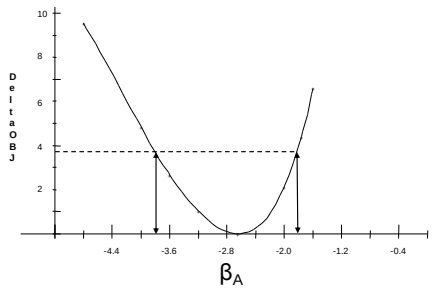
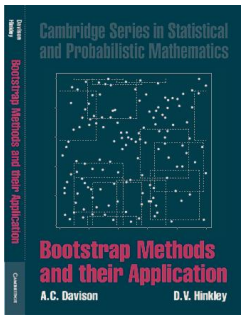
Slide 1	**Bootstrap and Confidence Intervals** Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2	Learn and Confirm Cycle ● Original idea from GE Box (1966) ● Translated to Drug Development Sheiner LB. Learning versus confirming in clinical drug development. *Clinical Pharmacology & Therapeutics* 1997;61(3):275-91 ©NHG Holford, 2015, all rights reserved.	Sheiner brought the idea of a learn and confirm cycle to drug development. The basic idea was originally devised by George Box (a famous statistician)
Slide 3	Confirming or Learning? ● Confirming tests the Yes/No Hypothesis ● If the question being asked has a **Yes/No** answer then it is a Confirming question ● If the question has a **How Much** answer then it is a Learning question ©NHG Holford, 2015, all rights reserved.	Confirming and learning require different kinds of answers.

Slide 4	**Confirming or Learning?** **Confirming** • Making sure • Outcome Expected • Analysis Assumptions Minimized E.g. Randomized Treatment Assignment • Questions for Drug Approval – E.g. • Does the drug work? • Can it be used safely in renal failure? **Learning** • Exploration • Outcome Unexpected • Assumption rich analysis – E.g. PKPD model • Questions for Drug Science – E.g. • How big an effect does the drug have? • What is the clearance in renal failure? Power Bias & Imprecision ©NHG Holford, 2015, all rights reserved.	Confirming answers are Yes or No. The rejection of the null hypothesis to accept a model answers the question 'Is this model better than the other?'. It is therefore a confirming question. Simulation can be used to define the power of a clinical trial to reject the null hypothesis. Learning answers describe how big something is. Estimation of model parameters answers learning type questions. Simulation can be used to learn the bias and imprecision of parameter estimates.
Slide 5	**Confidence in Population Models** ● How confident can you be in parameter estimates? ● Typical statistics » standard error » 95% confidence interval ©NHG Holford, 2015, all rights reserved.	Examining the distribution of uncertainty in parameter estimates is used to identify the standard error of the uncertainty (imprecision) and calculate a confidence interval.
Slide 6	**The Standard Error Problem** ● Standard errors (SE) are not confidence intervals (CI) ● CI using SE assumes a model – usually normal distribution ● Normal distribution is symmetrical ● What is the problem when using NONMEM? » Standard errors are asymptotic *estimates* – And may be unobtainable even if the model fit is good » Confidence intervals are often asymmetric ©NHG Holford, 2015, all rights reserved.	The standard error is of no use by itself. It can be used to compute a confidence interval under the assumption that the uncertainty is normally distributed. This is usually unreasonable for non-linear model parameters (such as Emax). It is common to find asymmetry in the uncertainty of a parameter.

