Meta-Regression

Subgroup Analysis

This vignette introduces the regression functionality of the `dtametaTMB` package for meta-analysis of diagnostic test accuracy (DTA) studies.

Validation

The subgroup HSROC and Reitsma implementations reproduce the Cochrane Handbook RF and Anti-CCP examples closely, including the baseline parameters (HSROC: accuracy, threshold, shape; Reitsma: logit sensitivity and specificity), between-study variance estimates, and subgroup effects on accuracy and threshold. The Schuetz CT/MRI analyses yielded results broadly consistent with the published subgroup parameter estimates and variance components. Likelihood-ratio tests led to identical substantive conclusions, although the LR statistics differed somewhat from the published values.

Dummy-coding vs. cell-means parameterization

For subgroup analyses, we distinguish between two equivalent parameterizations of the same model. In the reference-group parameterization, one subgroup serves as the baseline and the remaining subgroup effects are expressed as deviations from this reference. In the group-specific (cell-means) parameterization, each subgroup has its own parameter directly. The former is convenient for testing subgroup differences, whereas the latter is convenient for reporting subgroup-specific estimates and plotting subgroup-specific HSROC curves. The Reitsma subgroup model is fitted twice with both parameterizations. The subgroup HSROC model is estimated using a reference-group parameterization, and subgroup-specific parameters are recovered by evaluating the fitted linear predictors at subgroup-specific design points via Z_{pred}.

How do we include covariates in the Reitsma model?

For sensitivity in study i, we have the number of diseased individuals testing positive: $y_{Ai} \sim \mathcal{B}(n_{Ai}, \pi_{Ai})$.

Similarly for specificity, we have the number of non-diseased individuals testing negative: $y_{Bi} \sim \mathcal{B}(n_{Bi}, \pi_{Bi})$.

Now we introduce a p-dimensional design-vector z_i including study level covariates. Consequently, at the study level, we have

$$\begin{pmatrix} z_i^\top \mu_{Ai} \\ z_i^\top \mu_{Bi} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} z_i^\top \mu_{A} \\ z_i^\top \mu_{B} \end{pmatrix}, \Sigma \right), \quad \text{with} \quad \Sigma = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}.$$

Let's assume that z_i includes a single binary covariate representing two subgroups. Then using dummy coding with subgroup 1 being the reference, we have

$$z_i^\top \mu_{Ai} = \begin{cases} \mu_{Ai} & \text{for subgroup 1,} \\ \mu_{Ai} + \nu_{A2} & \text{for subgroup 2,} \end{cases} \qquad z_i^\top \mu_{Bi} = \begin{cases} \mu_{Bi} & \text{for subgroup 1,} \\ \mu_{Bi} + \nu_{B2} & \text{for subgroup 2,} \end{cases}$$

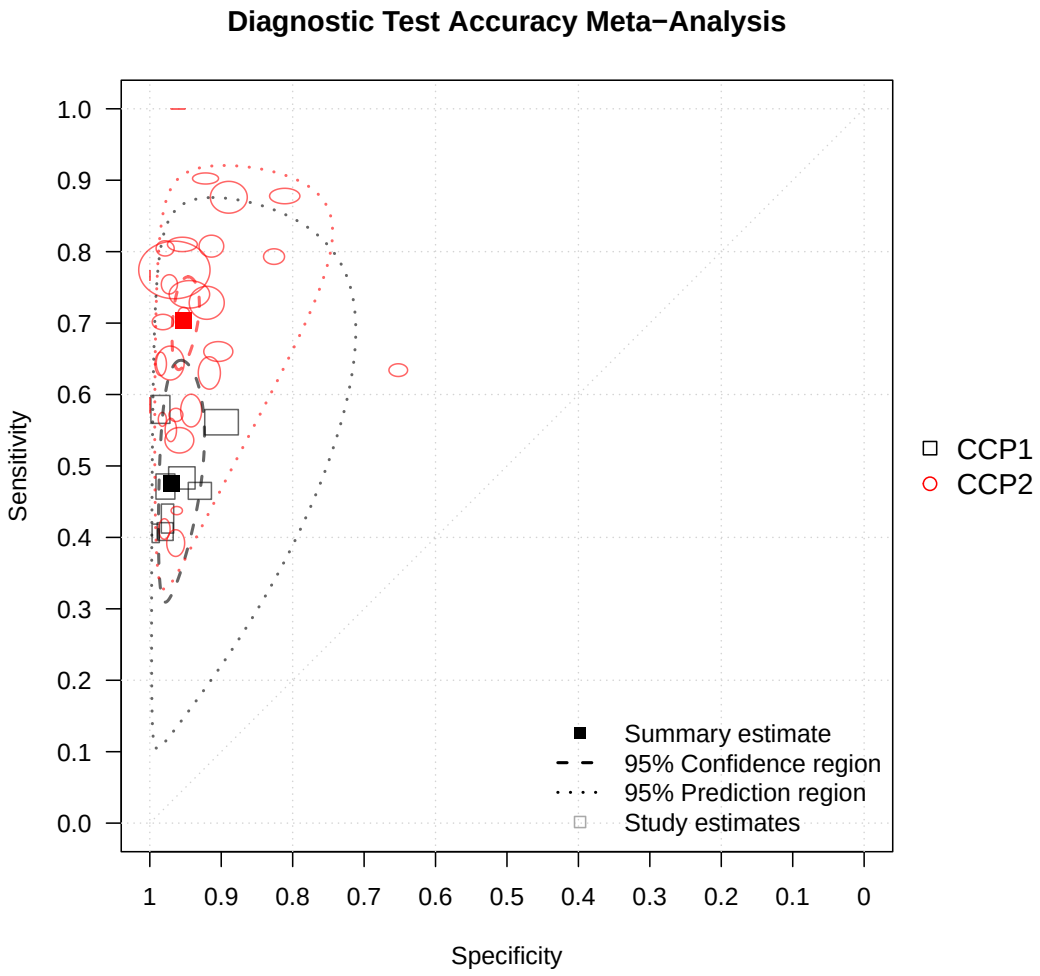
$$z_i^\top \mu_{A} = \begin{cases} \mu_{A} & \text{for subgroup 1,} \\ \mu_{A} + \nu_{A2} & \text{for subgroup 2,} \end{cases} \qquad z_i^\top \mu_{B} = \begin{cases} \mu_{B} & \text{for subgroup 1,} \\ \mu_{B} + \nu_{B2} & \text{for subgroup 2.} \end{cases}$$

```
data("anticcp")
reitsmasub <- fitReitsmaSubgroup(data=anticcp,
                                 TP=TP,
                                 FP=FP,
                                 FN=FN,
                                 TN=TN,
                                 study=study,
                                 subgroup=generation)
reitsmasub
#>
#> Reitsma Subgroup Model
#> ----------------------
#>
#> Number of studies   : 37
#> Number of subgroups : 2
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0004844247
#> -2 log likelihood   : 533.37 ( df = 7 )
```

```
#> AIC                 : 547.37
#> BIC                 : 558.646
#>
#> Use summary() for parameter estimates.
summary(reitsmasub)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                               Estimate   Std_Error
#> mu_A.CCP1                 -0.096538884 0.220320590
#> mu_B.CCP1                  3.446719200 0.298243690
#> mu_A.CCP2                  0.866038480 0.120876820
#> mu_B.CCP2                  3.016490600 0.162237540
#> sigma2_A.sens.log_sigma_A  0.359828710 0.102176500
#> sigma2_B.spec.log_sigma_B  0.539909310 0.180157230
#> sigma_AB                  -0.196844990 0.098353424
#> nu_A.CCP2                  0.962571630 0.251342040
#> nu_B.CCP2                 -0.430210700 0.337711820
#>
#> Sensitivity / specificity
#> -------------------------
#>           type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.CCP1 sens 0.47588401      0.95 0.37089964 0.58304390
#> mu_B.CCP1 spec 0.96913315      0.95 0.94594449 0.98255779
#> mu_A.CCP2 sens 0.70392072      0.95 0.65229087 0.75081294
#> mu_B.CCP2 spec 0.95331358      0.95 0.93693872 0.96559260
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>         Lambda       Theta       beta sigma2_alpha sigma2_theta
#> CCP1 3.0073766 -1.61053440 0.20288653   0.48784248   0.31880561
#> CCP2 3.6840001 -0.88349711 0.20288653   0.48784248   0.31880561
#>
#> Subgroups
#> ---------
#> [1] "CCP1" "CCP2"
```

How do I get a summary plot of the Reitsma model?

