TTE Modeling History

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Contents

1 Preamble

```
##==================================== PREAMBLE ========================================##
script.version <- "V2"      #
script.status  <- "DRAFT"   #
set.seed(11626)             # reproducibility
##------------------------------------------------------------------------------------##

## DIRECTORIES ----
project.dir <- file.path("",'pmx_bip','PMx_Playground','gbenitez',
                         "OTHER_PROJECTS",  'PostDoc_project_ISoP', '2018_TTE')
data.dir <-file.path(project.dir,"DATA")
nm.dir <-file.path(project.dir, 'NONMEM')

## Study specific terms
proj.no        <- "TTE_tutorial"
analysis.type  <- "TTE"
mod.type       <- 'Base'
run.log        <- "TTE_runlog.csv" # run record name
diagnostics    <- "VisualizeRunTTE_base.Rmd" # run diagnostics
hazVPC         <- "VisualizeRunTTE_hazard.Rmd" # run hazard based vpc

## Define path for figure output:
fig.dir <- file.path(nm.dir,
                     paste0("Modelling_history_plots_",mod.type,"_",script.version), "")
knitr::opts_chunk$set(fig.path = fig.dir, dev = c('pdf', 'png'),
                      fig.align = 'center', fig.height = 9, fig.width = 16,
                      out.width = '0.95\\linewidth')
##======================================================================================##
```

2 Best model & summary of work

3 Objectives

1. Develop a base time to event model for AZ Cediranib data, ProjectDataSphere # 78
2. Assess the impact of cateogical and continuous covariates on the hazard.

4 Modelling History

4.1 Run 1 : Exponential hazard

```
##=================================== Run notes  ====================================##
# Rationale:   Simplest hazard model to test
# Question:    Will an exponential hazard describe this data?
# Based on:    NA
# Description: h0(t) = lambda
##-----------------------------------------------------------------------------------##
show.mod(1, nm.dir) # print model
```

```
## ;; 1. Based on:
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    exponential hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;;    LAMBDA
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
##
##
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
##
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
##
## $PROBLEM    Base TTE model - Project DataSphere # 78
##
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-------------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
```

```
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
##
## $DATA    ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time, ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
##
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value exponential hazard h0(t) = lambda
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = LAMBDA
##
## DADT(1) = LAMBDA
##
## ;;================================= MODEL FIT ==================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX= LAMBDA
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
```

```
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA
## (0, 0.2) ; lambda
##
## $OMEGA
## 0  FIX   ; place holder
##
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9  NSIG=3 MSFO=msfb_1
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
## ;Sim_end
## ;;================================= TABLES ================================
##
## ;Sim_start : add/remove for simulation
## $TABLE NOPRINT ONEHEADER FILE=mytab1
```

```
## ID TIME DV EVID MDV PRED CHZ SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP
## ;Sim_end
##
## $TABLE NOAPPEND ONEHEADER NOPRINT FILE=sdtab1
## ID TIME SUR EVID
##
## $TABLE NOAPPEND ONEHEADER NOPRINT FILE=patab1
## ID LAMBDA ETAS(1:LAST)
##
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab1
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.1.0.1 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run1/run1
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:00"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   31.2"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.11"
## [19] ""
## [20] "Objective function value: 1037.8336"
## [21] ""
## [22] "Condition number: 1"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA               OMEGA      SIGMA    "
## [28] "lambda  0.3156  (0.05953)                         "
## [29] ""
## [30] "The relative standard errors for omega and sigma are reported on the approximate"
## [31] "standard deviation scale (SE/variance estimate)/2."
## [32] "------------------------------------------------------------------------"
```

