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A strategy for residual error modeling incorporating both scedasticity of variance and distribution shape

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Traditional error modeling
Models and assumptions

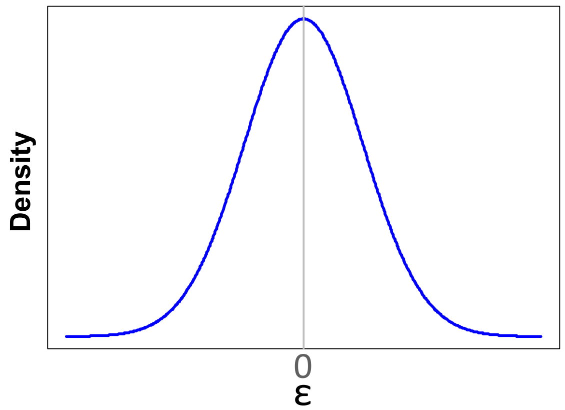
- **Models**

$$y = f(\theta, x, Z) + \varepsilon$$

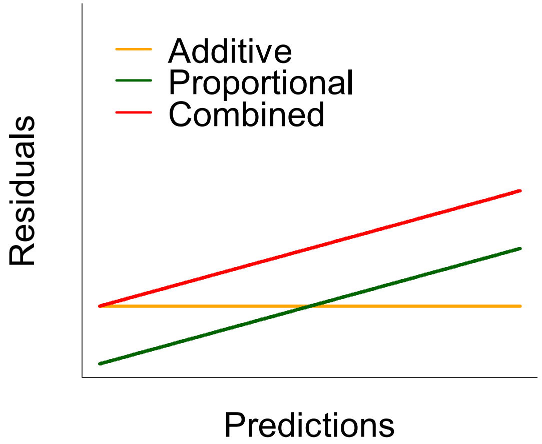
$$\varepsilon \sim N(0, var(\varepsilon))$$

$var(\varepsilon)$
σ^2_{add}
$\sigma^2_{prop} \times f(\theta, x, Z)^2$
$\sigma^2_{add} + \sigma^2_{prop} \times f(\theta, x, Z)^2$

- **Assumptions**



Normal distribution, mean 0



Fixed residual – prediction relationship

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What to do if assumptions do not hold?

Common answers, limitations, needs

Untransformed data
best case scenario

Fixed transformations
OFV not comparable
Time-consuming

Estimated transformations, different distribution
OFV comparable

Validity of assumptions on residuals

↓

Validity of likelihood calculation

↓

Validity of inference

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Alternative strategies

dTBS and Student's t-distribution

1 **dTBS**

Transform data and prediction so ε has a symmetric density

- Box-Cox (skewness) + Power term (scedasticity)

2 **t-distribution**

Change **distribution assumption**

- Student's t-distribution (heavy-tailed)

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Residual error modeling with dynamic Transform Both Sides (dTBS)

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Dynamic Transform Both Sides

Box-Cox transformation in NLMEM

$$h(y) \begin{cases} \lambda \neq 0 & \dfrac{y^{\lambda} - 1}{\lambda} \\ \lambda = 0 & \log(y) \end{cases}$$

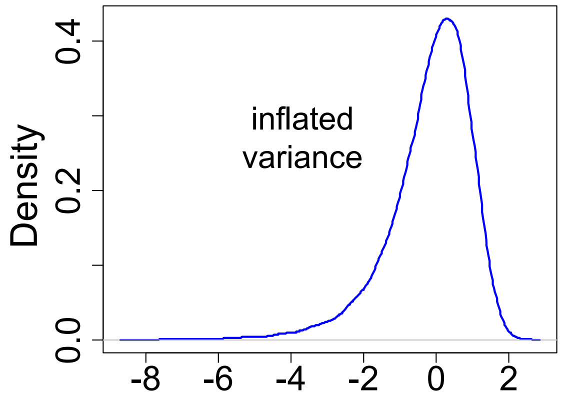
λ = 1	normal
λ = 0	log
λ > 1	*left* skewed
λ < 1	*right* skewed

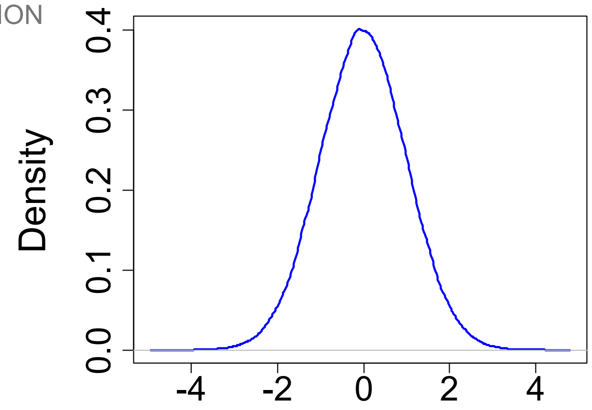
In NLMEM $\quad h(DV) = h(IPRED) + \varepsilon$

Untransformed scale:
skewed residuals

TRANSFORMATION

Transformed scale:
normal residuals





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Dynamic Transform Both Sides
Likelihood calculation given the transformation

- Likelihood of *untransformed* data– **allows OFV comparison**[1,2]

$$p(y) = \int p(y|b)p(b)db$$

$$p(y|b) = \prod \underbrace{\frac{1}{\sqrt{2\pi\sigma^2}} \times e^{-\frac{(\boldsymbol{h}(\boldsymbol{y})-\boldsymbol{h}(\hat{y}))^2}{2\sigma^2}}}_{\text{Likelihood of transformed data}} \times \underbrace{\frac{\boldsymbol{d\ h}(\boldsymbol{y})}{\boldsymbol{dy}}}_{\text{First derivative of Box Cox: } y^{\lambda-1}}$$

[1] Carroll & Ruppert. *Transformation and Weighting in Regression*. Chapman and Hall. 1998
[2] Oberg & Davidian. *Estimating Data Transformations in Nonlinear Mixed Effects Models*. Biometrics. 2000

Dynamic Transform Both Sides

Implementation in NONMEM

- **Dynamic** estimation of λ[1]

