Meta-analysis for diagnostic accuracy studies: A new statistical model using beta-binomial distributions and bivariate copulas

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Overview

- Introduction
- Current standard approach
- Our Model
- Copulas
- Two Examples: A simple one and a tricky one
- Future plans

Introduction: Definitons

- “Meta-analysis is a quantitative, systematic summary of a collection of separate studies for the purpose of obtaining information that cannot be derived from any of the studies alone “(Boissel et al., 1988)
- “There is an increasing interest in systematic reviews and meta-analyses of data from diagnostic accuracy studies” (Harbord, 2007)

Introduction:
Intervention studies with binary outcome

Study	Treatment	Control
1	0/17	3/18
2	245/1780	317/1802
3	47/590	63/595
…	…	…

Introduction: Intervention studies with binary outcome

Study	Treatment	Control	Effect size
1	0/17	3/18	RR_1= (0/17)/(3/18)
2	245/1780	317/1802	RR_2= …
3	47/590	63/595	RR_3= …
…	…	…	…
			RR_{MA}= …

Introduction: Diagnostic studies

Study	„Sick“ (Sensitivity)	„Healthy“ (Specificity)
1	0/17	3/18
2	245/1780	317/1802
3	47/590	63/595
…	…	…

Introduction: Diagnostic studies

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…	…	…

In general, there is no interest in merging sensitivity and specificity per study.

Introduction: Diagnostic studies

Study	„Sick“ (Sensitivity)	„Healthy“ (Specificity)
1	0/17	3/18
2	245/1780	317/1802
3	47/590	63/595
…	…	…
	Se_{MA}=…	Sp_{MA}=…

Generally, there is no interest in merging sensitivity and specificity per study.

Introduction: Diagnostic studies

Study	„Sick“ (Sensitivity)	„Healthy“ (Specificity)
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…	…	…

Generally, there is no interest in merging sensitivity and specificity per study.

Se_{MA}=… Sp_{MA}=…

… taking into account that each study reports two values that are (generally negatively) correlated

Current standard approach

Bivariate logistic regression model with random effects:

$$\text{Sensitivity } Se = \frac{TP}{TP+FN} \text{ and specificity } Sp = \frac{TN}{TN+FP}$$

(TP, FN, TN, FP represent the number of true positives, false nevatives, true negatives and false positives, respectively)

$$TP_i|Se_i \sim \text{Binomial}(TP_i + FN_i, Se_i),\ \text{logit}(Se_i) = \mu + \mathbf{U_i}\alpha + \phi_i$$
$$TN_i|Sp_i \sim \text{Binomial}(TN_i + FP_i, Sp_i),\ \text{logit}(Sp_i) = \nu + \mathbf{V_i}\beta + \psi_i$$
$$\begin{pmatrix}\phi_i \\ \psi_i\end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix}0 \\ 0\end{pmatrix}, \begin{pmatrix}\sigma^2_{\phi_i} & \rho_{\phi_i\psi_i} \\ \rho_{\phi_i\psi_i} & \sigma^2_{\psi_i}\end{pmatrix}\right]$$

$\text{logit}(p) = \log(p/(1-p))$, μ, ν intercepts for $\text{logit}(Se_i)$, $\text{logit}(Sp_i)$, U_i, V_i vectors of possibly available covariates

Current standard approach

Advantages:

- Bivariate modeling of sensitivity and specificity
  → allows correlation within studies
- Sensitivity and specificity can vary between the studies (random effects)
- Accesses individual patient data
- Meta-Regression is possible
- Empty Cells (Se, Sp = 100%) are possible
- Standard software is available (SAS PROCs NLMIXED, GLIMMIX)

Problems:

- Sensitivity and specificity are modeled on logit scale
  (interpretation of variance, correlation, …)
- Likelihood has no closed form (product of N integrals → approximative methods/ numerical or stochastical integration needed)
- Only one possible dependence structure

Our model

Analogous:
TP_i and TN_i are binomially distributed

$$TP_i|Se_i \sim \text{Binomial}(TP_i + FN_i, Se_i),$$
$$TN_i|Sp_i \sim \text{Binomial}(TN_i + FP_i, Sp_i),$$

