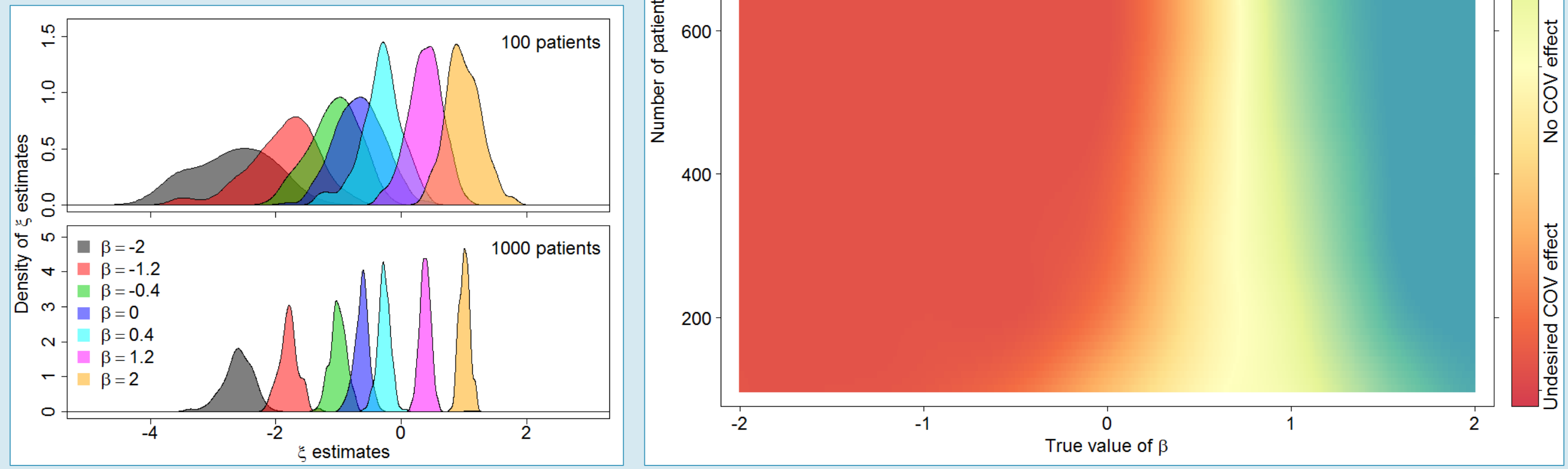
Cause-specific (CS) hazard modelling: investigates the effect of COV on the response rate and treats dropout the same as right-censoring. A widely used method is **Cox proportional hazard modelling** (Cox PH) [1], which is semiparametric and does not support simulation-based model diagnostics. Covariate effects can be visualised by indirectly calculating the cumulative incidence function (CIF). A parametric equivalent to CS modelling has been developed [2] and supports visual predictive checks (VPC) to qualify the covariate influence [3].

Sub-distribution (SD) hazard modelling: investigates the effect of COV on the individual risk (chance) of a response and on the competing risk, i.e. dropout. It differentiates between dropout and right-censoring. A widely used method is the **Fine-Gray model** [4], which is semiparametric and does not support simulation-based model diagnostics. A direct parametric modelling approach for the CIF of SD (CIF_{SD}) is presented here. It uses a modified three-parameter logistic function and a generalised odds-rate link function under the constraint that the asymptotes of CIF_{SD} for the competing events must add up to one [5]. The parametric model for CIF_{SD} can be used in simulation-based diagnostics (VPC).

Developers of cancer drugs use solely the CS approach to guide decisions. Payers are using the SD approach as they are interested in prolonging quality life. Patient advocacy groups have barely recognised the potential of the SD approach. The oncology divisions of regulatory agencies have traditionally shared the same interest in the CS model as drug developers, but recently have paid more attention to the patients’ interest in not wasting the limited resource of time.

SD approach serving the payers interest

- Fine-Gray model was used.
- The heat map on right shows where the desired effects can be found and at what cost.
- The ability of estimating the Fine-Gray regression parameter, ξ , is illustrated below.



