Reference profiles

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Objectif

- create datasets for the test files for functions
  - binning: npde.binning
  - plotting VPC and npde scatterplots:
  - computing reference profile: aux.npdeplot.meanprof, *transform mean profile*
  - computing prediction intervals: compute.bands, compute.bands.true, aux.npdeplot.computepi
- files needed for these different steps:
  - observed data (aka original data): **obsdat__** [eg *obsdat_ecopk*]
  - simulated data (simulations under the model using the design in the original dataset) **simdat__** [eg *simdat_ecopk*]
    * for convenience, also save a matrix with npde~N(0,1) (used to compute PI) of nrow=nrow(obsdat): **npdesim__** [eg *npdesim_ecopk*]
  - obsmat for npde, yobs, tnpde for some reference profile (eg dose=1000): **obsmat__**
  - pimat for npde, yobs, tnpde for some reference profile (eg dose=1000): **pimat__**

Setup, loading libraries

Example saved by Romain

- 3 categories of weight => need a more simple example without covsplit
  - also would need the same Y-axis (ie facet_grid plot) and not 3 separate plots => maybe make a second version outputting a single plot instead of a list of plots, with facet_grid
  - not a very good example as the PI overlap
  - plot with the 3 categories and with just one => works
- changed graphical options to default as was just too hideous
- a number of issues
  - pb with censored data being overlayed on the plot in excess
 - labels
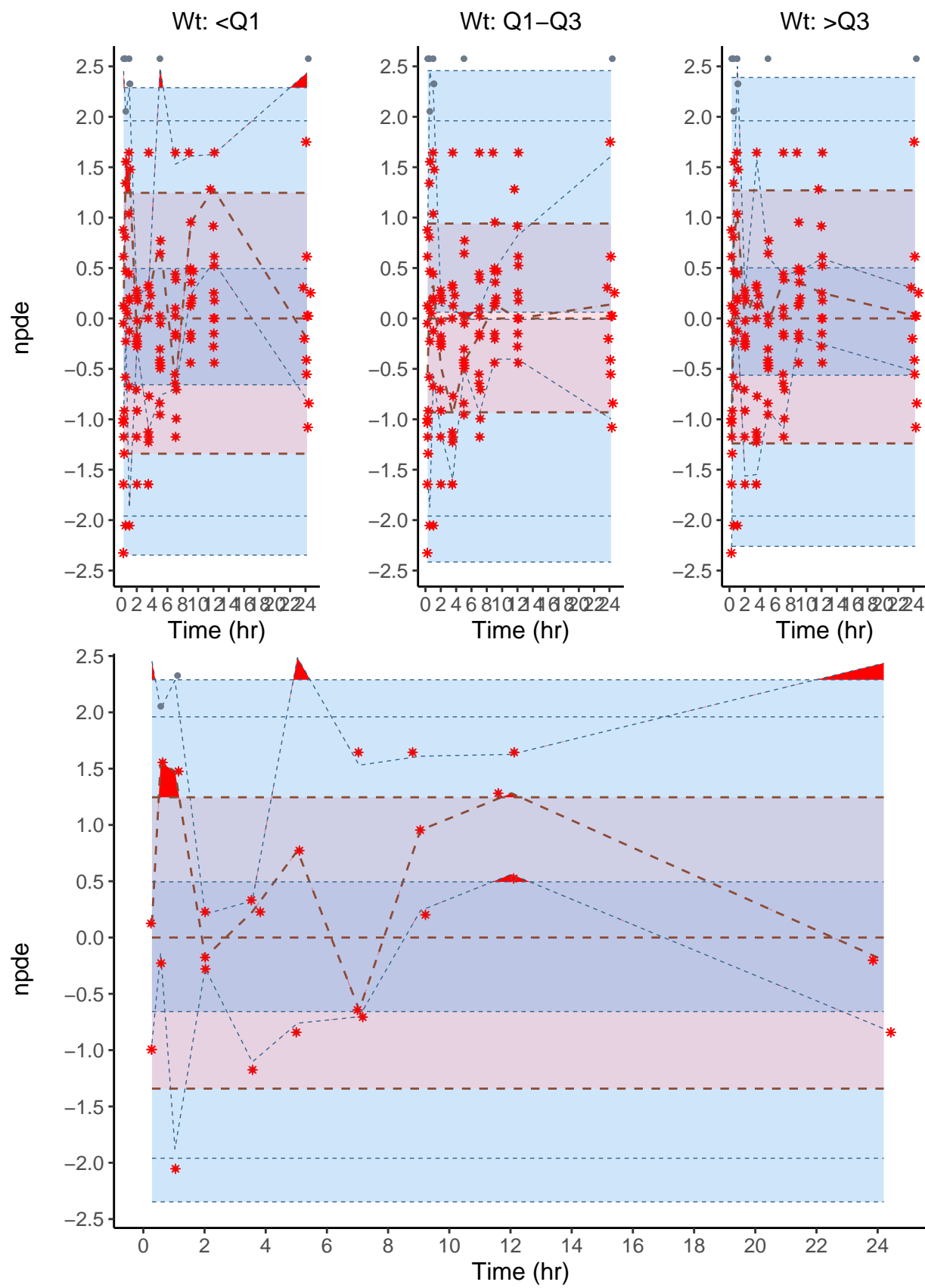
```
##        2.5%        50%      97.5%
## -1.956481  0.022429  1.971912
```