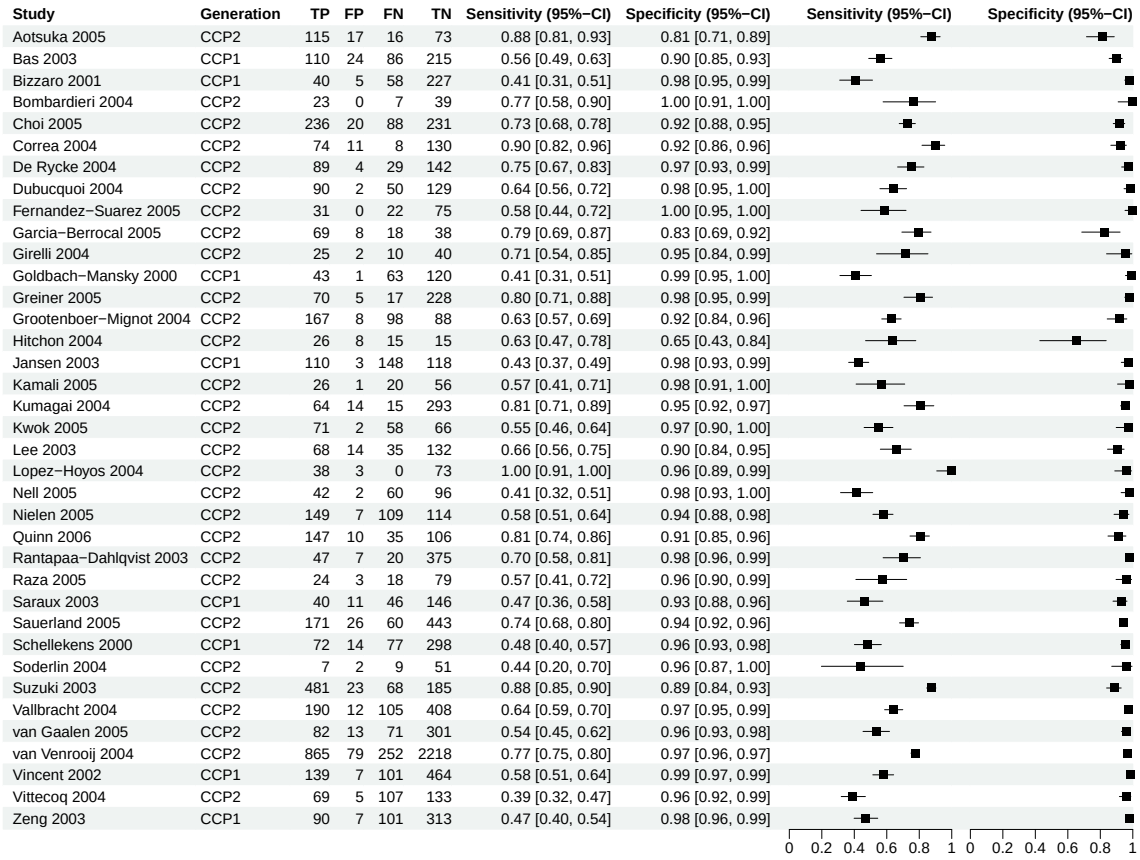
```
plot(reitsmasub,
     scale=0.01,
     nudge_legend=-0.2,
     size="se",
     col=c("black","red"))
```



How do I get a coupled forest plot?

Note: Rendering forest plots may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

```
forest(reitsmasub,subgroup_label="Generation")
```



Study	Generation	TP	FP	FN	TN	Sensitivity (95%−CI)	Specificity (95%−CI)
Aotsuka 2005	CCP2	115	17	16	73	0.88 [0.81, 0.93]	0.81 [0.71, 0.89]
Bas 2003	CCP1	110	24	86	215	0.56 [0.49, 0.63]	0.90 [0.85, 0.93]
Bizzaro 2001	CCP1	40	5	58	227	0.41 [0.31, 0.51]	0.98 [0.95, 0.99]
Bombardieri 2004	CCP2	23	0	7	39	0.77 [0.58, 0.90]	1.00 [0.91, 1.00]
Choi 2005	CCP2	236	20	88	231	0.73 [0.68, 0.78]	0.92 [0.88, 0.95]
Correa 2004	CCP2	74	11	8	130	0.90 [0.82, 0.96]	0.92 [0.86, 0.96]
De Rycke 2004	CCP2	89	4	29	142	0.75 [0.67, 0.83]	0.97 [0.93, 0.99]
Dubucquoi 2004	CCP2	90	2	50	129	0.64 [0.56, 0.72]	0.98 [0.95, 1.00]
Fernandez−Suarez 2005	CCP2	31	0	22	75	0.58 [0.44, 0.72]	1.00 [0.95, 1.00]
Garcia−Berrocal 2005	CCP2	69	8	18	38	0.79 [0.69, 0.87]	0.83 [0.69, 0.92]
Girelli 2004	CCP2	25	2	10	40	0.71 [0.54, 0.85]	0.95 [0.84, 0.99]
Goldbach−Mansky 2000	CCP1	43	1	63	120	0.41 [0.31, 0.51]	0.99 [0.95, 1.00]
Greiner 2005	CCP2	70	5	17	228	0.80 [0.71, 0.88]	0.98 [0.95, 0.99]
Grootenboer−Mignot 2004	CCP2	167	8	98	88	0.63 [0.57, 0.69]	0.92 [0.84, 0.96]
Hitchon 2004	CCP2	26	8	15	15	0.63 [0.47, 0.78]	0.65 [0.43, 0.84]
Jansen 2003	CCP1	110	3	148	118	0.43 [0.37, 0.49]	0.98 [0.93, 0.99]
Kamali 2005	CCP2	26	1	20	56	0.57 [0.41, 0.71]	0.98 [0.91, 1.00]
Kumagai 2004	CCP2	64	14	15	293	0.81 [0.71, 0.89]	0.95 [0.92, 0.97]
Kwok 2005	CCP2	71	2	58	66	0.55 [0.46, 0.64]	0.97 [0.90, 1.00]
Lee 2003	CCP2	68	14	35	132	0.66 [0.56, 0.75]	0.90 [0.84, 0.95]
Lopez−Hoyos 2004	CCP2	38	3	0	73	1.00 [0.91, 1.00]	0.96 [0.89, 0.99]
Nell 2005	CCP2	42	2	60	96	0.41 [0.32, 0.51]	0.98 [0.93, 1.00]
Nielen 2005	CCP2	149	7	109	114	0.58 [0.51, 0.64]	0.94 [0.88, 0.98]
Quinn 2006	CCP2	147	10	35	106	0.81 [0.74, 0.86]	0.91 [0.85, 0.96]
Rantapaa−Dahlqvist 2003	CCP2	47	7	20	375	0.70 [0.58, 0.81]	0.98 [0.96, 0.99]
Raza 2005	CCP2	24	3	18	79	0.57 [0.41, 0.72]	0.96 [0.90, 0.99]
Saraux 2003	CCP1	40	11	46	146	0.47 [0.36, 0.58]	0.93 [0.88, 0.96]
Sauerland 2005	CCP2	171	26	60	443	0.74 [0.68, 0.80]	0.94 [0.92, 0.96]
Schellekens 2000	CCP1	72	14	77	298	0.48 [0.40, 0.57]	0.96 [0.93, 0.98]
Soderlin 2004	CCP2	7	2	9	51	0.44 [0.20, 0.70]	0.96 [0.87, 1.00]
Suzuki 2003	CCP2	481	23	68	185	0.88 [0.85, 0.90]	0.89 [0.84, 0.93]
Vallbracht 2004	CCP2	190	12	105	408	0.64 [0.59, 0.70]	0.97 [0.95, 0.99]
van Gaalen 2005	CCP2	82	13	71	301	0.54 [0.45, 0.62]	0.96 [0.93, 0.98]
van Venrooij 2004	CCP2	865	79	252	2218	0.77 [0.75, 0.80]	0.97 [0.96, 0.97]
Vincent 2002	CCP1	139	7	101	464	0.58 [0.51, 0.64]	0.99 [0.97, 0.99]
Vittecoq 2004	CCP2	69	5	107	133	0.39 [0.32, 0.47]	0.96 [0.92, 0.99]
Zeng 2003	CCP1	90	7	101	313	0.47 [0.40, 0.54]	0.98 [0.96, 0.99]

How do I constrain parameters in the Reitsma model?

In sparse data one may wish to fix parameters of the random effects (variance-covariance matrix) at zero. This can be done via the `constrain` argument.

For example,

```
constrainA <- fitReitsmaSubgroup(data=anticcp,
                                 TP=TP,
                                 FP=FP,
                                 FN=FN,
                                 TN=TN,
                                 study=study,
                                 subgroup=generation,
                                 constrain="sigma2_A")
summary(constrainA)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                                 Estimate   Std_Error
#> mu_A.CCP1                 -5.4394046e-02 0.054985303
#> mu_B.CCP1                  3.4466250e+00 0.298754820
#> mu_A.CCP2                  9.1797945e-01 0.031391722
#> mu_B.CCP2                  2.9968587e+00 0.162162330
#> sigma2_A.sens.log_sigma_A  4.9303807e-32 0.000000000
#> sigma2_B.spec.log_sigma_B  5.3963306e-01 0.179976400
#> sigma_AB                   0.0000000e+00 0.000000000
#> nu_A.CCP2                  9.7237352e-01 0.063315273
#> nu_B.CCP2                 -4.4976608e-01 0.337953820
#>
#> Sensitivity / specificity
#> -------------------------
#>           type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.CCP1 sens 0.48640484      0.95 0.45954779 0.51334062
#> mu_B.CCP1 spec 0.96913033      0.95 0.94588841 0.98257334
#> mu_A.CCP2 sens 0.71463023      0.95 0.70191901 0.72701020
#> mu_B.CCP2 spec 0.95243201      0.95 0.93577764 0.96492938
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>          Lambda      Theta     beta sigma2_alpha  sigma2_theta
#> CCP1 -3128642.1 -1564321.1 35.73522 3.262267e-16 8.1556674e-17
#> CCP2 52800433.0 26400216.0 35.73522 3.262267e-16 8.1556674e-17
#>
#> Subgroups
```

```
#> ---------
#> [1] "CCP1" "CCP2"
```

fixes the logit sensitivity variance to zero. This also implies that the random effects covariance is zero. Note that you can also set `constrain` to `"sigma_AB"`, `"sigma2_B"`, or `"all"`.

