**Chapter 19 Online Appendix**

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# Online Appendix 19.A: Sample size estimation

The following is a listing of sample size estimation using both inferred ROC-AUC and wAFROC-AUC as figures of merit. The code listing of the relevant file mainwAFROCPowerDBMH.R follows.

### Online Appendix 19.A.1: Code listing

rm(list = ls()) #mainwAFROCPowerDBMH.R

library(ggplot2)

library(RJafroc)

source("loadDataFile.R")

# included datasets

fileName <- c("TONY", "VD", "FR", "FED", "JT", "MAG", "OPT", "PEN", "NICO", "RUS", "DOB1", "DOB2", "FZR" )

fileName <- fileName[4]

cat("fileName = ", fileName,"\n")

frocData <- loadDataFile(fileName)

retFileName <- paste0("ANALYZED/", "saveRetRoc", fileName)

if (!file.exists((retFileName))){

I <- length(frocData$modalityID)

J <- length(frocData$readerID)

s <- 1

for (i in 1:I){

for (j in 1:J){

cat("i = ", i, ", j = ", j, "\n")

CBM <- CBMFitR(rocData, i, j)

tempRoc <- FitRsmRocCurve(rocData, i, j, AUCCbm = CBM$AUC, zetaCbm = CBM$cutoffs, nLesDistr = nLesDistr)

retSmRoc[[s]] <- as.list(c(tempRoc,

list(nLesDistr = nLesDistr, CBMAUC = CBM$AUC, CBMmu = CBM$mu, CBMalpha = CBM$alpha, CBMcutoffs = CBM$cutoffs, i = i, j = j)))

s <- s + 1

}

}

save(retSmRoc, file = retFileName)

} else {

load(retFileName) # loads object retSmRoc, i.e., ROC data previously analyzed by RSM; this has parameter values

}

i1 <- 1;i2 <- 2 # FED data has 5 modalities; we choose to analyze the first two

cat("NH i1 = ", i1, "NH i2 = ", i2, "\n")

selectJ <- c(1, 2, 3, 4)

frocData <- ExtractDataset(frocData, trts = c(i1, i2), rdrs = selectJ)

J <- length(frocData$readerID)

K <- dim(frocData$NL)[3]

mu1 <- rep(NA, J);mu2 <- rep(NA, J);nu1 <- rep(NA, J);nu2 <- rep(NA, J);lambda1 <- rep(NA, J);lambda2 <- rep(NA, J)

S <- length(retSmRoc)

for (s in 1:S){

if (retSmRoc[[s]]$j %in% selectJ){

if (retSmRoc[[s]]$i == i1){

mu1[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$mu$mu)

lambda1[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$lambda$lambda)

nu1[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$nu$nu)

}else if (retSmRoc[[s]]$i == i2){

mu2[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$mu$mu)

lambda2[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$lambda$lambda)

nu2[retSmRoc[[s]]$j == selectJ] <- as.numeric(retSmRoc[[s]]$nu$nu)

}

}

}

mu <- rbind(mu1, mu2);lambda <- rbind(lambda1, lambda2);nu <- rbind(nu1, nu2)

muMed <- median(mu) # instead of average, use median to get representative value over whole dataset

nuMed <- median(nu) # do:

lambdaMed <- median(lambda) # do:

# construct lesion weights, assuming equally weighted lesions

nLesDistr <- retSmRoc[[1]]$nLesDistr

lesionWeights <- matrix(-Inf, nrow = nrow(nLesDistr), ncol = nrow(nLesDistr))

for (l in 1:nrow(nLesDistr)){

nLes <- nLesDistr[l, 1]

lesionWeights[l, 1:nLes] <- 1/nLes

}

# calculate NH values for ROC-AUC and wAFROC-AUC

aucRocNH <- RsmOperatingCharacteristics(muMed, lambdaMed, nuMed,

lesionDistribution = nLesDistr, lesionWeights = lesionWeights, type = "ROC")$aucROC

aucAfrocNH <- RsmOperatingCharacteristics(muMed, lambdaMed, nuMed,

lesionDistribution = nLesDistr, lesionWeights = lesionWeights, type = "wAFROC")$aucwAFROC