- Additional files[1,2]
  – data transformed during estimation
  – redefinition of likelihood

$$\underbrace{-2LL'}_{\text{Likelihood of untransformed data}} = \underbrace{-2LL}_{\text{Likelihood of transformed data}} - \underbrace{2(\lambda - 1)\log(y)}_{\text{Contribution of transformation}}$$

[1] Frame B. *Within Subject Random Effect Transformations with NONMEM VI*. Wolverine Pharmacometrics Corporation. 2009.
[2] Robert Bauer, adaptation courtesy for NM7

Dynamic Transform Both Sides

Power term for dynamic heteroscedasticity

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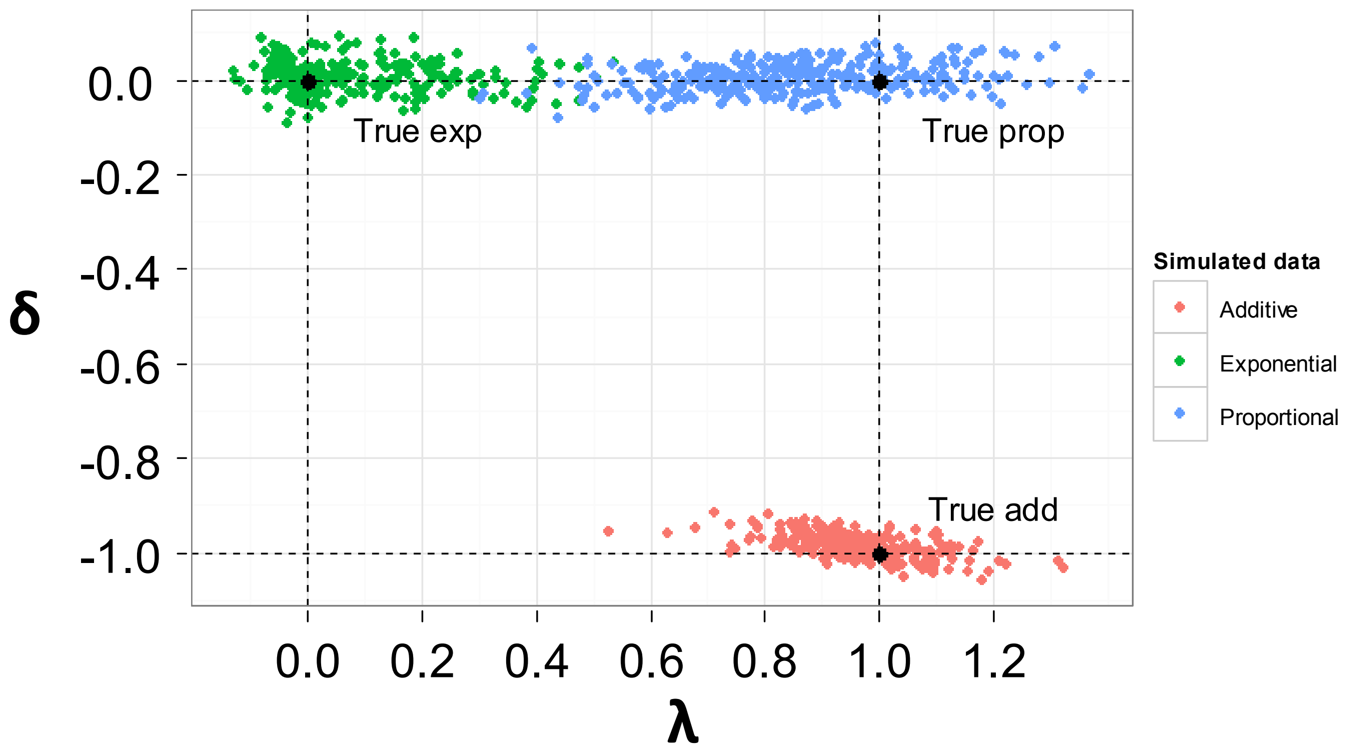
- **Power dTBS**: $\frac{\mathrm{DV}^{\lambda}-1}{\lambda} = \frac{\mathrm{IPRED}^{\lambda}-1}{\lambda} + \mathrm{IPRED}^{\zeta} * \varepsilon$
  $\varepsilon \sim N(0, \sigma^2)$
- Dynamic heteroscedasticity
- Parameterization: $\zeta = \lambda + \delta$

Model	**Equation**	$\widetilde{sd}$ **(ε) untransformed scale**	**sd (ε) transformed scale**
Power	$DV = IPRED + IPRED^{\zeta} * \varepsilon$	$\sigma \times IPRED^{\zeta}$	NA
Box-Cox	$h(DV) = h(IPRED) + \varepsilon$	$\sigma \times IPRED^{1-\lambda}$	σ
dTBS	$h(DV) = h(IPRED) + \mathrm{IPRED}^{\zeta} * \varepsilon$	$\sigma \times IPRED^{1-\lambda+\zeta}$	$\sigma \times IPRED^{\zeta}$