Constraining fixed effects is controlled by the `sensspec_constrain` argument. For example,

```
constrainsens <- fitReitsmaSubgroup(data=anticcp,
                                    TP=TP,
                                    FP=FP,
                                    FN=FN,
                                    TN=TN,
                                    study=study,
                                    subgroup=generation,
                                    sensspec_constrain="sens")
summary(constrainsens)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                               Estimate  Std_Error
#> mu_A.CCP1                  0.653305180 0.12740877
#> mu_B.CCP1                  3.081222100 0.32561613
#> mu_A.CCP2                  0.653305180 0.00000000
#> mu_B.CCP2                  3.118005800 0.17451227
#> sigma2_A.sens.log_sigma_A  0.541939800 0.14627725
#> sigma2_B.spec.log_sigma_B  0.577648680 0.19968290
#> sigma_AB                  -0.277162040 0.13981590
#> nu_A.CCP2                  0.000000000 0.00000000
#> nu_B.CCP2                  0.036831361 0.38577185
#>
#> Sensitivity / specificity
#> -------------------------
#>           type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.CCP1 sens 0.65775489      0.95 0.59954955 0.71157008
#> mu_B.CCP1 spec 0.95611150      0.95 0.92004997 0.97632597
#> mu_A.CCP2 sens 0.65775489      0.95 0.59954955 0.71157008
#> mu_B.CCP2 spec 0.95762939      0.95 0.94136328 0.96952925
#>
```

```
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> -------------------------------------------
#>         Lambda      Theta        beta sigma2_alpha sigma2_theta
#> CCP1 3.6962689 -1.1843237 0.031905471   0.56469478   0.41833574
#> CCP2 3.7324705 -1.2024245 0.031905471   0.56469478   0.41833574
#>
#> Subgroups
#> ---------
#> [1] "CCP1" "CCP2"
```

assumes equal (logit) sensitivities in all subgroups. Note that you can also set `sensspec_constrain` to `"spec"` or `c("sens","spec")`.

How can I compare `constrainsens` with the full model?

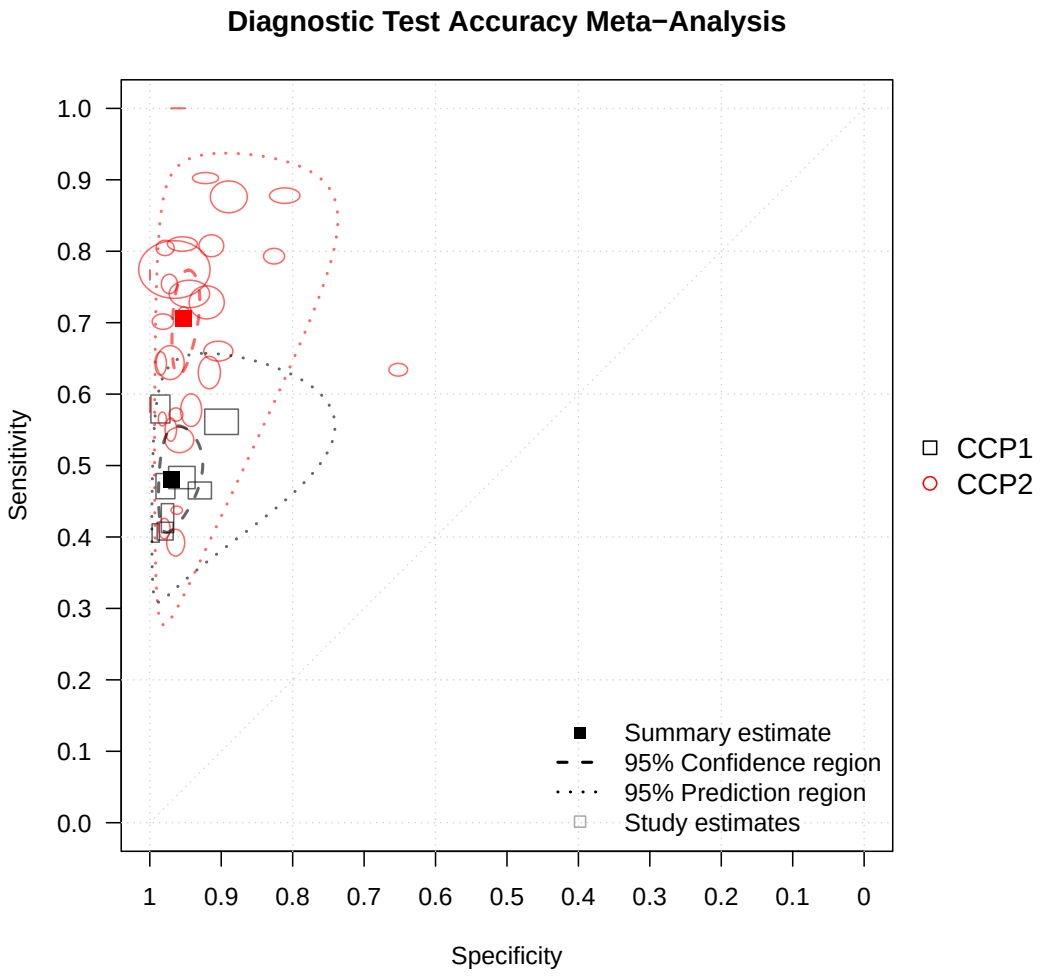
We can perform a likelihood ratio test via `anova`, essentially testing whether there exist subgroup differences in sensitivity.

```
anova(constrainsens,reitsmasub)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  6 -272.77
#> Model 2  7 -266.69       1 12.181  0.0004827 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

How do I allow for different subgroup-specific random-effects (co-)variances in the Reitsma model?

```
heteroskedastic <- fitReitsmaSubgroup(data=anticcp,
                                      TP=TP,
                                      FP=FP,
                                      FN=FN,
                                      TN=TN,
                                      study=study,
                                      subgroup=generation,
                                      variances="unequal")
plot(heteroskedastic,
     scale=0.01,
     nudge_legend=-0.2,
```

```
      size="se",
      col=c("black","red"))
```




```
anova(reitsmasub,heteroskedastic)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  7 -266.69
#> Model 2 10 -262.42       3 8.5306    0.03623 *
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

How do I fit the Reitsma subgroup model using the custom TMB backend?

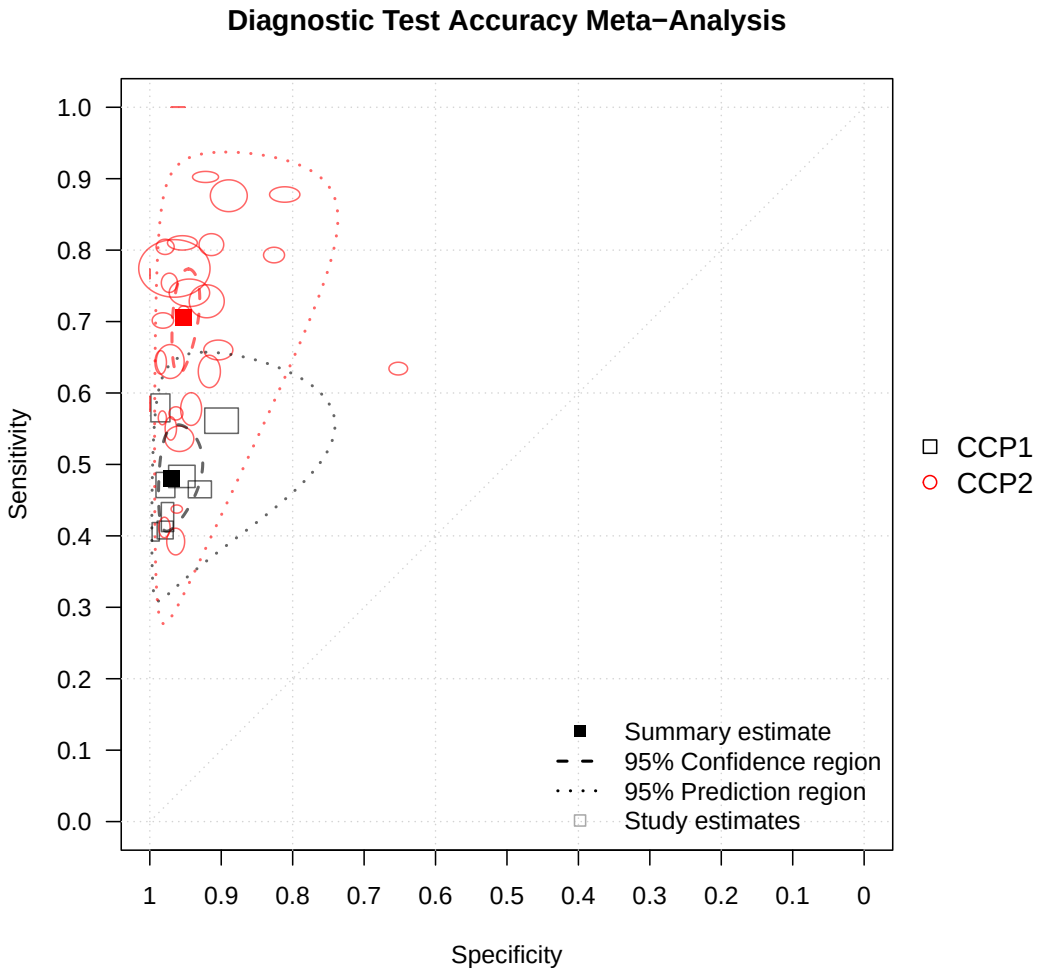
By default, `fitReitsmaSubgroup()` fits the Reitsma model using `glmmTMB`. The package also provides `fitReitsmaSubgroupTMB()`, which fits the same binomial-normal model using a custom Template Model Builder (TMB) template.