# following code calculates ROC-ES and wAFROC-ES

deltaMu <- seq(0.01, 0.2, 0.01) # values of deltaMu to scan below

esRoc <- array(dim = length(deltaMu));eswAfroc <- array(dim = length(deltaMu))

for (i in 1:length(deltaMu)) {

esRoc[i] <- RsmOperatingCharacteristics(muMed + deltaMu[i], lambdaMed, nuMed, lesionDistribution =

nLesDistr, lesionWeights = lesionWeights, type = "ROC")$aucROC - aucRocNH

eswAfroc[i] <- RsmOperatingCharacteristics(muMed+ deltaMu[i], lambdaMed, nuMed, lesionDistribution =

nLesDistr, lesionWeights = lesionWeights, type = "wAFROC")$aucwAFROC - aucAfrocNH

#cat("ES ROC, wAFROC = ", esRoc[i], eswAfroc[i],"\n")

}

#cat("\n")

a<-lm(eswAfroc~-1+esRoc) # fit values to straight line thru origin

effectSizeROC <- seq(0.01, 0.1, 0.01)

effectSizewAFROC <- effectSizeROC\*a$coefficients[1]

JTest <- 5;KTest <- 100

varCompROC <- DBMHAnalysis(frocData, fom = "HrAuc", option = "RRRC")$varComp

varCompwAFROC <- DBMHAnalysis(frocData, fom = "wAFROC", option = "RRRC")$varComp

cat("JTest = ", JTest, "KTest = ", KTest, "\n")

powerROC <- array(dim = length(effectSizeROC));powerwAFROC <- array(dim = length(effectSizeROC))

for (i in 1:length(effectSizeROC)) {

varYTR <- varCompROC$varComp[3]

varYTC <- varCompROC$varComp[4]

varYEps <- varCompROC$varComp[6]

powerROC[i] <- SsPowerGivenJK(JTest, KTest, alpha = 0.05, effectSize = effectSizeROC[i], option = "RRRC",

method = "DBMH", varYTR = varYTR, varYTC = varYTC, varYEps = varYEps)

varYTR <- varCompwAFROC$varComp[3]

varYTC <- varCompwAFROC$varComp[4]

varYEps <- varCompwAFROC$varComp[6]

powerwAFROC[i] <- SsPowerGivenJK(JTest, KTest, alpha = 0.05, effectSize = effectSizewAFROC[i], option = "RRRC",

method = "DBMH", varYTR = varYTR, varYTC = varYTC, varYEps = varYEps)

cat("ROC effect size = ,", effectSizeROC[i], "wAFROC effect size = ,", effectSizewAFROC[i],

", Statistical power ROC, wAFROC:", powerROC[i], ",", powerwAFROC[i], "\n")

}

df <- data.frame(esRoc = esRoc, eswAfroc = eswAfroc)

p <- ggplot(data = df, aes(x = esRoc, y = eswAfroc)) +

geom\_smooth(method = "lm", se = FALSE, color = "black", formula = y ~ x) +

geom\_point()

print(p)

df <- data.frame(powerROC = powerROC, powerwAFROC = powerwAFROC)

p <- ggplot(mapping = aes(x = powerROC, y = powerwAFROC)) +

geom\_line(data = df, size = 0.5)

print(p)

Line 8 defines the dataset to be loaded, namely the "FED" dataset, which is a 5-modality 4-radiologist FROC dataset. Place a break point at line 32 and click Source. Line 34 selects all four radiologists in the dataset and line 35 uses the ExtractDataset() function to extract data corresponding to the first two modalities only, as these are the ones regarded as NH modalities. Keep clicking on Next until the code pointer advances to line 36. Examination of the Environment panel reveals that now frocData is a 2-modality 4-reader dataset with 100 non-diseased and 100 diseased cases. Line 39 assigns memory to hold the parameters  where the appendage "1" applies to modality 1 and "2" applies to modality 2. Keep clicking on Next until the code pointer advances to line 42. Confirm (highlight and click Run) that the value of S is 20, since retSmRoc is a list with 20 elements; this comes from the 5 modalities x 4 readers.