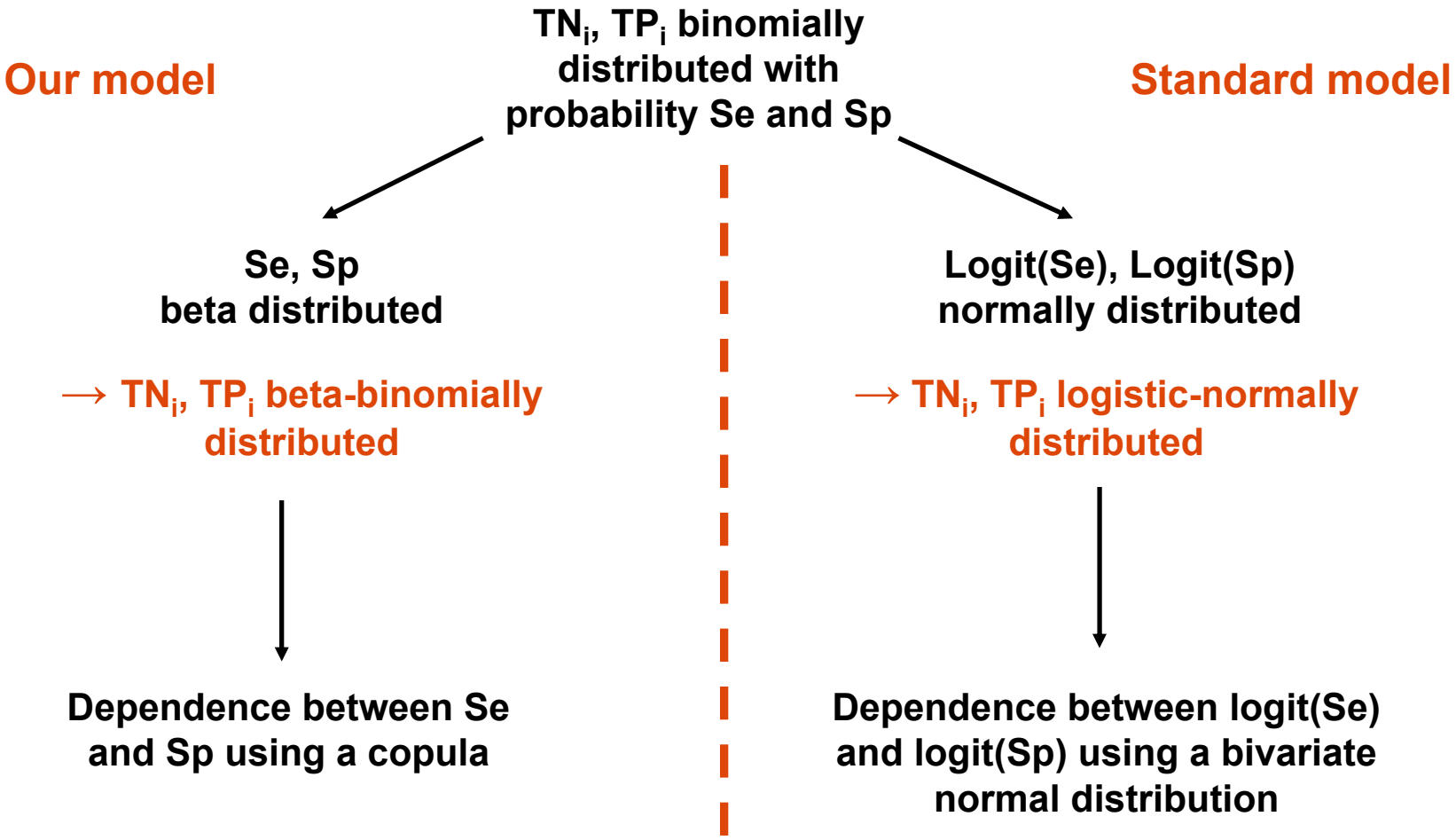
But:
Se_i and Sp_i are beta distributed
(=> Se_i and Sp_i are random effects)

$$\text{logit}(Se_i) = \mu + \mathbf{U_i}\alpha + \phi_i$$
$$\text{logit}(Sp_i) = \nu + \mathbf{V_i}\beta + \psi_i$$
$$\begin{pmatrix}\phi_i \\ \psi_i\end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix}0 \\ 0\end{pmatrix}, \begin{pmatrix}\sigma^2_{\phi_i} & \rho_{\phi_i\psi_i} \\ \rho_{\phi_i\psi_i} & \sigma^2_{\psi_i}\end{pmatrix}\right]$$

