Randomization and Mixture Approaches to Model Building

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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

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

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

The Confirming Question

- The most common Clinical Trial Simulation question:
  - » “Can the Null Hypothesis be rejected?”
- Frequentist Hypothesis testing requires
  - » specification of rejection level
    - – Alpha e.g. 0.05 [Type I Error criterion]
  - » calculation of a test statistic
    - – E.g. likelihood ratio
  - » prediction of P associated with test statistic
- How can P be predicted?

The Randomization Test

What is the True P Value?

- A critical issue for population model based analysis
- Assumption that NONMEM OBJ Function Difference is Chi-square distributed may be dubious for confirming trial decisions
- The OBJ Function difference is the Likelihood Ratio Test statistic
- Randomization Test uses computational power to ***estimate*** the true P value for a given data set and analysis method

Randomization Test

- Idea is to create a data set that would be expected if the Null Hypothesis was true
- Simplest case uses a binary covariate e.g. treatment assignment
- The original data has actual treatment assignment and outcome
- New data set is identical except for re-randomization of covariate so that the Null Hypothesis will be true (under randomization)

Randomization Test

There are (at least) 3 methods that can be considered for the randomisation of a covariate:

1. Sample from a parametric distribution for the covariate ('simulation')
2. Sample with re-sampling from the covariate empirical distribution (like bootstrap)
3. Sample by permutation of the covariate empirical distribution (no resampling)

RT Assignment Methods

Parametric Simulation

```
if (uran >= 0.5)
   rancov=1
else
   rancov=0
```

Empirical Permutation

```
if (nsub>1) {
   isub=int(nsub*uran)+1
   rancov=COV[isub]
   # remove COV[isub]
   for (i=isub; i<nsub; i++)
      COV[i]=COV[i+1]
   nsub--
} else
   rancov=COV[1]
```

Empirical ReSampling

```
isub=int(nsub*uran)+1
rancov=COV[isub]
```

Theophylline and Sex

- Randomized concentration controlled trial of theophylline

  Holford NHG, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? *Clinical Pharmacokinetics* 1993;25(6):495-505

- Simple Pharmacodynamic Model
- Does Sex affect Theophylline Emax?

Model for Sex

```
$PRED
   if (sex.eq.0) then ;female
      fsxemx=THETA(4)
   else
      fsxemx=1
   endif
   E0=      THETA(1)*EXP(ETA(1))
   EMAX=fsxemx*THETA(2)*EXP(ETA(2))
   EC50=THETA(3)*EXP(ETA(3))
   Y = E0 + EMAX*THEO/(THEO+EC50) + ERR(1)
```

Sex Change

Original

# ID	TIME	THEO	AGE	WT	SEX	RACE	DIAG	PEFR
1	0.01	1	27	57	0	1	1	200
1	1.51	20.7	27	57	0	1	1	300
2	0.01	0.1	21	76	0	1	1	110
2	1.42	25.5	21	76	0	1	1	200
2	4.42	26.2	21	76	0	1	1	325
3	0.01	0.1	26	67.5	1	1	1	150
3	1.01	11.7	26	67.5	1	1	1	400
3	3.76	7	26	67.5	1	1	1	420

Permuted

# ID	TIME	THEO	AGE	WT	SEX	RACE	DIAG	PEFR
1	0.01	1	27	57	0	1	1	200
1	1.51	20.7	27	57	0	1	1	300
2	0.01	0.1	21	76	1	1	1	110
2	1.42	25.5	21	76	1	1	1	200
2	4.42	26.2	21	76	1	1	1	325
3	0.01	0.1	26	67.5	0	1	1	150
3	1.01	11.7	26	67.5	0	1	1	400
3	3.76	7	26	67.5	0	1	1	420

NONMEM and RT

- Run Null and Alternate Models with Original Data
- Compute Original Data delta OBJ

  dOBJorg=original null OBJ minus original alternate OBJ
- Run Alternate Model with many (1000+) randomized data sets
- Compute Randomized Data delta OBJ

  dOBJ= original null OBJ minus randomized data set OBJ
- Sort on dOBJ and find quantile corresponding to dOBJorg