Click Next to bring the code-pointer to line 43. This line looks complicated: *carefully* highlight retSmRoc[[s]] and click Run, Online Appendix 19.A.2 (the author has compressed the listing be deleting blank lines) and an RSM predicted ROC plot and overlaid operating points for the first reader in the first modality is displayed in the Plots panel.

### Online Appendix 19.A.2: Code snippet

Browse[2]> retSmRoc[[s]]

$plots

$plots[[1]]

$mu

mu Modality Reader

1 3.67597138794971 1 1

$lambda

lambda Modality Reader

1 36.5574221504606 1 1

$lambdaP

lambdaP Modality Reader

1 9.94496917748065 1 1

$nu

nu Modality Reader

1 0.415773740358019 1 1

$nuP

nuP Modality Reader

1 0.783111606500295 1 1

$AUC

AUC Modality Reader

1 0.902039601221186 1 1

$zetas

zetaFwd1 zetaFwd2 zetaFwd3 zetaFwd4 zetaFwd5

1.500923 1.699539 2.102367 2.688416 3.698767

$gdnss

gdnss Modality Reader

1 <NA> 1 1

$nLesDistr

[,1] [,2]

[1,] 1 69

[2,] 2 20

[3,] 3 11

$CBMAUC

[,1]

[1,] 0.9020396

$CBMmu

[,1]

[1,] 3.063572

$CBMalpha

[,1]

[1,] 0.8291959

$CBMcutoffs

NULL

$i

[1] 1

$j

[1] 1

The object retSmRoc is list of 16 elements (for the curious, count the instances of $ in the above code snippet; or type str(retSmRoc[[s]]) at the Console prompt and view the last seven items of the ouput).

...

...

..$ nLesDistr : num [1:3, 1:2] 1 2 3 69 20 11

..$ CBMAUC : num [1, 1] 0.879

..$ CBMmu : num [1, 1] 1.65

..$ CBMalpha : num [1, 1] 1

..$ CBMcutoffs: NULL

..$ i : int 5

..$ j : int 4

The first element is huge as it contains plotting data for 8000 predicted ROC data points (probably overkill, but it was done to ensure the plot looks continuous). It can be ignored for now. The list member named $nLesDistr gives the histogram of the lesion distribution. The member named $CBMAUC gives the CBM-AUC, which is the constraint. The member named $CBMalpha is the alpha parameter of the CBM distribution.

The list member named $j is the reader number and the statements in lines 44 – 52 will only execute if retSmRoc[[s]]$j is one of the four readers. Its current value is one (confirm by careful highlighting retSmRoc[[s]]$j and clicking on Run). Click on Next: the code block from lines 45 – 47 will only execute if retSmRoc[[s]]$i == i1, i.e., the modality index corresponds to 1, which happens to be true (confirm by highlighting etc.). Click on Next: the next three lines extract the values of for radiologist 1 in modality 1 and saves it in the positions of the length 4 array mu1, lambda1 and nu1 that evaluate to TRUE; to understand this jargon, on line 45 highlight retSmRoc[[s]]$j == selectJ and click on Run: one should see: TRUE FALSE FALSE FALSE (emphasis added). So the result of the right hand side, which is  = 3.675971, is saved to the *first* position of the mu1 array. The next two lines save the corresponding values (36.55742 and 0.4157737) to the first positions in the lambda1 and nu1 arrays. The three value correspond to *i* = 1 and *j* = 1. If one keep clicking on Next, the code pointer will return to line 45, but this time s = 2, corresponding to *i* = 1 and *j* = 2. This continues until all readers in the first modality have been exhausted, and the arrays mu1, lambda1 and nu1 are fully populated. On the next iterations of the for-loop retSmRoc[[s]]$i equals 2, which cause parameter results for the second modality to be extracted in lines 49 – 51 and saved to the correct positions in the mu2, lambda2 and nu2 arrays.