Slide 7	**Log Likelihood Profile** ● Assume that change in log likelihood with different parameter values is Chi-square distributed ● Fix parameter of interest and refit the data ● Find parameter values which change log likelihood by CHIINV(1-CI,df=1) e.g. 3.84 for 95% CI ©NHG Holford, 2015, all rights reserved.	The log likelihood profile method does not assume symmetry of the parameter uncertainty but it does use the likelihood ratio test (LRT) based on the change in NONMEM objective function value to predict the probability of the confidence interval. This assumption is known to be only approximately true (see discussion of the randomization test).
Slide 8	**Log Likelihood Profile** **Tacrine Potency Parameter**  Holford NHG, Peace KE. Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proceedings of the National Academy of Sciences of the United States of America 1992;89(23):11471-11475 ©NHG Holford, 2015, all rights reserved.	A log likelihood profile (LLP) is illustrated here. The parameter is BetaA the potency parameter for the effect of tacrine at a dose of 80 mg/day. The approximate 95% confidence interval is shown under the assumption of the chi-square distribution. This LLP was obtained using the FO method and therefore the actual 95% CI is almost certainly wider than shown here.
Slide 9	**Resampling Methods** ● Jackknife (Quenouille 1949) » Used to estimate bias » Tukey (1958) proposed its use to estimate variance ● Bootstrap (Effron 1979) "A data set of size *n* has 2^n-1 nonempty subsets; the jackknife uses only *n* of them. The jackknife may be improved by using statistics based on … all 2^n-1subsets." Shao & Tu 1995 ©NHG Holford, 2015, all rights reserved.	Resampling methods have been proposed as a means to take advantage of the assumption that observations in a data set differ randomly and it is this random difference that gives rise to the uncertainty in a parameter. The Jackknife method takes subsets of the original data and obtains estimates of the parameter of interest. These are then combined to obtain an overall parameter estimate to describe the mean or the variance. The bootstrap is similar to the jackknife but creates datasets the same size as the original by re-sampling at random from the original data. This means that the same observation can appear more than once in the data set. Under the assumption that the random component of the observation is indeed random from observation to observation then it does not matter that an observation is resampled. The bootstrap method means that many more random data sets can be generated and this opens up the possibility to estimate more interesting statistics such as confidence intervals.

Slide 10	**Theoretical and Empirical Distributions** ● Theoretical distribution is based on a mathematical model for the distribution that might have given rise to the data e.g. normal ● Empirical distribution is derived from data ©NHG Holford, 2015, all rights reserved.	It is helpful to distinguish theoretical and empirical distributions. The bootstrap procedure constructs an empirical distribution. This is especially useful because the theoretical distribution may not be known.
Slide 11	**Bootstrap Methods** ● Davison & Hinkley 1997 ● Simulation methods » Parametric » Non-Parametric  ©NHG Holford, 2015, all rights reserved.	Davison & Hinkly describe the theory and application of bootstrap methods. They distinguish parametric bootstraps which rely on using parametric model to simulate data and non-parametric bootstraps which rely on resampling to obtain new randomly different datasets from original data.
Slide 12	**Bootstrap Samples** ● Parametric Sampling » Use a parametric model to simulate and sample from the theoretical distribution ● Non-parametric Sampling » Use the data and sample from the empirical distribution ● Compute statistics (e.g. 95% CI) from the Sample ©NHG Holford, 2015, all rights reserved.	Both the parametric and non-parametric bootstrap procedures can be used to generate samples from their respective distributions. The parametric method requires a full parametric model (e.g. PK model with population parameter variability and residual unidentified variability) while the non-parametric method only requires an original data set.

Slide 13

Non-Parametric Bootstrap

```
#Data is the empirical dist vector Fhat[] of length NSUB
#Let NBOOT be the number of bootstrap samples

for (i=1; i <= NBOOT; i++ ) {

#Sample the elements of Fhat NSUB times using a uniform random distribution

    for ( j=1; j <= NSUB; j++ ){
        jsub=int(NSUB*uran)+1
        BS[j] = Fhat[jsub]
     }
#Estimate parameter from the bootstrap sample e.g. the average

    Thetastar[i] = average(BS)
}

#Describe the distribution of Thetastar e.g. standard error

se = stdev(Thetastar)
```

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The basic bootstrap algorithm is shown using awk code. NBOOT is the number of bootstrap samples requested. This would typically be 1000 or more to obtain an estimate of the 95% confidence interval. Fhat is the empirical distribution i.e. the original data set. BS is a bootstrap data set obtained by resampling from Fhat. Nsub is the number of subjects. Thetastar is a vector of parameter estimates. In this case the average is computed for each BS sample data set. This step in the algorithm can be much more complex e.g. a NONEMM run using the BS data set can be used to estimate a full set of parameters.
In the last line of the algorithm a meta-analysis procedure is used to examine the results in Thetastar. In this case the standard deviation of the average values in Thetastar is used to estimate the standard error. The same Thetastar array could also be used to find the 90% confidence interval by looking for the values of Thetastar that are less than the 5%centile and greater than the 95%centile.