Directly modelling the CIF_{SD}

Mathematics:

A transformation of the model structure [4] was used for the direct regression modelling of the CIF_{SD}:

$$g_k\{F_k(t; \mathbf{z})\} = g_k\{F_k(t; \mathbf{0})\} + \xi_k^T \mathbf{z}$$

where, $F_k(t; \mathbf{z})$ are the cause k CIF_{SD} at time t given covariates $\mathbf{z}$, $F_k(t; \mathbf{0})$ is the baseline CIF_{SD}, the vector ξ_k contains the regression parameters, and g_k are non-decreasing inversible “link functions”.

For modelling, a generalised odds-rate link function was used:

$$g(u; \alpha) = \log \left[\frac{(1-u)^{-\alpha}-1}{\alpha} \right],$$

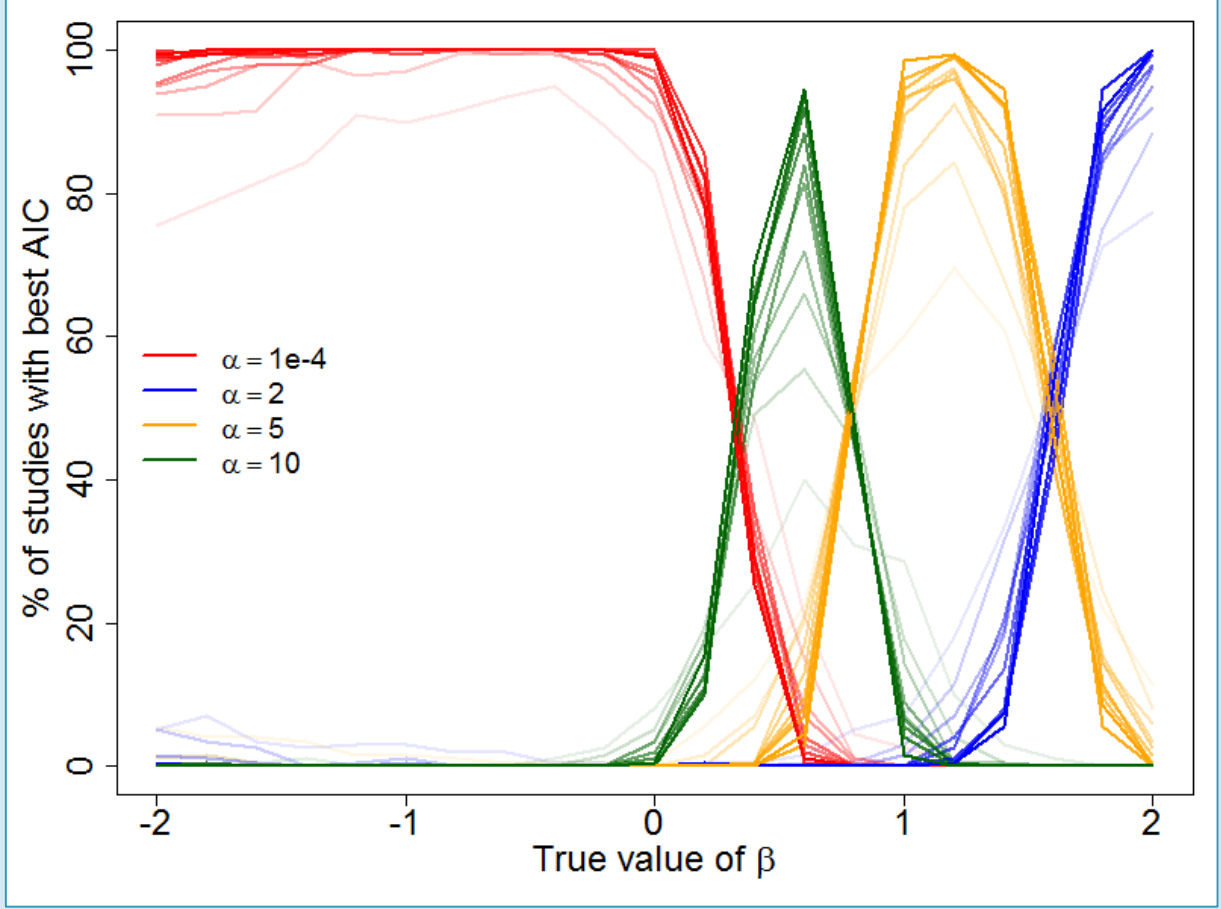
which includes both the proportional hazards ($\alpha \rightarrow 0$) and proportional odds models ($\alpha = 1$). The modified three-parameter logistic function [6] was used to model CIF_{SD}:

$$F_k(t) = \frac{p_k \exp(b_k(t - c_k)) - p_k \exp(-b_k c_k)}{1 + \exp(b_k(t - c_k))},$$

where p_k and b_k were estimated and c_k was fixed to 0, along with constrain $F_1(\infty; \mathbf{z}) + F_2(\infty; \mathbf{z}) = 1$.

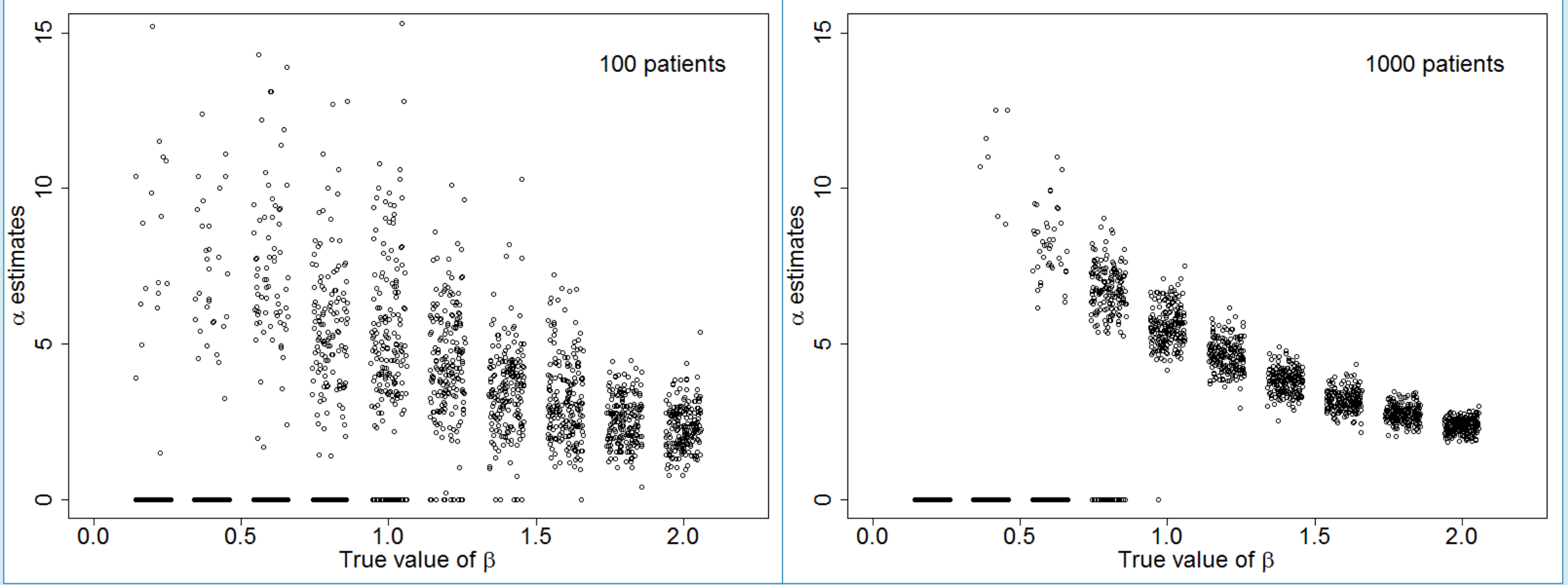
Fixing α :

The best model (based on AIC) for various values of β is shown, selecting α from the following list: 1e-4 (~ PH), 0.1, 0.5, 1, 2, 5, 10, and 20.