The custom TMB backend may offer improved numerical robustness in difficult or near-boundary cases.

```
data("anticcp")
reitsmasubTMB <- fitReitsmaSubgroupTMB(data=anticcp,
                                       TP=TP,
                                       FP=FP,
                                       FN=FN,
                                       TN=TN,
                                       study=study,
                                       variances="unequal",
                                       subgroup=generation)
reitsmasubTMB
#>
#> Reitsma Subgroup TMB Model
#> --------------------------
#>
#> Number of studies   : 37
#> Number of subgroups : 2
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 7.201756e-05
#> -2 log likelihood   : 524.839 ( df = 10 )
#> AIC                 : 544.839
#> BIC                 : 560.948
#>
#> Use summary() for parameter estimates.
summary(reitsmasubTMB)
#>
#> Summary: Reitsma Subgroup TMB Model
#> -----------------------------------
#>
#> Parameter estimates
#> -------------------
#>                   Estimate  Std. Error
#> mu_A.CCP1     -0.077734976 0.093745405
#> mu_A.CCP2      0.872414330 0.137541560
```

```
#> mu_B.CCP1      3.458614000 0.290964660
#> mu_B.CCP2      3.014784100 0.164919640
#> sigma2_A.CCP1  0.042771854 0.033050876
#> sigma2_A.CCP2  0.481452150 0.152370450
#> sigma2_B.CCP1  0.479322870 0.320124020
#> sigma2_B.CCP2  0.560479850 0.215712700
#> sigma_AB.CCP1 -0.062584493 0.079018858
#> sigma_AB.CCP2 -0.233390560 0.129708840
#> rho_AB.CCP1   -0.437092770 0.445469900
#> rho_AB.CCP2   -0.449289960 0.200921540
#> nu_A.CCP2      0.950149300 0.166450840
#> nu_B.CCP2     -0.443829930 0.334453170
#>
#> Sensitivity / specificity
#> -------------------------
#>           type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.CCP1 sens 0.48057604      0.95 0.43500175 0.52647587
#> mu_A.CCP2 sens 0.70524782      0.95 0.64630529 0.75804497
#> mu_B.CCP1 spec 0.96948699      0.95 0.94726671 0.98251710
#> mu_B.CCP2 spec 0.95323757      0.95 0.93652604 0.96571036
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>         Lambda       Theta        beta sigma2_alpha sigma2_theta
#> CCP1 1.7480891 -1.01627220 1.208247100   0.16119811   0.10288402
#> CCP2 3.8085824 -0.99809026 0.075993224   0.57214955   0.37642794
#>
#> Subgroups
#> ---------
#> [1] "CCP1" "CCP2"
```

```
plot(reitsmasubTMB,
     scale=0.01,
     nudge_legend=-0.2,
     size="se",
     col=c("black","red"))
```



How do we include covariates in the Rutter and Gatsonis model?

The number of diseased individuals from study i who test positive is denoted by $y_{i1} \sim \mathcal{B}(n_{i1}, \pi_{i1})$.

Similarly, the number of non-diseased individuals who test positive is $y_{i2} \sim \mathcal{B}(n_{i2}, \pi_{i2})$.

Now we introduce a p-dimensional design-vector z_i including study level covariates. Consequently, at the study level, we have

$$\text{logit}(\pi_{ij}) = \left(z_i^\top \theta_i + z_i^\top \alpha_i x_{ij}\right) \exp(-z_i^\top \beta x_{ij}),$$

$$z_i^\top \alpha_i \sim \mathcal{N}(z_i^\top \Lambda, \sigma_\alpha^2), \qquad z_i^\top \theta_i \sim \mathcal{N}(z_i^\top \Theta, \sigma_\theta^2),$$

where

$$x_{ij} = \begin{cases} -0.5 & \text{for non-diseased individuals,} \\ 0.5 & \text{for diseased individuals.} \end{cases}$$

Let's assume that z_i includes a single categorical covariate representing three subgroups. Then using dummy coding with subgroup 1 being the reference, we have

$$z_i^\top \theta_i = \begin{cases} \theta_i & \text{for subgroup 1,} \\ \theta_i + \gamma_2 & \text{for subgroup 2,} \\ \theta_i + \gamma_3 & \text{for subgroup 3,} \end{cases} \qquad z_i^\top \alpha_i = \begin{cases} \alpha_i & \text{for subgroup 1,} \\ \alpha_i + \xi_2 & \text{for subgroup 2,} \\ \alpha_i + \xi_3 & \text{for subgroup 3,} \end{cases}$$

$$z_i^\top \beta = \begin{cases} \beta & \text{for subgroup 1,} \\ \beta + \delta_2 & \text{for subgroup 2,} \\ \beta + \delta_3 & \text{for subgroup 3,} \end{cases}$$

$$z_i^\top \Lambda = \begin{cases} \Lambda & \text{for subgroup 1,} \\ \Lambda + \xi_2 & \text{for subgroup 2,} \\ \Lambda + \xi_3 & \text{for subgroup 3,} \end{cases} \qquad z_i^\top \Theta_i = \begin{cases} \Theta & \text{for subgroup 1,} \\ \Theta + \gamma_2 & \text{for subgroup 2,} \\ \Theta + \gamma_3 & \text{for subgroup 3.} \end{cases}$$

Note: For prediction `fitRutterGatsonisSubgroup()` uses the prediction matrix

$$Z_{\text{pred}} = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix}$$

for the case above and therefore recovers the threshold, accuracy, and shape parameters for each subgroup as if it were the reference group.

How do I perform a Rutter and Gatsonis meta-regression with a single categorical study-level covariate?

```
data("RF")
RF2        <- RF[RF$method %in% c("LA","ELISA","Nephelometry"),]
RF2$method <- factor(RF2$method,levels=c("LA","ELISA","Nephelometry"))
ruttergatsonissub <- fitRutterGatsonisSubgroup(data=RF2,
                                               TP=TP,
                                               FP=FP,
```

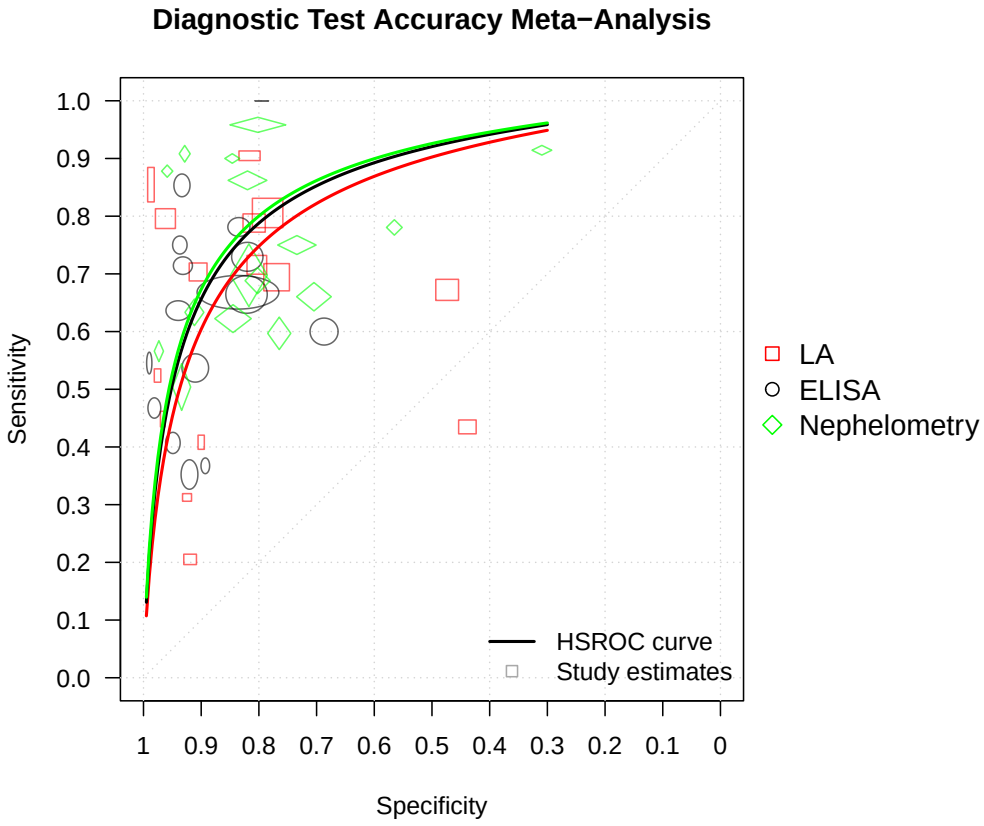
```
                                                    FN=FN,
                                                    TN=TN,
                                                    study=study,
                                                    subgroup=method,
                                                    constrain="shape") # assumes equal
                                                                       # shapes in subgroups
```

```
ruttergatsonissub
#>
#> Rutter & Gatsonis Subgroup Model
#> --------------------------------
#>
#> Number of studies   : 47
#> Number of subgroups : 3
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0002867077
#> -2 log likelihood   : 753.722 ( df = 9 )
#> AIC                 : 771.722
#> BIC                 : 788.374
#>
#> Use summary() for parameter estimates.
summary(ruttergatsonissub)
#>
#> Summary: Rutter & Gatsonis Subgroup Model
#> -----------------------------------------
#>
#> Parameter estimates
#> -------------------
#>                         Estimate  Std. Error
#> Lambda_LA            2.456309800 0.323577140
#> xi_ELISA             0.248533990 0.439541130
#> xi_Nephelometry      0.331428920 0.442600640
#> Theta_LA            -0.550060260 0.213340320
#> gamma_ELISA         -0.196255960 0.260961790
#> gamma_Nephelometry   0.495863020 0.262230320
#> beta_LA              0.197677370 0.169839730
#> delta_ELISA          0.000000000 0.000000000
#> delta_Nephelometry   0.000000000 0.000000000
#> sigma2_alpha         1.277914900 0.308524820
#> sigma2_theta         0.476839640 0.113444950
#> Lambda_LA            2.456309800 0.323577140
```

```
#> Lambda_ELISA         2.704843800 0.326954560
#> Lambda_Nephelometry  2.787738800 0.305779190
#> Theta_LA            -0.550060260 0.213340320
#> Theta_ELISA         -0.746316220 0.209913080
#> Theta_Nephelometry  -0.054197236 0.212131240
#> beta_LA              0.197677370 0.169839730
#> beta_ELISA           0.197677370 0.169839730
#> beta_Nephelometry    0.197677370 0.169839730
#> logitsens            0.826168420 0.286300410
#> logitsens            1.051312600 0.286070100
#> logitsens            1.126406200 0.276895840
#> sens                 0.695544150 0.060627687
#> sens                 0.741026870 0.054898582
#> sens                 0.755175060 0.051194078
#>
#> Sensitivity / specificity
#> -------------------------
#>       subgroup       spec conflevel  logitsens  Std_Error   CI_Lower  CI_Upper
#> 1           LA 0.84615385      0.95 0.82616842 0.28630041 0.26502992 1.3873069
#> 2        ELISA 0.84615385      0.95 1.05131260 0.28607010 0.49062549 1.6119997
#> 3 Nephelometry 0.84615385      0.95 1.12640620 0.27689584 0.58370030 1.6691121
#>         Sens SensCI_Lower SensCI_Upper
#> 1 0.69554415   0.56587235   0.80016196
#> 2 0.74102687   0.62025377   0.83368883
#> 3 0.75517506   0.64191840   0.84145740
#>
#> Recovered bivariate parameters (Reitsma)
#> ----------------------------------------
#>               mu_A.sens mu_B.spec sigma2_A.sens sigma2_B.spec    sigma_AB
#> LA           0.61427837 1.9629508    0.65348637    0.97036902 -0.15736092
#> ELISA        0.54906437 2.3167723    0.65348637    0.97036902 -0.15736092
#> Nephelometry 1.21359400 1.5985037    0.65348637    0.97036902 -0.15736092
#>
#> Subgroups
#> ---------
#> [1] "LA"           "ELISA"        "Nephelometry"
```