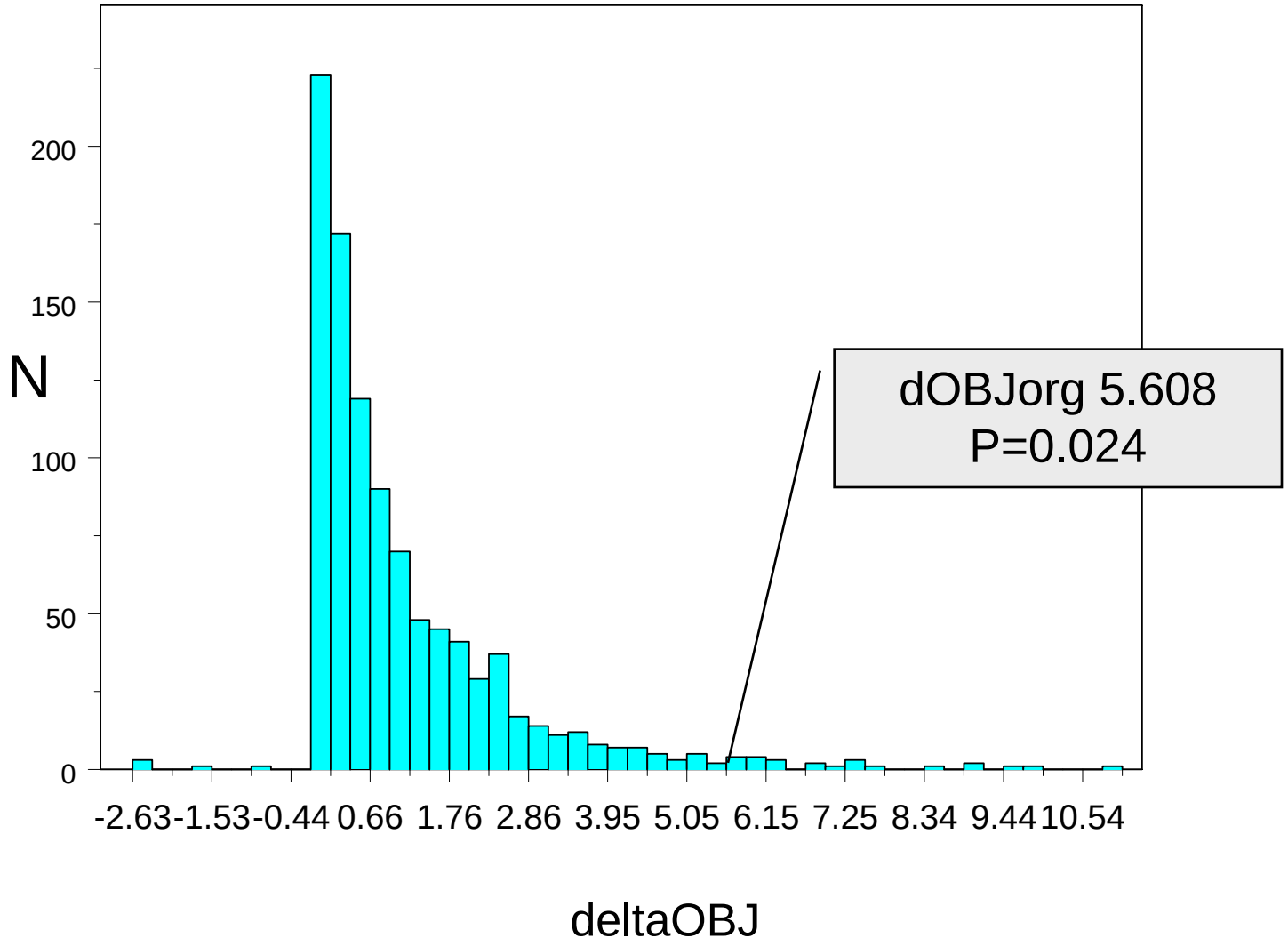
WFN nmrt

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

```
nmrt SEX theopdsex 1 1000
```

- SEX is an example of the covariate that will be permuted to generate null data sets
- Results in theopd.rt_SEX directory in theopd.txt

Null Distribution (FOCE)