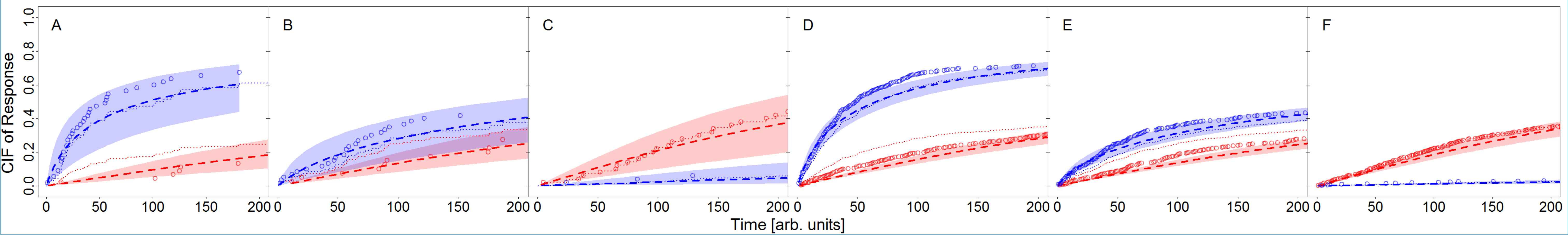


Estimating α :

The plots below demonstrate how the estimated value of α changes while the covariate influence, β , approaches the influence ($\gamma=1$) of the competing event, i.e. dropout. More patients afford better estimates.



Directly modelling the CIF_{SD} provides informative VPCs for the SD approach:



VPC of a single study with 100 patients. The median and pointwise 95% CI of the model-predicted CIF_{SD} is shown, stratified by COV=1 (blue) and COV=0 (red). The comparison with the observed data is facilitated by showing the cumulative count (on probability scale) of the response events while COV=1 (blue circles) and COV=0 (red circles). The comparison with the CIF_{SD} derived from the semiparametric SD approach is shown for COV=1 (blue dots) and COV=0 (red dots). Panel A, B, and C show simulations where COV=1 has a stronger effect on response than on dropout ($\beta = 2$), where COV=1 has almost the same effect on response and on dropout ($\beta = 0.8$), and where COV=1 has the opposite effect on response than on dropout ($\beta = -2$), respectively. The VPCs for dropout are not shown. The estimated α values in Panels A, B, and C were 2.91, 5.72, and 10^{-4} (approaching the proportional hazard model), respectively. Panels D, E, and F show VPC for studies with 1000 patients with same β of A, B, and C. The estimated α values in Panels D, E, and F were 2.58, 6.59, and 10^{-4} (approaching the proportional hazard model), respectively.

Discussion

- Changing the parameter α of the generalised odds-rate link function showed that log-minus-log was not always the best model according to the Akaike information criterion (AIC). Therefore, the directly modelled CIF_{SD} with a fixed α might fail to correctly estimate the covariate effect on the response risk.
- Under SD approach, clinical studies show only positive results when the effect on response is distinctly stronger than the effect on dropout.

Conclusion

- The CS and SD approaches serve the different interests well. Developers could embrace the SD approach without being forced to conduct larger trials. With the SD approach developers of better tolerated cancer treatments could differentiate their asset against competitors.
- With the direct parametric modelling of the CIF_{SD}, VPCs can qualify the SD approach.

References:

- David, C. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society*, 34(2), 187-220.
- Holford, N. (2013). A time to event tutorial for pharmacometricians. *CPT: Pharmacometrics & Systems Pharmacology*, 2(e43), 1-8.
- Grevel J (2017). Time to event modelling of competing risks. Submission ID DDMODEL00000243 in *DDMoRe Model Repository*, URL: <http://repository.ddmore.eu/model/DDMODEL00000243>.
- Fine, J. P., & Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association*, 94(446), 496-509.
- Shi, H., Cheng, Y., & Jeong, J. H. (2013). Constrained parametric model for simultaneous inference of two cumulative incidence functions. *Biometrical Journal*, 55(1), 82-96.
- Cheng, Y. (2009). Modeling cumulative incidences of dementia and dementia-free death using a novel three-parameter logistic function. *The International Journal of Biostatistics*, 5(1), Article 29.