How do I get a summary plot of the Rutter and Gatsonis subgroup model?

```r
plot(ruttergatsonissub,
     specrange=c(0.3,0.995),
     size="se",
     col=c("red","black","green"),
     scale=0.015)
```

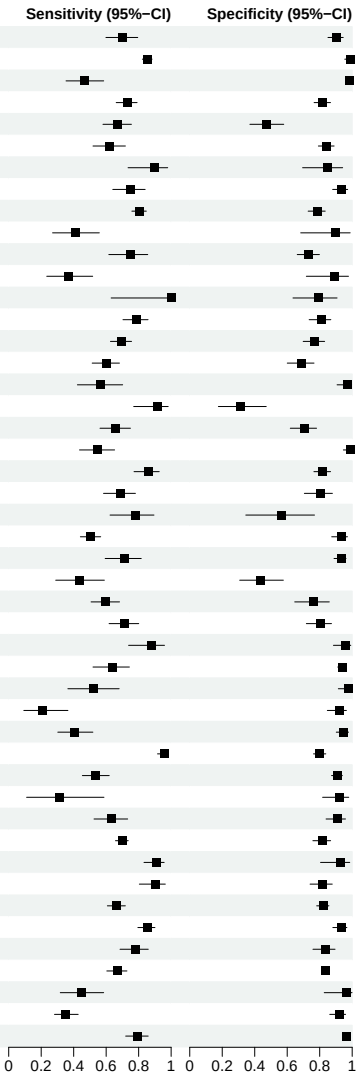


How do I get a coupled forest plot?

Note: Rendering forest plots may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

```r
forest(ruttergatsonissub,subgroup_label = "Method")
```

Study	Method	TP	FP	FN	TN	Sensitivity (95%−CI)	Specificity (95%−CI)
Aho 1999	LA	64	16	27	153	0.70 [0.60, 0.79]	0.91 [0.85, 0.94]
Anuradha 2005	LA	482	2	82	153	0.85 [0.82, 0.88]	0.99 [0.95, 1.00]
Banchuin 1992	ELISA	36	6	41	313	0.47 [0.35, 0.58]	0.98 [0.96, 0.99]
Bas 2003	ELISA	143	43	53	196	0.73 [0.66, 0.79]	0.82 [0.77, 0.87]
Berthelot 1995	LA	80	50	39	45	0.67 [0.58, 0.76]	0.47 [0.37, 0.58]
Bizzaro 2001	Nephelometry	61	36	37	196	0.62 [0.52, 0.72]	0.84 [0.79, 0.89]
Bombardieri 2004	Nephelometry	27	6	3	33	0.90 [0.73, 0.98]	0.85 [0.69, 0.94]
Carpenter 1989	ELISA	60	8	20	119	0.75 [0.64, 0.84]	0.94 [0.88, 0.97]
Choi 2005	LA	261	54	63	197	0.81 [0.76, 0.85]	0.78 [0.73, 0.83]
Cordonnier 1996	LA	20	2	29	18	0.41 [0.27, 0.56]	0.90 [0.68, 0.99]
Das 2004	Nephelometry	42	46	14	127	0.75 [0.62, 0.86]	0.73 [0.66, 0.80]
Davis 1989	ELISA	18	3	31	25	0.37 [0.23, 0.52]	0.89 [0.72, 0.98]
de Bois 1996	ELISA	8	8	0	31	1.00 [0.63, 1.00]	0.79 [0.64, 0.91]
De Rycke 2004	LA	93	28	25	118	0.79 [0.70, 0.86]	0.81 [0.73, 0.87]
Despres 1994	LA	143	39	63	130	0.69 [0.63, 0.76]	0.77 [0.70, 0.83]
Dubucquoi 2004	ELISA	84	41	56	90	0.60 [0.51, 0.68]	0.69 [0.60, 0.77]
Fernandez−Suarez 2005	Nephelometry	30	2	23	73	0.57 [0.42, 0.70]	0.97 [0.91, 1.00]
Girelli 2004	Nephelometry	32	29	3	13	0.91 [0.77, 0.98]	0.31 [0.18, 0.47]
Goldbach−Mansky 2000	Nephelometry	70	39	36	93	0.66 [0.56, 0.75]	0.70 [0.62, 0.78]
Gomes−Daudrix 1994	ELISA	48	1	40	99	0.55 [0.44, 0.65]	0.99 [0.95, 1.00]
Greiner 2005	Nephelometry	75	42	12	191	0.86 [0.77, 0.93]	0.82 [0.76, 0.87]
Grootenboer−Mignot 2004	Nephelometry	64	18	29	73	0.69 [0.58, 0.78]	0.80 [0.71, 0.88]
Hitchon 2004	Nephelometry	32	10	9	13	0.78 [0.62, 0.89]	0.57 [0.34, 0.77]
Jansen 2003	Nephelometry	130	8	128	113	0.50 [0.44, 0.57]	0.93 [0.87, 0.97]
Jonsson 1998	ELISA	50	14	20	191	0.71 [0.59, 0.82]	0.93 [0.89, 0.96]
Kamali 2005	LA	20	32	26	25	0.43 [0.29, 0.59]	0.44 [0.31, 0.58]
Kwok 2005	Nephelometry	77	16	52	52	0.60 [0.51, 0.68]	0.76 [0.65, 0.86]
Lee 2003	LA	73	22	29	90	0.72 [0.62, 0.80]	0.80 [0.72, 0.87]
Lopez−Hoyos 2004	Nephelometry	36	3	5	70	0.88 [0.74, 0.96]	0.96 [0.88, 0.99]
Rantapaa−Dahlqvist 2003	ELISA	49	23	28	359	0.64 [0.52, 0.74]	0.94 [0.91, 0.96]
Raza 2005	LA	22	2	20	80	0.52 [0.36, 0.68]	0.98 [0.91, 1.00]
Saraux 1995	LA	8	8	31	91	0.21 [0.09, 0.36]	0.92 [0.85, 0.96]
Saraux 2003	ELISA	35	8	51	149	0.41 [0.30, 0.52]	0.95 [0.90, 0.98]
Sauerland 2005	Nephelometry	161	89	7	360	0.96 [0.92, 0.98]	0.80 [0.76, 0.84]
Schellekens 2000	ELISA	80	28	69	284	0.54 [0.45, 0.62]	0.91 [0.87, 0.94]
Soderlin 2004	LA	5	4	11	49	0.31 [0.11, 0.59]	0.92 [0.82, 0.98]
Spiritus 2004	Nephelometry	57	9	33	93	0.63 [0.53, 0.73]	0.91 [0.84, 0.96]
Suzuki 2003	Nephelometry	383	38	166	170	0.70 [0.66, 0.74]	0.82 [0.76, 0.87]
Swedler	Nephelometry	89	3	9	39	0.91 [0.83, 0.96]	0.93 [0.81, 0.99]
Thammanichanond 2005	LA	57	25	6	111	0.90 [0.80, 0.96]	0.82 [0.74, 0.88]
Vallbracht 2004	ELISA	196	75	99	345	0.66 [0.61, 0.72]	0.82 [0.78, 0.86]
van Leeuwen 1988	ELISA	163	10	28	140	0.85 [0.80, 0.90]	0.93 [0.88, 0.97]
Vasiliauskiene 2001	ELISA	75	21	21	106	0.78 [0.69, 0.86]	0.83 [0.76, 0.89]
Visser 1996	ELISA	157	287	78	1466	0.67 [0.60, 0.73]	0.84 [0.82, 0.85]
Vittecoq 2001	LA	26	1	32	29	0.45 [0.32, 0.58]	0.97 [0.83, 1.00]
Vittecoq 2004	ELISA	62	11	114	127	0.35 [0.28, 0.43]	0.92 [0.86, 0.96]
Winkles 1989	LA	113	19	29	481	0.80 [0.72, 0.86]	0.96 [0.94, 0.98]



How do I constrain parameters in the Rutter and Gatsonis subgroup model?