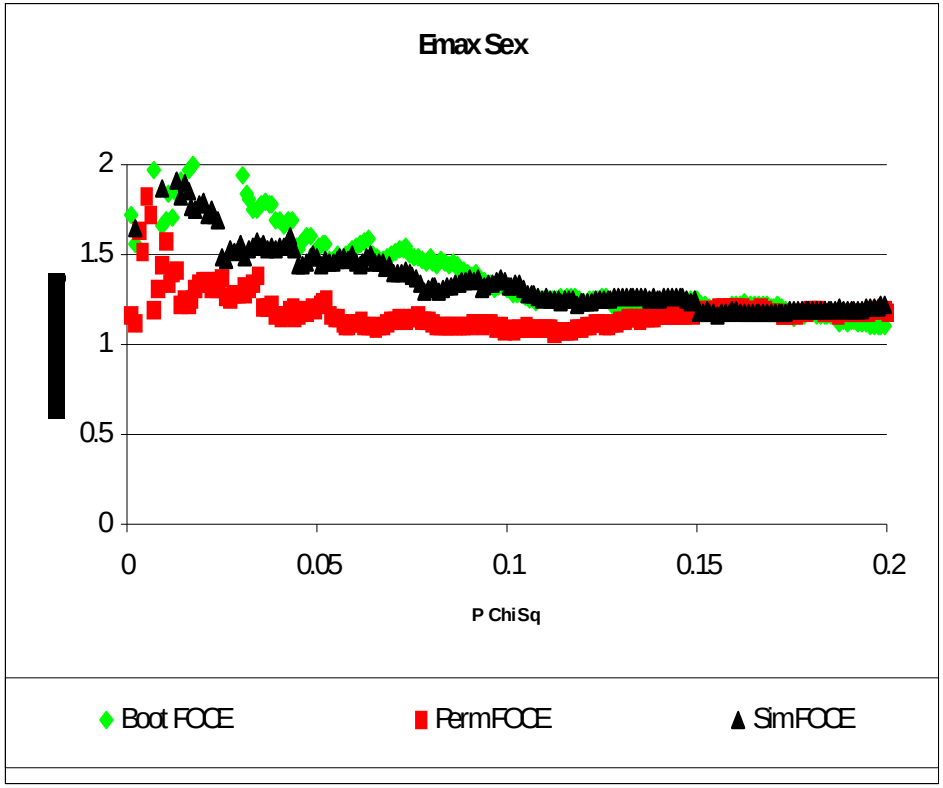


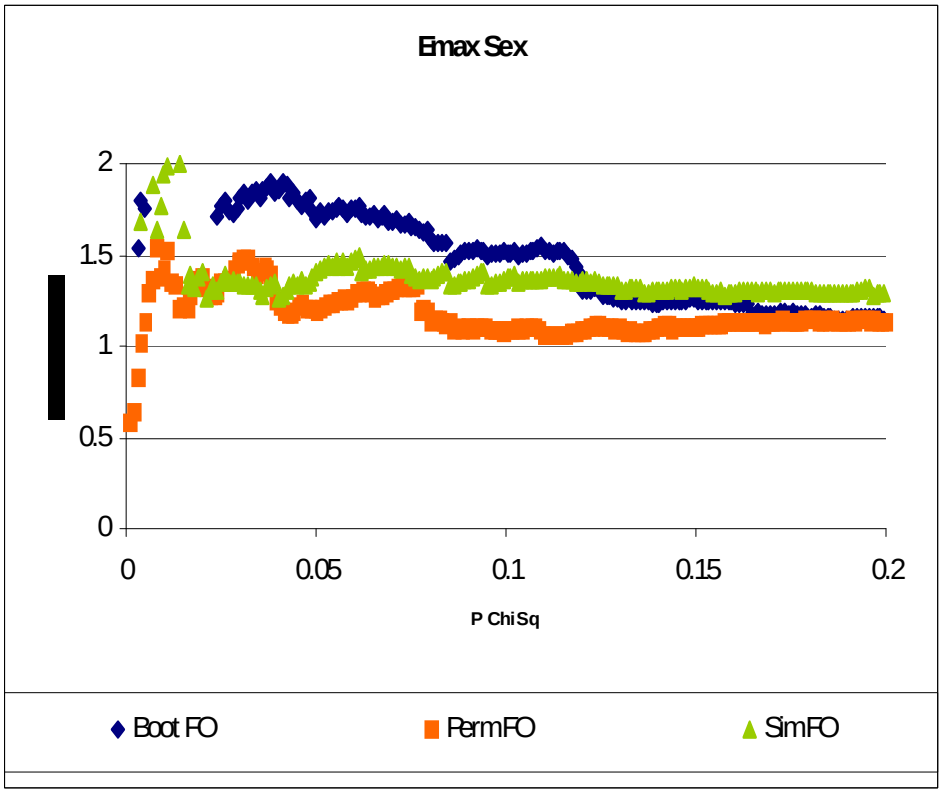
True P and Critical DOBJ Values

Rep	Dobj	Obj	P Chisq	P Quant	Quant/ChisQ	Decision
890	5.625	5795.706	0.017706	0.023139	1.306831	
170	5.608	5795.723	0.017879	0.024145	1.350485	Reject
464	5.568	5795.763	0.018292	0.025151	1.374994	
…						
112	4.163	5797.168	0.041316	0.049296	1.193135	
894	4.161	5797.17	0.041365	0.050302	1.216048	
25	4.146	5797.185	0.041733	0.051308	1.229431	
…						
864	3.911	5797.42	0.047971	0.055332	1.153445	
265	3.828	5797.503	0.050403	0.056338	1.11775	
545	3.777	5797.554	0.051962	0.057344	1.103582	

Original Data dOBJorg FOCE =5.608

Theophylline Emax and Sex





http://wfn.sourceforge.net/wfnrt.htm

Theophylline Emax and Sex

Estimation Method	Randomization Method	Successful Runs %	$\chi 2$ P	Quantile P	DOBJ(0.05,1)
FOCE[1]	Parametric	99.7	0.018	0.028	4.506
5.608	Non-Parm	99.7	0.018	0.033	4.570
	Permutation	99.4	0.018	0.024	4.163
FO[1]	Parametric	99.7	0.051	0.073	4.407
3.816	Non-Parm	99.7	0.051	0.080	4.741
	Permutation	99.5	0.051	0.065	4.115

- DOBJ FOCE $\chi 2$ P closer to true P value?
- Method Permutation closer to $\chi 2$ P?

1=Compaq Visual Fortran 6.6 Update A

Randomization Test of SEX and WT

Covariate	Parameter	Obj[1]	dOBJ	Randomization Test Probability[3]	PPV[2] Emax
None	-	5801.3	5.599	0.024	0.27
Sex	Emax	5795.7			0.22
Weight[4]	Emax,E0	5813.5	0.235	0.635	0.43
Sex Weight[4]	Emax Emax, E0	5813.3			0.43

1=NONMEM V 1.1 FOCE
2=Population Parameter Variability (sqrt(ω^2))
3=Compaq Visual Fortran 6.6 Update C
4=Allometric model on Emax and E0

Likelihood Ratio Test Results

- Seems to be a smaller Emax in women
  Against biological expectation (no effect)

- Adding weight worsens objective function and PPV suggesting no effect of weight on PEFR
  Against biological expectation (increase with size)

Mixed up about Sex? Is there another Way?

- A Bayesian approach is to estimate the probability of one model being favoured over another model

