

Introduction

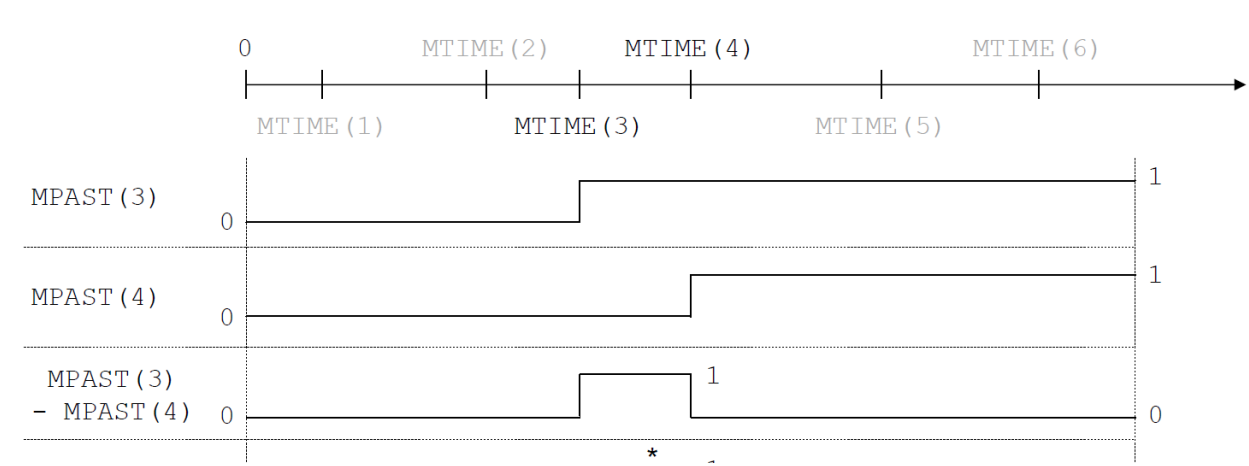
A change-point model is a model in which a parameter's value discontinuously changes at a given time (named change-point). It can be used to modify model behaviour (e.g. shift in absorption parameter value) or update the system (e.g. Enterohepatic recycling). In addition to parameter values, such models require the definition of change-point, and its implementation in NONMEM is not as intuitive as it looks, especially in repeated doses and at steady state.

Three methods of change-point definition were evaluated:

Change-point methods using MTIME (**MTIME_meth**)

- the reference method, using model event time parameter (MTIME) directly implemented in NONMEM, MTIME parameter defines a time at which the system is updated.
- Adapted to NONMEM subroutines

Fig.1: Change-point model : MTIME (from Uppsala lecture)