Sourcing new changes and plotting the same data with new code

Debugging aux.npdeplot.plot

- **Problems**
    - binf, bsup should be lower and upper bounds of PI, but then bmed should be the median (ie theoretical) value OR binf, bsup, bmed are the 3 PI, and 0025, 05 and 0975 are the respective percentiles for each pi
    - is dotline useful ? (either use quantile or fill quantile with theoretical value)
    - need the same names in both pimat and obsmat to be less confusing
        * for groups = should be grp, but **change to xbin** (because grp and group could be covariate names)
        * why is category different than cov and why is there also covariate ?
        * xcent: ok as name of bin center
    - we don't need covariates and category both, this function is only supposed to be called with one covariate at a time (the split is done in the function calling it)
- **TODO** change name or remove dotline, should be ther + names not consistent
    - type of pi: pinf, pmid, psup (3 PI, eg 0.025, 0.5 and 0.975 for 95% PI, controlled by vpc.interval)
    - boundaries of pi: lower, median, upper
    - => pinf.lower, pinf.median, pinf.upper, etc...
    - grouping factor: grp for both obsmat and pimat
    - x-value for bin: xcent (ok)
    - observed percentiles: obs.inf obs.med obs.sup
    - removed dotline
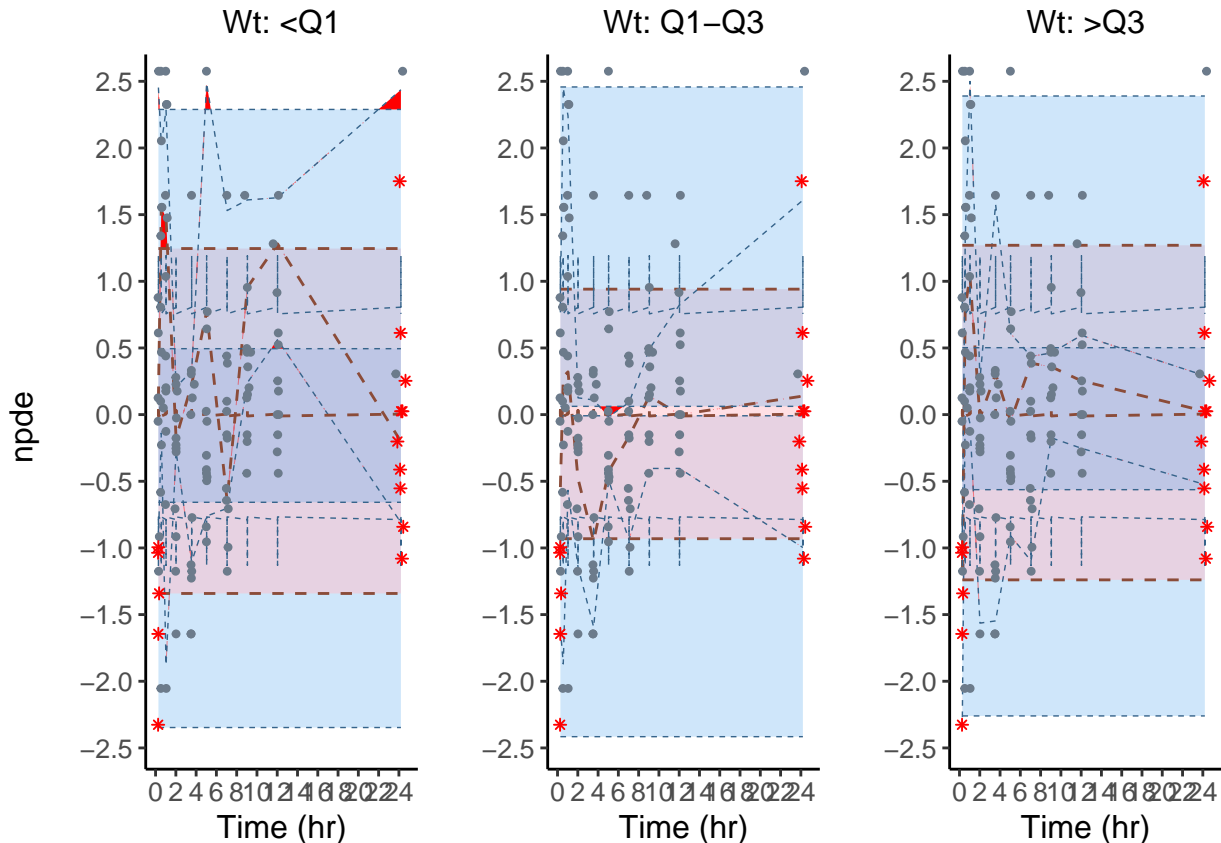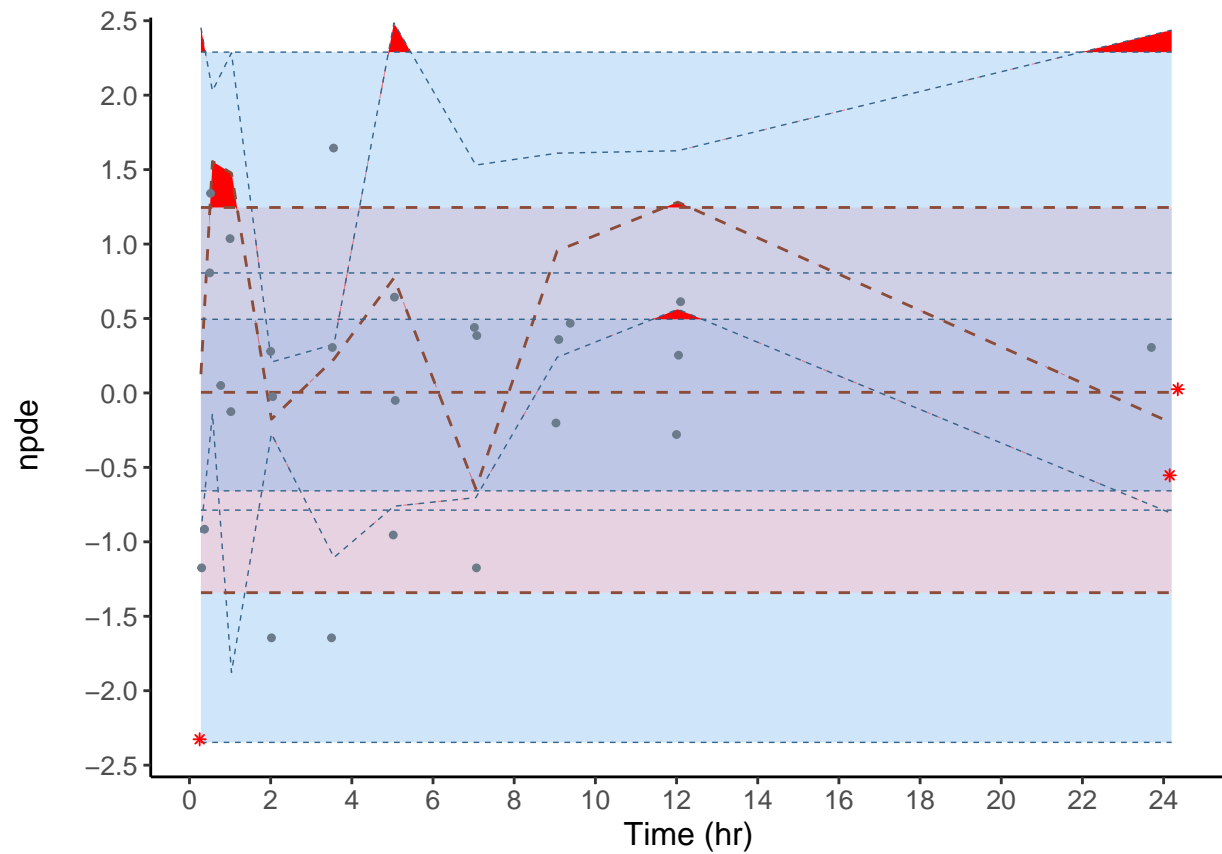
Checking a few options