Exit debug mode (red-square button), remove any existing break point by clicking on it, insert a break point at line 62 and click Source. The RSM parameters are contained in mu, lambda and nu, which can be displayed by executing the command lines (the ones preceded with ">") in code snippet Online Appendix 19.A.3. Each parameter has two rows, corresponding to modalities 1 and 2 and 4 columns, corresponding to the four radiologists. Since some of the parameters can vary over large ranges, it is more prudent to take *medians* as representative of the 8 datasets, last three command lines in Online Appendix 19.A.3.

### Online Appendix 19.A.3: Code snippet

Browse[2]> mu

[,1] [,2] [,3] [,4]

mu1 3.675971 5.437591 2.617286 0.3358064

mu2 4.129106 2.959226 4.428728 1.2263501

Browse[2]> lambda

[,1] [,2] [,3] [,4]

lambda1 36.55742 2.098421 25.95178 0.04292726

lambda2 40.97380 1.342264 43.35359 0.64008142

Browse[2]> nu

[,1] [,2] [,3] [,4]

nu1 0.4157737 0.1324396 0.5027167 5.344361

nu2 0.2543416 0.3507453 0.1824401 1.892815

Browse[2]> muMed

[1] 3.317599

Browse[2]> lambdaMed

[1] 14.0251

Browse[2]> nuMed

[1] 0.3832595

Move the cursor to line 69 by clicking on Next many times or using the "*get me out of this loop*" button. Lines 65 – 66 calculate the lesion distribution vector nLesDistr and the lesion weights vector lesionWeights (this example assumes equal weighting).

### Online Appendix 19.A.4: Code snippet

Browse[2]> nLesDistr

[,1] [,2]

[1,] 1 69

[2,] 2 20

[3,] 3 11

Browse[2]> lesionWeights

[,1] [,2] [,3]

[1,] 1.0000000 -Inf -Inf

[2,] 0.5000000 0.5000000 -Inf

[3,] 0.3333333 0.3333333 0.3333333

This example tells us that there are 69 cases with 1 lesion, 20 with 2 lesions and 11 with 3 lesions. The corresponding weights are 1, 1/2 and 1/3, respectively. The –Inf's indicate lesions not present.

Keep clicking on Next to get past lines 69 – 71. These compute ROC-AUC and wAFROC-AUC. Use code snippet commands in Online Appendix 19.A.5 to print out the values (highlight and click Run).

### Online Appendix 19.A.5: Code snippet

Browse[2]> aucRocNH

[1] 0.8768796

Browse[2]> aucAfrocNH

[1] 0.6983678

Notice that the wAFROC FOM is smaller than the ROC FOM. This is usually the case unless the lesions are easily visible. Keep clicking on Next. Lines 75 – 83 increases muMed from 0.01 to 0.2 in steps of 0.01 (line 75). For each new value it calculates the ROC-AUC effect-size, esRoc, and the wAFROC-AUC effect-size, eswAfroc and saves the values in arrays dimensioned at line 76. An Excel file PowerComparison.xlsx in the online material showing that eswAfroc is a nearly linear function of esRoc (straight line fit constrained to run through the origin, slope = 2.023665, R2 = 0.9999844, contained in summary(a)$r.squared). In other words the wAFROC effect-size is about twice the ROC effect-size. Instead of going through Excel, line 86 calculates the regression (the ‑1 ensures the fit goes through the origin, as it must, because for zero , both FOMs must be at their null hypotheses values). Line 87 creates an effectSizeROC array that runs from 0.01 to 0.1 in steps of 0.01. Line 88 multiplies it by a factor 2.024, the value of a$coefficients[1], to create the corresponding effectSizeswAFROC array.