- NONMEM can use a mixture model to estimate this probability

Thanks to Steve Duffull for suggesting this approach

Mixture on Models

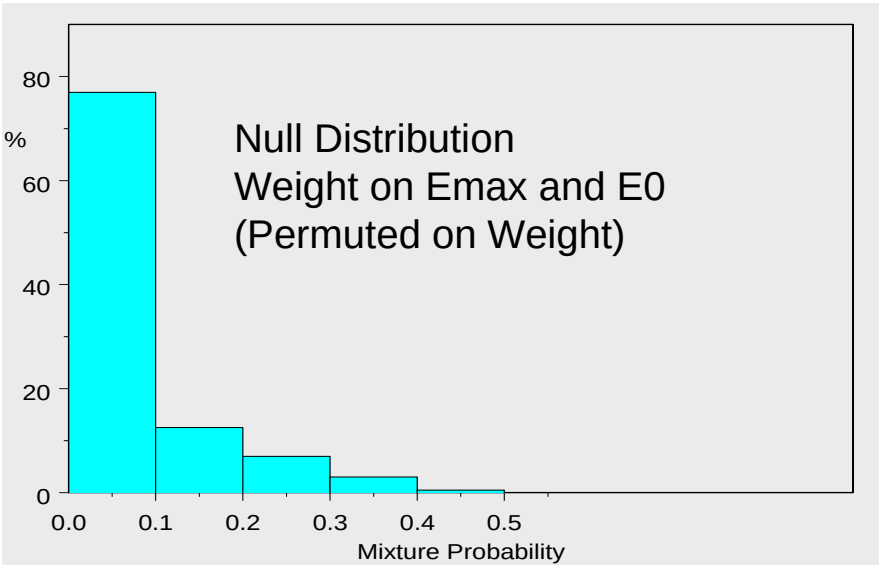
```
$PRED

   IF (MIXNUM.EQ.1) THEN ; sex effect model
      IF (SEX.NE.1) THEN
         FSXM=THETA(4) ;female
      ELSE
         FSXM=1  ;male
      ENDIF
   ELSE
      FSXM=1 ; no effect of sex
   ENDIF

   E0  =THETA(1)*EXP(ETA(1))
   EMAX=FSXM*THETA(2)*EXP(ETA(2))
   EC50=THETA(30*EXP(ETA(3))

   Y   =E0 + EMAX*THEO/(THEO+EC50) + EPS(1)

$MIX
  NSPOP=2
  P(1)=THETA(5)   ; Prob of sex effect model
  P(2)=1-THETA(5) ; Prob of no sex effect
```

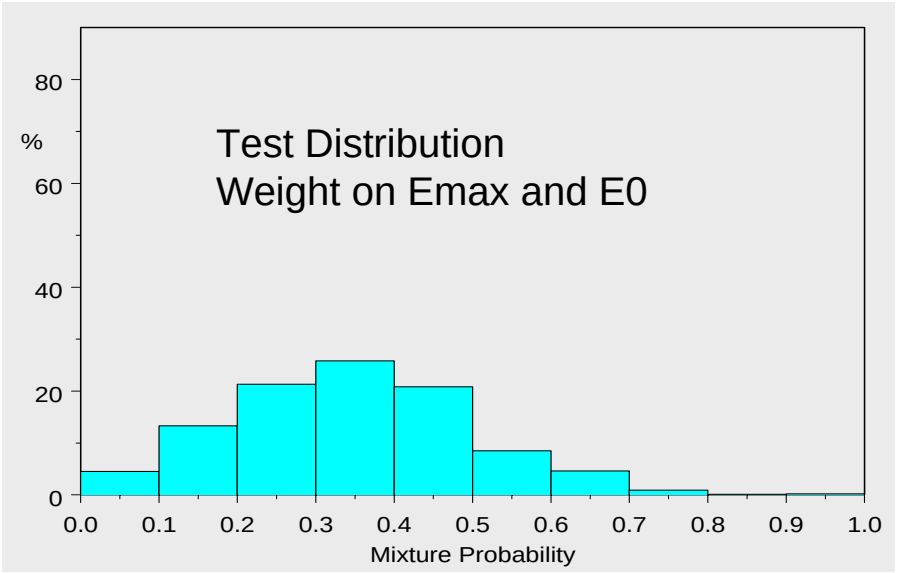
Mixture Model Method

- Specify both models in the same problem
- Estimate the mixture probability for each model
- Bootstrap the mixture model
- Examine distribution of mixture probability

