

Example Multistate Model Code

```
;; 1. Based on: 500
;; 2. Description: Final multistate model with dose introduced on all
transitions
;; x1. Author: Uppsala

$SIZES      PD=-500
$PROBLEM    TRAP 2L_NSCLC multistate model
$INPUT      C DOMAIN=DROP SEQ USUBJID SUBJID ID SITEID STDY XDATE=DROP
            CTIME=DROP TIME TAPD TAFT WEEKI DAY CYCLE TIMEN TAPDN
            EPOCHN AMT RATE DV DV2 SIMFL SIMFL2 VISITT FLAG EOTFL EVID
            MDV CMT BLOQ FLAGIMP FLLATS NFLATS TSSRC COHORT TTYPE
            TTYPE2 TRT01AN AGE SEX RACE RACE2 WT EGFR ALB CRP LDH NLR
            INR PLAT WBC TB1 TB2 SMOKING PDL1 TGFB1 ECOG METAS METASL
            MSI HISTOL NNTL CMCOR PMBIO PMAB TMB
$DATA      ../.../Data_management/Data/ms-spec16-1.csv IGNORE=@
            IGNORE=(SIMFL2.EQ.1) IGNORE=(CMT.EQ.7) WIDE
$SUBROUTINE ADVAN13 TOL=6
$MODEL      NCOMP=6

$PK
IF(TRT01AN.EQ.10) CDOSE = 1
IF(TRT01AN.EQ.11) CDOSE = 0

IF(METAS.EQ.1) METASX=0
IF(METAS.EQ.0) METASX=1

BSV        = ETA(1) ; place holder
WEEK=TIME/24/7

IF(NEWIND.NE.2) DV1 = 1
IF(NEWIND.NE.2) XDV = 1
IF(NEWIND.NE.2) PPDV = 1
SPDV = PPDV

IF(NEWIND.NE.2) FLDV3 = 0

; Sim_start: add for simulation
IF(DV.GE.1) DV1 = DV
IF(DV.GE.1) XDV = DV
;Sim_end

;----- GompertzMakeham -----
ALPH = 1.8645e-04
BETA =0.11425
CVALUE =0.0007
GAMA =0.1
ASMFL=0

X1 = EXP(BETA*AGE-30)
Y1 = (ALPH*GAMA)/BETA
GGM = CVALUE + ((ALPH*X1)/(1+(Y1*(X1-1))))

GMTY = 1/GGM
```

```

;----- Mean transit times -----

MTT12  = THETA(1)*24*7      ;From stable to decrease
MTT13  = THETA(2)*24*7      ;From stable to progression
MTT14  = THETA(3)*24*7      ;From stable to unknown
MTT16  = 52.1429*GMTY*24*7  ;From stable to Death

MTT23  = THETA(4)*24*7      ;From decrease to progression
MTT24  = THETA(5)*24*7      ;From decrease to unknown
MTT26  = THETA(6)*24*7      ;From decrease to Death

MTT36  = THETA(7)*24*7      ;From progression to Death

MTT46  = THETA(8)*24*7      ;From unknown to Death

MTT15  = THETA(9)*24*7      ;From stable to dropout
MTT35  = THETA(9)*24*7      ;From progression to dropout
MTT45  = THETA(9)*24*7      ;From unknown to dropout
HZA13  = THETA(10) *EXP(THETA(22)*CDOSE)
HZA36  = THETA(11) *EXP(THETA(23)*CDOSE)

;----- Initialize location probabilities -----
IF(NEWIND.NE.2) THEN
BIO1   = 1
BIO2   = 0
BIO3   = 0
BIO4   = 0
BIO5   = 0
BIO6   = 0
ENDIF

;----- "Bioavailability" factors -----
F1      = BIO1
F2      = BIO2
F3      = BIO3
F4      = BIO4
F5      = BIO5
F6      = BIO6

;-----
;--Differential equations for the probability of each score
HZL13=1/MTT13
HZL36=1/MTT36

$DES
DEL = 1E-16
WB13 = HZL13*HZA13*(HZL13*(T+DEL))**(HZA13-1)
WB36 = HZL36*HZA36*(HZL36*(T+DEL))**(HZA36-1)

K12    = 1/(MTT12) *EXP(THETA(13)*CDOSE)
K13    = WB13*EXP(METASX*THETA(12)) *EXP(THETA(14)*CDOSE)
K14    = 1/(MTT14) *EXP(THETA(15)*CDOSE)
K16    = 1/(MTT16)

K23    = 1/(MTT23) *EXP(THETA(16)*CDOSE)
K24    = 1/(MTT24) *EXP(THETA(17)*CDOSE)