In the Rutter and Gatsonis model, all parameter constraints are controlled by `constrain`, i.e.,

- `constrain="sigma2_alpha"` sets σ_α^2 to zero,
- `constrain="sigma2_theta"` sets σ_θ^2 to zero,

- `constrain="accuracy"` assumes equal accuracy parameters across subgroups, i.e. $\xi_2 = \xi_3 = \cdots = 0$,
- `constrain="threshold"` assumes equal threshold parameters across subgroups, i.e. $\gamma_2 = \gamma_3 = \cdots = 0$,
- `constrain="shape"` assumes equal shape parameters across subgroups, i.e. $\delta_2 = \delta_3 = \cdots = 0$,
- `constrain="shape_zero"` fixes all shape parameters at zero.

Constraints can also be combined, for example `constrain=c("shape","sigma2_theta")`.

How do I use the general Rutter and Gatsonis regression function?

This method is for advanced users who feel comfortable specifying their own design and prediction matrices. For study-level covariates, the design matrix Z needs two identical consecutive rows per study, one for the diseased and one for the non-diseased. Of note, there are neither `plot()` nor `forest()` methods for `fitRutterGatsonisReg()`.

Let's reproduce the subgroup-analysis from before.

```
# Specify design matrix Z
Z  <- model.matrix(~method,data=RF2)
# For study level-covariates, we need to two identical consecutive
# rows per study (diseased and non-diseased).
Z2 <- Z[rep(seq_len(nrow(Z)), each = 2), , drop = FALSE]
# Specify prediction matrix Z_pred
Z_pred <- matrix(c(1,0,0,1,1,0,1,0,1),ncol=3,nrow=3,byrow=T)
constrain <- list(shape_coef=factor(c(1, rep(NA, ncol(Z2) - 1))))

ruttergatsonisreg <- fitRutterGatsonisReg(data=RF2,
                                          TP=TP,
                                          FP=FP,
                                          FN=FN,
                                          TN=TN,
                                          study=study,
                                          Z=Z2,
                                          Z_pred=Z_pred,
                                          map=constrain)

ruttergatsonisreg
#>
#> Rutter & Gatsonis Regression Model
#> ----------------------------------
#>
```

```
#> Number of studies : 47
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.0003981125
#> -2 log likelihood : 753.722 ( df = 9 )
#> AIC               : 771.722
#> BIC               : 788.374
#>
#> Use summary() for parameter estimates.
summary(ruttergatsonisreg)
#>
#> Summary: Rutter & Gatsonis Regression Model
#> -------------------------------------------
#>
#> Parameter estimates
#> -------------------
#>                    Estimate  Std. Error
#> accuracy_coef   2.456306200 0.323578110
#> accuracy_coef   0.248536610 0.439542730
#> accuracy_coef   0.331419970 0.442602170
#> threshold_coef -0.550050810 0.213340320
#> threshold_coef -0.196254760 0.260962000
#> threshold_coef  0.495866140 0.262230550
#> shape_coef      0.197682730 0.169839700
#> shape_coef      0.000000000 0.000000000
#> shape_coef      0.000000000 0.000000000
#> sigma2_alpha    1.277925600 0.308528070
#> sigma2_theta    0.476840430 0.113445210
#> Lambda_Pred     2.456306200 0.323578110
#> Lambda_Pred     2.704842800 0.326955320
#> Lambda_Pred     2.787726100 0.305780160
#> Theta_Pred     -0.550050810 0.213340320
#> Theta_Pred     -0.746305570 0.209913120
#> Theta_Pred     -0.054184665 0.212131320
#> beta_Pred       0.197682730 0.169839700
#> beta_Pred       0.197682730 0.169839700
#> beta_Pred       0.197682730 0.169839700
#> logitsens       0.826166620 0.286300670
#> logitsens       1.051312600 0.286070290
#> logitsens       1.126395500 0.276896050
#> sens            0.695543770 0.060627783
#> sens            0.741026870 0.054898619
```

```
#> sens            0.755173080 0.051194397
#>
#> Sensitivity / specificity
#> -------------------------
#>         spec conflevel  logitsens  Std_Error   CI_Lower  CI_Upper       Sens
#> 1 0.84615385      0.95 0.82616662 0.28630067 0.26502762 1.3873056 0.69554377
#> 2 0.84615385      0.95 1.05131260 0.28607029 0.49062509 1.6120000 0.74102687
#> 3 0.84615385      0.95 1.12639550 0.27689605 0.58368917 1.6691018 0.75517308
#>   SensCI_Lower SensCI_Upper
#> 1   0.56587179   0.80016175
#> 2   0.62025368   0.83368888
#> 3   0.64191584   0.84145602
```

How do I compare models?

In the previous section we fitted the `RF` data set using the Rutter and Gatsonis subgroup model while keeping the shape parameter equal across all subgroups `constrain="shape"`. Now let's fit the full model allowing for different shape parameters across subgroups and check whether the data lend support to this approach. In addition, let's also consider a model that constrains both `shape` and `accuracy`.

```
ruttergatsonissubfull <- fitRutterGatsonisSubgroup(data=RF2,
                                                   TP=TP,
                                                   FP=FP,
                                                   FN=FN,
                                                   TN=TN,
                                                   study=study,
                                                   subgroup=method,
                                                   constrain=NULL)
ruttergatsonissubfull
#>
#> Rutter & Gatsonis Subgroup Model
#> --------------------------------
#>
#> Number of studies   : 47
#> Number of subgroups : 3
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0001936155
#> -2 log likelihood   : 753.553 ( df = 11 )
#> AIC                 : 775.553
```

```
#> BIC                 : 795.905
#>
#> Use summary() for parameter estimates.
summary(ruttergatsonissubfull)
#>
#> Summary: Rutter & Gatsonis Subgroup Model
#> ----------------------------------------
#>
#> Parameter estimates
#> -------------------
#>                         Estimate  Std. Error
#> Lambda_LA             2.42435650 0.330490060
#> xi_ELISA              0.29743443 0.513150050
#> xi_Nephelometry       0.37161351 0.450864220
#> Theta_LA             -0.50294636 0.244516610
#> gamma_ELISA          -0.25783318 0.370244910
#> gamma_Nephelometry    0.39706424 0.359443140
#> beta_LA               0.27775702 0.266422660
#> delta_ELISA          -0.10290405 0.426607590
#> delta_Nephelometry   -0.16039260 0.397537120
#> sigma2_alpha          1.27305060 0.307984420
#> sigma2_theta          0.47624252 0.113436600
#> Lambda_LA             2.42435650 0.330490060
#> Lambda_ELISA          2.72179090 0.392992730
#> Lambda_Nephelometry   2.79597000 0.307080030
#> Theta_LA             -0.50294636 0.244516610
#> Theta_ELISA          -0.76077954 0.278169440
#> Theta_Nephelometry   -0.10588212 0.263228630
#> beta_LA               0.27775702 0.266422660
#> beta_ELISA            0.17485297 0.333210110
#> beta_Nephelometry     0.11736442 0.295002910
#> logitsens             0.81868527 0.275188790
#> logitsens             1.06266640 0.324053890
#> logitsens             1.12065150 0.288348430
#> sens                  0.69395719 0.058444763
#> sens                  0.74319976 0.061846941
#> sens                  0.75410954 0.053467971
#>
#> Sensitivity / specificity
#> -------------------------
#>       subgroup       spec conflevel  logitsens  Std_Error   CI_Lower  CI_Upper
#> 1           LA 0.84615385      0.95 0.81868527 0.27518879 0.27932515 1.3580454
```

```
#> 2        ELISA 0.84615385      0.95 1.06266640 0.32405389 0.42753242 1.6978003
#> 3 Nephelometry 0.84615385      0.95 1.12065150 0.28834843 0.55549896 1.6858041
#>         Sens SensCI_Lower SensCI_Upper
#> 1 0.69395719   0.56938077   0.79544184
#> 2 0.74319976   0.60528428   0.84524723
#> 3 0.75410954   0.63541045   0.84367155
#>
#> Recovered bivariate parameters (Reitsma)
#> ----------------------------------------
#>               mu_A.sens mu_B.spec sigma2_A.sens sigma2_B.spec    sigma_AB
#> LA           0.61726846 1.9706516    0.60182246    1.04887820 -0.15797987
#> ELISA        0.54987796 2.3155155    0.66705102    0.94631215 -0.15797987
#> Nephelometry 1.21846130 1.5947581    0.70652253    0.89344424 -0.15797987
#>
#> Subgroups
#> ---------
#> [1] "LA"           "ELISA"        "Nephelometry"
ruttergatsonissubacc <- fitRutterGatsonisSubgroup(data=RF2,
                                                  TP=TP,
                                                  FP=FP,
                                                  FN=FN,
                                                  TN=TN,
                                                  study=study,
                                                  subgroup=method,
                                                  constrain=c("shape","accuracy"))
ruttergatsonissubacc
#>
#> Rutter & Gatsonis Subgroup Model
#> --------------------------------
#>
#> Number of studies   : 47
#> Number of subgroups : 3
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0005592484
#> -2 log likelihood   : 754.332 ( df = 7 )
#> AIC                 : 768.332
#> BIC                 : 781.283
#>
#> Use summary() for parameter estimates.
summary(ruttergatsonissubacc)
#>
```

```
#> Summary: Rutter & Gatsonis Subgroup Model
#> ----------------------------------------
#>
#> Parameter estimates
#> -------------------
#>                         Estimate  Std. Error
#> Lambda_LA             2.65810190 0.191815720
#> xi_ELISA              0.00000000 0.000000000
#> xi_Nephelometry       0.00000000 0.000000000
#> Theta_LA             -0.55746273 0.212932400
#> gamma_ELISA          -0.19386257 0.260935930
#> gamma_Nephelometry    0.49703130 0.262130440
#> beta_LA               0.18948853 0.164729720
#> delta_ELISA           0.00000000 0.000000000
#> delta_Nephelometry    0.00000000 0.000000000
#> sigma2_alpha          1.29063570 0.312335810
#> sigma2_theta          0.47671067 0.113444250
#> Lambda_LA             2.65810190 0.191815720
#> Lambda_ELISA          2.65810190 0.191815720
#> Lambda_Nephelometry   2.65810190 0.191815720
#> Theta_LA             -0.55746273 0.212932400
#> Theta_ELISA          -0.75132530 0.208099240
#> Theta_Nephelometry   -0.06043143 0.209582940
#> beta_LA               0.18948853 0.164729720
#> beta_ELISA            0.18948853 0.164729720
#> beta_Nephelometry     0.18948853 0.164729720
#> logitsens             1.00734590 0.165264820
#> logitsens             1.00734590 0.165264820
#> logitsens             1.00734590 0.165264820
#> sens                  0.73250042 0.032382577
#> sens                  0.73250042 0.032382577
#> sens                  0.73250042 0.032382577
#>
#> Sensitivity / specificity
#> -------------------------
#>       subgroup       spec conflevel logitsens  Std_Error   CI_Lower CI_Upper
#> 1           LA 0.84615385      0.95 1.0073459 0.16526482 0.68343284 1.331259
#> 2        ELISA 0.84615385      0.95 1.0073459 0.16526482 0.68343284 1.331259
#> 3 Nephelometry 0.84615385      0.95 1.0073459 0.16526482 0.68343284 1.331259
#>         Sens SensCI_Lower SensCI_Upper
#> 1 0.73250042   0.66450444   0.79104882
#> 2 0.73250042   0.66450444   0.79104882
```

```
#> 3 0.73250042   0.66450444   0.79104882
#>
#> Recovered bivariate parameters (Reitsma)
#> ----------------------------------------
#>               mu_A.sens mu_B.spec sigma2_A.sens sigma2_B.spec    sigma_AB
#> LA           0.70184091 2.0739910    0.66138418    0.96614309 -0.15405174
#> ELISA        0.52550245 2.2871192    0.66138418    0.96614309 -0.15405174
#> Nephelometry 1.15394330 1.5275659    0.66138418    0.96614309 -0.15405174
#>
#> Subgroups
#> ---------
#> [1] "LA"           "ELISA"        "Nephelometry"
```