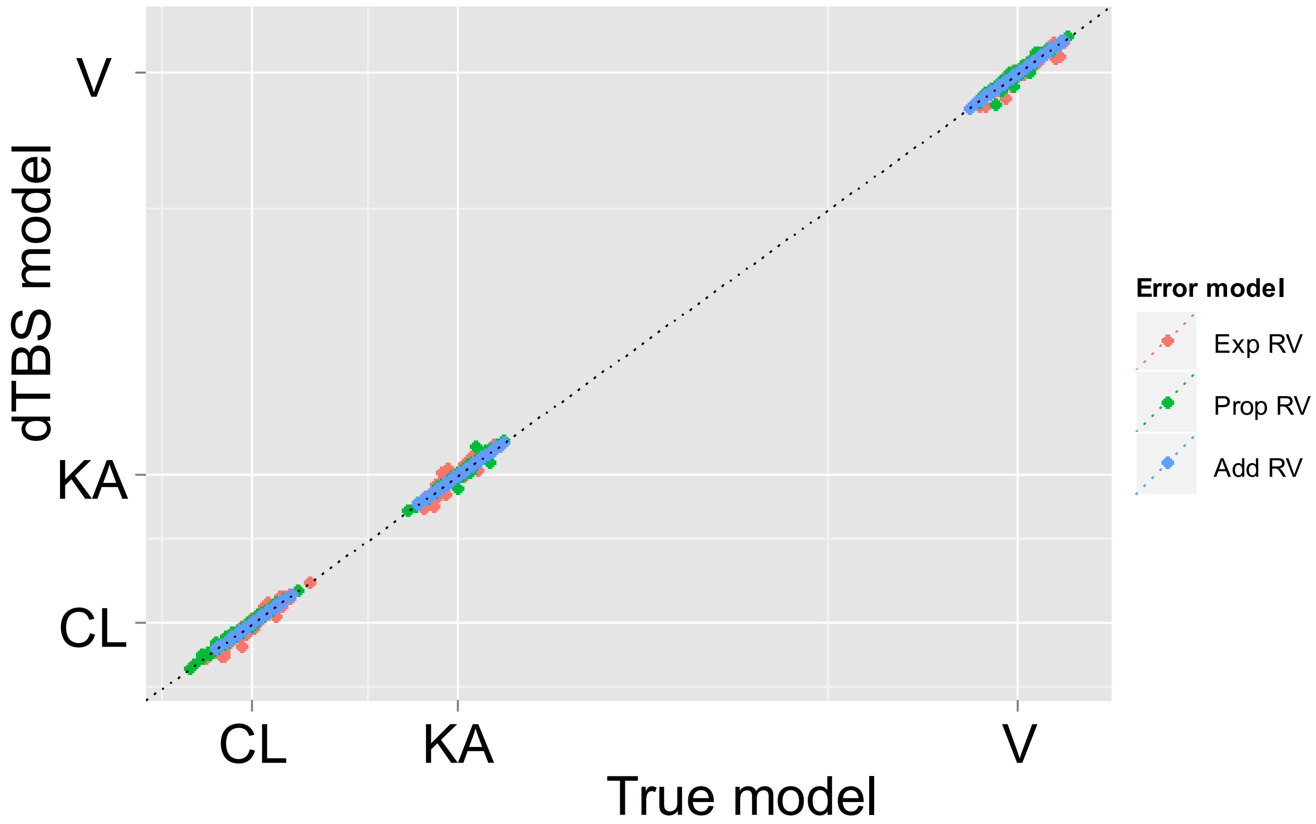
Dynamic Transform Both Sides
Simulation : estimation of λ and δ

- Simulation **additive, proportional and exponential** error models
- Estimation dTBS + true model



Dynamic Transform Both Sides

Simulation : satisfactory estimation of model parameters



Dynamic Transform Both Sides

Real data examples

Compound	Data	Model	RV model	Fixed transfo.	Obs.
ACTH & Cortisol	PD	turnover	combined	-	364
Cladribine	PK	IV 3 CMT	combined	-	488
Cyclophosphamide & metabolite	PK	4 CMT, CL induction	combined	-	383
Ethambutol	PK	2 CMT, transit	combined	-	1869
Moxonidine	PK	Oral 1 CMT	additive	Log	1021
Moxonidine	PD	E_{max}	additive	Log	1364
Paclitaxel	PD	Neutrophil	additive	Box-Cox	530
Pefloxacin	PK	IV 1 CMT	proportional	-	337
Phenobarbital	PK	IV 1 CMT	proportional	-	155
Prazosin	PK	Oral 1 CMT	proportional	-	887

Dynamic Transform Both Sides

Real data examples: dTBS estimates & OFV drop

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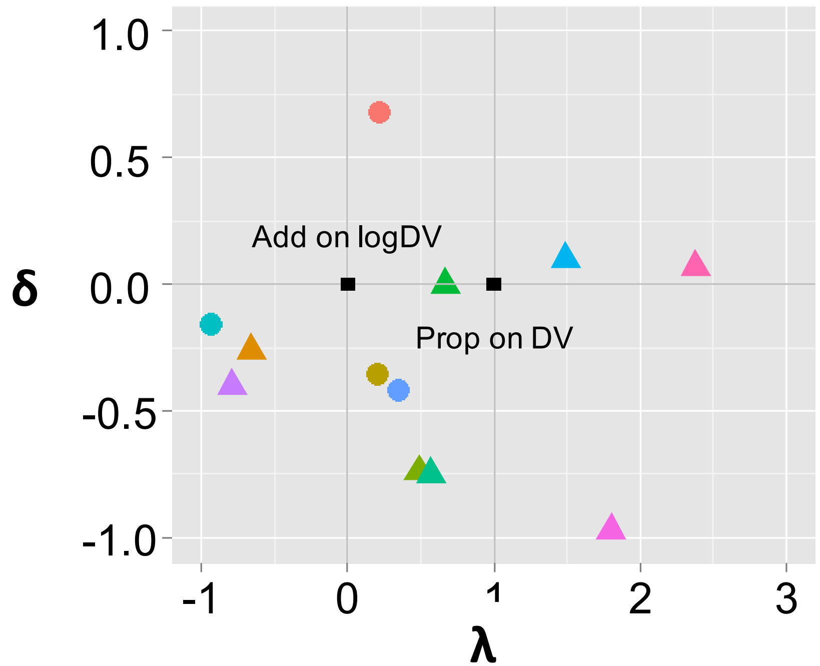
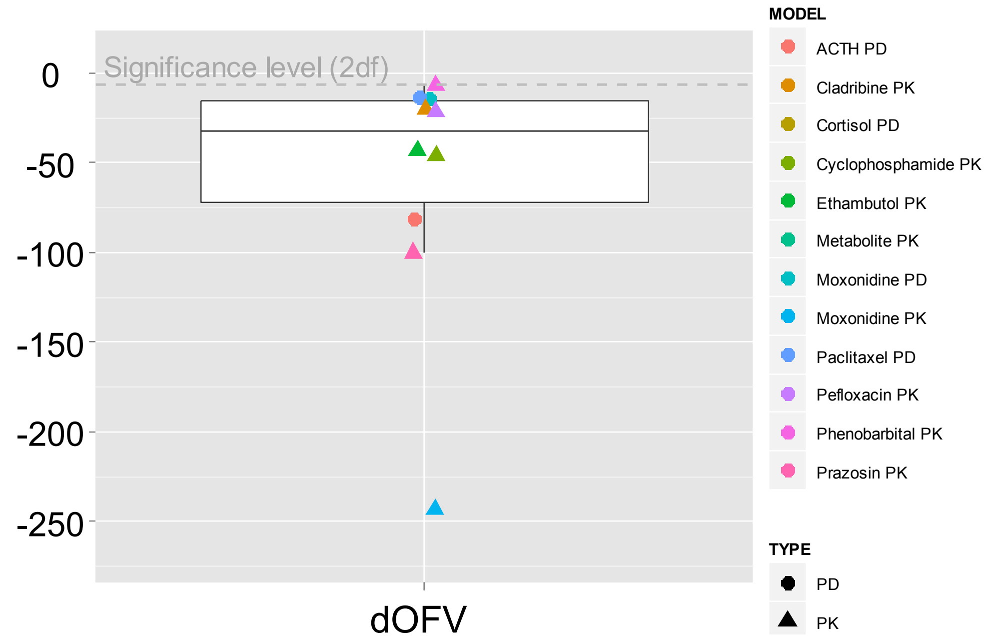
λ	δ
[-0.94; 2.38]	[-0.97; 0.68]