Advantage:
TP_i and TN_i are beta-binomially distributed

Last step:
Modeling the dependence between Se_i and Sp_i by using copulas

Our model


Our model
TN_i, TP_i binomially distributed with probability Se and Sp
Standard model
Se, Sp beta distributed
→ TN_i, TP_i beta-binomially distributed
Logit(Se), Logit(Sp) normally distributed
→ TN_i, TP_i logistic-normally distributed
Dependence between Se and Sp using a copula
Dependence between logit(Se) and logit(Sp) using a bivariate normal distribution

Copulas

Definition:

Every function $C : [0,1] \times [0,1] \to [0,1]$ that satisfies

(i) $C(u,0) = 0 = C(0,v), \ \forall\ u,v \in [0,1]$

(ii) $C(u,1) = u, \ C(1,v) = v, \ \forall\ u,v \in [0,1]$

(iii) $\forall\ u_1, u_2, v_1, v_2 \in [0,1]$ with $u_1 \leq u_2, \ v_1 \leq v_2$:

$$\Delta := C(u_2,v_2) - C(u_2,v_1) - C(u_1,v_2) + C(u_1,v_1) \geq 0$$

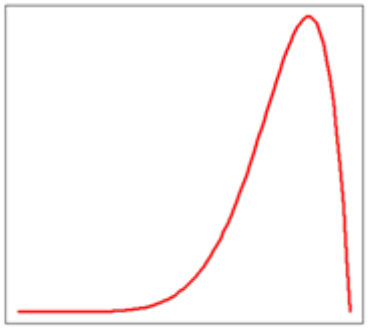
is a **copula**.

Important:

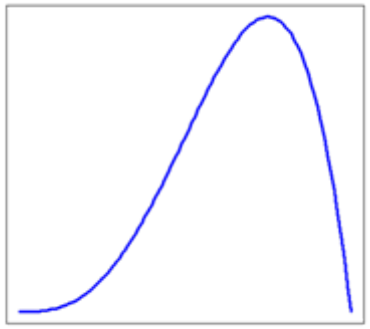
- A bivariate copula is a bivariate distribution on [0,1] x [0,1] with uniform margins
- Most copulas have an explicit density

$\longrightarrow$ Likelihood of the our model is a product of the likelihoods of the copula and of the margins

Copulas

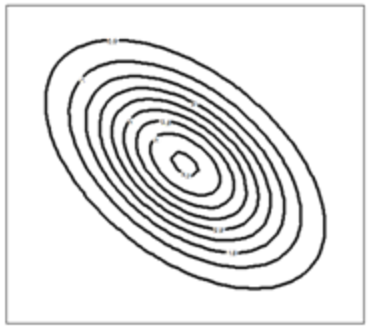


Sens ~ F



Spec ~ G

+



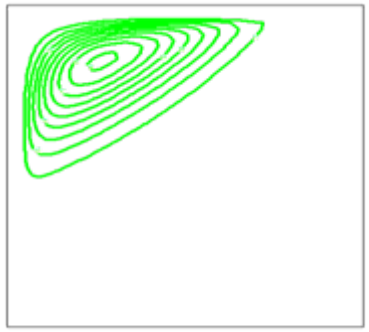
Copula C

Gaussian copula
(ρ = -0.5)

H(x,y) = C(F(x),G(y))

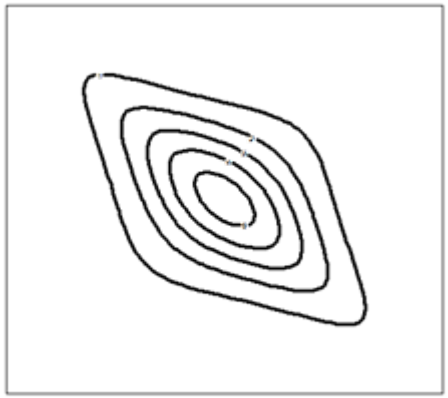
(Sklar)