- plot.box=TRUE
  - fails miserably with Japanese warnings :-)
  - seems to be missing some boxes (only 6 and should be 10, ie 5 doesn't show (or maybe does but flat ?))
  - prediction intervals don't show and only weird lines appear
- check the labels for the different options (x, pred, cov, . . .)

Wt: <Q1 : Wt   Wt: <Q1 : Wt   Wt: <Q1 : Wt

5
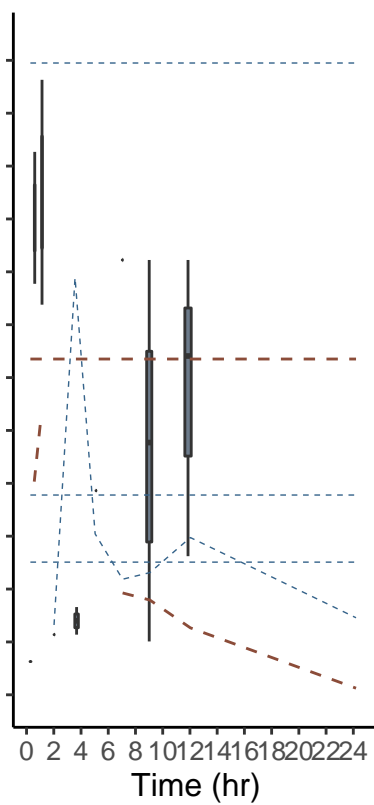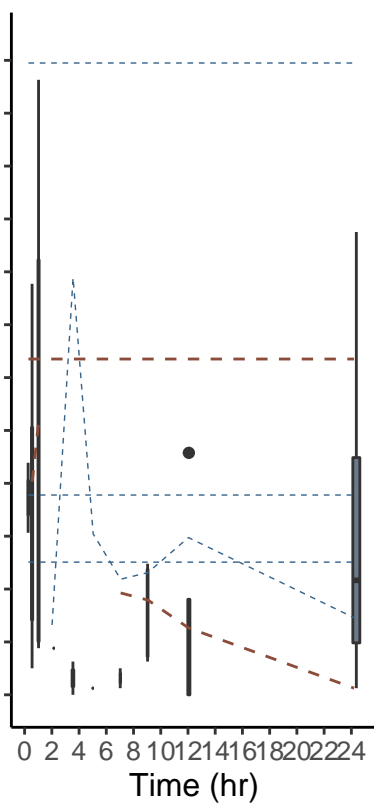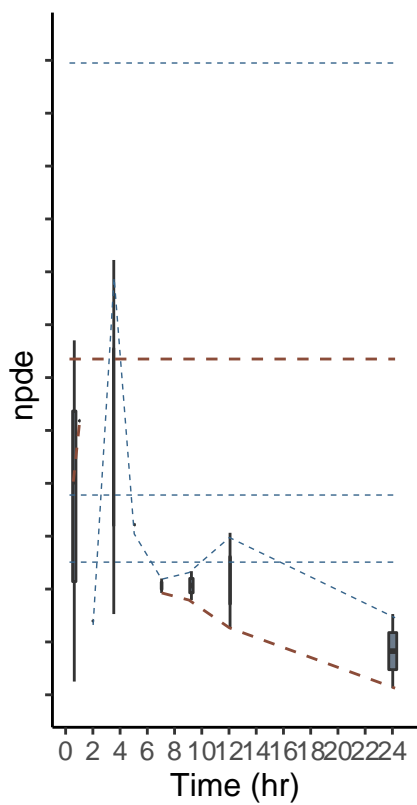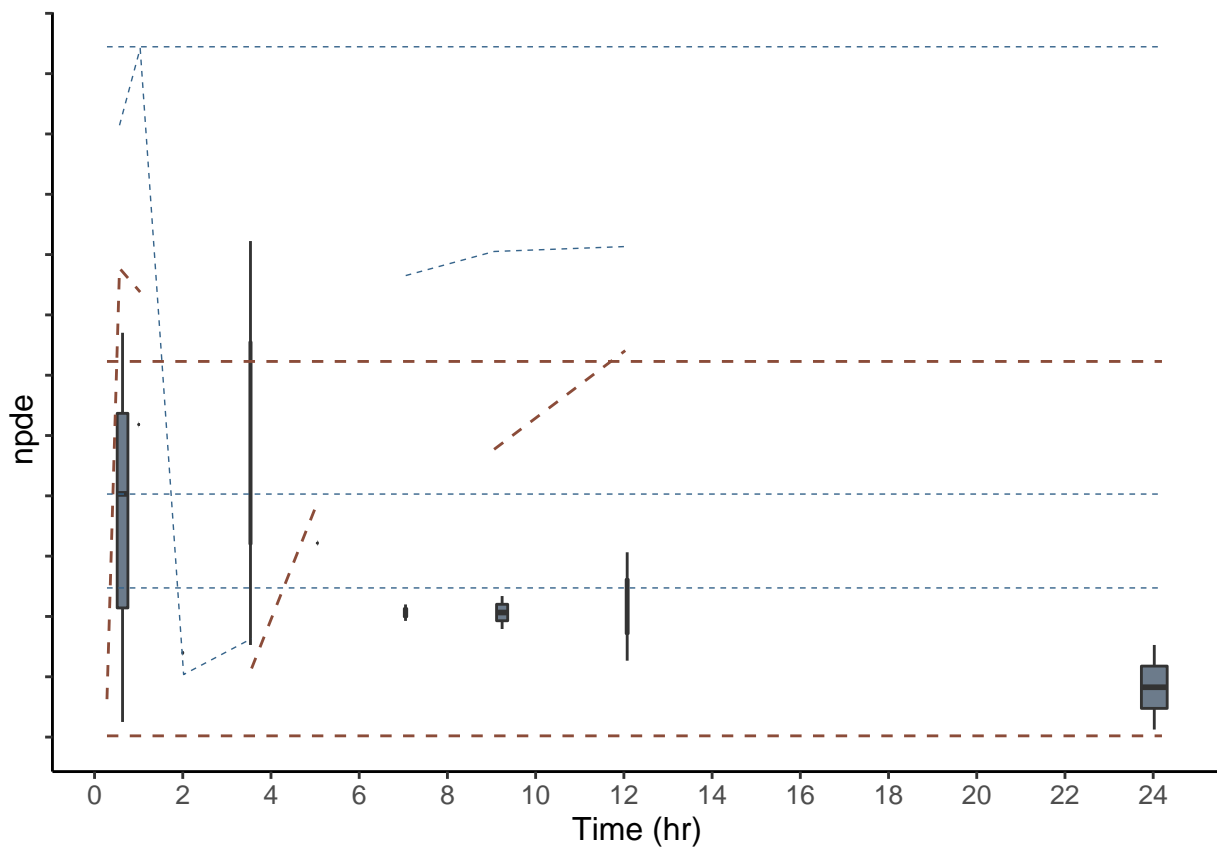
One-compartment PK example with covariates, different doses and different sampling schedules

