



# Estimating a Cox proportional hazard model in NONMEM

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## Background and Objectives

Traditionally the most commonly used model for survival analysis is the Cox proportional hazard (Cox PH) model [1]. The Cox PH model is a semi-parametric model that makes a parametric assumption regarding the effect of the covariates on the hazard function, but makes no assumption about the shape of the hazard function (i.e. the baseline hazard). This can be interpreted as it is the influence of the covariates that are of interest, not the nature of the hazard function as such.

As time to event models are increasingly used within the field of pharmacometrics it would be convenient to be able to add the Cox PH model to the battery of survival models to be tested in NONMEM and to be used within other procedures such as scm or randtest in PsN [2]. Hence, the objective of this work was to implement the Cox PH model in NONMEM® [3].

## Methods and Materials

The log partial likelihood for the Cox PH model for all event times is expressed as:

$$\log L(\beta) = \sum_{j=1}^N \left\{ X_j \beta - \log \left[ \sum_{k \in R_j} \exp(X_k \beta) \right] \right\}$$

where N is the number of events in the data set,  $X_j$  is the covariate vector for subject with an event at time  $j$ ,  $R_j$  is the set of subjects at risk at time  $j$ ,  $X_k$  is the covariate vector for subject  $k$ ,  $\beta$  is the covariate coefficient vector. If the data set contains ties, i.e. several events at the same time point, the log partial likelihood for the Cox PH model with the Breslow approximation [4] was used:

$$\log L(\beta) = \sum_{j=1}^N \left\{ S_j \beta - d_j \log \left[ \sum_{k \in R_j} \exp(X_k \beta) \right] \right\}$$

where  $S_j = \sum_{i \in D_j} X_i$ ;  $D_j$  is the set of subjects having an event at time  $j$  and  $d_j$  is the number of events at time  $j$ . Both of the definitions of the likelihood were implemented in NONMEM® (version 7.3); code displayed in figure 1.

As the risk set at time  $j$  ( $R_j$ ) consists of the included subjects with event/censoring time  $\geq j$  the data set was sorted according to decreasing event times, enabling the inner sums to be calculated on the fly. The implementation was tested on a data set which was simulated based on the survival model presented in Bruno et al [5]. Four covariates were tested: baseline tumor size (BASE), tumor size at week 6 (TSR6), number of metastases (META) and ECOG status. The result from NONMEM® was compared to a Cox PH model run in R (version 3.1.0) using the coxph function from the survival package (version 2.37-7), with and without the Breslow option.

To evaluate the behaviour in NONMEM, the Cox PH Breslow model were applied to 200 simulated data sets. The simulations were made assuming a baseline Weibull hazard distribution model.

## Results

The estimated covariate coefficients and standard errors (SE) in NONMEM and R are displayed in table I-II (without and with ties).

| Covariate | NONMEM (SE)             | R (SE)                  |
|-----------|-------------------------|-------------------------|
| BASE      | 0.002842<br>(0.0002905) | 0.002847<br>(0.0002911) |
| TSR6      | 0.9632<br>(0.09246)     | 0.9633<br>(0.09246)     |
| ECOG      | 0.4684<br>(0.04798)     | 0.4684<br>(0.04798)     |
| META      | 0.3102<br>(0.05221)     | 0.3103<br>(0.05221)     |

Table I. Estimated covariate coefficients from NONMEM and R

| Covariate | NONMEM (SE)             | R (SE)                 |
|-----------|-------------------------|------------------------|
| BASE      | 0.002828<br>(0.0002898) | 0.002847<br>(0.000291) |
| TSR6      | 0.9621<br>(0.09245)     | 0.9633<br>(0.1667)     |
| ECOG      | 0.4678<br>(0.04798)     | 0.4683<br>(0.04798)    |
| META      | 0.3098<br>(0.05221)     | 0.3104<br>(0.05221)    |

Table II. Estimated covariate coefficients from NONMEM and R with Breslow approximation

When applied on the 200 simulated data sets, the Cox PH model had no fail runs whereas the Weibull model (true model) failed in 23 cases. Although the Cox PH model was somewhat slower to run in NONMEM® than R, the Cox PH model was about 15 times faster to run than the Weibull model (in NONMEM®).