(Sens,Spec) ~ H

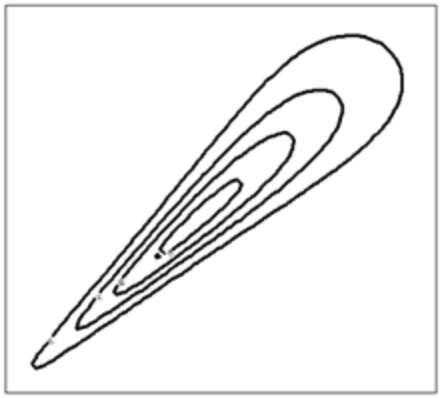


A copula describes the functional relationship between the marginal distributions and the related joint distribution.

Copulas

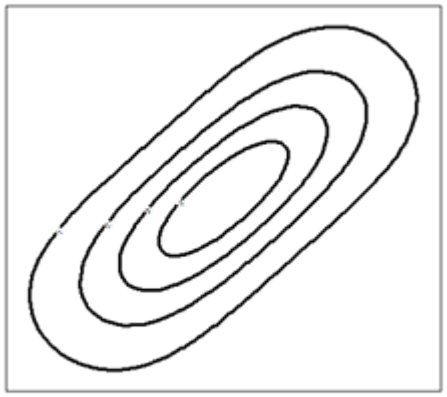


t-Copula

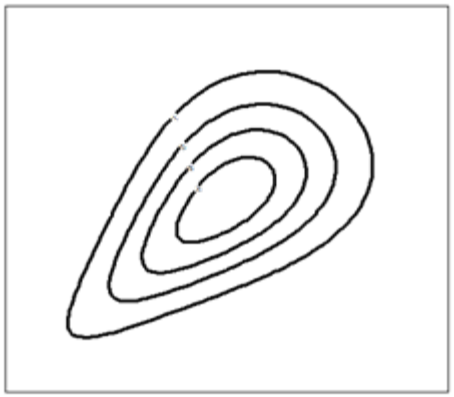


Clayton-Copula

Frank-Copula



AMH-Copula



Back to our model

Advantages:

- Modelling sensitivity and specificity on the original scale
- Closed Likelihood
  - Numerical stability
  - No need for numerical or stochastic integration
  - „Exact“ LR-test theory is applicable [MCMC: length of chain?, GQ: number of quadrature points?, effective degrees of freedom for random effects)
- Different copulas enable different dependence structures
  → optimisation via goodness of fit criteria
- Same number of parameters as compared to the standard model

Disadvantage:

- Standard model with bivariate normal distribution of the logits of sensitivity and specificity is slightly more flexible (Johnson, 1987)

Our Model:
SAS PROC NLMIXED

```
proc nlmixed data=scheidler . . .;
        …
       pi_sens = exp(b_sens)/(1 + exp(b_sens));
       pi_spec = exp(b_spec)/(1 + exp(b_spec));

       alpha_sens1 = pi_sens*(1-rho_sens)/rho_sens ; alpha_sens2 = (1- pi_sens)*(1-rho_sens)/rho_sens ;
       alpha_spec1 = pi_spec*(1-rho_spec)/rho_spec ; alpha_spec2 = (1- pi_spec)*(1-rho_spec)/rho_spec ;

       do i=0 to TP;
            f_senspdf = exp(lgamma(K+1)+lgamma(TP+alpha_sens1)+lgamma(K-i+alpha_sens2)+lgamma(alpha_sens1+alpha_sens2)
                        -lgamma(i+1)-lgamma(K-i+1)-lgamma(K+alpha_sens1+alpha_sens2) -lgamma(alpha_sens1)-lgamma(alpha_sens2));
            F_sens = F_sens + f_senspdf;
       end;

       do i=0 to TN;
            f_specpdf = exp(lgamma(G+1)+lgamma(i+alpha_spec1)+lgamma(G-i+alpha_spec2)+lgamma(alpha_spec1+alpha_spec2)
                        -lgamma(i+1)-lgamma(G-i+1)-lgamma(G+alpha_spec1+alpha_spec2) -lgamma(alpha_spec1)-lgamma(alpha_spec2));
            F_spec = F_spec + f_specpdf;
       end;
       u = quantile('Gauss',F_sens);v = quantile('Gauss',F_spec);


       ll_sens= lgamma(K+1)+lgamma(TP+alpha_sens1)+lgamma(K-TP+alpha_sens2)+lgamma(alpha_sens1+alpha_sens2)
               -lgamma(TP+1)-lgamma(K-TP+1)-lgamma(K+alpha_sens1+alpha_sens2) -lgamma(alpha_sens1)-lgamma(alpha_sens2);
       ll_spec= lgamma(G+1)+lgamma(TN+alpha_spec1)+lgamma(G-TN+alpha_spec2)+lgamma(alpha_spec1+alpha_spec2)
               -lgamma(TN+1)-lgamma(G-TN+1)-lgamma(G+alpha_spec1+alpha_spec2) -lgamma(alpha_spec1)-lgamma(alpha_spec2);

       ll_Gaussian= -log(sqrt(2*3.141*(1-normalcorr**2))) -(u**2 + v**2- 2*normalcorr*u*v)*normalcorr/(2*(1-normalcorr**2))
             -logpdf('Gauss',u) -logpdf('Gauss',v);

       ll = ll_sens + ll_spec + ll_Gaussian;

       model dummy ~ general(ll);

       estimate "Sensitivity"  exp(b_sens)/(1 + exp(b_sens)) ;
       estimate "Specificity"  exp(b_spec)/(1 + exp(b_spec)) ;
run;
```