Slide 14

Resampling for Regression

- Model Based Resampling
  - » Fit model and then sample from residuals
    - – But problem with heteroscedastic error

$$Y_j^* = \hat{\beta}_0 + \hat{\beta}_1 \bullet X_j + \varepsilon_j^*$$

- Resampling Cases
  - » Sampling unit is a “case” of X,Y pairs
    - – But distorts original design
  - » Population analysis samples individuals as the “case”

$$Y_j^* = Y_i; X_j^* = X_i$$

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Davison & Hinckley point out the difficulty of sampling random observations when doing regression. Ideally one would sample from the residuals of the regression predictions but it there is heteroscedasticity then this cannot be done simply. The alternative is to sample from each subject as a ‘case’. This preserves the heteroscedasticity but distorts the design of the trial if there is substantial difference from subject to subject in their dose and sampling times. It seems unlikely that these design differences would be important in determining the outcome of typical PKPD data analyses.

Slide 15

WFN nmbs

- Any model/data
  - » Care with paths for user defined $SUB
- WFN command:

```
nmbs theopd 1 1000
```

- Results in theopd.bs directory in theopd.txt

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Wings for NONMEM has an nmbs command to automatically create bootstrap data sets and run NONMEM models. The only restriction is to be sure that any paths that exist in $SUB recognize that the bootstrap NONMEM run is two levels down from the parent directory. It is usually easier to give a fully qualified path for any $SUB user defined subroutines.
The bootstrap results are found in the a *.bs folder in a *.txt file. The *.txt file has the parameter estimates for each bootstrap replicate on one line of the file. They are tab delimited and can be easily read into Excel for further analysis.

Slide 16

Theophylline Example

Raw Results from 1000 Replications

#Rep	Obj	Min	Cov	POPE0	POPEMAX	POPEC50	EMSEX
1	5793.0	MINIMIZATION_SUCCESSFUL	ABORTED	158	147	8.85	0.754
2	5468.5	MINIMIZATION_SUCCESSFUL	OK	147	216	11	0.891
3	6037.1	MINIMIZATION_SUCCESSFUL	OK	127	230	9.05	0.801
4	5556.8	MINIMIZATION_SUCCESSFUL	OK	137	205	8.91	0.932
5	5400.9	MINIMIZATION_SUCCESSFUL	ABORTED	153	266	15.3	0.817
6	6152.6	MINIMIZATION_SUCCESSFUL	ABORTED	144	255	11.1	0.823

Successful Runs Sorted on Emax

Index	Rep	Obj	Min	Cov	POPE0	**POPEMAX**	POPEC50	EMSEX
1	732	5719.6	MINIMIZATION_SUCCESSFUL	OK	148	116	6.64	1.38
2	216	5936.6	MINIMIZATION_SUCCESSFUL	ABORTED	148	121	4.97	1.11
3	169	6002.0	MINIMIZATION_SUCCESSFUL	OK	155	129	5.13	0.963
24	74	5877.8	MINIMIZATION_SUCCESSFUL	OK	133	155	4.27	0.877
25	435	5587.2	MINIMIZATION_SUCCESSFUL	OK	156	**155**	6.76	0.919
26	337	6094.8	MINIMIZATION_SUCCESSFUL	OK	159	156	5.26	0.879
974	539	5460.3	MINIMIZATION_SUCCESSFUL	ABORTED	148	313	17.9	0.697
975	858	6098.0	MINIMIZATION_SUCCESSFUL	ABORTED	117	**313**	13.7	0.730
976	675	5492.8	MINIMIZATION_SUCCESSFUL	OK	156	314	19.7	0.640
998	873	5460.5	MINIMIZATION_SUCCESSFUL	ABORTED	136	349	15.8	0.671
999	986	5716.5	MINIMIZATION_SUCCESSFUL	ABORTED	139	358	22.6	0.741
1000	18	5928.1	MINIMIZATION_SUCCESSFUL	ABORTED	139	363	23.9	0.647