Creating datafile

- one-compartment PK model:
  - parameters: ka~LN(2,0.2), V~LN(V_0,0.2), CL~LN(CL_0, 0.2) (20% IIV)
  - covariate effects: V_0(sex=0)=10, V_0(sex=1)=6; CL_0= 1 + 0.3*log(age/40)
- design:
  - 100 subjects: 50 male, 50 female, age ranging from 30 to 70
  - 5 groups, in each group, following time sequences: 20 subjects with full (2-24 every 2h), 20 initial (1-6h then 12, 24), 10 sparse (1, 2, 5, 10, 24)
  - doses: c(10,20,50,100,1000) cycling every 5 subjects
- save to or read from file (save once with createDat set to TRUE)

Computing PI for a VPC using the same data

Creating the PI to plot a VPC, using all times

- across all doses (very large)
- PI only for the dose=1000 group (but will still have covariate effects, uncorrected here (could correct using pcVPC))

Using new code to plot scatterplots and VPC on simulated data

Binning

TODO create unitary tests for binning (including different binning methods +++) + advice on binning for *pred*

```
##                 xaxt grp
## (-0.5,1]    0.812500    1
## (1,2]       2.000000    2
## (2,3.43]    3.000000    3
## (3.43,5]    4.428571    4
## (5,6]       6.000000    5
## (6,10]      9.200000    6
## (10,13.1]  12.000000    7
## (13.1,18]  16.000000    8
## (18,23.3]  21.000000    9
## (23.3,24]  24.000000   10
```