- 100% dOFV > 5.99
- **Mean drop -60**





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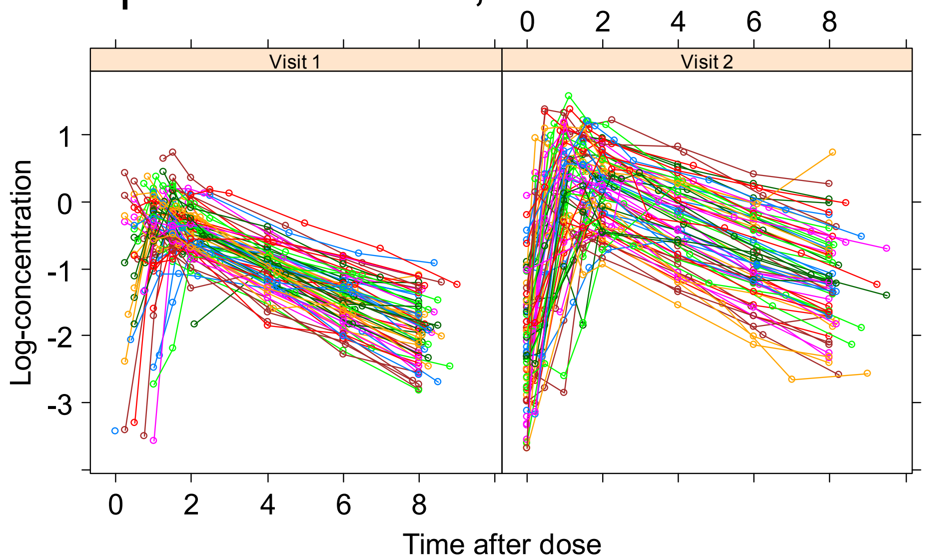
Dynamic Transform Both Sides

Moxonidine PK example: data and model

- **Data:** rich
  - 74 patients, 1021 observations
  - 3 possible doses, 2 occasions



- **Model**:
  - Additive error on log-transformed data
  - 1 CMT, first-order absorption, lag time

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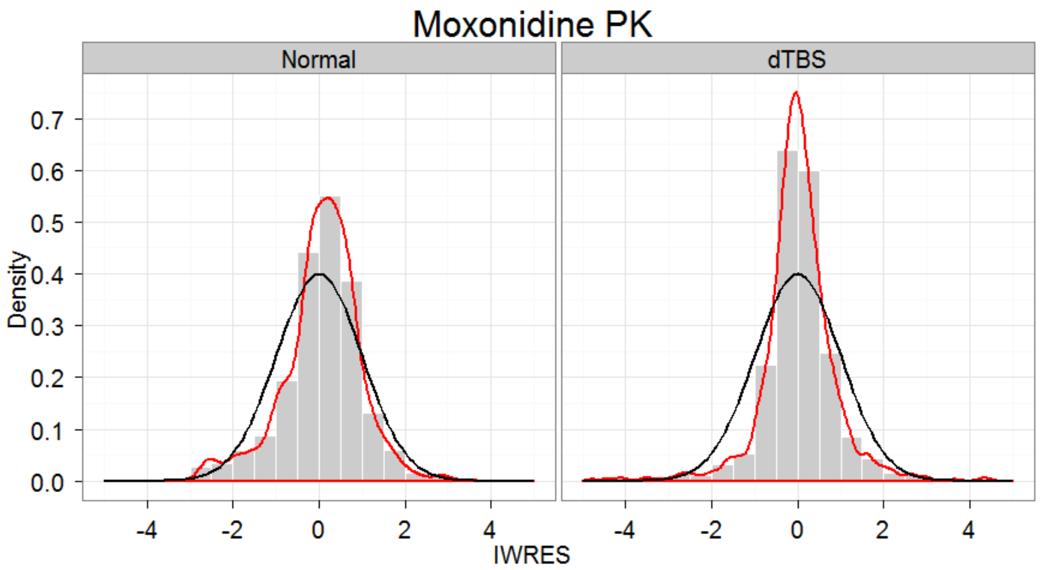
Dynamic Transform Both Sides

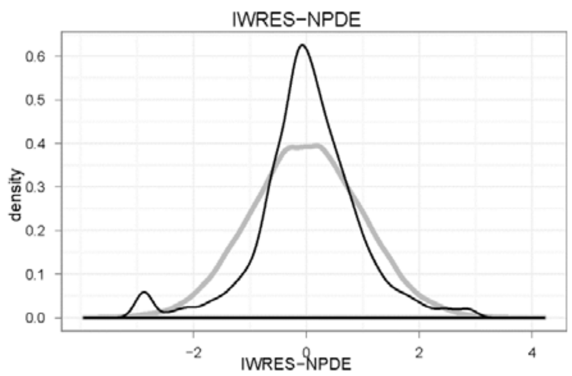
Moxonidine example: OFV and parameter estimates