The bias (relative estimation error, REE) and imprecision (relative root mean squared error, rRMSE) for the Cox PH model are displayed in table III.

| Covariate | REE (%) | rRMSE (%) |
|-----------|---------|-----------|
| BASE      | 0.09591 | 0.5358    |
| TSR6      | -10.76  | 23.92     |
| ECOG      | -1.763  | 7.862     |
| META      | -0.9006 | 12.18     |

Table III. Bias and imprecision of 200 simulated overall survival data sets

```

;;; Make sure that you are working with decreasing times
...
$ABB COMRES=4 ; COMRES=1 if no ties (i.e. not Breslow approx)
SPRED
IF (NEWIND.EQ.0) THEN ;For first record
  COM(1) = 0 ; Placeholder for overall Cum risk set sum
  COM(2) = 0 ; Placeholder for last time of event or censoring time
  COM(3) = 0 ; Tie contribution
  COM(4) = 0 ; Tie count

ENDIF
;-----Covariate relationships-----
RFBASE = RFTSR6 = RFECOG = RFMETA = 0
RFBASE = THETA(1)*BASE
RFTSR6 = THETA(2)*TSR6
RFECOG = THETA(3)*ECOG
RFMETA = THETA(4)*META
RFCOV = RFBASE+RFTSR6+RFECOG+RFMETA+ETA(1) ; ETA fixed to zero to infer population
TVRF = RFCOV
RF = TVRF
Y=0

;*****
; If all event times are unique in the dataset (i.e. no ties)
; use this part of the code
IF (TIME.NE.0) THEN
  COM(1) = COM(1)+EXP(RF) ; Increase risk set (if censoring time or event)
ENDIF

IF (TIME.NE.0.AND.DV.EQ.1) THEN ; Update partial likelihood if event
  Y=-2*(RF-LOG(COM(1)))
ENDIF
;*****

; If there are several events at the same time point (i.e. ties)
; use this part of the code
IF (TIME.NE.0.AND.TIME.NE.COM(2)) THEN ; End of tie region
  IF (COM(4).NE.0) THEN ; If we had events during the tie region
    Y=-2*(COM(3)-COM(4)*LOG(COM(1))) ; Breslow approximation
  ENDIF
  COM(3) = 0
  COM(4) = 0
ENDIF

IF (DV.EQ.1) THEN ; Update tie sum if event
  COM(3) = COM(3)+RF
ENDIF
IF (TIME.NE.0) THEN ; Update tie count
  COM(1) = COM(1)+EXP(RF) ; Increase risk set (censoring time or event)
  COM(2) = TIME
  IF (DV.EQ.1) THEN ; Only add event time to ties
    COM(4) = COM(4)+1
  ENDIF
ENDIF

; Last record for last individual, add contrb to part. likelihood if event
IF (TIME.NE.0.AND.NDREC.EQ.LIREC.AND.NIREC.EQ.NINDR) THEN
  IF (COM(4).NE.0) THEN
    Y=-2*(COM(3)-COM(4)*LOG(COM(1)))
  ENDIF
ENDIF
;*****
...
$ESTIM MAXEVAL=9999 METHOD=0 -2LL SIGL=9 NSIG=3 PRINT=1
$COV MATRIX=R

```

Figure 1. NONMEM code for the implementation of the partial likelihood for the Cox proportional hazard model with and without the Breslow approximation.

## Conclusion

- ✓ The likelihood for the Cox PH model with and without the Breslow approximation was successfully implemented in NONMEM® with the condition that the subjects in the data set are ordered by decreasing event times.

## References

- [1] Cox D.R. Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B (Methodological), Vol. 34, No. 2. (1972), pp.187-220.
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- [4] Breslow N. Covariance analysis of censored survival data. Biometrics. 1974 Mar;30(1):89-99.
- [5] R Bruno et al. Simulations to Assess Phase II Noninferiority Trials of Different Doses of Capecitabine in Combination With Docetaxel for Metastatic Breast Cancer. CPT Pharmacometrics Syst Pharmacol. 2012;26;1:e19