4.1.0.2 Diagnostic plots

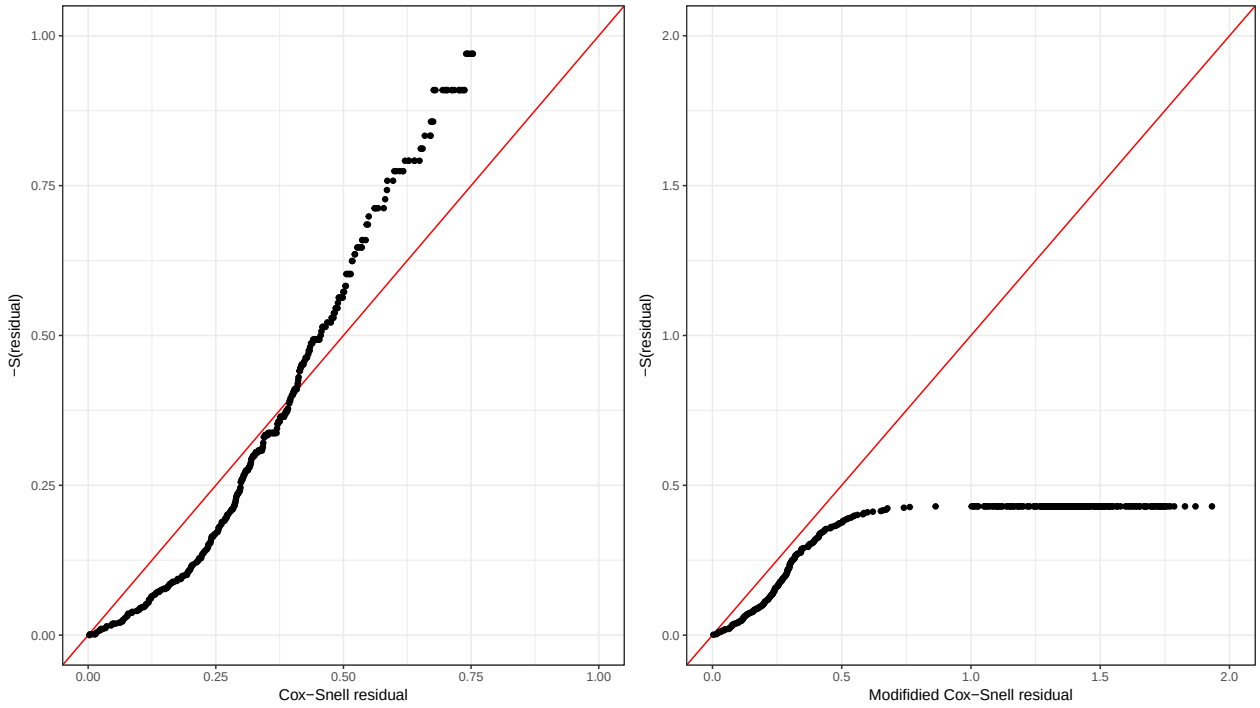


Figure 1: Residual-based diagnostics

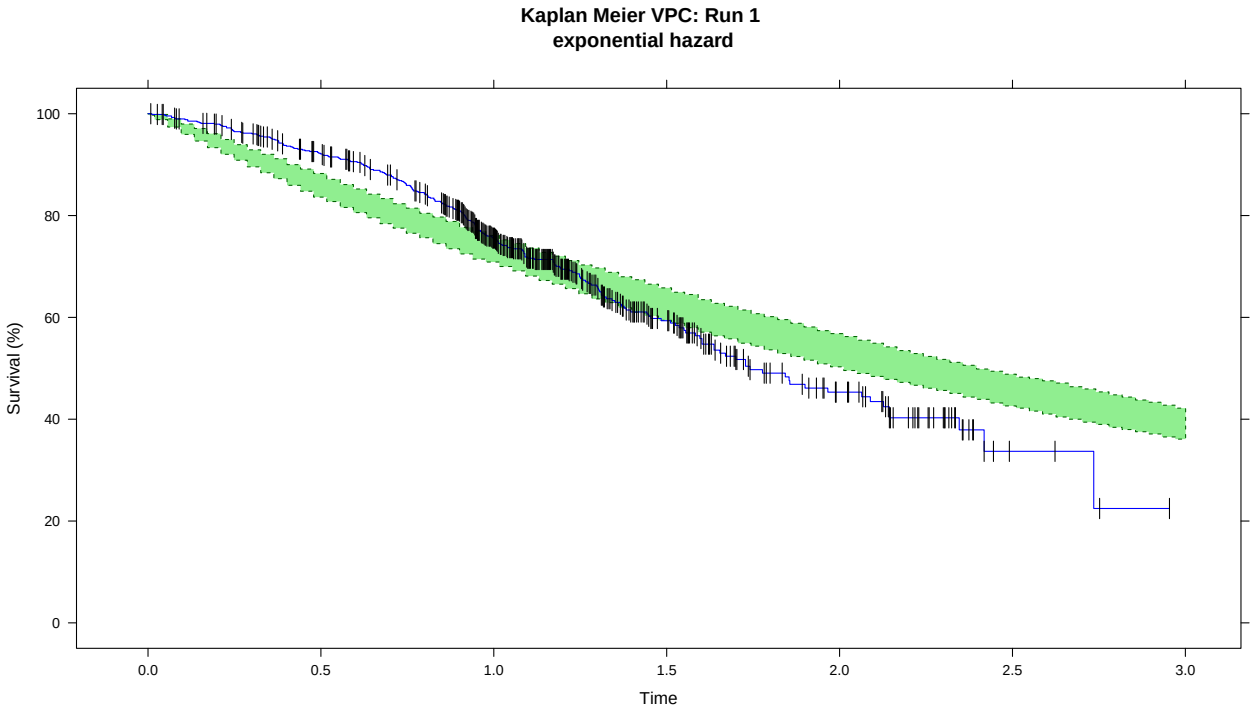


Figure 2: Simulation-based diagnostic: Kaplan Meier plot

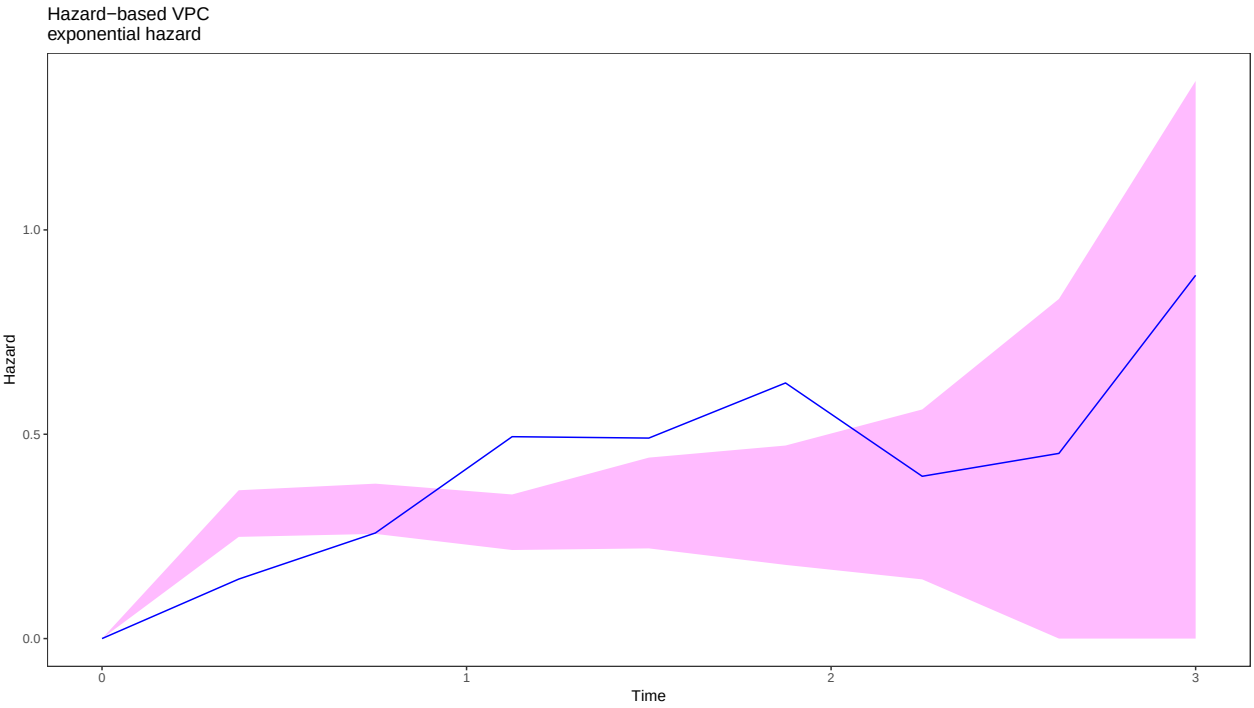


Figure 3: Simulation-based diagnostic: Hazard based VPC

4.2 Run 2: Gompertz hazard

```
##======================================= Run notes  =======================================##
# Rationale:   Test models with increasing complexity
# Question:    Will a Gompertz hazard describe this data?
# Based on:    NA
# Description: h0(t) = lambda * exp(delta*t)
##-------------------------------------------------------------------------------------------##
show.mod(2, nm.dir) # print model
```

```
## ;; 1. Based on: 1
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Gompertz hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-----------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
##
```

```
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  DELTA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Gompertz hazard h0(t) = lambda * exp(delta*t)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = LAMBDA * EXP(DELTA*(T+DEL))
##
## DADT(1) = BASE
##
## ;;================================= MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
```

```
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX= LAMBDA * EXP(DELTA*(TIME+DELX))
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.316) ; lambda