Creating pimat for the npde

Compute PI, using simulated values for npde in N(0,1)

```
##          grp xcent category pinf.lower pmid.lower psup.lower pinf.median
## X60        1   0.5      all  -2.425248 -0.2963501   1.304350   -1.834215
## X100       2   1.0      all  -2.370190 -0.2432410   1.416334   -1.884664
## X100.1     3   2.0      all  -2.370190 -0.2432410   1.416334   -1.884664
## X40        4   3.0      all  -2.517751 -0.3777325   1.119632   -1.744514
## X80        5   4.0      all  -2.442602 -0.2579136   1.361685   -1.837915
## X60.1      6   5.0      all  -2.425248 -0.2963501   1.304350   -1.834215
```

```
## X80.1    7   6.0       all  -2.442602 -0.2579136   1.361685    -1.837915
## X40.1    8   8.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X60.2    9  10.0       all  -2.425248 -0.2963501   1.304350    -1.834215
## X80.2   10  12.0       all  -2.442602 -0.2579136   1.361685    -1.837915
## X40.2   11  14.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X40.3   12  16.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X40.4   13  18.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X40.5   14  20.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X40.6   15  22.0       all  -2.517751 -0.3777325   1.119632    -1.744514
## X100.2  16  24.0       all  -2.370190 -0.2432410   1.416334    -1.884664
##         pmid.median psup.median pinf.upper pmid.upper psup.upper   obs.inf
## X60    -0.008464578    1.831309  -1.316745  0.3286482   2.436604 -1.954261
## X100   -0.004378835    1.859389  -1.437663  0.2440337   2.377141 -1.782612
## X100.1 -0.004378835    1.859389  -1.437663  0.2440337   2.377141 -2.264534
## X40     0.008658287    1.740091  -1.166079  0.3896442   2.488034 -3.171491
## X80     0.008013737    1.832194  -1.386740  0.2799098   2.413168 -2.123336
## X60.1  -0.008464578    1.831309  -1.316745  0.3286482   2.436604 -1.842304
## X80.1   0.008013737    1.832194  -1.386740  0.2799098   2.413168 -1.704525
## X40.1   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.815107
## X60.2  -0.008464578    1.831309  -1.316745  0.3286482   2.436604 -1.706134
## X80.2   0.008013737    1.832194  -1.386740  0.2799098   2.413168 -1.845161
## X40.2   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.880031
## X40.3   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.510640
## X40.4   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.868667
## X40.5   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.828610
## X40.6   0.008658287    1.740091  -1.166079  0.3896442   2.488034 -1.883965
## X100.2 -0.004378835    1.859389  -1.437663  0.2440337   2.377141 -1.624436
##          obs.median  obs.sup
## X60    -0.09733499 2.182355
## X100   -0.05676337 1.919444
## X100.1 -0.18879379 1.747523
## X40    -0.23108683 1.708377
## X80     0.02498215 1.875161
## X60.1  -0.01469505 1.658127
## X80.1   0.02420463 1.949936
## X40.1   0.04493230 1.780580
## X60.2  -0.26331270 1.903362
## X80.2   0.22065761 2.250403
## X40.2  -0.10972884 2.137150
## X40.3  -0.08561940 2.291986
## X40.4   0.11468376 1.621968
## X40.5   0.08927355 1.860865
## X40.6  -0.04334040 1.535363
## X100.2  0.06178032 1.851554
```
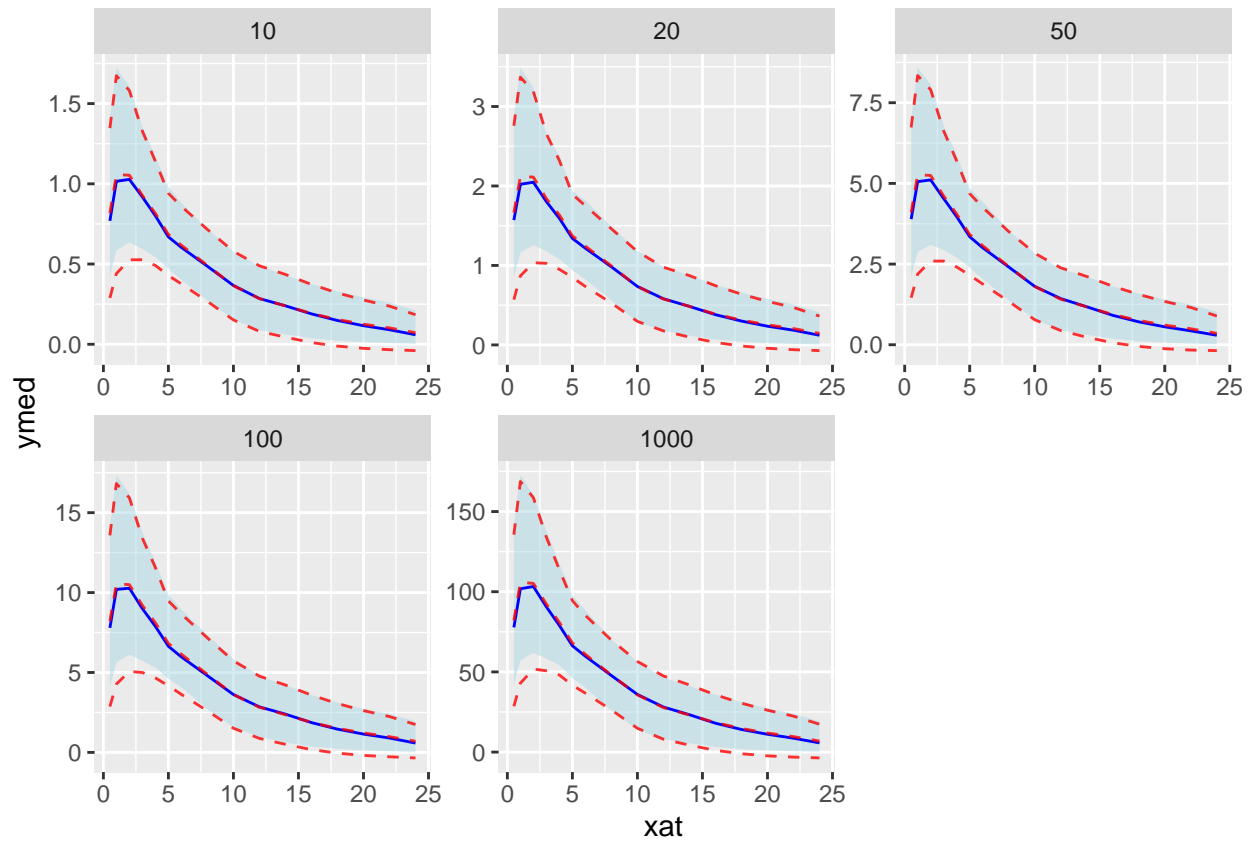
Create corresponding obsmat and plot result
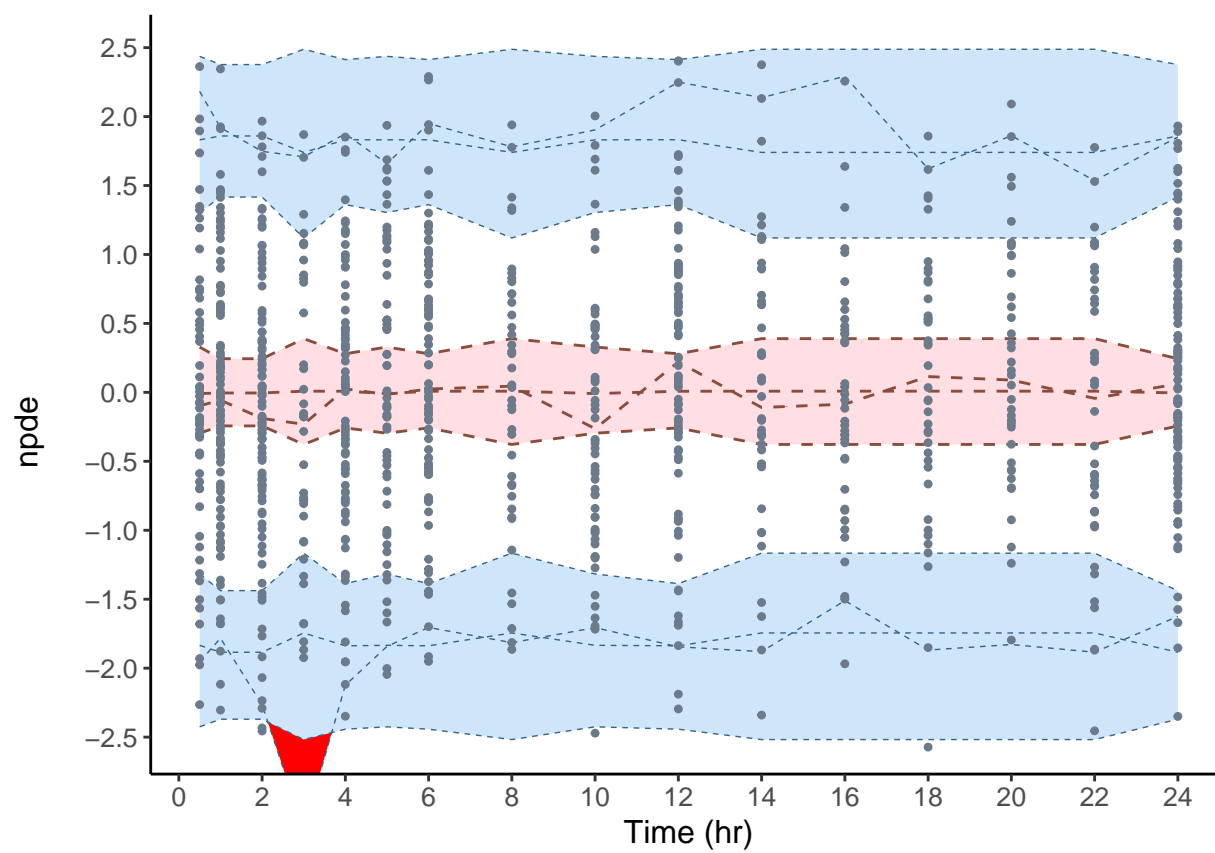