Line 90 sets the number of readers in the *pivotal* or test study as 5 and the corresponding number of cases to 100 (which is actually half that in the pilot study). Lines 91 – 92 perform DBMH analysis twice, once using fom = "HrAuc" and once using fom = "wAFROC", and extracts the two sets of pseudovalue variance components from the returned objects.

Exit debug mode, clear any existing break points and insert a new break point at line 100 and click Source. Lines 97 – 99 extract the pseudovalue treatment-reader (line 97), treatment-case (line 98) and error (line 99) variance components. Line 100 calculates power for the ROC method. Lines 103 – 106 repeat these steps for wAFROC analysis (fom = "wAFROC"). The function SSPowerGivenJK() computes statistical power for specified values of treatment-reader, treatment-case and error pseudovalue variance components and effect-size. Note the consistent usage of inferred ROC-AUC derived quantities in lines 97 – 101 and the consistent usage of wAFROC-AUC derived quantities in lines 103 – 107. All three variance components and effect-sizes are affected by the choice of FOM.

Remove all break points and click on Source. The results in a more readable format are in the Excel file PowerComparison.xlsx in the online material. The observed wAFROC effect-size was -0.00686, see red font near bottom of Online Appendix 19.A.8, which is too small to reach 80% power, even with the number of cases inflated to 200 and the number of readers reduced to 4 (the actual conditions of the study, Online Appendix 19.A.7). It is not surprising that the study did not find a significant difference between these two modalities.

### Online Appendix 19.A.6: Code output

JTest = 4 KTest = 200

ROC effect-size = , 0.01 wAFROC effect-size = , 0.02023665 , Statistical power ROC, wAFROC: 0.06936532 , 0.4445016

ROC effect-size = , 0.02 wAFROC effect-size = , 0.04047331 , Statistical power ROC, wAFROC: 0.1288161 , 0.9535477

ROC effect-size = , 0.03 wAFROC effect-size = , 0.06070996 , Statistical power ROC, wAFROC: 0.2291864 , 0.9997675

ROC effect-size = , 0.04 wAFROC effect-size = , 0.08094661 , Statistical power ROC, wAFROC: 0.3642924 , 0.9999999

ROC effect-size = , 0.05 wAFROC effect-size = , 0.1011833 , Statistical power ROC, wAFROC: 0.517793 , 1

ROC effect-size = , 0.06 wAFROC effect-size = , 0.1214199 , Statistical power ROC, wAFROC: 0.6672359 , 1

ROC effect-size = , 0.07 wAFROC effect-size = , 0.1416566 , Statistical power ROC, wAFROC: 0.7927595 , 1

ROC effect-size = , 0.08 wAFROC effect-size = , 0.1618932 , Statistical power ROC, wAFROC: 0.8841596 , 1

ROC effect-size = , 0.09 wAFROC effect-size = , 0.1821299 , Statistical power ROC, wAFROC: 0.9420896 , 1

ROC effect-size = , 0.1 wAFROC effect-size = , 0.2023665 , Statistical power ROC, wAFROC: 0.9741633 , 1

To put the previous values in perspective the following lists the results of DBMH analysis of the extracted 2-modality dataset. The important result is the small observed effect-size, in red font. The choice of 0.03 for the postulated effect size is not unreasonably large as the lower limit of the 95% CI is -0.028.