## (0.2)    ;delta
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_2
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
```

```
##
## ;Sim_end
##
## ;;================================ TABLES ================================
##
## ;Sim_start : add/remove for simulation
## $TABLE      NOPRINT ONEHEADER FILE=mytab2 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## ;Sim_end
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab2 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab2 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.2.0.3 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run2/run2
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:08"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   39"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.22"
## [19] ""
## [20] "Objective function value: 991.7985"
## [21] ""
## [22] "Condition number: 8.54"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA              OMEGA      SIGMA    "
## [28] "lambda  0.1707  (0.1059)                        "
## [29] " delta  0.7818  (0.1297)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

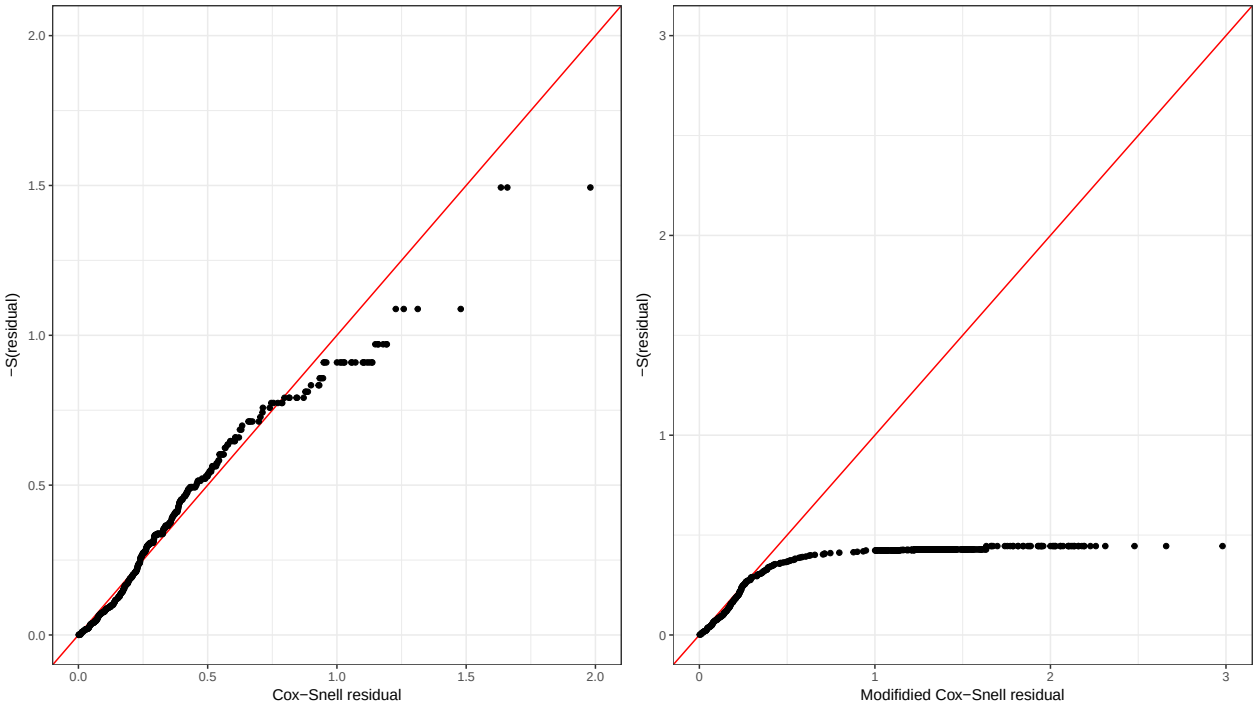


Figure 4: Residual-based diagnostics

4.2.0.4 Diagnostic plots

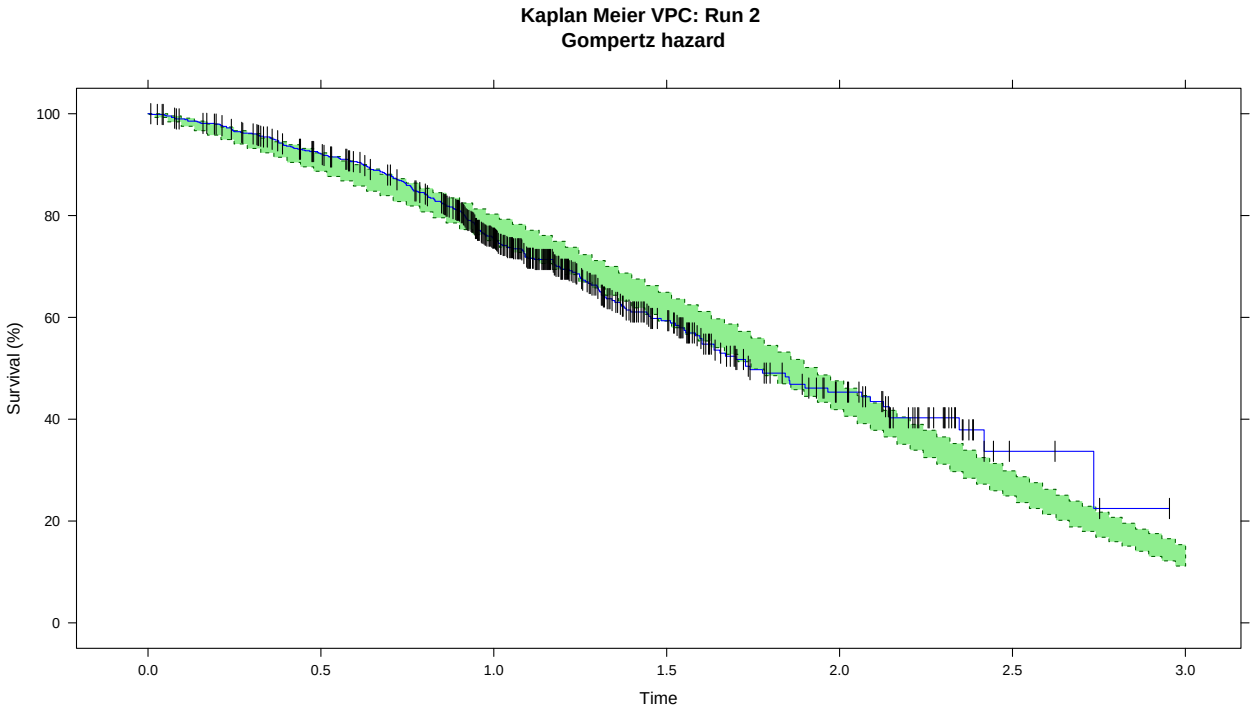


Figure 5: Simulation-based diagnostic

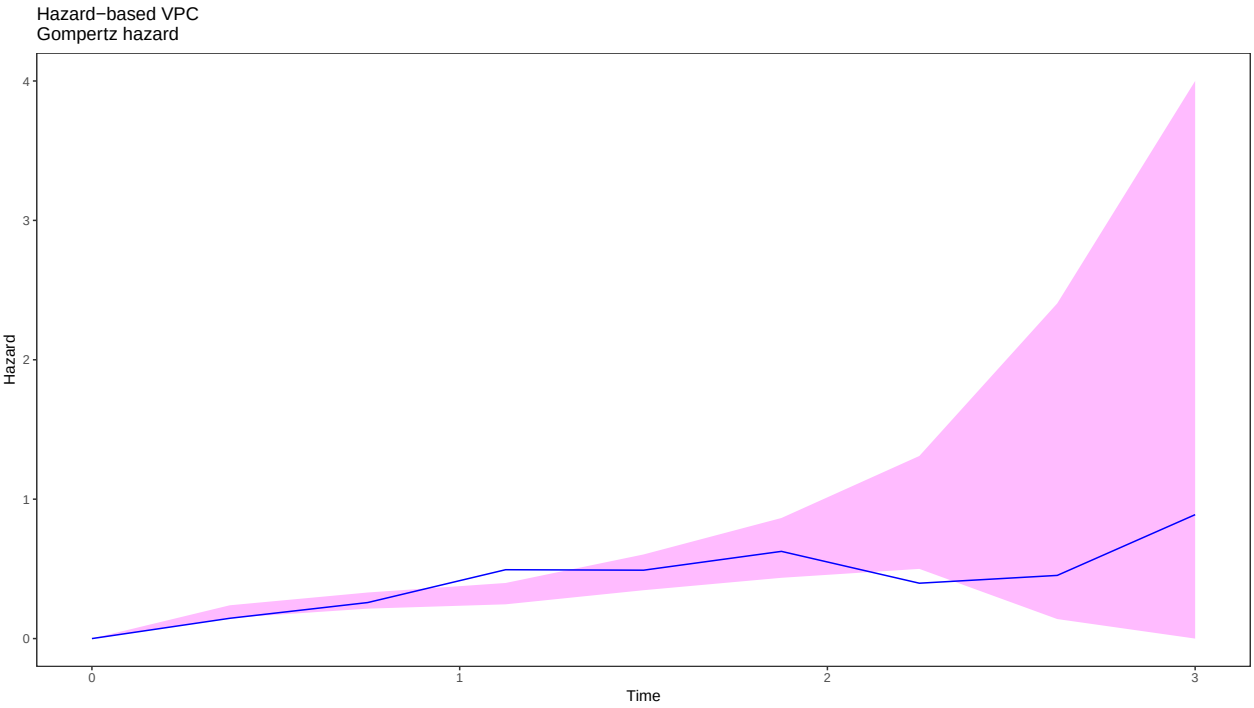


Figure 6: Simulation-based diagnostic: Hazard based VPC

4.3 Run 3 - Weibull hazard