Our Model:
SAS PROC NLMIXED

```
proc nlmixed data=scheidler . . .;
        …
       pi_sens = exp(b_sens)/(1 + exp(b_sens));
       pi_spec = exp(b_spec)/(1 + exp(b_spec));

       alpha_sens1 = pi_sens*(1-rho_sens)/rho_sens ; alpha_sens2 = (1- pi_sens)*(1-rho_sens)/rho_sens ;
       alpha_spec1 = pi_spec*(1-rho_spec)/rho_spec ; alpha_spec2 = (1- pi_spec)*(1-rho_spec)/rho_spec ;

       do i=0 to TP;
            f_senspdf = exp(lgamma(K+1)+lgamma(TP+alpha_sens1)+lgamma(K-i+alpha_sens2)+lgamma(alpha_sens1+alpha_sens2)
                        -lgamma(i+1)-lgamma(K-i+1)-lgamma(K+alpha_sens1+alpha_sens2) -lgamma(alpha_sens1)-lgamma(alpha_sens2));
            F_sens = F_sens + f_senspdf;
       end;

       do i=0 to TN;
            f_specpdf = exp(lgam                                              spec1+alpha_spec2)
                        -lgam                                                 a_spec1)-lgamma(alpha_spec2));
            F_spec = F_spec + f_
       end;
       u = quantile('Gauss',F_se

       ll_sens= lgamma(K+1)+lgamma(TP+alpha_sens1)+lgamma(K-TP+alpha_sens2)+lgamma(alpha_sens1+alpha_sens2)
               -lgamma(TP+1)-lgamma(K-TP+1)-lgamma(K+alpha_sens1+alpha_sens2) -lgamma(alpha_sens1)-lgamma(alpha_sens2);
       ll_spec= lgamma(G+1)+lgamma(TN+alpha_spec1)+lgamma(G-TN+alpha_spec2)+lgamma(alpha_spec1+alpha_spec2)
               -lgamma(TN+1)-lgamma(G-TN+1)-lgamma(G+alpha_spec1+alpha_spec2) -lgamma(alpha_spec1)-lgamma(alpha_spec2);

       ll_Gaussian= -log(sqrt(2*3.141*(1-normalcorr**2))) -(u**2 + v**2- 2*normalcorr*u*v)*normalcorr/(2*(1-normalcorr**2))
             -logpdf('Gauss',u) -logpdf('Gauss',v);

       ll = ll_sens + ll_spec + ll_Gaussian;

       model dummy ~ general(ll);

       estimate "Sensitivity"  exp(b_sens)/(1 + exp(b_sens)) ;
       estimate "Specificity"  exp(b_spec)/(1 + exp(b_spec)) ;
run;
```

But: No random statement needed, we are only using the NL*-part of PROC NLMIXED!