Reference profiles

Testing the function to compute the reference profile with different options: - reference profiles for the different doses, shown as facet graph

Reference profiles across different doses

Reference profile for ages between 40 and 55

- poor reference profile in this case as too heterogenous (all doses)
- peak at time=3 because only dose=1000 for this timepoint so mean much higher
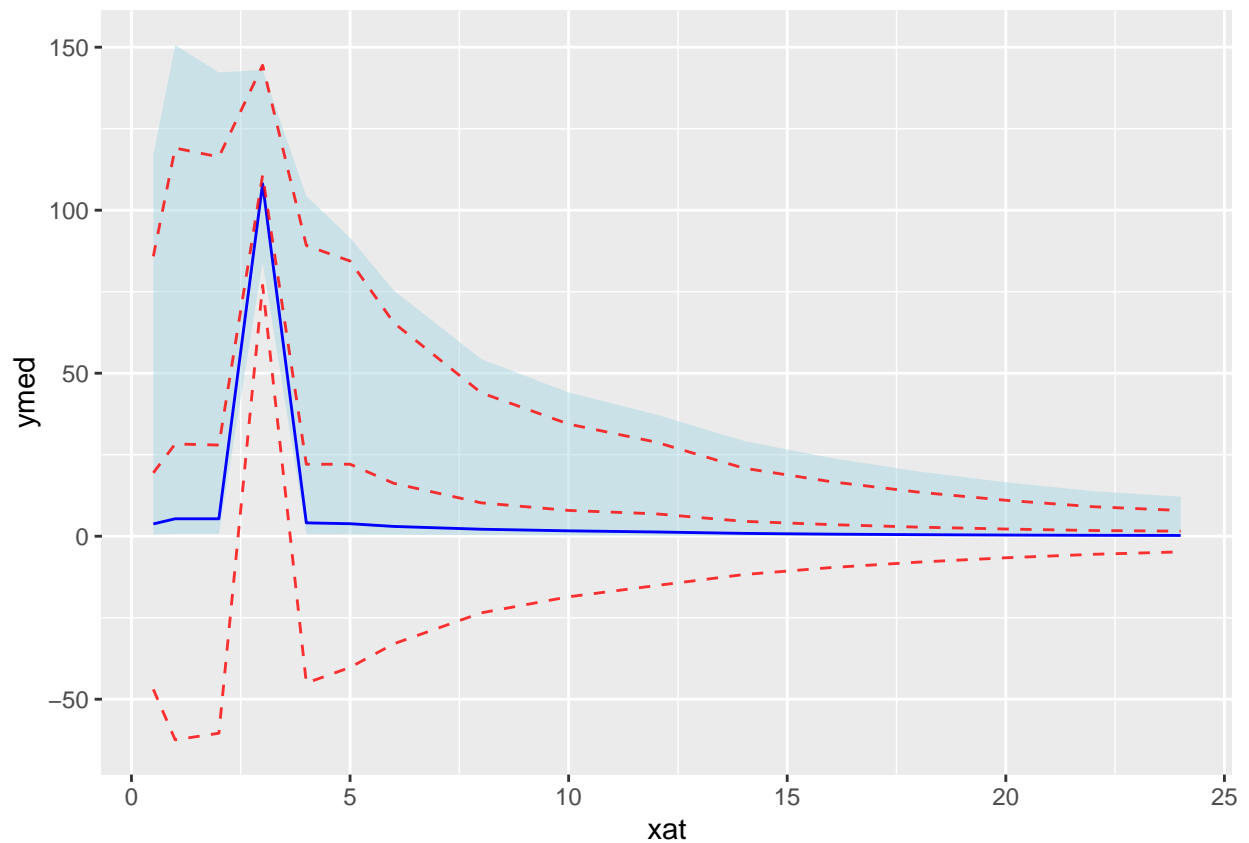
```
##
##              10     20     50    100   1000
##     0.5  1200   1200   1200   1200   1200
##     1    1200   1200   1200   1200   1400
##     2    1200   1200   1200   1200   1400
##     3       0      0      0      0    200
##     4     800    800    800    800   1000
##     5     400    400    400    400    600
##     6     800    800    800    800   1000
##     8     800    800    800    800    800
##     10   1200   1200   1200   1200   1200
##     12    800    800    800    800   1000
##     14    800    800    800    800    800
##     16    800    800    800    800    800
##     18    800    800    800    800    800
##     20    800    800    800    800    800
##     22    800    800    800    800    800
##     24   1200   1200   1200   1200   1400
```

Scatterplots with reference plots

### Transformation for reference plots

Transforming obsmat and pimat:

- pimat

- the PI are initially computed as the quantiles (eg 0.05, 0.5, 0.95 for a 90% PI) of the npde in npdesim (assuming they were computed from the observation matrix)
- the reference profile had us compute the mean and SD of the observations, eg $E(f(\phi|\theta))$ and $SD(f(\phi|\theta))$
- obsmat
  - for npde: we have the values of the npde
    * transformation
      · $E(f(\phi|\theta)) + \text{npde}_{ij} \times SD(f(\phi|\theta))$ (?)
      · same transformation applied to the boundaries, medians of the PI and of the empirical percentiles
  - for npd same