```
##=================================== Run notes  ====================================##
# Rationale:   Test models with increasing complexity
# Question:    Will a Weibull hazard describe this data?
# Based on:    NA
# Description: h0(t) = lambda * exp(delta*t)
##-------------------------------------------------------------------------------------##
show.mod(3, nm.dir) # print model
```

```
## ;; 1. Based on: 2
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
```

```
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
##
## $SUBROUTINE ADVAN=6 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================ RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
```

```
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ========================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ==================================
##
## $THETA  (0,0.171) ; lambda
##  (0, 0.2) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ==============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_3
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
##
## $TABLE      NOPRINT ONEHEADER FILE=mytab3 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab3 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab3 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.3.0.5 Run summary

```
##  [1] "-------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run3/run3
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:11"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   44.39"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.67"
## [19] ""
## [20] "Objective function value: 979.5856"
## [21] ""
## [22] "Condition number: 3.943"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "         THETA               OMEGA      SIGMA    "
## [28] "lambda  0.4379  (0.05053)                        "
## [29] " gamma    1.59  (0.05795)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------"
```

4.3.0.6 Diagnostic plots

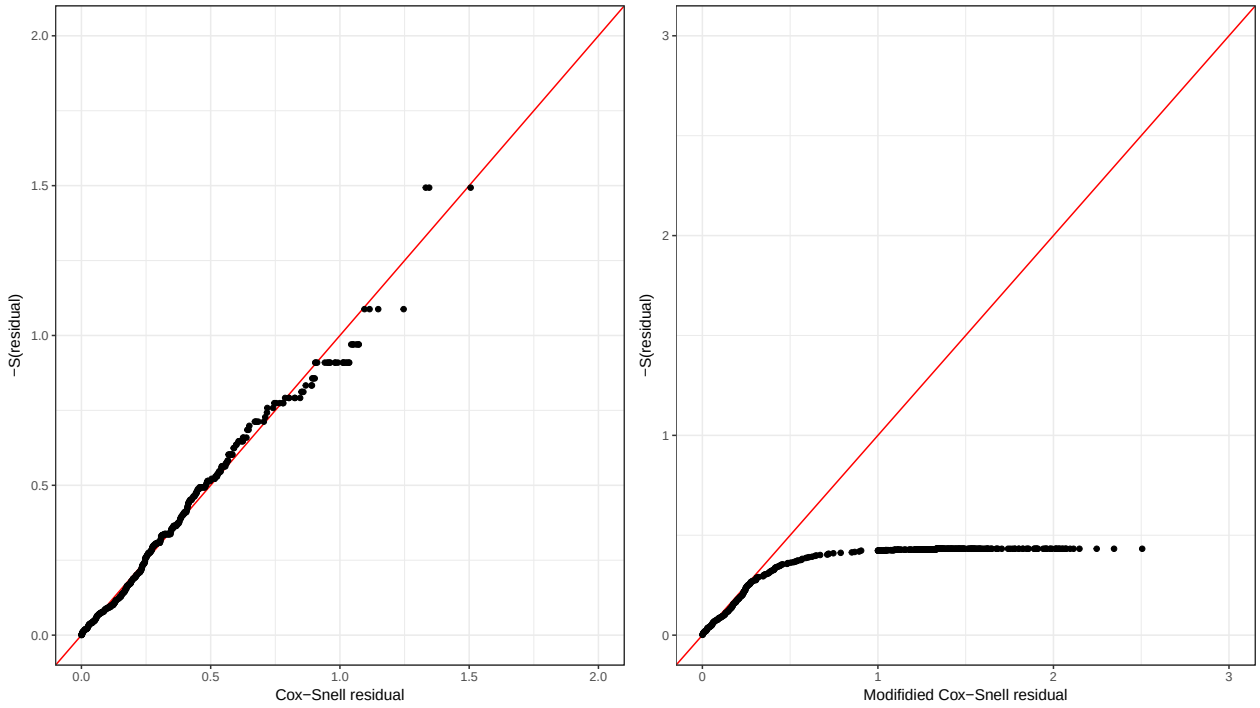


Figure 7: Residual-based diagnostics

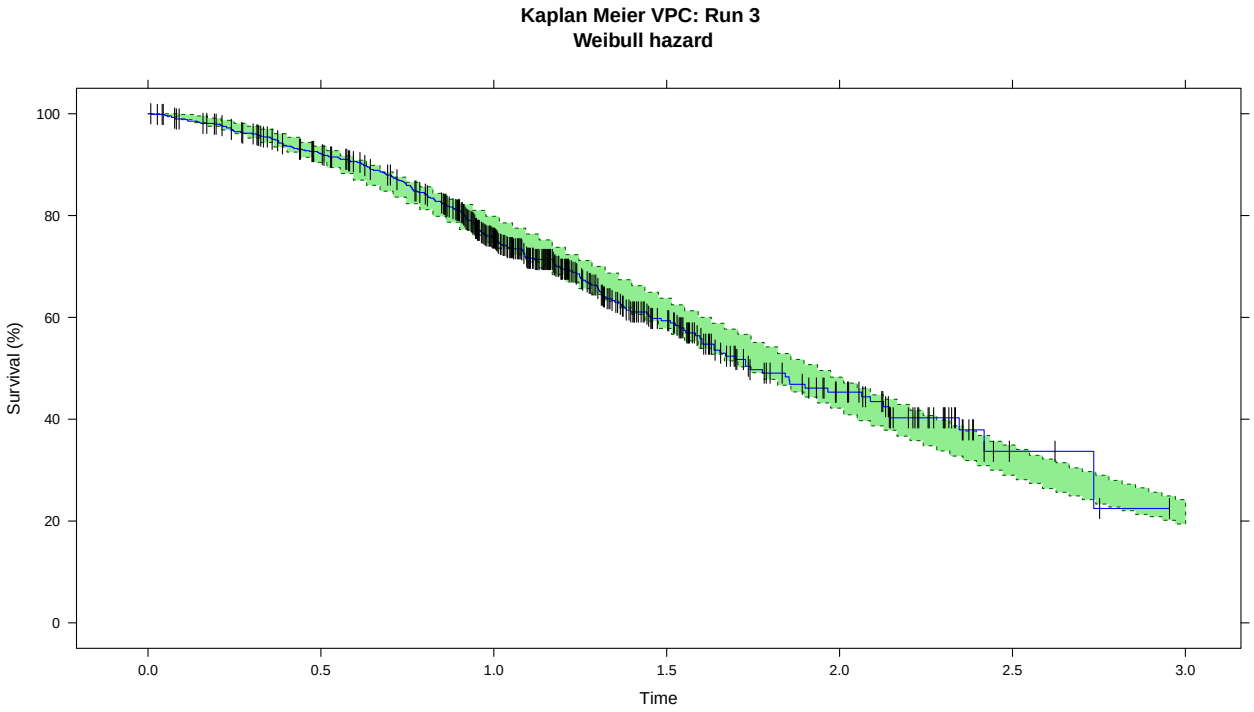


Figure 8: Simulation-based diagnostic

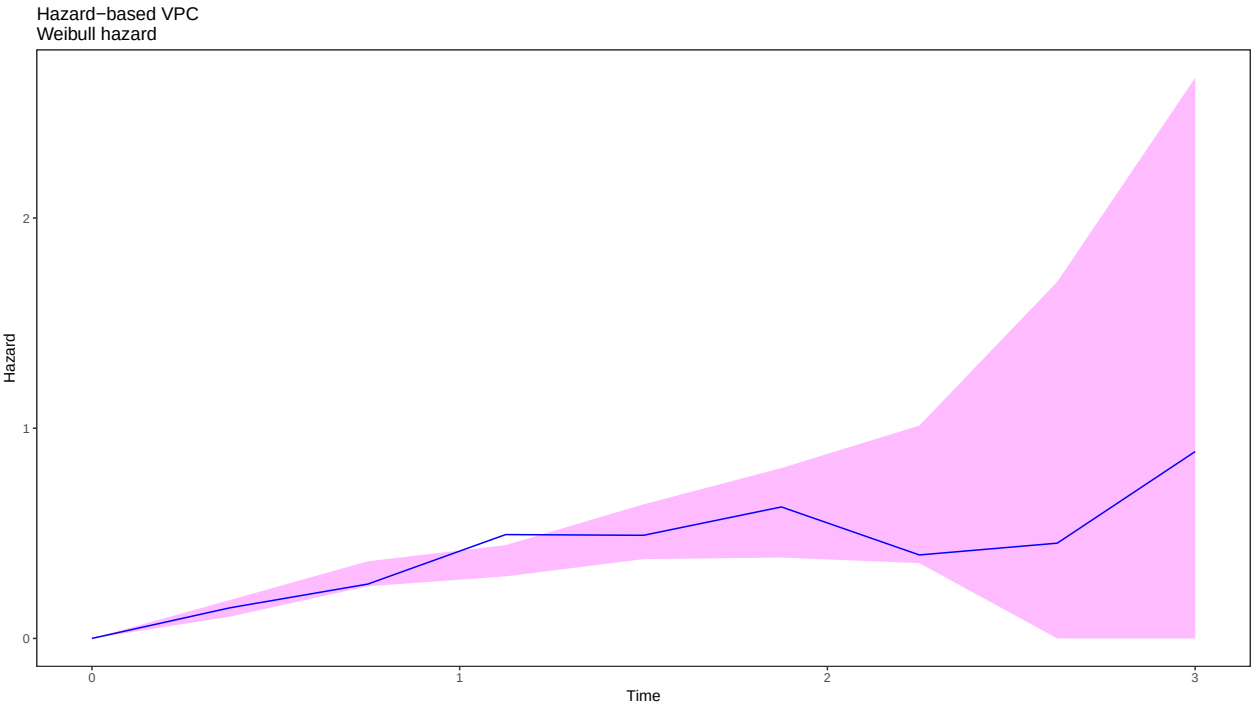


Figure 9: Simulation-based diagnostic: Hazard based VPC

4.4 Run 4 - Log-logistic hazard

```
##===================================== Run notes  ======================================##
# Rationale:   Test models with increasing complexity
# Question:    Will a log logistic hazard describe this data?
# Based on:    NA
# Description: h0(t) = h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
##-------------------------------------------------------------------------------------##
show.mod(4, nm.dir) # print model
```

```
## ;; 1. Based on: 3
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVE
##
## ;-----------------------------------------------------data description
## ; ID, subject identifier
## ; TIME, in years
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
## ; CENS, censored event, 0 = no, 1 = yes
## ; MAXT, last recorded event per patient (either death or censor)
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
## ; GENDER, bianry covariate (0=male,1=female)
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
## ; BLAGE, categorical, age group in years
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
## ; BLALB, continuous, ALB test values at baseline
## ; BLALP, continuous, ALP test values at baseline
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
## ; OSTIM, observed time in days to event or censor time
##
## ;-------------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## ;Sim_start : remove from simulation model
```

```
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================= DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = ga
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE
##
## ;;================================= MODEL FIT ===================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
```

```
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES ====================================
##
## $THETA  (0.2) ; delta
##  (0,1) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_4
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================= TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab4 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTI
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab4 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab4 ID DELTA GAMMA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.4.0.7 Run summary