95% CI for Emax is 155 to 313

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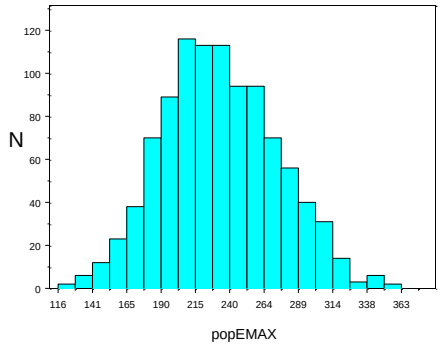
The theopdsex example is shown here. The Raw Results table shows the first 6 replications. The Successful Runs tables shows the same results sorted on the POPEMAX value. The lower 2.5% centile and upper 97.5%centile can be identified from their index in the table and the corresponding POPEMAX estimates used to define the 95% confidence interval for Emax.

Slide 17

Distribution of Emax (FOCE)



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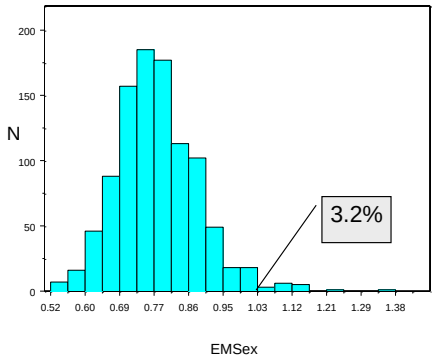
The bootstrap distribution of Emax is shown here. It looks reasonably symmetrical and even normal in shape.

Slide 18

Distribution of EMSex (FOCE)



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When the sex on Emax model is used the estimate of the reduction of Emax in females is shown above. The mode is about 0.75 which means the typical Emax is 25% lower in females. Only 3.2% of estimates are greater than 1 which provides strong support that this parameter is different inf females.

Slide 19

NONMEM Non-Parametric Bootstrap

- $SIMULATION OPTION

BOOTSTRAP=n
With the BOOTSTRAP option, NONMEM does not perform the usual simulation activity of randomly creating DV values for a new data set, but rather selects a random set of subjects from an existing "template" data set (which must already have legitimate DV values).

The BOOTSTRAP number n refers to how many subjects are to be randomly selected from the data set. Setting -1 means to randomly select as many subjects as are in the data set. For example, if 400 subjects are in the simulation template data set, then 400 subjects are randomly selected. The random source is, in effect, uniform, because any subject is equally probable.

```
$PROB theophylline pharmacodynamics
$DATA theopd.dat
$INPUT ID TIME THEO AGE WT SEX RACE DIAG DV
$SIML (20150716) BOOTSTRAP=-1 SUBP=2
$ESTIM METHOD=COND INTER PRINT=0
```

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Slide 20

WFN nmbsi

- Uses $SIM BOOTSTRAP=-1
- WFN command:

```
nmbsi theopd 1 100
```

- Results in theopd%NMDIR% directory in theopd.smy
- Bootstrap results are stochastically the same with nmbs and nmbsi

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Wings for NONMEM has an nmbs command to automatically create bootstrap data sets and run NONMEM models. The only restriction is to be sure that any paths that exist in $SUB recognize that the bootstrap NONMEM run is two levels down from the parent directory. It is usually easier to give a fully qualified path for any $SUB user defined subroutines.
The bootstrap results are found in the a *.bs folder in a *.txt file. The *.txt file has the parameter estimates for each bootstrap replicate on one line of the file. They are tab delimited and can be easily read into Excel for further analysis.

Slide 21

Parametric Bootstrap

- Random effects (parameters and residual error) are simulated instead of sampling from original dataset
- Fixed effects may use the same covariate distribution as original dataset or use simulated covariate distribution
- Distribution of bootstrap parameter estimates can be used to calculate estimation bias
- "Gold Standard" method for imprecision (confidence intervals, standard error)

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Slide 22

What is the Truth?