## First step: compute and check the mean profile for all possible time points

Not all time points/bins are represented in the subset used for the reference profile: spline interp
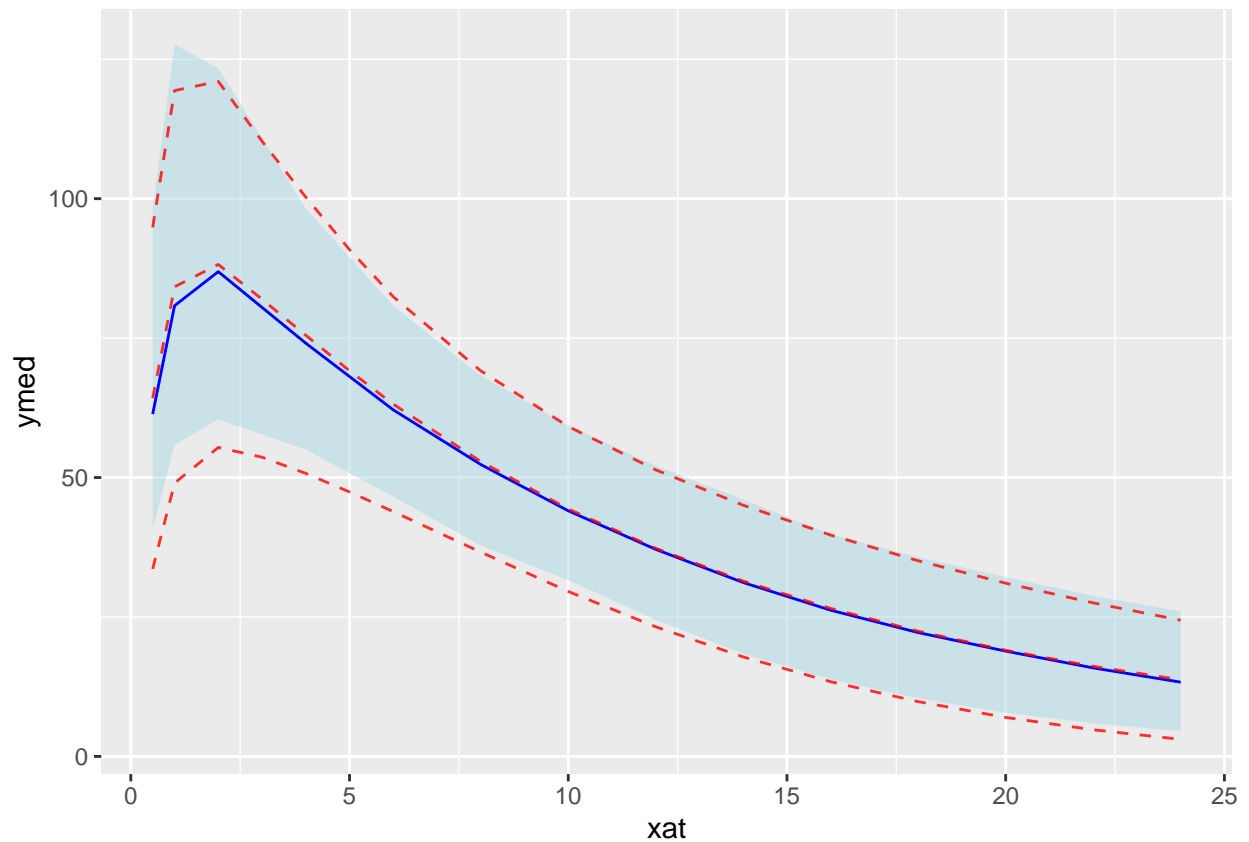
We should see close agreement between the ribbon and the lines from the reference profile.