```
##  [1] "-------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run4/run4
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:04"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   39.55"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.4"
## [19] ""
## [20] "Objective function value: 982.6190"
## [21] ""
## [22] "Condition number: 1.758"
## [23] ""
## [24] "Number of observation records: 690"
## [25] "Number of individuals: 690"
## [26] ""
## [27] "        THETA               OMEGA      SIGMA    "
## [28] "delta  -1.137  (0.07126)                        "
## [29] "gamma   1.831  (0.06489)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "-------------------------------------------------------------------------------"
```

4.4.0.8 Diagnostic plots

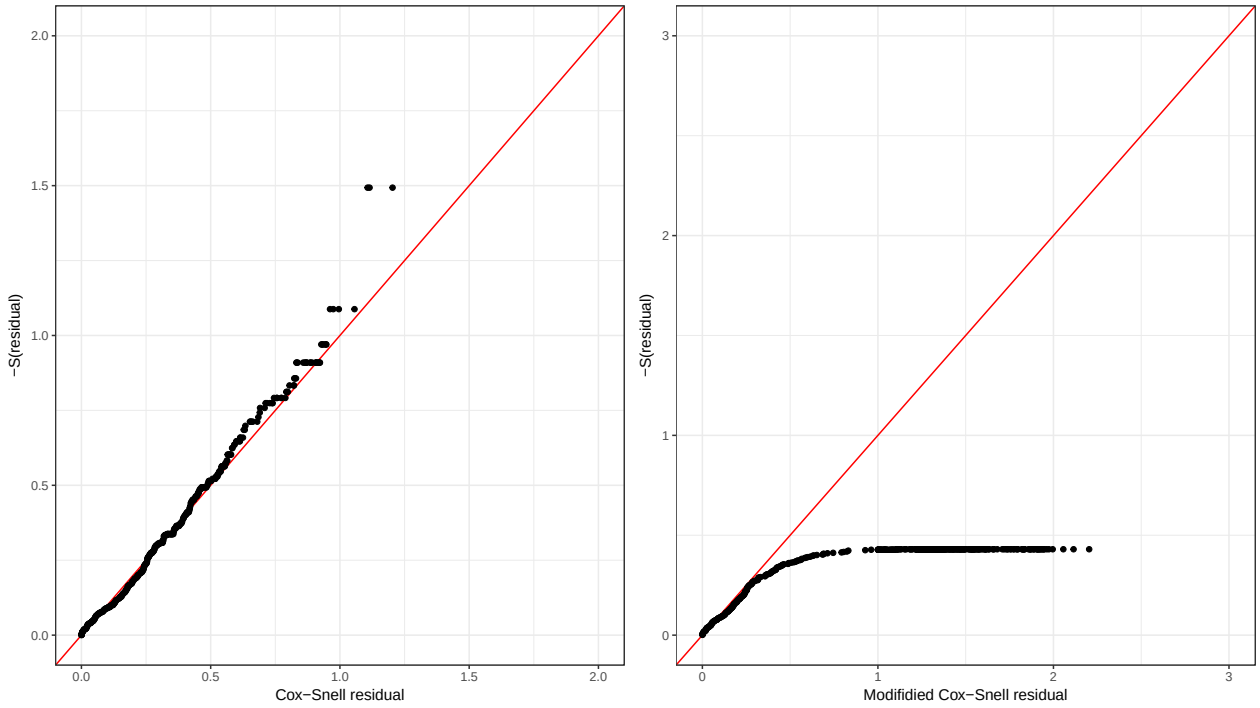


Figure 10: Residual-based diagnostics

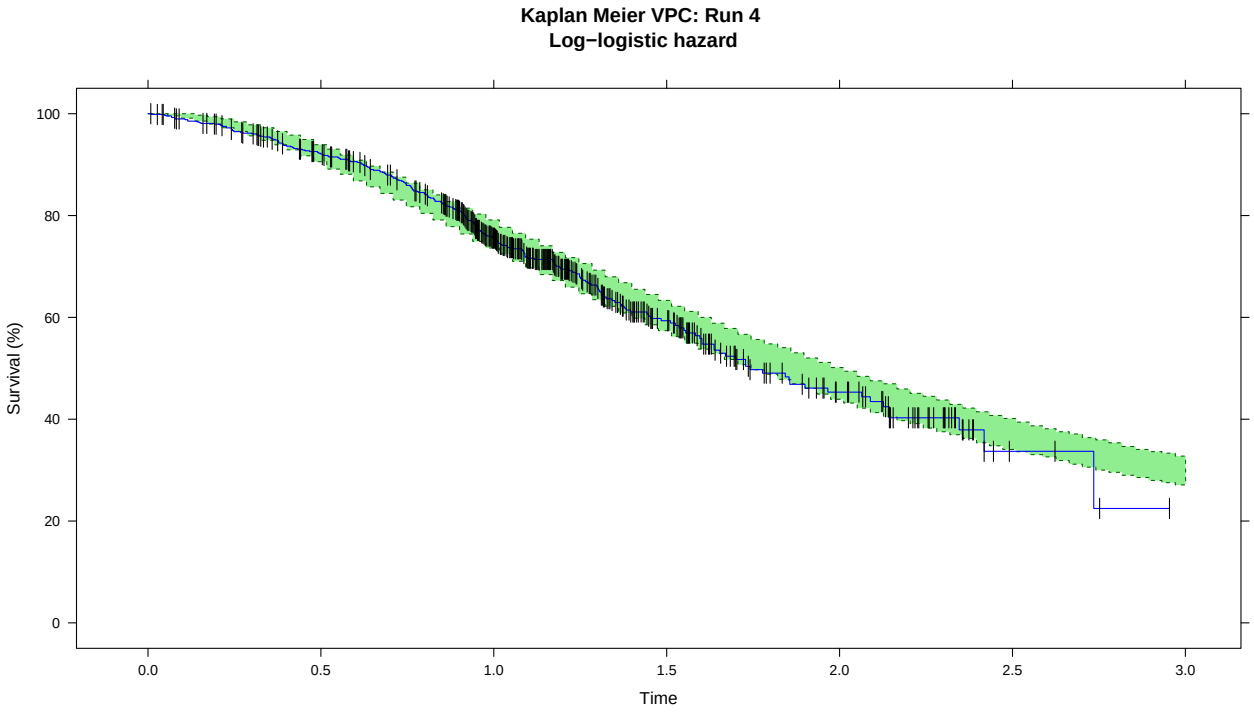


Figure 11: Simulation-based diagnostic

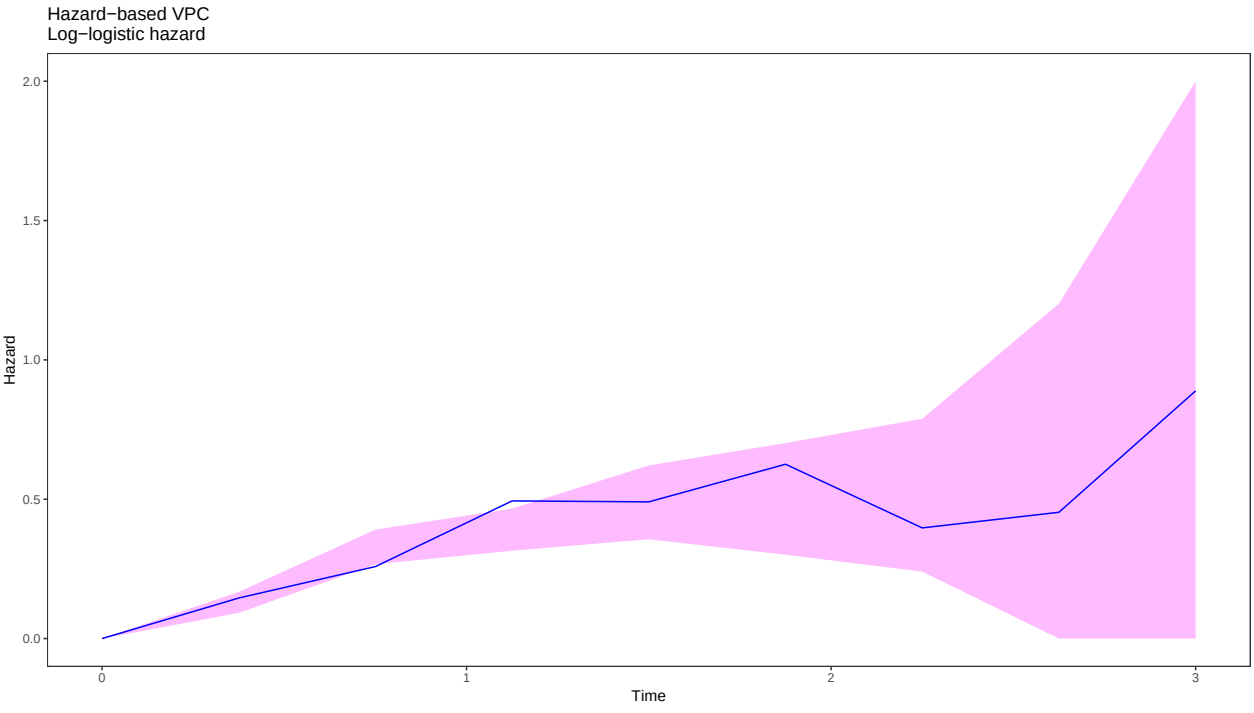


Figure 12: Simulation-based diagnostic: Hazard based VPC

4.5 Run 5 - Weibull Hazard (ignore patients missing LDH data)

```
##===================================== Run notes  ======================================##
# Rationale:   Model data for subjects with baseline LDH data
# Question:    Will a Weibull hazard describe this data?
# Based on:    3
# Description: h0(t) = lambda * exp(delta*t)
##-------------------------------------------------------------------------------------##
# next.mod(3,5,nm.dir)
show.mod(5, nm.dir) # print model
```

```
## ;; 1. Based on: 3
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    Weibull hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-------------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
```

```
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=6
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  LAMBDA = THETA(1) * EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================ DIFFERENTIAL EQUATIONS ================================
## ; Typical Value Weibull hazard h0(t) = lambda*gamma*t^(gamma-1)
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = (LAMBDA*GAMMA)*(LAMBDA*(T+DEL))**(GAMMA-1)
##
## DADT(1) = BASE
##
## ;;================================ MODEL FIT ================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-------------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
## ENDIF
##
```

```
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=(LAMBDA*GAMMA)*(LAMBDA*(TIME+DELX))**(GAMMA-1)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  (0,0.438) ; lambda
##  (0,1.59) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
##             NSIG=3 MSFO=msfb_5
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
```

```
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab5 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab5 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab5 ID LAMBDA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.5.0.9 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run5/run5
##  [4] ""
##  [5] "Successful minimization                                          [    OK   ]   "
##  [6] "No rounding errors                                               [    OK   ]   "
##  [7] "No zero gradients                                                [    OK   ]   "
##  [8] "No final zero gradients                                          [    OK   ]   "
##  [9] "Hessian not reset                                                [    OK   ]   "
## [10] "No parameter near boundary                                       [    OK   ]   "
## [11] "Covariance step                                                  [    OK   ]   "
## [12] ""
## [13] "Condition number                                                 [    OK   ]   "
## [14] "Correlations                                                     [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:04"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   34.56"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   0.64"
## [19] ""
## [20] "Objective function value: 940.9514"
## [21] ""
## [22] "Condition number: 4.01"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "         THETA              OMEGA      SIGMA    "
## [28] "lambda  0.4347  (0.0513)                        "
## [29] " gamma    1.61  (0.0595)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

- Similar final estimates for lambda (run3: 0.4379) and gamma (run3: 1.59)