Methods

Coding implementation

Fig.2: Control streams using MTIME for single dose (left) and repeated doses (right) examples

```

$PK
CL = THETA(1)*EXP(ETA(1))
V2 = THETA(2)*EXP(ETA(2))
K = CL/V2

MTIME(1)=THETA(3)*EXP(ETA(3))
MTDIFF=1
XKA1=THETA(4)*EXP(ETA(4))
XKA2=THETA(5)*EXP(ETA(5))

KA=XKA1*(1-MPAST(1))+XKA2*(MPAST(1))

$SIZES PCT=5
$PK
.....
MTIME(1)=THETA(3)*EXP(ETA(3))
MTDIFF=1
MTIME(2) = 24
MTIME(3) = MTIME(1) + 24
MTIME(4) = 48
MTIME(5) = MTIME(1) + 48

XKA1=THETA(4)*EXP(ETA(4))
XKA2=THETA(5)*EXP(ETA(5))

KASD = XKA1 + (XKA2-XKA1)*MPAST(1)
KA01=XKA1+(XKA2-XKA1)*MPAST(1)+(XKA1-XKA2)*MPAST(2)
KA02=KA01+(XKA2-XKA1)*MPAST(3)+(XKA1-XKA2)*MPAST(4)
KA03 = KA02 + (XKA2-XKA1)*MPAST(5)
KA = KA03

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Change-point methods using a dummy compartment (**CMT_meth**)

- the use of a fictive change point compartment (CMT) with an associated lag time [1];

Fig.3: Change-point model : CMT_meth

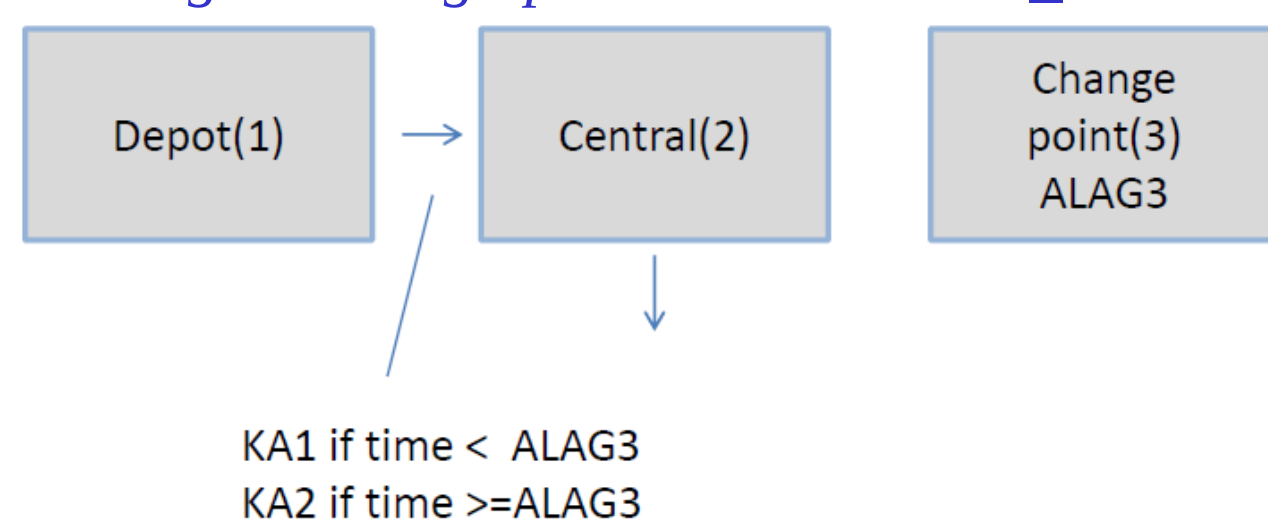


Table 1: Dataset sample for CMT_meth

ID	TIME	AMT	CMT	EVID	MDV
1	0	100	1	1	1
1	0	99	3	1	1
1	0	0	2	0	0
1	0.25	0	2	0	0
1	0.5	0	2	0	0
1	0.75	0	2	0	0

Fig.4: Control stream for the CMT_meth and dataset sample

```

$MODEL
COMP = (DEPOT) ; absorption compartment
COMP = (CENTRAL) ; central compartment
COMP = (CHANGE) ; Change point

$PK
IF(NEWIND.LT.2) THEN
I1=0
I3=0
ENDIF
IF(I1.EQ.1) Z=0
IF(I3.EQ.1) Z=1
I1=0
I3=0
IF(DOSREC(AMT).NE.0.AND.DOSREC(AMT).NE.99) I1=1
IF(DOSREC(AMT).EQ.99) I3=1

CL = THETA(1)*EXP(ETA(1))
V2 = THETA(2)*EXP(ETA(2))
XKA1=THETA(3)*EXP(ETA(3))
XKA2=THETA(4)*EXP(ETA(4))
KA=XKA1*(1-Z)+XKA2*Z
ALAG3=THETA(6)*EXP(ETA(6))

$DES ; differential equations
DADT(1)=(-1-Z)*(-XKA1)*A(1)+Z*(-XKA2)*A(1)
DADT(2)=(1-Z)*(XKA1)*A(1)+Z*(XKA2)*A(1)-K*A(2)
DADT(3)=0