How do I get the log likelihood, the AIC, and the BIC of a model?

```
logLik(ruttergatsonissubfull)
#> 'log Lik.' -376.7765 (df=11)
AIC(ruttergatsonissubfull)
#> [1] 775.5531
BIC(ruttergatsonissubfull)
#> [1] 795.9047

logLik(ruttergatsonissub)
#> 'log Lik.' -376.8612 (df=9)
AIC(ruttergatsonissub)
#> [1] 771.7223
BIC(ruttergatsonissub)
#> [1] 788.3736

logLik(ruttergatsonissubacc)
#> 'log Lik.' -377.1659 (df=7)
AIC(ruttergatsonissubacc)
#> [1] 768.3318
BIC(ruttergatsonissubacc)
#> [1] 781.2829
```

How do I perform a likelihood ratio test of the two models?

The tests below formally investigate whether the HSROC curve shapes and/or accuracy parameters are equal in all subgroups.

```
anova(ruttergatsonissub,
      ruttergatsonissubfull)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  9 -376.86
#> Model 2 11 -376.78       2 0.1692     0.9189
anova(ruttergatsonissubacc,
      ruttergatsonissub)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  7 -377.17
#> Model 2  9 -376.86       2 0.6095     0.7373
anova(ruttergatsonissubacc,
      ruttergatsonissubfull)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  7 -377.17
#> Model 2 11 -376.78       4 0.7787     0.9413
```

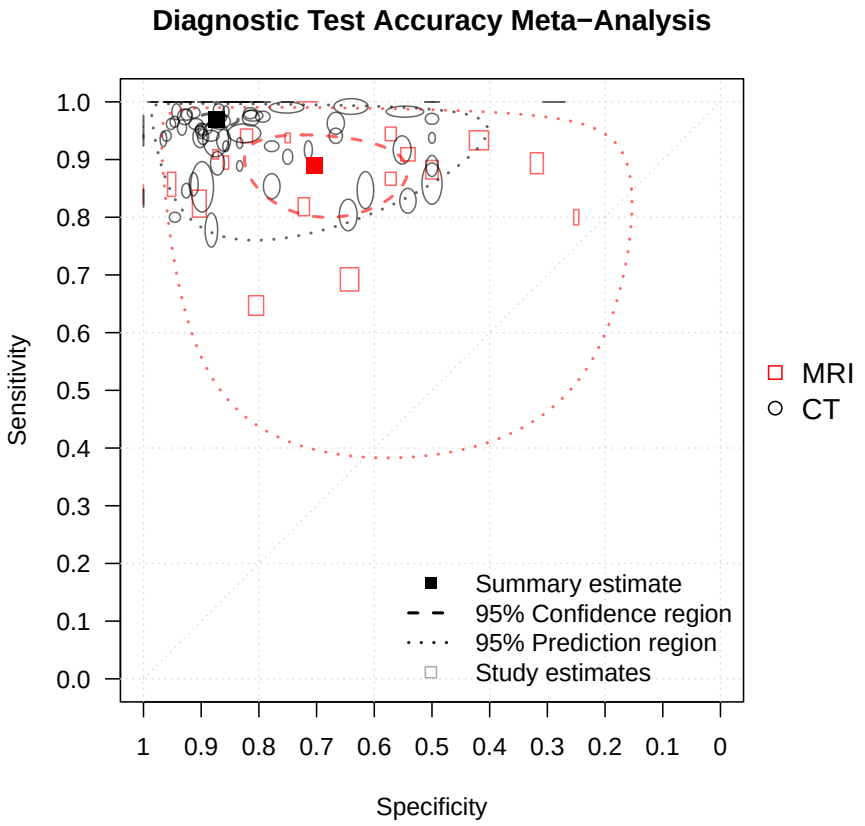
How do I replicate results from the Cochrane Handbook with respect to the `schuetz` data set?

What are the results for the full data set?

```
data(schuetz)
head(schuetz)
#>   test          study TP FP FN TN indirect
#> 1   CT Achenbach 2005 25  4  0 19        1
#> 2   CT   Alkadhi 2008 57 12  2 79        1
#> 3   CT  Andreini 2007 17  0  0 44        1
#> 4   CT    Bayrak 2008 64  4  0 32        1
#> 5  MRI    Bedaux 2002  7  1  0  1        1
#> 6  MRI   Bogaert 2003 12  3  3  1        1
schuetz$test   <- factor(schuetz$test,levels=c("MRI","CT"))
schuetzreitsma <- fitReitsmaSubgroup(data=schuetz,
                                     TP=TP,FP=FP,FN=FN,TN=TN,
                                     study=study,
                                     subgroup=test,
                                     variances="common")
schuetzreitsma
#>
#> Reitsma Subgroup Model
#> ----------------------
```

```
#>
#> Number of studies   : 108
#> Number of subgroups : 2
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0009488887
#> -2 log likelihood   : 951.843 ( df = 7 )
#> AIC                 : 965.843
#> BIC                 : 984.618
#>
#> Use summary() for parameter estimates.
summary(schuetzreitsma)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                              Estimate  Std_Error
#> mu_A.MRI                   2.09345490 0.26392178
#> mu_B.MRI                   0.86047288 0.25722689
#> mu_A.CT                    3.48272650 0.15698592
#> mu_B.CT                    1.92906950 0.12066660
#> sigma2_A.sens.log_sigma_A 0.85004519 0.21954718
#> sigma2_B.spec.log_sigma_B 0.85268704 0.16833879
#> sigma_AB                   0.18575027 0.13420795
#> nu_A.CT                    1.38928530 0.30152230
#> nu_B.CT                    1.06858890 0.28340397
#>
#> Sensitivity / specificity
#> -------------------------
#>          type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.MRI sens 0.89026540      0.95 0.82866250 0.93154909
#> mu_B.MRI spec 0.70275944      0.95 0.58814870 0.79651089
#> mu_A.CT  sens 0.97019227      0.95 0.95988410 0.97791261
#> mu_B.CT  spec 0.87314639      0.95 0.84456148 0.89711495
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>        Lambda      Theta        beta sigma2_alpha sigma2_theta
#> MRI 2.9548851 0.61763696 0.001551535    2.0742307   0.33280741
#> CT  5.4130029 0.77892791 0.001551535    2.0742307   0.33280741
```