### Online Appendix 19.A.7: Code output

> ret <- DBMHAnalysis(frocData, fom = "wAFROC", option = "RRRC")

> ret

$fomArray

Rdr - 1 Rdr - 3 Rdr - 4 Rdr - 5

Trt - 1 0.7792667 0.7248917 0.7036250 0.8050917

Trt - 2 0.7870000 0.7269000 0.7226167 0.8037833

$anovaY

Source SS DF MS

1 T 0.01880327 1 0.018803266

2 R 2.33024767 3 0.776749224

3 C 130.13175366 199 0.653928410

4 TR 0.02382003 3 0.007940011

5 TC 27.33988244 199 0.137386344

6 RC 73.93443040 597 0.123843267

7 TRC 57.74518265 597 0.096725599

8 Total 291.52412012 1599 NA

$anovaYi

Source DF 1 2

1 R 3 0.4420838 0.3426054

2 C 199 0.3754000 0.4159148

3 RC 597 0.1088409 0.1117280

$varComp

varComp

Var(R) 0.0018542289

Var(C) 0.0611780498

Var(T\*R) -0.0004439279

Var(T\*C) 0.0101651862

Var(R\*C) 0.0135588340

Var(Error) 0.0967255991

$fRRRC

[1] 0.3868925

$ddfRRRC

[1] 112.3997

$pRRRC

[1] 0.5351971

$ciDiffTrtRRRC

Treatment Estimate StdErr DF t Pr > t CI Lower CI Upper

1 1 - 2 -0.00685625 0.01102279 112.3997 -0.6220068 0.5351971 -0.02869565 0.01498315

$ciAvgRdrEachTrtRRRC

Treatment Area StdErr DF CI Lower CI Upper

1 1 0.7532187 0.02976245 7.708447 0.6841319 0.8223056

2 2 0.7600750 0.02843396 10.692084 0.6972717 0.8228783

This concludes the explanation of the sample size estimation procedure.

As an exercise, the reader should repeat the analysi for the Franken and Van Dyke datasets and compare them to the results obtained in **Chapter 11**.

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Fig. 17.1

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Fig. 17.3

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Fig. 17.10

Table 17.3

17.5.1

17.5.2

17.6.1

17.6.2

17.7.2

17.8 Search performance

17.9 Class. Performance

17.10 IsFrocGood

17.10.1 Clinical relevance

17.11.2.1 Eng Code

17.11

demo

17.11.4

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Table 17.2

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Fig. 20.1

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# Cross-references

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**Part B**

**Part C**

**Part D**

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**Chapter 02**

**Chapter 03**

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Figure 1.A.5.1

Figure 1.A.5.2

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2.9.2 PPV NPV

Table 2.1

Table 2.2

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Table 3.2

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Table 4.1 Roc counts table

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Fig. 5.1 operating point convention

Fig. 5.2

Fig. 5.3

Table 5.1

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Fig. 6.4

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7.3.2

Fig. 7.1

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Eqn.(7.6)

Fig. 8.1

Table 8.1

Fig. 9.1

Fig. 9.2

Fig. 9.3

Fig. 9.4

Fig. 9.5

(9.24) dds

(9.34) Definition of ncp

(9.35) Eqn. AH – RRRC

(9.24)

(9.34)

(9.35)

(9.43)

(9.44)

(9.43)

(9.44)

(9.52)

(9.53)

9.10.2.2 Interactions

Table 9.1

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9.13: Meaning of pseudovalues

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Fig. 9.A.3.1

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10.2.5.1

10.2 1RIT

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10.7 1TMultipleR

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Table 11.1 2 types of errors

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11.8.1

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Table 14.C.1

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Fig. 14.6

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Fig. 15.7

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16.4

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17.3

Fig. 17.1

Fig. 17.2

17.5.1

17.5.2

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Fig. 17.4

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Fig. 17.10

Table 17.1

Table 17.2

Table 17.3

17.5.1

17.5.2

17.6.1

17.6.2

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17.11.2.1

17.11.4

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Fig. 19.1

Fig. 19.2

Fig. 19.3

Table 19.1

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18.2.3

18.7 Sample size

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18.5.2

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18.5.4

Fig. 18.1

Fig. 18.2

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Online Appendix 19.A.8

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Fig. 20.1

Fig. 20.2

Fig. 20.3

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Fig. 22.1

Fig. 22.2

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Table 22.3

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