Fix the value of the DE describing the change-point
compartment to zero

Indicator variable (Z) used to switch between rate
constants

Doserec(amt): array with current values of the PK system

ALAG3 is the changing-point

```

Change-point method using a function (**FCT_meth**)

- A change point function (FCT) with an analytical expression of a rectangular wave function.

Fig.5: rectangular function

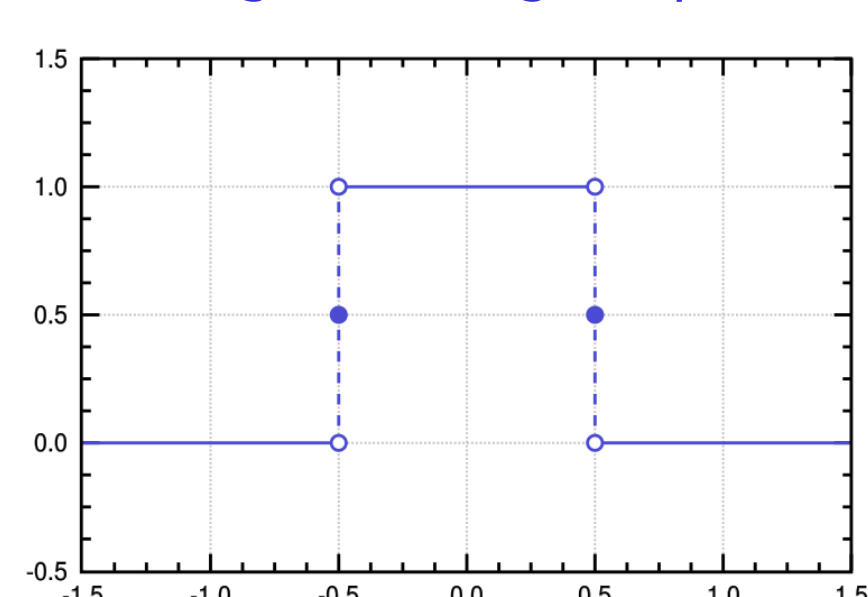


Fig.6: Control stream for the FCT_meth

```

$PK
CL = THETA(1)*EXP(ETA(1))
V = THETA(2)*EXP(ETA(2))

XKA1 = THETA(3)*EXP(ETA(3))
XKA2 = THETA(4)*EXP(ETA(4))
MMI = THETA(6)*EXP(ETA(6))

$DES
PER = 2 * 3.141593 * MMI / 24
SI1 = SIN((3.141593 - AA)/2)
SI2 = SIN(2 * 3.141593 * T / 24 + (3.141593 - AA)/2)
CREN = (SQRT((SI2-SI1)**2) - (SI2 - SI1))/(2*SQRT(0.000001 + (SI2 - SI1)**2))
KA = XKA1 + (XKA2 - XKA1) * CREN