- Bias: Easy
  - » True parameters for fixed and random effects used for simulation
  - » Compared to bootstrap average estimate
- Uncertainty: Tricky
  - » 95SE: Standard error describing the 95% bootstrap confidence interval for the parameters
  - » Compared to bootstrap average asymptotic standard error

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Slide 23

NONMEM and Monolix Estimation Methods

- Parametric Bootstrap
  - » 100 simulated data sets
  - » Initial estimates "jitter" x 3 or x 1/3 true value (J3)
- NONMEM
  - » FOCEI
  - » AUTO (SAEM ln mu-transformed)
  - » A10k1k (like AUTO but 10,000 burnin, 1,000 accumulation)
- Monolix
  - » SAEM (ln transformed internally)
  - » p5p2 (500 burnin, 200 accumulation, Auto option)
  - » A10k1k (like p5p2 but 10,000 burnin, 1,000 accumulation)

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Slide 24

Warfarin PKPD Parameter Bias

Warfarin J3		NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method		FOCE	SAEM	SAEM	SAEM	SAEM
Option		INTER	AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL	MDL
POP_CL	0.1	-0.09%	0.58%	0.56%	-11.8%	-11.7%
POP_V	8	17.2%	-0.08%	-0.10%	9.2%	9.2%
POP_KA	2	222%	-4.5%	-5.0%	370084%	#########
POP_TLAG	1	48%	-3.5%	-4.5%	-19%	-18%
RUV_ADD	1	5.6%	-1.3%	-1.4%	19.1%	19.1%
RUV_PROP	0.1	57.2%	2.0%	2.2%	11.6%	12.0%
PPV_CL	0.316	-4.3%	-0.51%	-0.51%	-17.7%	-18%
PPV_V	0.316	57.4%	0.45%	0.40%	57%	80%
PPV_KA	0.316	130%	-63%	-66%	4.9%	4.9%
PPV_TLAG	0.316	338%	-9%	-7%	102%	103%
Corr CL V	0.1	0.8%	24%	23%	-239%	-238%
Average Time	sec	10.3	53.5	51.3	42.0	42.4
Max Time	sec	51.5	102.5	80.6	82.0	91.0
Success	%	100	100	100	98	98

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MU coding and EXIT for FOCE and NONMEM SAEM
Combined2 error model
Initial estimates "jitter" x 3 or x 1/3 true value (J3)

Slide 25

Warfarin PKPD Uncertainty

Warfarin J3	NONMEM	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM lnMU	FOCE	SAEM lnMU	SAEM lnMU	SAEM	SAEM
Option	AUTO	INTER	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_CL	6%	-5%	10%	11%	-7.4%	-7.2%
POP_V	6%	-19%	7%	7%	11.5%	12.7%
POP_KA	29%	-47%	171%	36%	46%	45%
POP_TLAG	18%	-80%	75%	47%	29%	31%
RUV_ADD	6%	-23%	7%	4.0%	3185%	3190%
RUV_PROP	11%	1.4%	43%	36%	-28%	-28%
PPV_CL	15%	-8.5%	5%	-2.3%	29.6%	39.8%
PPV_V	12%	-6%	28%	27%	643%	647%
PPV_KA	77%	101%	364%	359%	-83%	-83%
PPV_TLAG	42%	-7%	163%	145%	50%	52%
Corr CL V	158%					
SE success	%	5	100	100	98	98

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MU coding and EXIT for FOCE and NONMEM SAEM
Combined2 error model
Initial estimates "jitter" x 3 or x 1/3 true value (J3)

Slide 26

Parametric Bootstrap Comparison of Estimation

- Based on parameter and standard error bias the FOCE estimation method is better in some cases and SAEM is a better method in others
- Both NONMEM and Monolix asymptotic standard errors are often poor descriptions of uncertainty relative to the bootstrap 95 SE

Holford, N. H. G. (2014). Evaluation of NONMEM and Monolix by Parametric Bootstrap. PAGE. Alicante. http://www.page-meeting.org/default.asp?abstract=3143

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Slide 27

Practical Matters

- What if my preferred final model does not complete the $COV step?
- What do I do with bootstrap runs that do not minimize successfully?