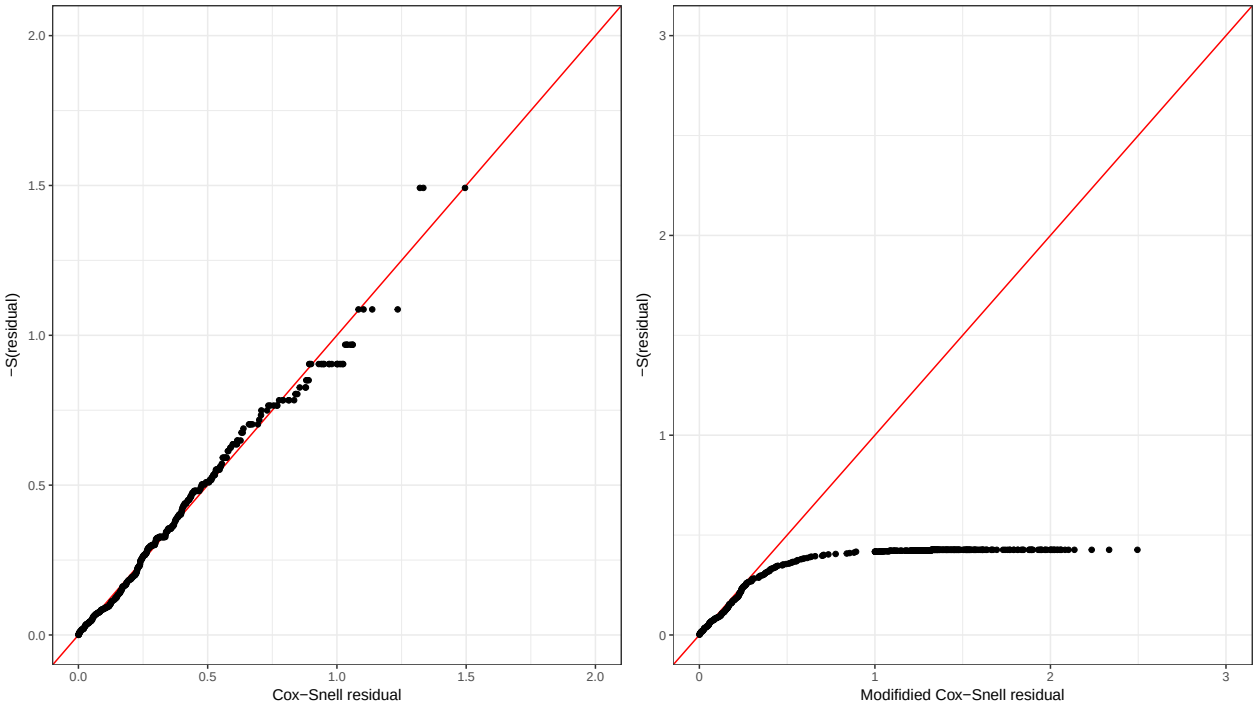


Figure 13: Residual-based diagnostics

4.5.0.10 Diagnostic plots

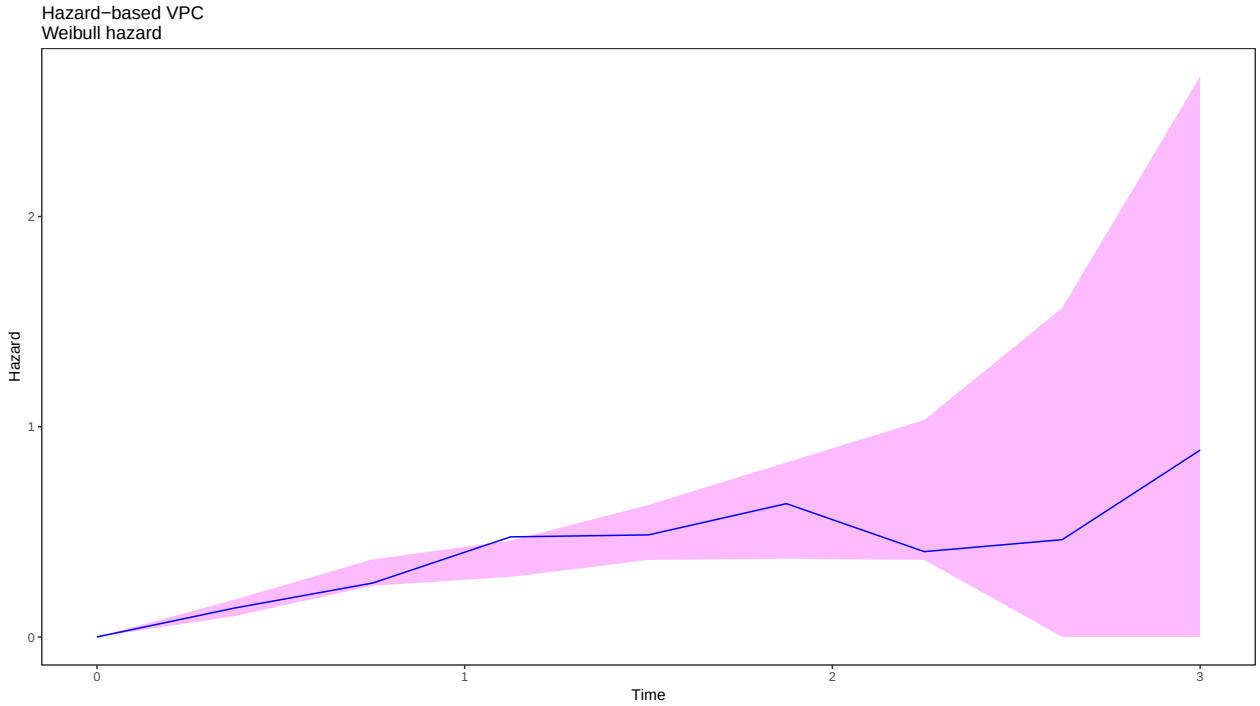
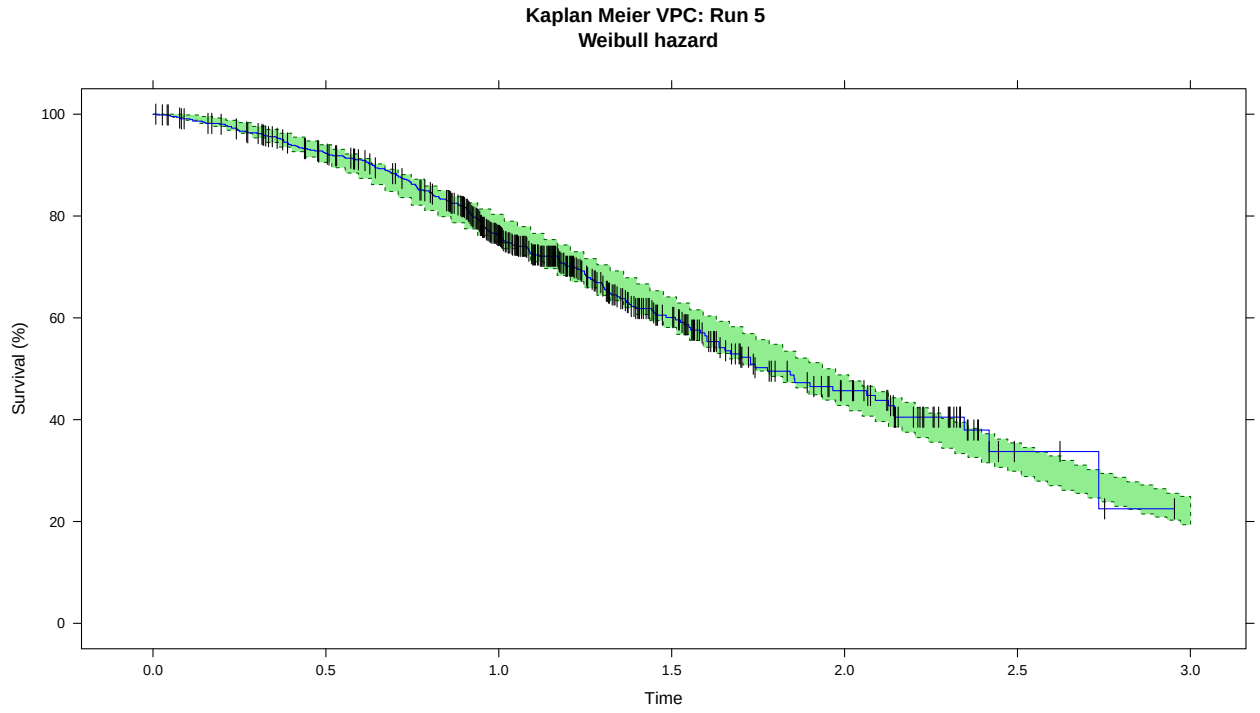