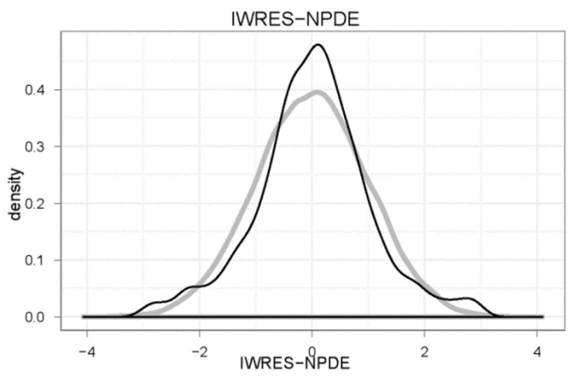
Parameter	Fixed log Value	Fixed log RSE(%)	dTBS Value	dTBS RSE(%)
OFV	-2173	-	-2416	-
dOFV	0	-	**- 243**	-
λ (-)	0	-	**1.5**	*6.3*
ζ (-)	0	-	**1.6**	-
Δ (ζ-λ)	0	-	0.1	*39*
CL ($L.h^{-1}$)	27	*1.2*	26	*3.4*
V (L)	110	*2.6*	108	*3.3*
KA (h^{-1})	4.5	*9*	4.9	*18*
LAG (h)	0.24	*1.3*	0.23	*2.3*
RV (na)	0.33	*1.3*	0.25	*4.1*
IIV CL (%)	27	*10*	25	*11*
Cor IIV CL-V (-)	0.74	-	0.70	-
IIV V (%)	24	*13*	24	*10*
IIV KA (%)	168	*12*	136	*14*
IOV CL (%)	12	*18*	17	*11*
IOV KA (%)	71	*18*	88	*16*

- Important OFV drop
- λ ≈ ζ ≈ 1.5: left skewness
- Parameter estimates changed (RV on different scales)

Dynamic Transform Both Sides
Moxonidine example: IWRES distribution

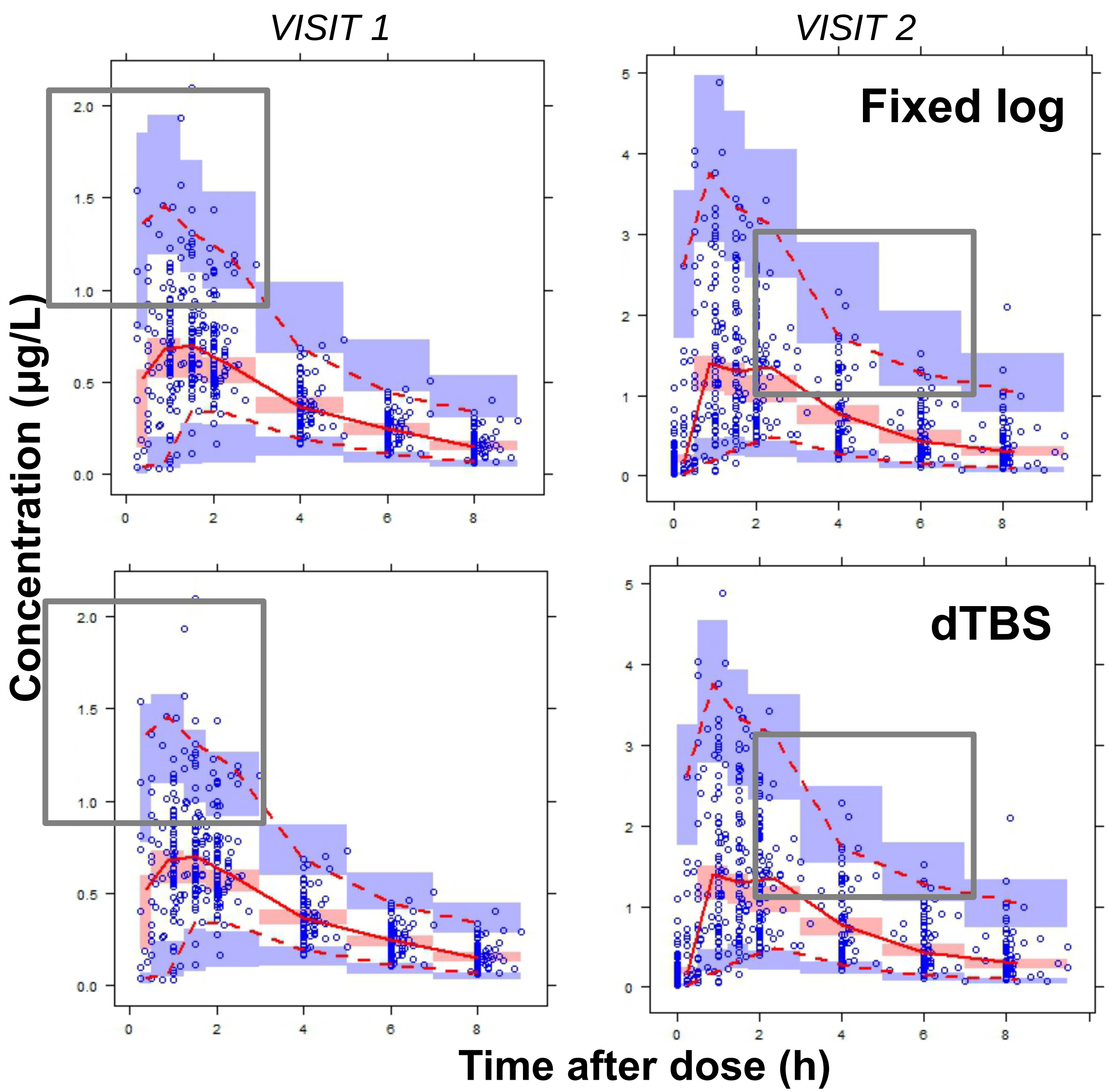






Dynamic Transform Both Sides

Moxonidine example: prediction properties



- **Narrower CI** with dTBS
- E.g. highest upper bound of CI_{95} 95^{th} perc. = **2 vs 1.6** (log vs dTBS)
- ***more precise predictions***