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With simple data sets it is common for nearly all boostrap runs to complete successfully. It is not usual to run the $COV step at the same time because this takes extra time and the $COV estimates are not as useful as the bootstrap estimates of uncertainty. However, with more complex problems NONMEM may finish in a variety of ways these include: 1) $COV OK 2) Minimization successful but $COV failed 3) Minimization terminated due to rounding errors 4) Other errors eg. Next iteration would produce an infinite objective function value.

Slide 28

Methods

- Original Data set (Matthews et al. 2004)
  - » 697 patients; 2567 concentrations
- Final Model terminated
  - » MINIMIZATION TERMINATED DUE TO PROXIMITY OF LAST ITERATION EST. TO A VALUE AT WHICH THE OBJ. FUNC. IS INFINITE

Matthews I, Kirkpatrick C, Holford NHG. Quantitative justification for target concentration intervention - Parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. British Journal of Clinical Pharmacology 2004;58(1):8-19

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A recent publication has used bootstraps to obtain confidence intervals on parameters for a model that terminated with 'MINIMIZATION TERMINATED DUE TO PROXIMITY OF LAST ITERATION EST. TO A VALUE AT WHICH THE OBJ. FUNC. IS INFINITE'. This model was preferred as the final model because it expressed a pathophysiological reason for why some patients have low serum creatinine concentrations in comparison to their expected aminoglycoside clearance.

Slide 29

The Final Model Context

Model building – model description and objective function value

	Model components						
Model number	Size Model	CPR Model	RF Model	Low SCr Model	Obj	ΔObj	ΔNpar
1	Weight	Age, Sex	Age, Sex	Cr_{OPT}	5288.2	−569.1	6
2	Weight	Age, Sex	Age	Cr_{OPT}	5288.4	−568.9	5
3	Weight	Age, Sex	Age	RUCr	5296.7	−560.6	3 (1)
4	Weight	C&G	C&G	RUCr + RFV	5304.2	−553.1	1 (5)
5	Weight	Age, Sex	Age	F_{CPR}	5306.6	−550.7	4
6	Weight	C&G	C&G	Cr_{OPT}	5308.7	−548.6	(5)
7	Weight	C&G	C&G	RUCr	5310.1	−547.2	(2)
8	Weight	Age, Sex	–	–	5342.6	−514.7	2
9	Weight	C&G	–	–	5380.8	−476.5	(2)
10	Weight	C&G	C&G	RUCK	5410.7	−446.6	(5)
11	–	–	Age	–	5563.5	−293.8	1
12	–	Std	–	–	5759.2	−98.1	0
13	Weight	–	–	–	5803.2	−54.1	0
14	–	–	–	–	5857.3	0	0

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Model 5 estimates the fractional reduction in creatinine production rate in patients with serum creatinine less than 0.06 mmol/L. This was preferred over a similar model which empirically the serum creatinine to 0.06 if it was less than 0.06 (Model 6). Model 6 converged successfully and had similar parameters to Model 5. It did not seem reasonable that the Model 5 parameter estimates should be discarded simply because of the termination message from NONMEM.

Slide 30

Methods II

- Original Data Set
  - » Bootstrap of final model
  - » Initial estimates equal to final estimates at termination
- Simulated Data Set
  - » Model identical to Original Data
  - » Parameters obtained from average of 1055 bootstrap runs of original data
  - » Bootstrap of a single simulated data set

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Bootstraps were performed on the original data and also a data set obtained by simulating from the mean boostrap parameters obtained from the original data set.

Slide 31

Methods III

- Compilers
  - » Compaq Visual Fortran 6.6 Update C
    - – F77OPT =/fltconsistency /optimize:4 /fast
  - » GNU Fortran (GCC 3.1) 3.1 20020514
    - – F77OPT =-fno-backslash –O
- Platform
  - » Windows 2000
  - » Dual AMD MP2000

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Two compilers were compared. The Compaq df compiler is aggressively optimized while the GNU g77 compiler uses default optimization. It was expected that the GNU compiler might have better numerical performance while the df compiler would be faster.
All runs were performed on AMD MP2000 processors.