Figure 14: Simulation-based diagnostic: Hazard based VPC



4.6 Run 6 - Log-logistic hazard (ignore patients missing LDH data)

```
##------------------------------------ Run notes  ------------------------------------##
# Rationale:   Test models with increasing complexity
# Question:    Will a log logistic hazard describe this data?
# Based on:    NA
# Description: h0(t) = h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k)
##------------------------------------------------------------------------------------##
# next.mod(4,6,nm.dir)
show.mod(6, nm.dir) # print model
```

```
## ;; 1. Based on: 4
## ;; 2. Description:
## ;;    TTE model
## ;; 3. Label:
## ;;    log-logistic hazard
## ;; 4. Structural model:
## ;;    Hazard compartment
## ;; 5. Covariate model:
## ;; 6. Interindividual variability:
## ;; 7. Interoccasion variability:
## ;; 8. Residual variability:
## ;; 9. Estimation:
## ;;    LAPLACE
## ;Sim_start : add to simulation model
## ;$SIZES NO=79 LIM6=500
## ;Sim_end
## ; notes $SIZES
## ; NO= MAX NO. OF OBSERVATION RECORDS / INDIVIDUAL RECORD
## ; LIM6 = size of buffer 6 - temporary disk file
## $PROBLEM    Base TTE model - Project DataSphere # 78
## $INPUT      ID TIME STIME EVID DV CENS MAXT NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## ;-------------------------------------------------------data description
##
## ; ID, subject identifier
##
## ; TIME, in years
##
## ; STIME, flag which indicates if time was observed (STIME=0) or time is simulated (STIME=2)
##
## ; EVID, EVID=3 reset the system at time zero/each new ID; EVID=0 indicates an observation
##
## ; DV, DV = 0 (no event observed = right censored (TRUE), DV = 1, an event occured at time = TIME
##
## ; CENS, censored event, 0 = no, 1 = yes
##
## ; MAXT, last recorded event per patient (either death or censor)
##
## ; NOLDH, missing LDH flag 0 = no, 1 = yes
##
## ; GENDER, bianry covariate (0=male,1=female)
##
## ; BLLDH, binary, 0 = within range, 1 = LDH > 1.5  upper limit of normal
```

```
##
## ; BLAGE, categorical, age group in years
##
## ; BLWHOSTAT, binary, WHO status 0 = normal, 1 = WHO level > 0
##
## ; BLALB, continuous, ALB test values at baseline
##
## ; BLALP, continuous, ALP test values at baseline
##
## ; BLWHOLEVEL, categorical, WHO status 0 - 4
##
## ; OSTIM, observed time in days to event or censor time
##
## ;-----------------------------------------------------
## $DATA      ../../DATA/ProjectDataSphere78_tte_V2.csv IGNORE=@
##
## IGNORE(NOLDH.EQ.1) ; 24 patients missing LDH data
##
## ;Sim_start : remove from simulation model
## IGNORE=(STIME.EQ.2) ; simulated time,ignored for estimation
## ;IGNORE=(STIME.EQ.0) ;; observed time, ignore for simulation
##
## ;Sim_end
## $SUBROUTINE ADVAN=6 TOL=9
## $MODEL      COMP=(HAZARD)
## ;;============================ PARAMETER DEFINITIONS ============================
## $PK
##  DELTA = THETA(1)* EXP(ETA(1))
##  GAMMA = THETA(2)
##
## ;;================================= DIFFERENTIAL EQUATIONS ==================================
## ; Typical Value Log-logistic hazard,  h0(t) = exp(delta) kt^(k-1) / (1+ exp(delta)*t^k), where k = g
##
## $DES
## DEL = 1E-6  ; to keep from taking 0**power
##
## BASE = EXP(DELTA)*GAMMA*(T+DEL)**(GAMMA-1) / (1 + EXP(DELTA)*(T+DEL)**GAMMA)
##
## DADT(1) = BASE
##
## ;;================================= MODEL FIT ===================================
##
## $ERROR
## IF(NEWIND.NE.2)  OLDCHZ=0    ;reset the cumulative hazard
##
## ;Sim_start
##    CHZ = A(1)                    ; hazard up to the event
## ;  CHZ = A(1)- OLDCHZ            ;cumulative hazard from previous time point in data set
## ;  OLDCHZ = A(1)                 ;rename old cumulative hazard
## ;Sim_end
## ;-----------------------------
## IF(DV.EQ.0) THEN             ; censored
##  SUR = EXP(-CHZ)
##  Y = SUR
```

```
## ENDIF
##
## ;------------------------------
## IF(DV.EQ.1) THEN             ; exact time
##  DELX = 1E-6
##  BASEX=EXP(DELTA)*GAMMA*(TIME+DELX)**(GAMMA-1) / (1 + EXP(DELTA)*(TIME+DELX)**GAMMA)
##  HAZNOW= BASEX
##  SUR = EXP(-CHZ)
##  Y = SUR*HAZNOW
## ENDIF
##
## ;;================================= RESIDUALS CALCULATIONS ================================
##
## ;where events DV = 1 and censoring DV = 0
##
## ;Martingale residual: rM = (1-CENSOR) + log(SURV)
## MARTRES = (DV) - CHZ
##
## ;deviance residual = sign(rM) * SQRT(-2*(rM + (1-CENS)*log(-log(SURV))))
##  SIGNRM = 1
##  IF (MARTRES < 0) SIGNRM = -1
##
## IF (MDV.EQ.1) THEN
##   DEVRES = 0
## ELSE
##   DEVRES = SIGNRM * SQRT(-2 * (MARTRES + (DV)*LOG(CHZ)))
## ENDIF
##
## IWRES = 1
##
##
## ;;================================= SIMULATION ============================================
## ;Simulation for model evaluation
##
## IF (ICALL.EQ.4) THEN
## CALL RANDOM (2,R)
##    DV=0
##    RTTE = 0
## IF(TIME.GT.MAXT) RTTE=1
## IF(R.GE.SUR) THEN
##    DV=1
##    RTTE = 1
## ENDIF
## ENDIF
##
## ;;================================= INITIAL ESTIMATES =====================================
##
## $THETA  -1.14 ; delta
##  (0,1.83) ; gamma
## $OMEGA  0  FIX  ; place holder
## ;;============================== ESTIMATION METHOD ============================
## ;Sim_start : add/remove for simulation
## $COVARIANCE PRINT=E
## $ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1 SIGL=9
```

```
##             NSIG=3 MSFO=msfb_6
## ;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
##
## ;Sim_end
##
## ;;================================ TABLES ================================
## $TABLE      NOPRINT ONEHEADER FILE=mytab6 ID TIME DV EVID MDV PRED CHZ
##             SUR HAZNOW MARTRES DEVRES NOLDH GENDER BLLDH BLAGE
##             BLWHOSTAT BLALB BLALP BLWHOLEVEL OSTIM
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=sdtab6 ID TIME SUR EVID
## $TABLE      NOAPPEND ONEHEADER NOPRINT FILE=patab6 ID DELTA GAMMA
##             ETAS(1:LAST)
## ;$TABLE NOAPPEND ONEHEADER NOPRINT FILE=catab
##
## ;ID NOLDH GENDER BLLDH BLAGE BLWHOSTAT BLALB BLALP BLWHOLEVEL

## NULL
```

4.6.0.11 Run summary

```
##  [1] "------------------------------------------------------------------------"
##  [2] ""
##  [3] "/pmx_bip/PMx_Playground/gbenitez/OTHER_PROJECTS/PostDoc_project_ISoP/2018_TTE/NONMEM/run6/run6
##  [4] ""
##  [5] "Successful minimization                                        [    OK   ]   "
##  [6] "No rounding errors                                             [    OK   ]   "
##  [7] "No zero gradients                                              [    OK   ]   "
##  [8] "No final zero gradients                                        [    OK   ]   "
##  [9] "Hessian not reset                                              [    OK   ]   "
## [10] "No parameter near boundary                                     [    OK   ]   "
## [11] "Covariance step                                                [    OK   ]   "
## [12] ""
## [13] "Condition number                                               [    OK   ]   "
## [14] "Correlations                                                   [    OK   ]   "
## [15] ""
## [16] "Total run time for model (hours:min:sec):                  0:01:09"
## [17] "Estimation time for subproblem, sum over $EST (seconds):   33.8"
## [18] "Covariance time for subproblem, sum over $EST (seconds):   1.33"
## [19] ""
## [20] "Objective function value: 944.1242"
## [21] ""
## [22] "Condition number: 1.828"
## [23] ""
## [24] "Number of observation records: 666"
## [25] "Number of individuals: 666"
## [26] ""
## [27] "       THETA               OMEGA      SIGMA    "
## [28] "delta  -1.17  (0.07111)                        "
## [29] "gamma  1.851  (0.06659)                        "
## [30] ""
## [31] "The relative standard errors for omega and sigma are reported on the approximate"
## [32] "standard deviation scale (SE/variance estimate)/2."
## [33] "------------------------------------------------------------------------"
```

- Similar final estimate for delta (run4: -1.137) and gamma (run4: 1.831)