```

```

K26    = 1/(MTT26) *EXP(THETA(18)*CDOSE)

K36    = WB36  *EXP(THETA(19)*CDOSE)
K46    = 1/(MTT46) *EXP(THETA(20)*CDOSE)

K15    = 1/(MTT15) *EXP(THETA(21)*CDOSE)
K25    = 0 ;no observed transition from response to dropout
K35    = 1/(MTT35) *EXP(THETA(21)*CDOSE)
K45    = 1/(MTT45) *EXP(THETA(21)*CDOSE)

DADT(1) = - A(1) * (K12 + K13 + K14 + K15 + K16)
; STABLE
DADT(2) =  A(1) * K12 - A(2) * K26 - A(2) * K25 - A(2) * K24 - A(2) *
K23 ; DECREASE
DADT(3) =  A(1) * K13 + A(2) * K23 - A(3) * K35 - A(3) * K36
; PROGRESSION
DADT(4) =  A(1) * K14 + A(2) * K24 - A(4) * K45 - A(4) * K46
; UNKNOWN
DADT(5) =  A(1) * K15 + A(2) * K25 + A(3) * K35 + A(4) * K45
; DROPOUT
DADT(6) =  A(1) * K16 + A(2) * K26 + A(3) * K36 + A(4) * K46
; DEATH

;-----

$ERROR
P_1 = A(1) ; Probability of observing STABLE
P_2 = A(2) ; Probability of observing DECREASE
P_3 = A(3) ; Probability of observing PROGRESSION
P_4 = A(4) ; Probability of observing UNKNOWN
P_5 = A(5) ; Probability of observing DROPOUT
P_6 = A(6) ; Probability of observing DEATH
;-----

; -----Cumulative probabilities -----

CUP1 = A(1) ; 1
CUP2 = A(1) + A(2) ; 1 + 2
CUP3 = A(1) + A(2) + A(3) ; 1 + 2 + 3
CUP4 = A(1) + A(2) + A(3) + A(4) ; ; 1 + 2 + 3 + 6
CUP5 = A(1) + A(2) + A(3) + A(4) + A(5); ; 1 + 2 + 3 + 6
CUP6 = A(1) + A(2) + A(3) + A(4) + A(5) + A(6) ; ; 1 + 2 + 3 + 6

;---- Model prediction -----
IF(DV.EQ.1.AND.EVID.EQ.0) Y = P_1
IF(DV.EQ.2.AND.EVID.EQ.0) Y = P_2
IF(DV.EQ.3.AND.EVID.EQ.0) Y = P_3
IF(DV.EQ.4.AND.EVID.EQ.0) Y = P_4
IF(DV.EQ.5.AND.EVID.EQ.0) Y = P_5
IF(DV.EQ.6.AND.EVID.EQ.0) Y = P_6

TOT = P_1 + P_2 + P_3 + P_4 + P_5 + P_6