Second step: transform observations as tnpde_ij = E(t_ij) + SD(t_ij)* npde_ij

## Should superimpose approximately to the reference profile

11
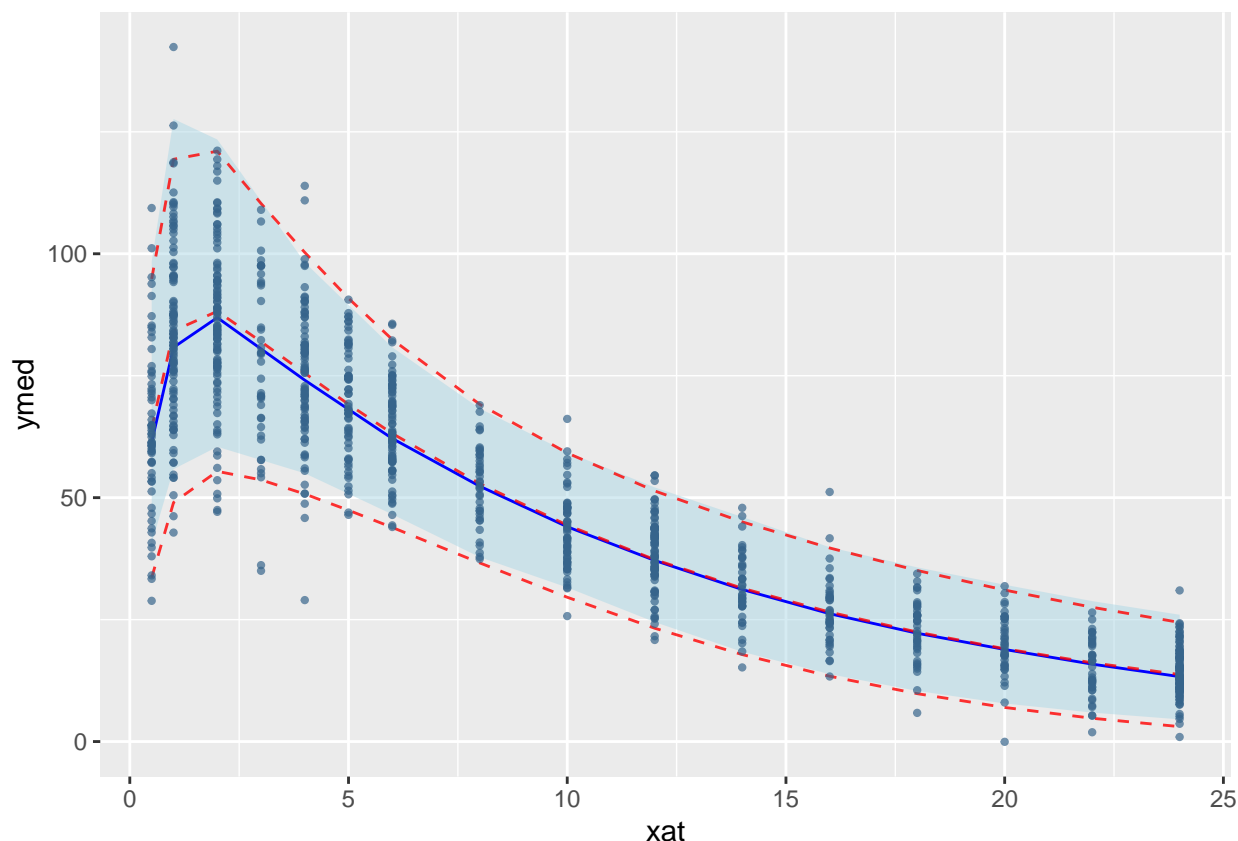
```
## Third step: compute PI using aux.npdeplot.computepi (done above)

##        grp xcent category pinf.lower  pmid.lower psup.lower pinf.median
## X60      1   0.5      all  -2.425248  -0.2963501   1.304350   -1.834215
## X100     2   1.0      all  -2.370190  -0.2432410   1.416334   -1.884664
## X100.1   3   2.0      all  -2.370190  -0.2432410   1.416334   -1.884664
## X40      4   3.0      all  -2.517751  -0.3777325   1.119632   -1.744514
## X80      5   4.0      all  -2.442602  -0.2579136   1.361685   -1.837915
## X60.1    6   5.0      all  -2.425248  -0.2963501   1.304350   -1.834215
##        pmid.median psup.median pinf.upper pmid.upper psup.upper   obs.inf
## X60   -0.008464578    1.831309  -1.316745  0.3286482   2.436604 -1.954261
## X100  -0.004378835    1.859389  -1.437663  0.2440337   2.377141 -1.782612
## X100.1 -0.004378835   1.859389  -1.437663  0.2440337   2.377141 -2.264534
## X40    0.008658287    1.740091  -1.166079  0.3896442   2.488034 -3.171491
## X80    0.008013737    1.832194  -1.386740  0.2799098   2.413168 -2.123336
## X60.1 -0.008464578    1.831309  -1.316745  0.3286482   2.436604 -1.842304
##         obs.median  obs.sup
## X60    -0.09733499 2.182355
## X100   -0.05676337 1.919444
## X100.1 -0.18879379 1.747523
## X40    -0.23108683 1.708377
## X80     0.02498215 1.875161
## X60.1  -0.01469505 1.658127

## Fourth step: transform PI

## Fifth step: plot
```
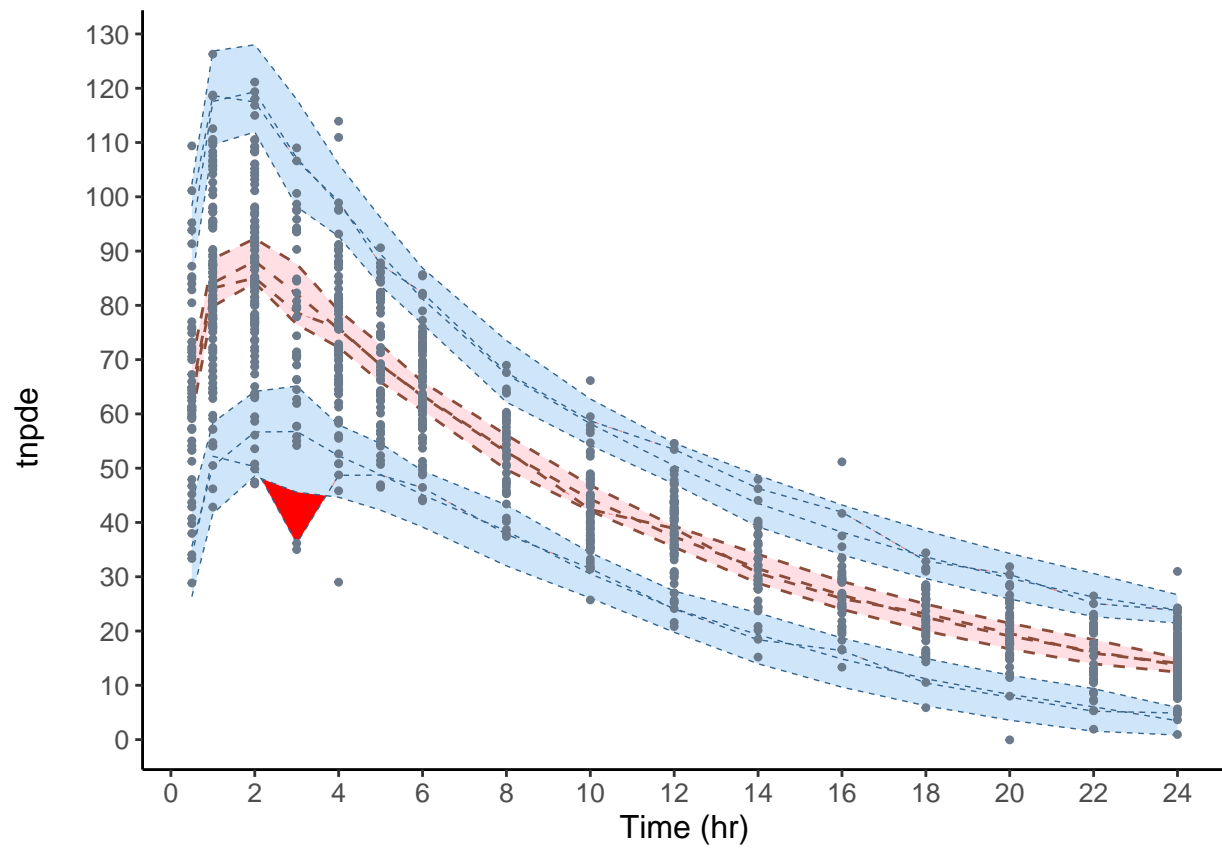
Works, PI for dose=1000 are much larger for VPC than npde when they should be relatively similar + t