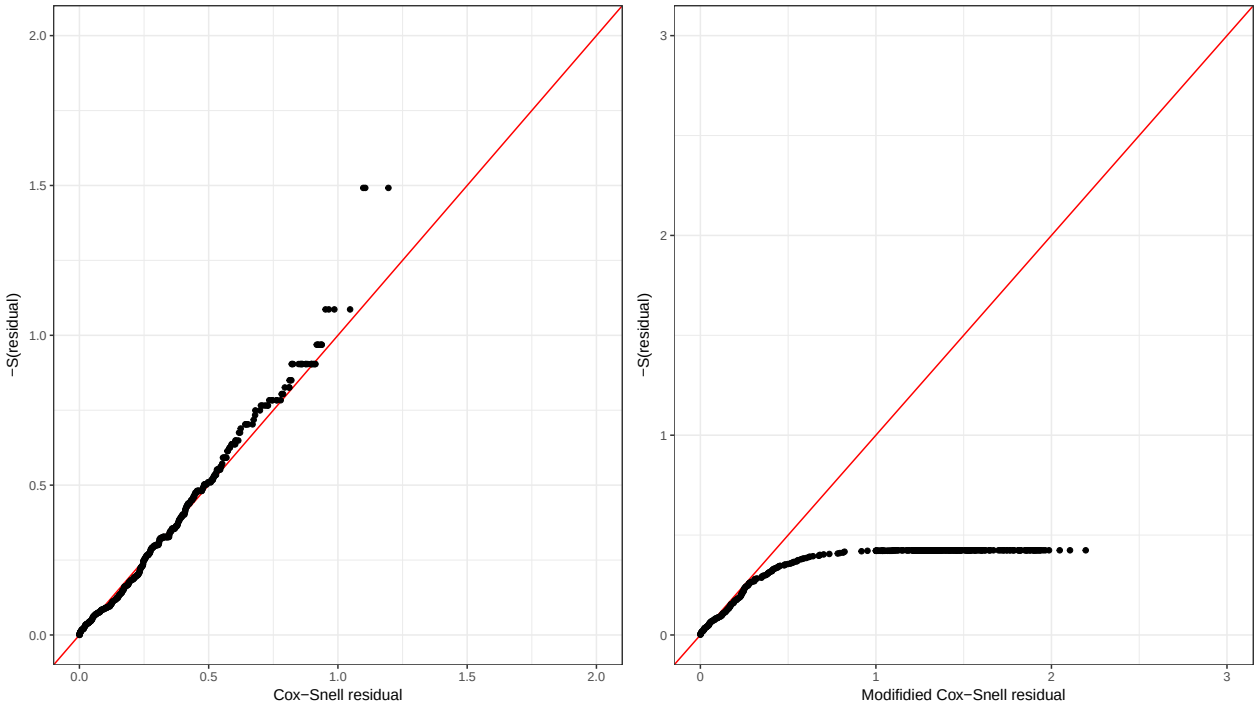


Figure 15: Residual-based diagnostics

4.6.0.12 Diagnostic plots

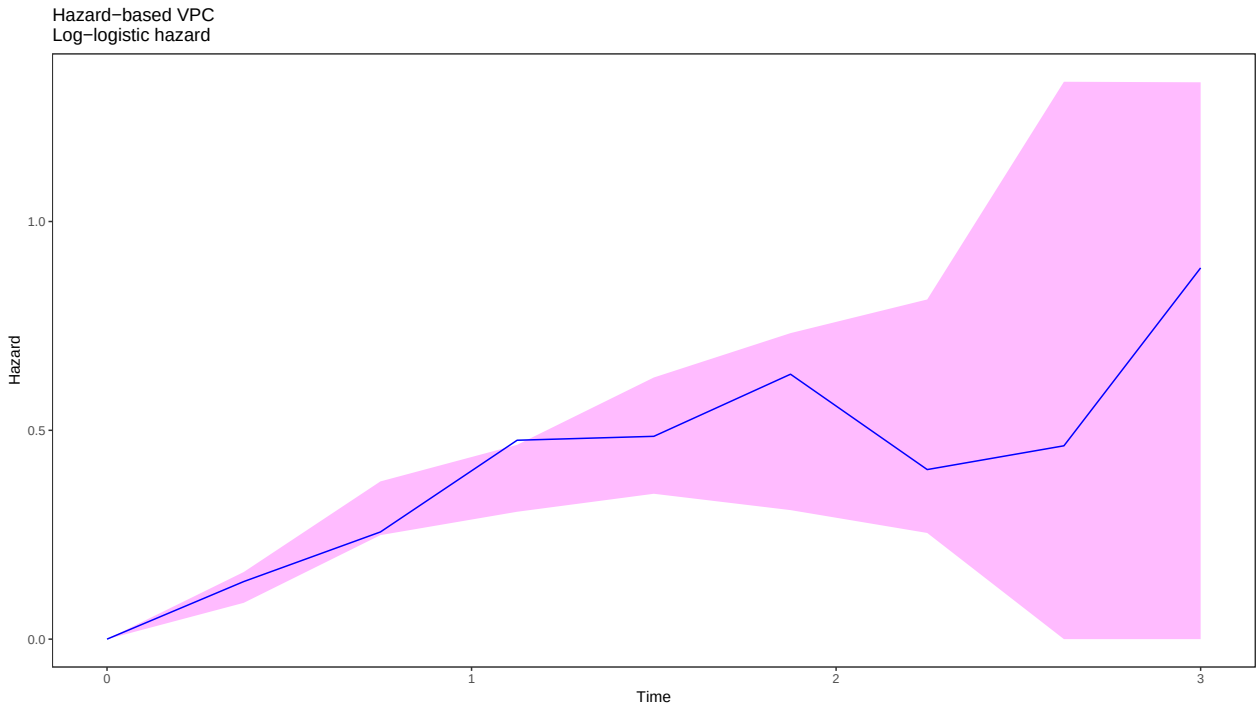
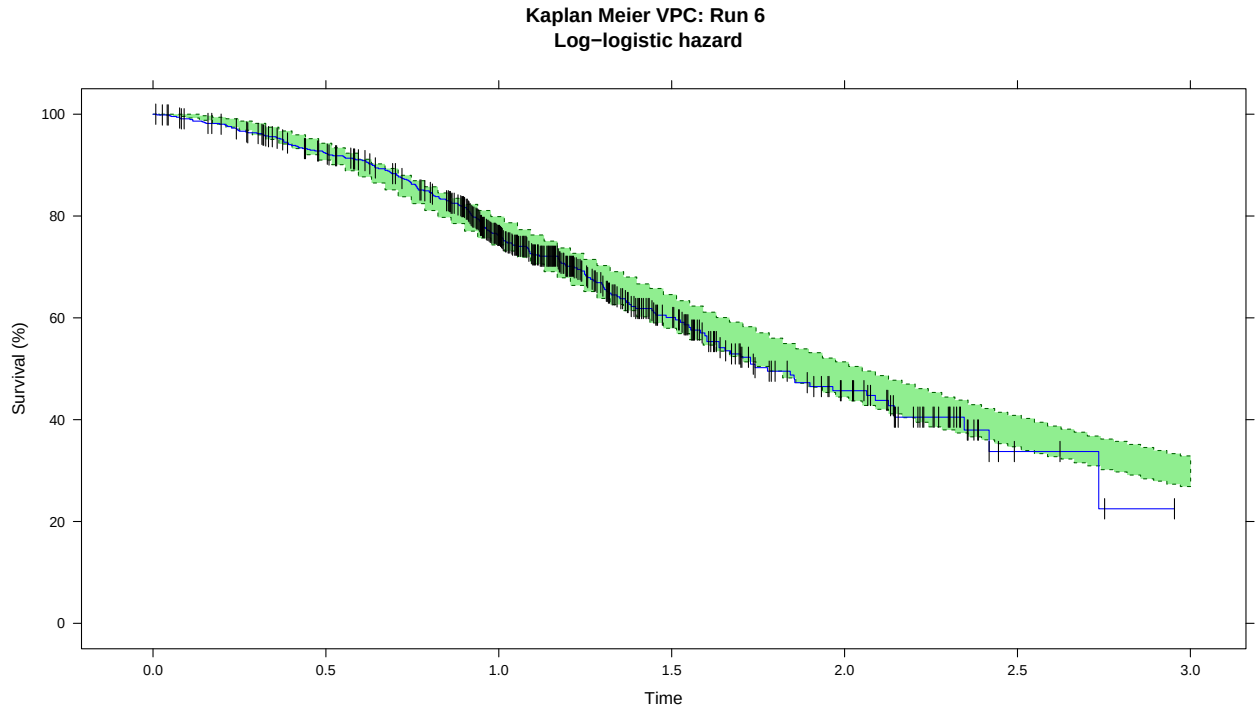


Figure 16: Simulation-based diagnostic: Hazard based VPC



5 Postamble

```
## R version 3.4.3 (2017-11-30)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Red Hat Enterprise Linux Server release 6.5 (Santiago)
##
## Matrix products: default
## BLAS: /apps/phaser/prod/R-3.4.3/lib64/R/lib/libRblas.so
## LAPACK: /apps/phaser/prod/R-3.4.3/lib64/R/lib/libRlapack.so
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
##  [3] LC_TIME=en_US.UTF-8        LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
##  [9] LC_ADDRESS=C               LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
##
## attached base packages:
## [1] grid      stats     graphics  grDevices utils     datasets  methods
## [8] base
##
## other attached packages:
##  [1] xpose_0.4.1      xpose4_4.6.0     dplyr_0.7.4      xtable_1.8-2
##  [5] GGally_1.3.2     gridExtra_2.3    ggplot2_2.2.1    metrumrg_5.55
##  [9] MASS_7.3-47      XML_3.98-1.9     lattice_0.20-35  reshape_0.8.7
## [13] stringr_1.2.0    base64enc_0.1-3  rmarkdown_1.8    tidyselect_0.2.3
## [17] knitr_1.18       tidyr_0.7.2
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.14       bindr_0.1          pillar_1.0.1
##  [4] compiler_3.4.3     RColorBrewer_1.1-2 plyr_1.8.4
##  [7] iterators_1.0.9    tools_3.4.3        digest_0.6.13
## [10] evaluate_0.10.1    tibble_1.4.1       gtable_0.2.0
## [13] pkgconfig_2.0.1    rlang_0.1.6        foreach_1.4.4
## [16] yaml_2.1.16        bindrcpp_0.2       rprojroot_1.3-2
## [19] glue_1.2.0         R6_2.2.2           udunits2_0.13
## [22] tweenr_0.1.5       purrr_0.2.4        magrittr_1.5
## [25] units_0.5-1        codetools_0.2-15   splines_3.4.3
## [28] backports_1.1.2    scales_0.5.0       htmltools_0.3.6
## [31] assertthat_0.2.0   ggforce_0.1.1      colorspace_1.3-2
## [34] stringi_1.1.6      lazyeval_0.2.1     munsell_0.4.3
## [37] gam_1.14-4
```