Slide 32

NONMEM Termination Type

	Data df	Data g77	Sim df
Runs	3141	924	3125
SUCCESS	30%	27%	46%
$COV	18%	9%	15%
INF OBJ	9%	12%	10%

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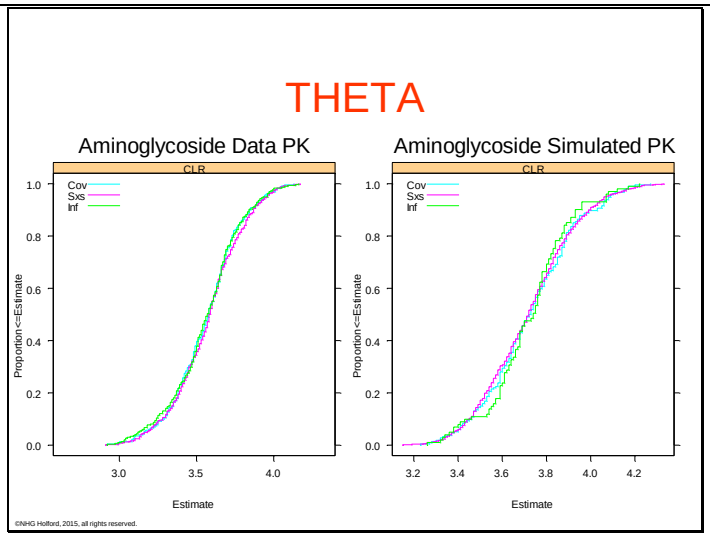
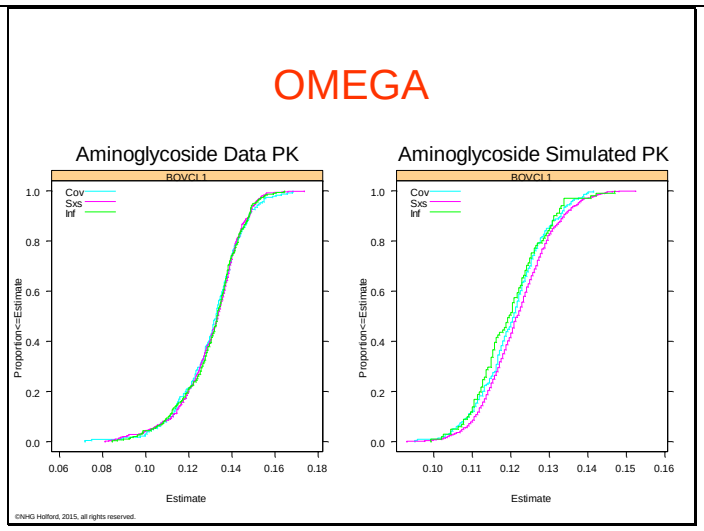
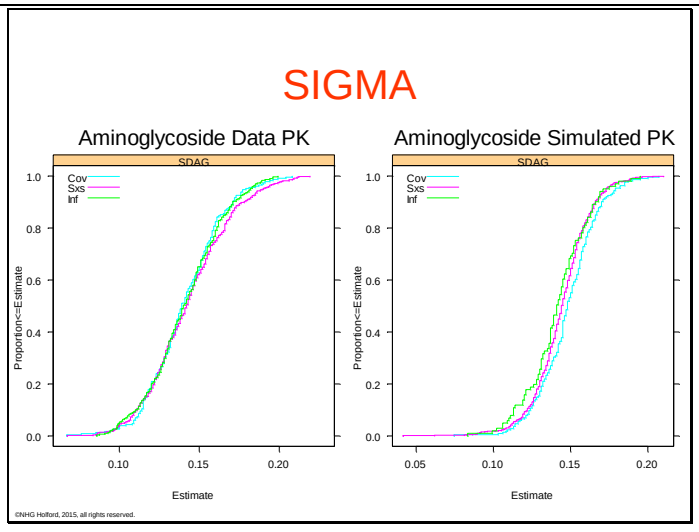
The two compilers gave broadly similar results for the types of termination. However, somewhat unexpectedly the g77 compiler was only able to complete the covariance step in half of the runs for which the df compiler was successful.
The simulated data set had more successful runs but % lower successful $COV.