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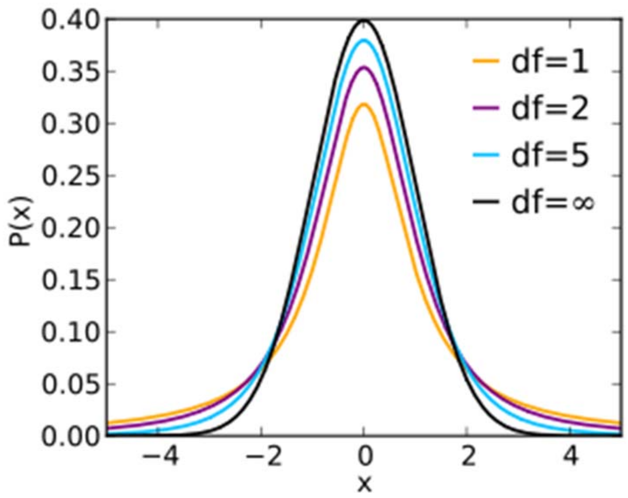
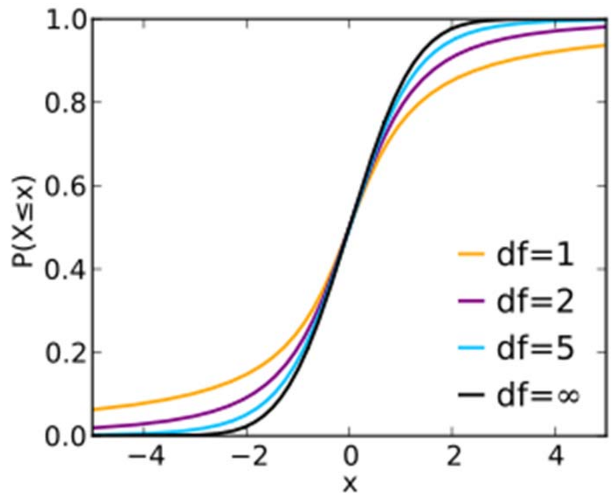
Residual error modeling with Student's t-distribution

Student's t-distribution
Function characteristics

- Parameter: **degrees of freedom** ν (df)
- Symmetric around 0, heavy-tailed
- Variance = $\frac{\nu}{\nu-2} > 1$ for $\nu > 2$
- Approaches normal distribution when $\nu \to \infty$





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Student's t-distribution

Implementation: redefinition of likelihood

- **Estimation**

- Likelihood based on pdf of t-distribution[1]

$$\boldsymbol{p}(\boldsymbol{y}|\nu,\sigma,\mu) = \frac{\Gamma(\frac{\nu+\mathbf{1}}{\mathbf{2}})}{\Gamma(\frac{\nu}{\mathbf{2}})\sqrt{\boldsymbol{\pi}\nu\boldsymbol{\sigma}^{2}}}\left(\mathbf{1}+\frac{\mathbf{1}}{\nu}\frac{(\boldsymbol{x}-\boldsymbol{\mu})^{2}}{\boldsymbol{\sigma}^{2}}\right)^{-\frac{\nu+\mathbf{1}}{\mathbf{2}}}$$

- Function Γ: Nemes approximation[2]
- ν ≥ 3: stability and full distribution definition

[1] Jackman, Simon. *Bayesian Analysis for the Social Sciences*. Wiley. 2009
[2] Nemes, Gergő. *New asymptotic expansion for the Gamma function*. Archiv der Mathematik . 2010

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Student's t-distribution
Real data examples

Compound	Data	Model	RV model	Fixed transfo.	Obs.
Moxonidine	PK	Oral 1 CMT	additive	Log	1021
Pefloxacin	PK	IV 1 CMT	proportional	-	337
Phenobarbital	PK	IV 1 CMT	proportional	-	155
Prazosin	PK	Oral 1 CMT	proportional	-	887

Compound	dOFV	ν
Moxonidine	- 400	3
Pefloxacin	- 16	4.7
Phenobarbital	0	∞
Prazosin	- 169	3

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Student's t-distribution

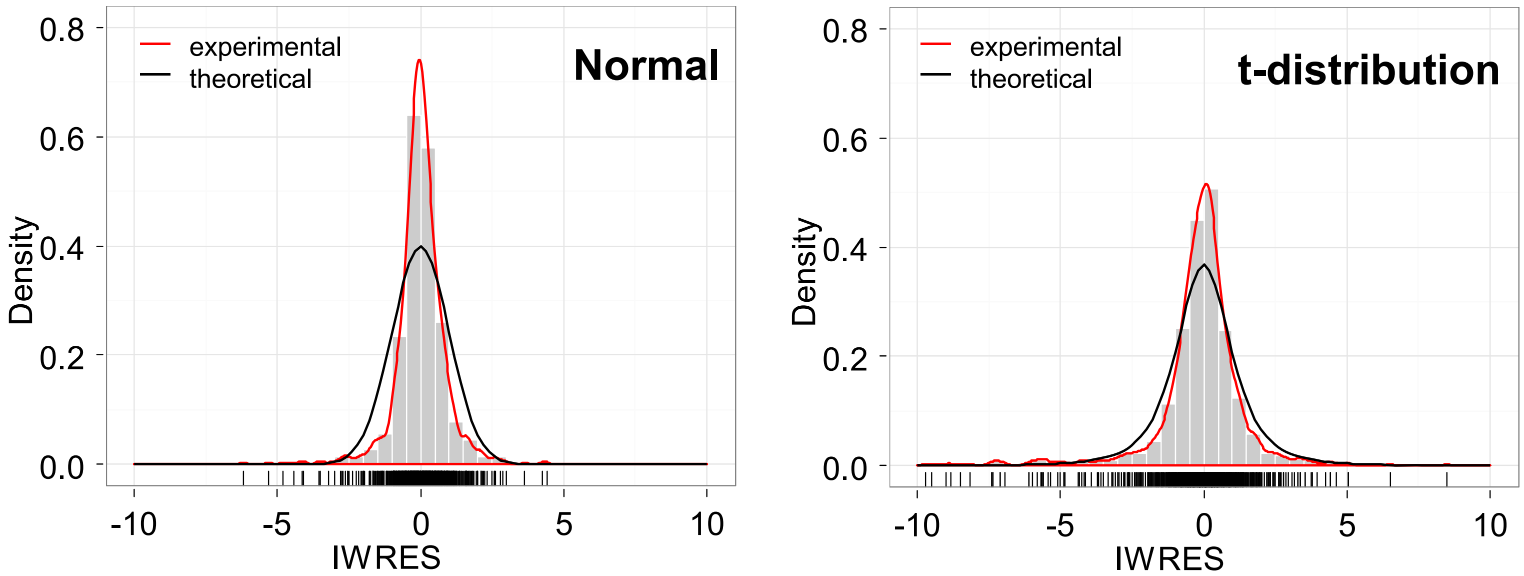
Moxonidine example: OFV and parameter estimates