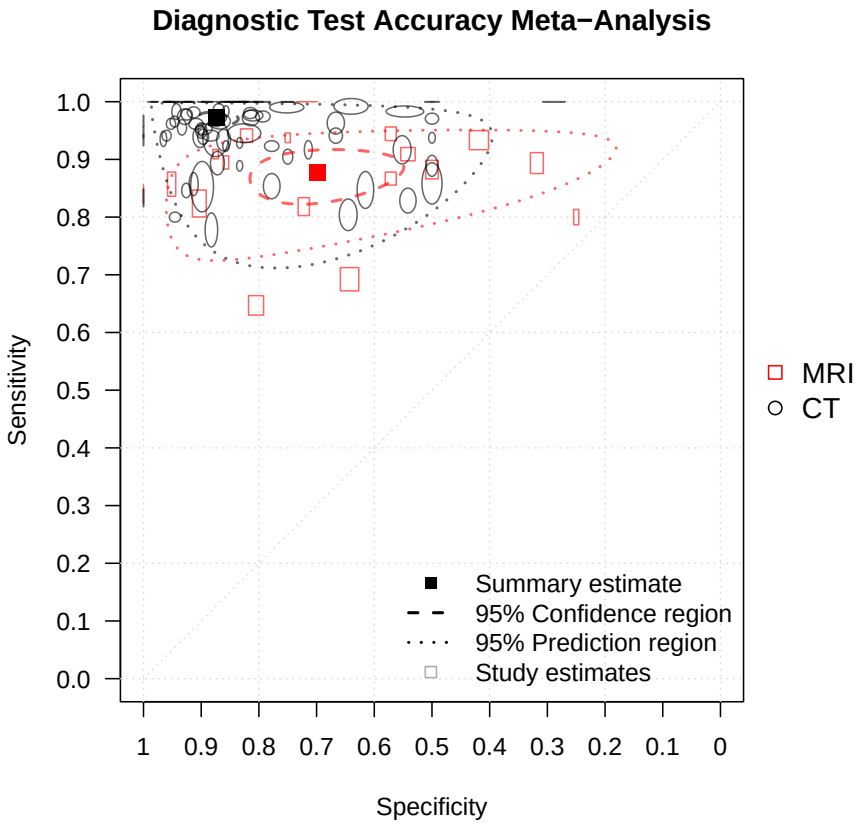
```
#>
#> Subgroups
#> ---------
#> [1] "MRI" "CT"
plot(schuetzreitsma,
     nudge_legend=-0.2,
     size="se",
     col=c("red","black"))
```




```
schuetzreitsma1 <- fitReitsmaSubgroup(data=schuetz,
                                      TP=TP,FP=FP,FN=FN,TN=TN,
                                      study=study,
                                      subgroup=test,
                                      variances="unequal")
schuetzreitsma1
#>
```

```
#> Reitsma Subgroup Model
#> ----------------------
#>
#> Number of studies   : 108
#> Number of subgroups : 2
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 0.0001117501
#> -2 log likelihood   : 943.305 ( df = 10 )
#> AIC                 : 963.305
#> BIC                 : 990.127
#>
#> Use summary() for parameter estimates.
summary(schuetzreitsma1)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                 Estimate  Std_Error
#> mu_A.MRI      1.96704120 0.16243413
#> mu_B.MRI      0.84102032 0.24063701
#> sigma2_A.MRI  0.11264202 0.16001562
#> sigma2_B.MRI  0.71212692 0.34247434
#> sigma_AB.MRI -0.14620818 0.13705823
#> mu_A.CT       3.55943060 0.17395078
#> mu_B.CT       1.93164220 0.12246545
#> sigma2_A.CT   1.10692640 0.30999078
#> sigma2_B.CT   0.88004569 0.19038875
#> sigma_AB.CT   0.30489374 0.17465399
#> nu_A.CT       1.59239900 0.23799792
#> nu_B.CT       1.09062870 0.27000566
#>
#> Sensitivity / specificity
#> -------------------------
#>          type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.MRI sens 0.87729295      0.95 0.83871205 0.90766116
#> mu_B.MRI spec 0.69868006      0.95 0.59130927 0.78795796
#> mu_A.CT  sens 0.97233226      0.95 0.96152431 0.98016685
#> mu_B.CT  spec 0.87343107      0.95 0.84443634 0.89767647
#>
```

```
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> -------------------------------------------
#>        Lambda      Theta        beta sigma2_alpha sigma2_theta
#> MRI 3.6494747 1.29435110  0.92202065   0.27403018   0.21471572
#> CT  5.4067108 0.65771141 -0.11468430   2.58376400   0.34104725
#>
#> Subgroups
#> ---------
#> [1] "MRI" "CT"
plot(schuetzreitsma1,
     nudge_legend=-0.2,
     size="se",
     col=c("red","black"))
```




```
schuetzreitsma2 <- fitReitsmaSubgroup(data=schuetz,
                                      TP=TP,FP=FP,FN=FN,TN=TN,
```

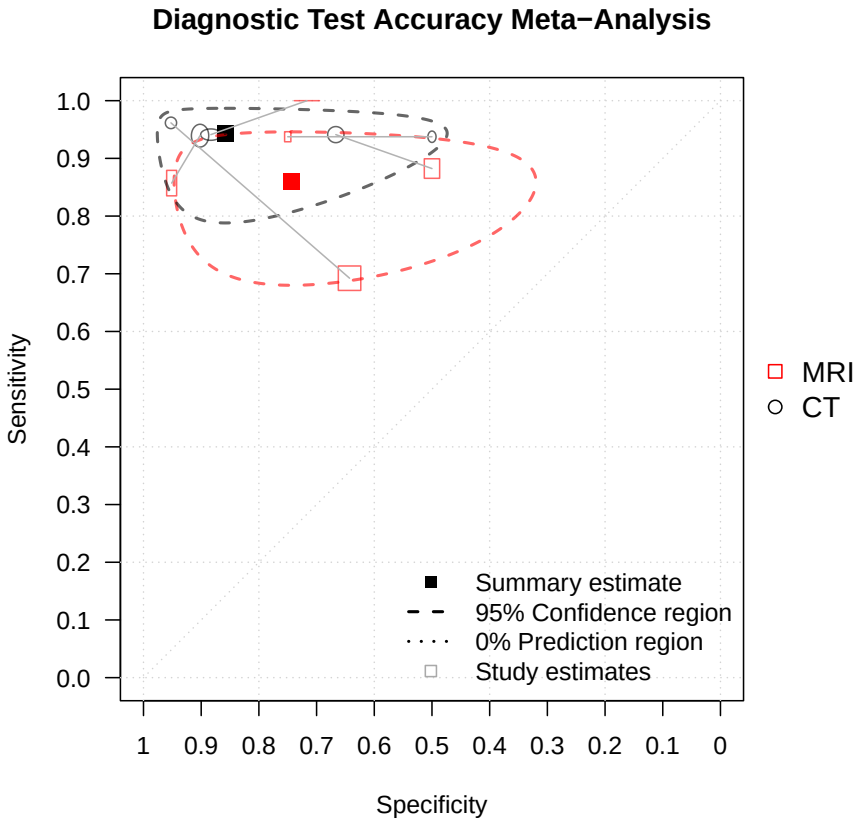
```
                                        study=study,
                                        subgroup=test,
                                        sensspec_constrain="sens")
schuetzreitsma3 <- fitReitsmaSubgroup(data=schuetz,
                                        TP=TP,FP=FP,FN=FN,TN=TN,
                                        study=study,
                                        subgroup=test,
                                        sensspec_constrain="spec")
anova(schuetzreitsma,schuetzreitsma1)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  7 -475.92
#> Model 2 10 -471.65       3 8.5381    0.03611 *
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
anova(schuetzreitsma2,schuetzreitsma)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  6 -485.79
#> Model 2  7 -475.92       1 19.745  8.848e-06 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
anova(schuetzreitsma3,schuetzreitsma)
#>         Df  logLik Df.diff  Chisq Pr(>Chisq)
#> Model 1  6 -482.64
#> Model 2  7 -475.92       1 13.432  0.0002474 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

What are the results for the direct comparisons?

```
schuetz2 <- subset(schuetz,indirect==0)
schuetzreitsma4 <- fitReitsmaSubgroup(data=schuetz2,
                                        TP=TP,FP=FP,FN=FN,TN=TN,
                                        study=study,
                                        subgroup=test,
                                        constrain="sigma2_A")
schuetzreitsma4
#>
#> Reitsma Subgroup Model
#> ----------------------
#>
```

```
#> Number of studies   : 10
#> Number of subgroups : 2
#> Optimizer           : Converged
#> Hessian             : Positive definite
#> Max |grad|          : 1.866797e-05
#> -2 log likelihood   : 88.734 ( df = 5 )
#> AIC                 : 98.734
#> BIC                 : 100.247
#>
#> Use summary() for parameter estimates.
summary(schuetzreitsma4)
#>
#> Summary: Reitsma Subgroup Model
#> -------------------------------
#>
#> Parameter estimates
#> -------------------
#>                                Estimate  Std_Error
#> mu_A.MRI                  1.8082893e+00 0.24124001
#> mu_B.MRI                  1.0631770e+00 0.41604406
#> mu_A.CT                   2.8134122e+00 0.34318787
#> mu_B.CT                   1.8013974e+00 0.43628527
#> sigma2_A.sens.log_sigma_A 4.9303807e-32 0.00000000
#> sigma2_B.spec.log_sigma_B 5.8153371e-01 0.43286772
#> sigma_AB                  0.0000000e+00 0.00000000
#> nu_A.CT                   1.0051219e+00 0.41949313
#> nu_B.CT                   7.3821676e-01 0.60559889
#>
#> Sensitivity / specificity
#> -------------------------
#>          type   Estimate conflevel   CI_Lower   CI_Upper
#> mu_A.MRI sens 0.85915500      0.95 0.79174360 0.90730054
#> mu_B.MRI spec 0.74329721      0.95 0.56162156 0.86745121
#> mu_A.CT  sens 0.94339630      0.95 0.89480371 0.97028818
#> mu_B.CT  spec 0.85831895      0.95 0.72036925 0.93441053
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>        Lambda    Theta     beta  sigma2_alpha  sigma2_theta
#> MRI 105972100 52986049 35.77261 3.3865514e-16 8.4663784e-17
#> CT  164875820 82437911 35.77261 3.3865514e-16 8.4663784e-17
#>
```

```
#> Subgroups
#> ---------
#> [1] "MRI" "CT"
plot(schuetzreitsma4,predlevel=0.000001,
     nudge_legend=-0.2,
     size="se",scale=0.0025,
     connectstudies = TRUE,
     col=c("red","black"))
```



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