Step 1: Probability of Weight on Emax and E0

1000 Permutations/Bootstraps

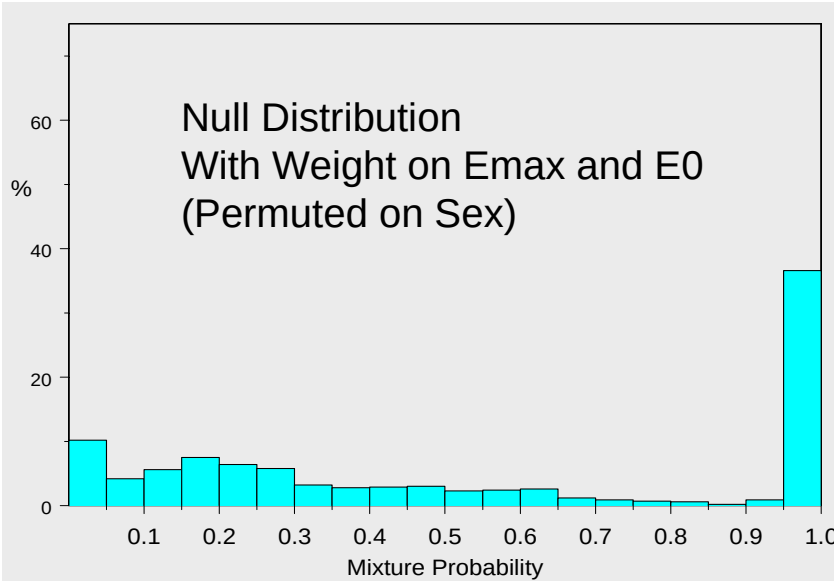


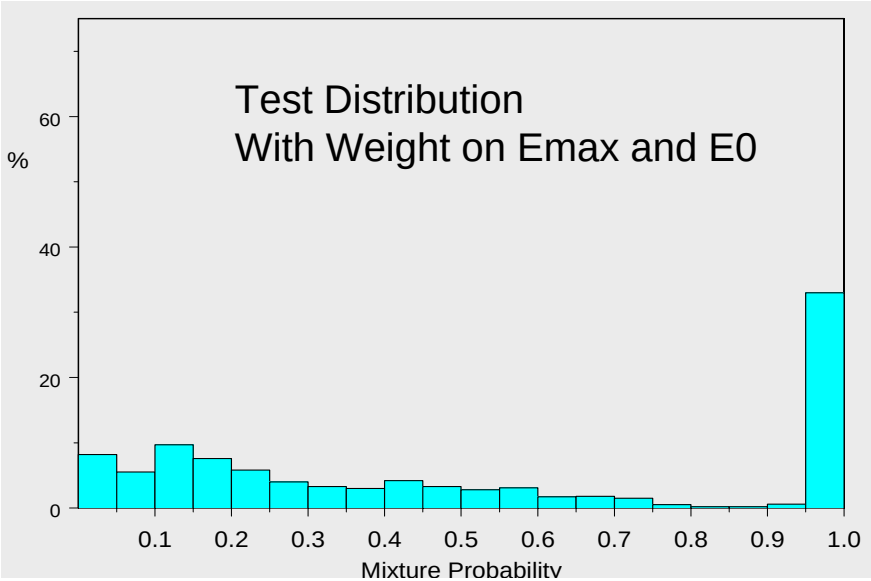


Step 2: Probability of Sex on Emax

With and Without Weight on Emax and E0

1000 Permutations/Bootstraps





Fractional Change of Emax in Females
1000 Bootstraps

	Weight on Emax and E0	Without Weight
Average	0.96	0.78
95% CI	0.72 – 1.24	0.06-1.01

Mixture Probability Results

- Distribution when weight is included is very different from the null when any weight effect has been removed by permutation

- No support for a sex effect
  Confirms biological expectation

- Suggests a weight effect on Emax and E0
  Confirms biological expectation

Statistics

- “Significance”
  - » Count of Mixture Prob > 0.5
- “Weight of Evidence”
  - » Average of Mixture Probability
- Odds
  - » For = Weight/(1-Weight)
  - » Against=(1-Weight)/Weight

Mixture Model Odds SEX and WT

	Mixture P Significance	**Mixture P Weight**	**Odds For**	**Odds Against**
No Weight	0.86	0.83	4.75	0.21
Weight on Emax	0.73	0.73	2.73	0.37
Weight on Emax and E0	0.45	0.52	1.07	0.93

Conclusion

- Females appear to have a smaller theophylline Emax for PEFR
- This difference is no longer supported when body size is used to explain between subject differences in Emax and baseline PEFR
- Mixture models are an alternative to the randomization test for model building