Slide 33		The empirical cumulative distribution function for some key parameters is shown. It indicates that for both the original data (left) and simulated data (right) that the distributions of the parameters from the bootstrap datasets are essentially the same. Clinically unimportant differences in the mean parameter value and in the tails are shown but for all practical purposes the parameters are indistinguishable based on the termination type.
Slide 34		
Slide 35		

Slide 36

$COV Error
$COV/BS StDev -1

		COV	SXS	RND	INF
data df	THETA	-1%	0%	3%	4%
data g77	THETA	-6%	-5%	-5%	2%
sim df	THETA	-9%	-9%	-10%	-11%

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The estimated standard error obtained from the mean of the $COV estimates is compared to the standard deviation of the boostrap estimates. It shows that for all cases the difference is small. The simulated data set tends to have about a 10% underestimate of the true (bootstrap) standard error when it is computed from $COV. This might be expected from the asymptotic properties of the $COV standard error.

Slide 37

Bootstrap 80% Confidence Interval

- BSCI: Empirical
  - » 10%centile to 90%centile
- BSSE: Asymptotic Normal Distribution
  - » 1.28*2 * Bootstrap StDev
- BS Asymptotic Error
  - » (BSSE/BSCI-1)*100

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A second comparison is made of the $COV and bootstrap predictions of the 80% confidence interval. The bootstrap CI was obtained from the 10%centile to 90%centile values in the bootstrap distribution. The bootstrap standard error was also used to predict a 80% CI based on the normal distribution assumption.

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BS StDev
Normal Distribution Assumption
Error

	Stats	COV	SXS	RND	INF
	THETA	-21%	-23%	-21%	-21%
Data df	OMEGA	-23%	-21%	-20%	-20%
	SIGMA	-19%	-22%	-23%	-22%
	THETA	-15%	-19%	-22%	-20%
Data g77	OMEGA	-19%	-22%	-20%	-19%
	SIGMA	-22%	-23%	-23%	-15%
	THETA	-21%	-21%	-21%	-20%
Sim df	OMEGA	-21%	-17%	-21%	-22%
	SIGMA	-21%	-21%	-21%	-20%
	Average	**-20%**	**-21%**	**-21%**	**-20%**

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The standard error prediction of the 80%CI was consistently about 20% lower than the bootstrap empirical distribution CI. Once again this is compatible with the asymptotic prediction based on using SE.

Slide 39	## Conclusions - NONMEM termination status is not a useful predictor of parameter reliability *when the final model is acceptable 'in context'* - Compaq compiler is superior to g77 compiler in completing $COV step - $COV slightly underestimates SE - SE prediction of parameter confidence interval underestimates the empirical bootstrap interval ©NHG Holford, 2015, all rights reserved.	In conclusion, for this specific data set and model it seems that one should not rely on the NONMEM termination type as a measure of parameter reliability. This result may have more generalizable application provided one is confident that the model is a good description of the data and is not stuck at a local minimum (e.g. by comparison with other similar models).
Slide 40	## References Efron B. Bootstrap methods: another look at the jackknife. The Annals of Statistics 1979;7(1):1-26 Efron B, Tibshirani R. Statistical data analysis in the computer age. Science 1991;253(5018):390-395 Holford NH, Peace KE. Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proceedings of the National Academy of Sciences of the United States of America 1992;89(23):11471-11475 Quenouille M. Approximation tests of correlation in time series. Journal of the Royal Statistical Society B 1949;11:18-84 Stine (annotated bibliography) http://www.icpsr.umich.edu/TRAINING/Biblio95/stine.html Tukey J. Bias and confidence in not quite large samples. Annals of Mathematical Statistics 1958;29:614 ©NHG Holford, 2015, all rights reserved.	