```

```

;-----
; Sim_start: remove for simulation
;   IF(ICALL.EQ.4) THEN
;
;       IF (EVID.EQ.0) THEN
;       CALL RANDOM (2,R)
;       USUR=R
;       ENDIF
;
;       DV1=SPDV
;       IF(VISITT.EQ.1.AND.USUR.LE.CUP1.AND.EVID.EQ.0) DV1=1
;       IF(VISITT.EQ.1.AND.USUR.GT.CUP1.AND.USUR.LE.CUP2.AND.EVID.EQ.0) DV1=2
;       IF(VISITT.EQ.1.AND.USUR.GT.CUP2.AND.USUR.LE.CUP3.AND.EVID.EQ.0) DV1=3
;       IF(VISITT.EQ.1.AND.USUR.GT.CUP3.AND.USUR.LE.CUP4.AND.EVID.EQ.0) DV1=4
;       IF(VISITT.EQ.1.AND.USUR.GT.CUP4.AND.USUR.LE.CUP5.AND.EVID.EQ.0) DV1=5
;       IF(VISITT.EQ.1.AND.USUR.GT.CUP5.AND.EVID.EQ.0) DV1=6
;
;       XDV  = DV1
;       IF(SPDV.EQ.5) XDV=5
;       IF(EVID.EQ.0) PPDV=XDV
;   ENDIF
;Sim_end
;----- Update Bioavailability factors -----

BIO1=0
BIO2=0
BIO3=0
BIO4=0
BIO5=0
BIO6=0

IF(XDV.EQ.1)  BIO1 = 1
IF(XDV.EQ.2)  BIO2 = 1
IF(XDV.EQ.3)  BIO3 = 1
IF(XDV.EQ.4)  BIO4 = 1
IF(XDV.EQ.5)  BIO5 = 1
IF(XDV.EQ.6)  BIO6 = 1

$THETA  (0,33.8359) ; 1  MTT12
(0,11.0384) ; 2  MTT13
(0,136.222) ; 3  MTT14
(0,72.0868) ; 4  MTT23
(0,258.656) ; 5  MTT24
(0,540.396) ; 6  MTT26
(0,65.0001) ; 7  MTT36
(0,133.42) ; 8  MTT46
(0,228.091) ; 9  MTT15 MTT35 MTT45
(0,0.582216) ; 10 HZA13
(0,0.944962) ; 11 HZA36
-1.42388 ; 12 METAS13
0.227429 ; 13 DOSE12
0.433809 ; 14 DOSE13
1.02555 ; 15 DOSE14
-0.155306 ; 16 DOSE23
-0.516235 ; 17 DOSE24
0.255654 ; 18 DOSE26
0.362582 ; 19 DOSE36
0.018097 ; 20 DOSE46

```

```

-1.12903 ; 21 DOSE5
-0.671522 ; 22 DOSE13s
-0.568961 ; 23 DOSE36s
$OMEGA 0 FIX ; eta as a placeholder

;Sim_start : add/remove for simulation
;$SIGMA 0 FIX
;$SIMULATION (12345) (123 UNIFORM) (123 UNIFORM) NSUB=1 ONLYSIM
$ESTIMATION METHOD=1 LIKE LAPLACE NUMERICAL SLOW PRINT=1 SIGL=9
                MAXEVALS=9999 CTYPE=4 NSIG=2 MSFO=run509.msf
$COVARIANCE MATRIX=R
;Sim_end

$TABLE          ID SUBJID DAY XDV TIME TAFT TRT01AN FLLATS AMT Y EVID MDV
                CMT DV BIO1 BIO2 BIO3 BIO4 BIO5 BIO6 F1 F2 F3 F4 F5 F6 P_1
                P_2 P_3 P_4 P_5 P_6 K12 K13 K14 K15 K16 K23 K24 K25 K26
                K35 K36 K45 K46 NOPRINT FILE=sdtab509
;vpc run509.mod -samples=500 -dv=XDV -idv=WEEK -rplots=2 -levels=1,2,3,4,5
;                -flip_com -dir=vpc509vpc -seed=12345 -stratify_on=CDOSE

```