Reference profile for an extreme case (review R2 AAPS J)

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Objective

Reference profiles

tnpde_{ij} are defined as $\text{tnpde}_{ij} = E(ysim^{ref}_{bin(t_{ij})}) + SD(ysim^{ref}_{bin(t_{ij})})\text{npde}_{ij}$ where $bin(t_{ij})$ denotes the bin in which lies the time t_{ij} corresponding to npde_{ij}, and $E(ysim^{ref}_{bin(t_{ij})})$ and $SD(ysim^{ref}_{bin(t_{ij})})$ are respectively the mean and standard deviation of the simulated data in the bin that belong to individuals in the reference group. Therefore, if under the model we expect: $\text{npde}_{ij} \sim \mathcal{N}(0,1)$ then it follows that $\text{tnpde}_{ij} \sim \mathcal{N}(E(ysim^{ref}_{bin(t_{ij})}), SD(ysim^{ref}_{bin(t_{ij})}))$

Setup, loading libraries

Creating datafile

- one-compartment PK model:
  - parameters: ka~LN(2,0.2), V~LN(V_0,0.2), CL~LN(CL_0=1, 0.2) (30% IIV)
  - covariate effects: V_0(sex=0)=10, V_0(sex=1)=6
- design:
  - 120 subjects: 60 male, 60 female
  - rich design (0.5, 1, then 2 to 24h every 2h)
  - 3 dose groups (10, 100, 1000) with 20 subjects of each gender
- save to or read from file (save once with createDat set to TRUE)

```
##   id time        y sex dose
## 1  1  0.5 0.4184108   0   10
## 2  1  1.0 0.5583849   0   10
## 3  1  2.0 0.5949278   0   10
## 4  1  6.0 0.4500934   0   10
## 5  1 12.0 0.2864061   0   10
## 6  1 24.0 0.1159664   0   10
```

```
##   irep id time        y sex dose
## 1    1  1  0.5 0.8698659   0   10
## 2    1  1  1.0 1.1235929   0   10
## 3    1  1  2.0 1.1471404   0   10
## 4    1  1  6.0 0.7828710   0   10
## 5    1  1 12.0 0.4305826   0   10
## 6    1  1 24.0 0.1302523   0   10
```

Compute npde

Use only a subset, too many points here

```
## ------------------------------------------------
## Distribution of npde :
##       nb of obs: 720
##            mean= -0.02292   (SE= 0.036 )
##        variance= 0.9538   (SE= 0.05 )
##        skewness= -0.08749
##        kurtosis= 0.1521
## ------------------------------------------------
## Statistical tests (adjusted p-values):
##    t-test              : 1
##    Fisher variance test  : 1
##    SW test of normality  : 1
##    Global test           : 1
## ---
## Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
## ------------------------------------------------
```