DADT(1)=-KA*A(1)
DADT(2)= KA*A(1) - A(2)*CL/V

```

Each method was evaluated with a simulated population PK example: a 1 compartment model with a changing first-order absorption rate. Simulations were performed after **single administration (SD)**, **repeated doses (RD)** and at **steady state (SS)** and the simulated median profile were plotted. Graphical comparison and run time duration were used to evaluate each method. Practical constraints in terms of coding and/or data preparation were also discussed.

Results

Table 2: PK parameters

KA1	0.01
KA2	0.1
CHANGE-point	5
CL/F	10
V/F	100

Table 3: methods evaluation

😊	Correct simulation of PK profiles, and easy implementation of the change point method.
😐	Correct simulation of PK profiles, but difficult implementation of the change point method.
😞	Incorrect simulation of PK profiles

Fig.7: simulation after single dose administration

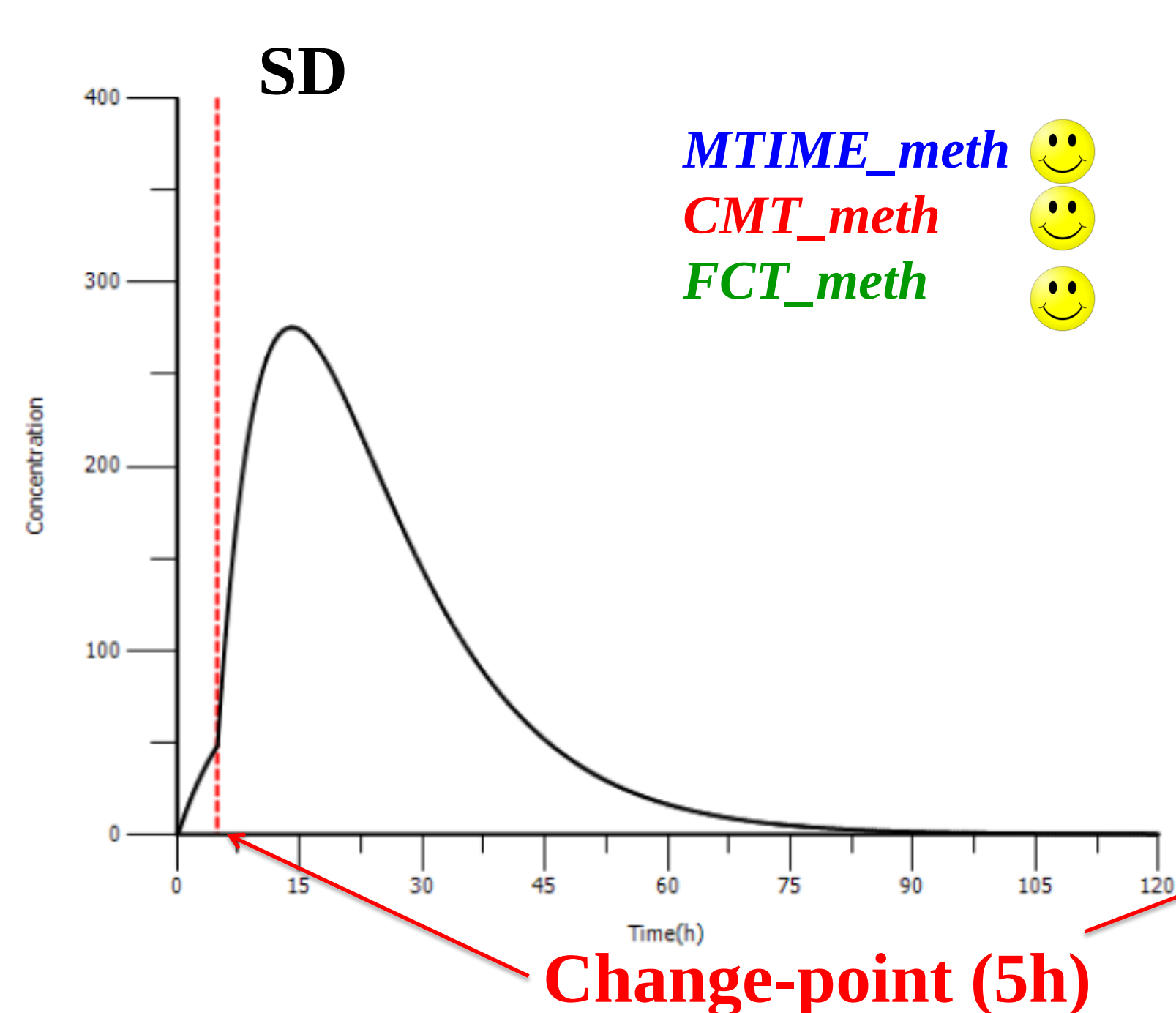


Fig.8: simulation after repeated dose administration

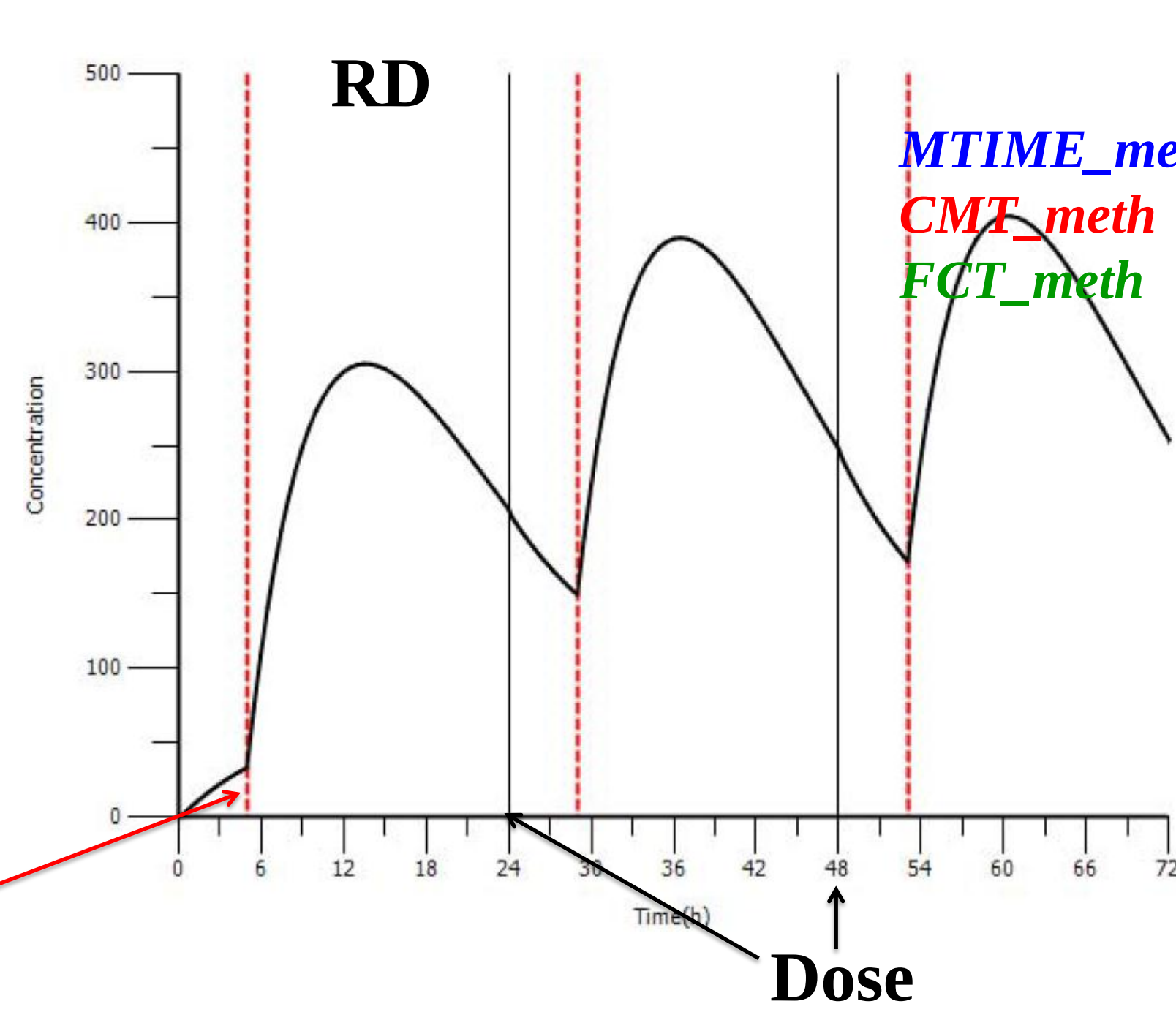
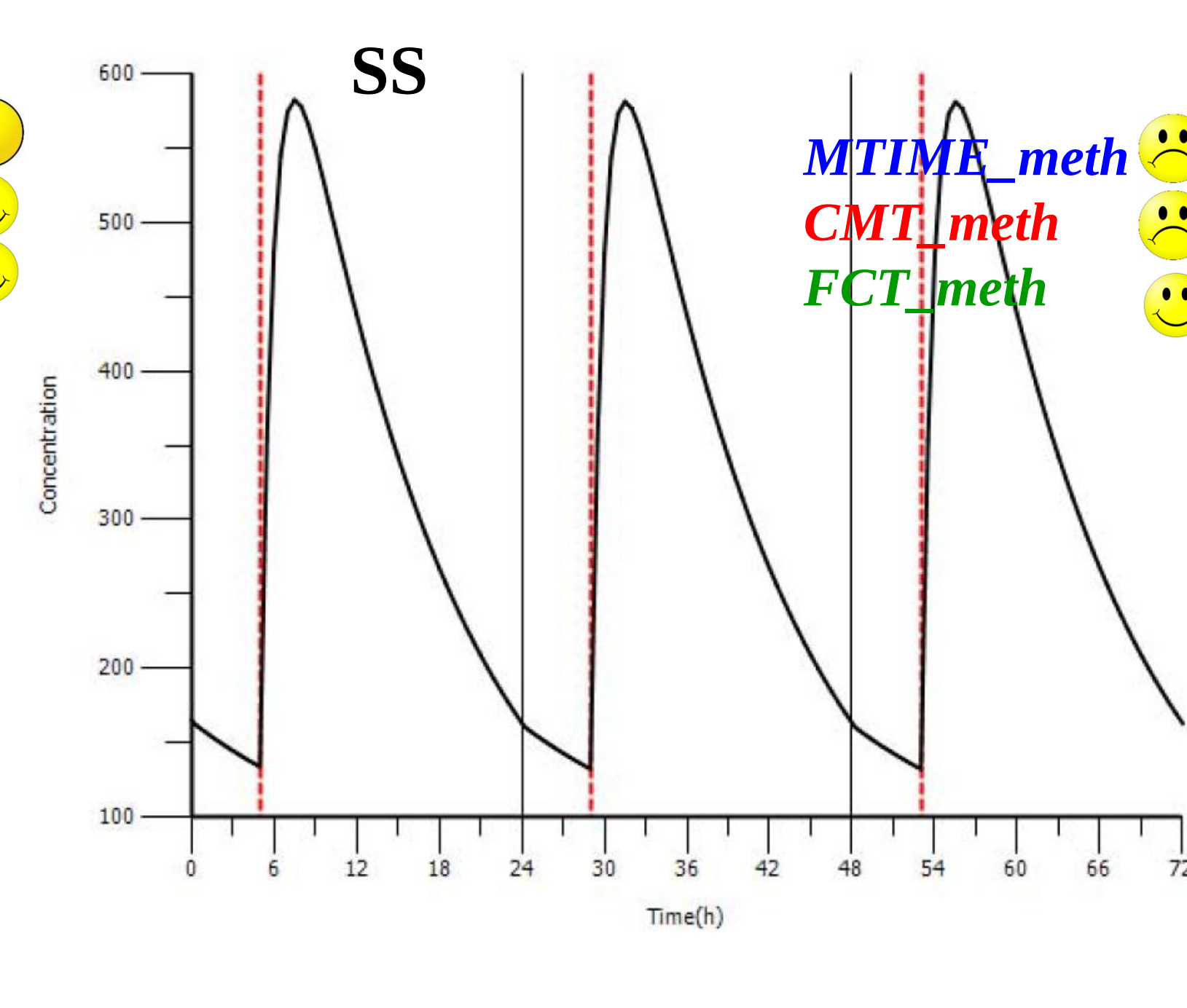


Fig.9: simulation at steady state



After single administration, the three methods give the same expected results. After multiple administrations, no difference in term of simulation output is observed between the three methods. As the reference method **MTIME_meth** allows the use of an adapted NONMEM subroutine, run duration is smaller than **CMT_meth** and **FCT_meth**, which require using differential equations. At steady state (using the implemented NONMEM SS option) only the **FCT_meth** is able to give the correct simulation results. From a practical point of view, **MTIME_meth** involves heavy code adjustment and **CMT_meth** requires specific dataset modification, while **FCT_meth** can be used without significant modifications of both code and dataset.

Conclusions

In order to implement a change-point model after a single dose administration, the **MTIME_meth** was the easiest way to do it, allowing to the modeller to use NONMEM subroutines.

For multiple dosing, the **CMT_meth** and **FCT_meth** are good alternatives when the number of doses increases. However, only the **FCT_meth** is able to perform correct simulation at steady state using NONMEM SS option.