Parameter	Normal	t-distribution
OFV	1221	820
dOFV	0	**- 400**
DF	∞	**3**
CL ($L.h^{-1}$)	26	26
V (L)	107	102
KA (h^{-1})	5.4	4.7
LAG (h)	0.24	0.24
RV (na)	0.33	0.17
IIV CL (%)	27%	28%
Cor IIV CL-V (-)	0.74	0.77
IIV V (%)	24%	23%
IIV KA (%)	162%	150%
IOV CL (%)	12%	12%
IOV KA (%)	63%	20%

- Important OFV drop
- DF at lower boundary
- Variance = 3

- Changes in absorption parameters

Student's t-distribution
Moxonidine PK: Residual distribution



- Better agreement between experimental and theoretical IWRES distribution for t-distribution

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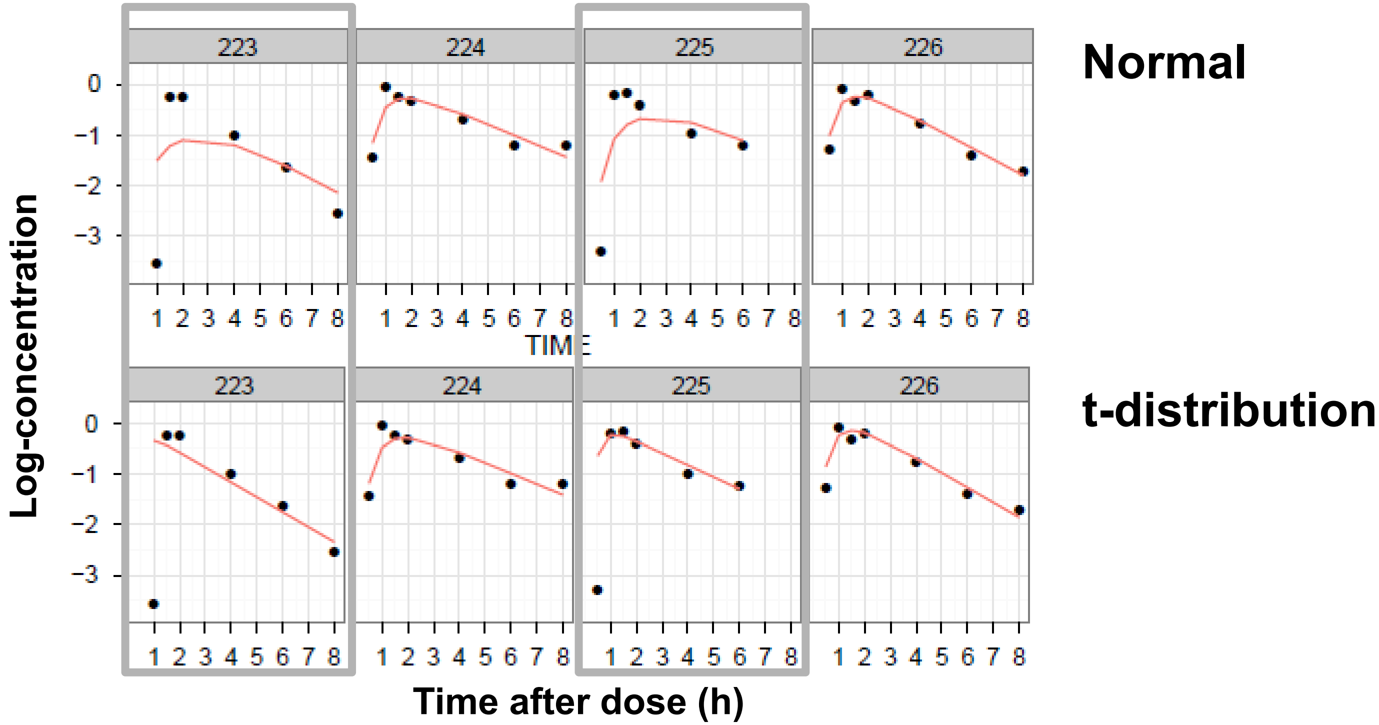
Student's t-distribution
Moxonidine example: Individual fits



- Better global fit by allowing some predictions to be further away from observations

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Conclusion

New possibilities for residual error modeling

dTBS

- **Dynamic**
- OFVs comparable
- Handles **skewness** and complex **scedasticity**
- Data: PK, particular assays…
- **Universal** model

t-distribution

- **Dynamic**
- OFVs comparable
- Way to leverage **outlier** information
- Data: multiple baselines, protocol deviations…

- Could be used jointly
- Can improve quality of parameter estimates and predictions

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Innovative Medicines Initiative

efpia

Drug Disease Model Resources ddmore

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Additional slides

- *dTBS ccontra and contr files*
- *dTBS model file code*
- *dTBS simulation code*
- *t-distribution simulation code*
- *Type I error investigation for dTBS and t-distribution*

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Dynamic Transform Both Sides

ccontra and contr files

ccontra

```
 subroutine ccontr (icall,c1,c2,c3,ier1,ier2)
      USE ROCM_REAL,   ONLY: theta=>THETAC,y=>DV_ITM2
      USE NM_INTERFACE,ONLY: CELS
!      parameter (lth=40,lvr=30,no=50)
!      common /rocm0/ theta (lth)
!      common /rocm4/ y
!      double precision c1,c2,c3,theta,y,w,one,two
      double precision c1,c2,c3,w,one,two
      dimension c2(:),c3(:,:)
      data one,two/1.,2./
      if (icall.le.1) return
      w=y(1)

      if(theta(7).eq.0) y(1)=log(y(1))
      if(theta(7).ne.0) y(1)=(y(1)**theta(7)-one)/theta(7)

      call cels (c1,c2,c3,ier1,ier2)
      y(1)=w
      c1=c1-two*(theta(7)-one)*log(y(1))

      return
      end
```

DV transformation

Redefinition of log-likelihood

contr

```
subroutine contr
(icall,cnt,ier1,ier2)
      double precision cnt
      call ncontr
(cnt,ier1,ier2,l2r)
      return
      end
```

Dynamic Transform Both Sides

Model file example: Modification of $ERROR

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Power RUV

Transform. of IPRED

```
$ ERROR

IPR1 = A(2)/V
IF(IPR1.LE.0) IPR1 = 0.001

LAMBDA = THETA(7)
ZETA   = LAMBDA + THETA(6)

W    = THETA(5)*IPR1**ZETA

IPRED = IPR1

IPRTR=IPRED
 IF (LAMBDA .NE. 0 .AND. IPRED .NE.0) THEN
    IPRTR=(IPRED**LAMBDA-1)/LAMBDA
 ENDIF
 IF (LAMBDA .EQ. 0 .AND. IPRED .NE.0) THEN
    IPRTR=LOG(IPRED)
 ENDIF
 IF (LAMBDA .NE. 0 .AND. IPRED .EQ.0) THEN
    IPRTR=-1/LAMBDA
 ENDIF
 IF (LAMBDA .EQ. 0 .AND. IPRED .EQ.0) THEN
    IPRTR=-1000000000
 ENDIF
 IPRED=IPRTR
```

Transform. of IWRES

```
 IRES  = IPRED-DV
 IWRES = IRES/W

IWRTR=IWRES

 IF (LAMBDA.NE.0 .AND. DV.NE.0 .AND.
    W.NE.0) THEN
   IWRTR=((DV**LAMBDA-1)/LAMBDA-IPRED)/W
 ENDIF
 IF (LAMBDA.EQ.0 .AND. DV.NE.0 .AND.
    W.NE.0) THEN
   IWRTR=(LOG(DV)-IPRED)/W
 ENDIF
 IF (LAMBDA.NE.0 .AND. DV.EQ.0 .AND.
    W.NE.0) THEN
   IWRTR=(-1/LAMBDA-IPRED)/W
 ENDIF
 IF (LAMBDA.EQ.0 .AND. DV.EQ.0 .AND.
    W.NE.0) THEN
   IWRTR=(-1000000000-IPRED)/W
 ENDIF

IWRES=IWRTR

Y=IPRED+EPS(1)*W
```

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Dynamic Transform Both Sides

Model file : other changes and simulation code

```
$SUBROUTINE ADVAN2 TRANS1  CONTR=contr.txt CCONTR=ccontra_nm7.txt
```

Additional files needed

```
$THETA  0.0001               ;DELTA_ZETA
$THETA  1                    ;LAMBDA

$ESTIMATION METHOD=1 INTER MAXEVALS=9999
```

dTBS SIMULATION ON UNTRANSFORMED SCALE

```
IF (ICALL.EQ.4 .AND. LAMBDA.EQ.0) THEN
  Y=EXP(Y)
ENDIF
IF (ICALL.EQ.4 .AND. LAMBDA.NE.0) THEN
  Y=((Y*LAMBDA)+1)**(1/LAMBDA)
ENDIF
```

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Student's t-distribution
Model file example

```
$ERROR
DF    = THETA(5)            ; degrees of freedom of Student distribution
W = THETA(4)*IPRED
SIG1  = W                   ; scaling factor for standard deviation of RUV
IWRES=(DV-IPRED)/SIG1

PHI=(DF+1)/2                ; Approximation of gamma function
INN=PHI+1/(12*PHI-1/(10*PHI))
GAMMA=SQRT(2*3.14159265/PHI)*(INN/EXP(1))**PHI

PHI2=DF/2                   ; Approximation of gamma function
INN2=PHI2+1/(12*PHI2-1/(10*PHI2))
GAMMA2=SQRT(2*3.14159265/PHI2)*(INN2/EXP(1))**PHI2

COEFF=GAMMA/(GAMMA2*SQRT(DF*3.14159265))/SIG1
BASE=1+IWRES*IWRES/DF
IF(BASE.EQ.0) BASE=0.000001
POW=-(DF+1)/2
L=COEFF*BASE**POW
Y=-2*LOG(L)

$EST MAXEVAL=9999 -2LL METH=1 LAPLACE
```

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Student’s t-distribution
Simulation code example

```
$ERROR

IPRED = ((DOSE/V)*(KA/C))*(A-B)

W = THETA(4)*IPRED
IWRES=(DV-IPRED)/W
DF = THETA(5)

IF (ICALL.EQ.4)
Y = IPRED +
W*EPS(1)*(1+((EPS(1)**2+1)/(4*DF))+((5*EPS(1)**4+16*EPS(1)**2+3)/(96*DF**
2))+((3*EPS(1)**6+19*EPS(1)**4+17*EPS(1)**2-15)/(384*DF**3)))

$SIGMA 1FIX
```

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Dynamic Transform Both Sides

Type I error rate not increased

Methods	
10,000 simulations 1 CMT PK model, exponential error model (40%)	
Re-estimation true model (λ = δ = 0)	*Re-estimation* dTBS model(λ = δ = est)

↓

Results
dOFV (alternative-true) > 5.99 in **5.04%** of cases

↓

Conclusion
Estimation of dTBS parameters **does not lead to increased type I error rate**

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Student's t-distribution

Type I error rate not increased

Methods	
10,000 simulations 1 CMT PK model, normally distributed additive error model	
Re-estimation true normal model	*Re-estimation* t-distributed error model

Results
dOFV (alternative-true) > 3.84 in **4.13%** of cases

Conclusion
Estimation of ν parameter **does not lead to increased type I error rate**