Standard Model:
SAS PROC NLMIXED

```
proc nlmixed data=scheidler . . .;
        …
     p_sens= exp(b_sens + u_sens)/(1+(exp(b_sens + u_sens)));
     p_spec= exp(b_spec + u_spec)/(1+(exp(b_spec + u_spec)));

     ll_sens = TP*log(p_sens) +  (K-TP)*log(1-p_sens);
     ll_spec = TN*log(p_spec) +  (G-TN)*log(1-p_spec);

     ll=ll_sens +ll_spec;

     model dummy ~ general(ll);

     estimate "Sensitivity" exp(b_sens)/(1+(exp(b_sens)));
     estimate "Specificity" exp(b_spec)/(1+(exp(b_spec)));

     random u_sens u_spec ~ normal([0,0],[sd_sens,cov_sens_spec,sd_spec]) subject=study;
run;
```

The simple example

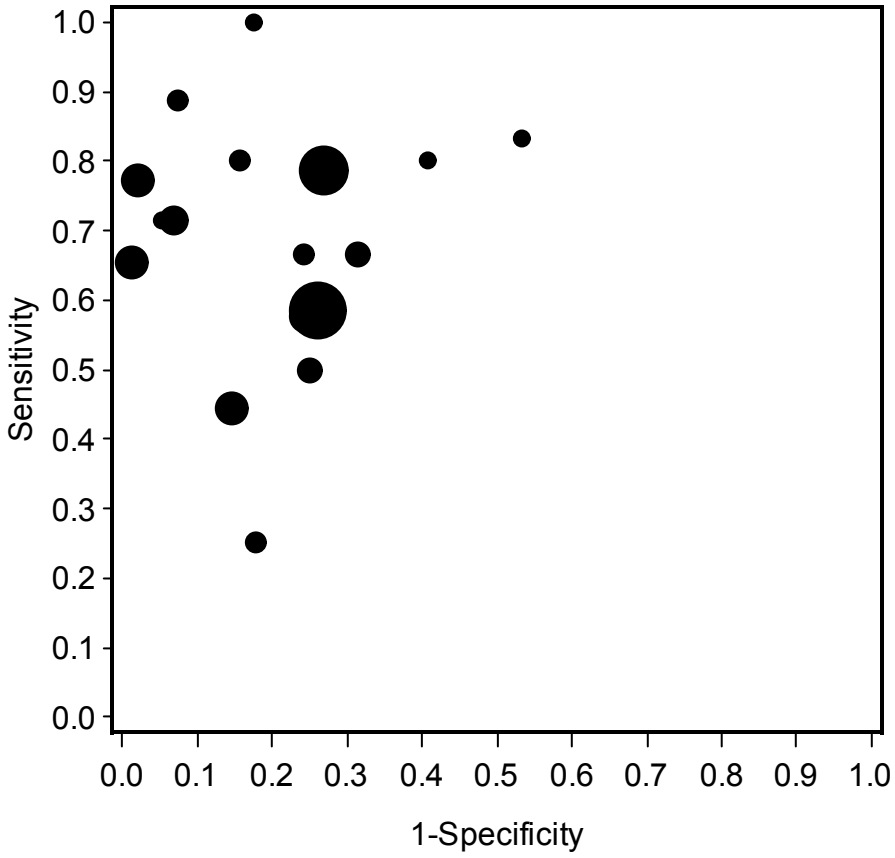
From: Scheidler et al. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis.

Aim: Validation of lymphangiography for diagnosing lymph node metastases in patients with cervical cancer

Gold standard: Histological/cytological specimen taken from surgery or biopsy of lymph nodes

Source, y	N*	Sensitivity, No. (%)	Specificity, No. (%)
Kindermann et al,[29] 1970	111	19/29 (66)	81/82 (99)
Lecart and Lenfant,[32] 1971	32	8/10 (80)	13/22 (59)
Piver et al,[42] 1971	103	41/53 (77)	49/50 (98)
Piver and Barlow,[43] 1973	26	5/7 (71)	18/19 (95)
Kolbenstvedt,[31] 1975	300	45/77 (58)	165/223 (74)
Leman et al,[19] 1975	48	8/10 (80)	32/38 (84)
Brown et al,[41] 1979	21	5/6 (83)	7/15 (47)
Lagasse et al,[48] 1979	95	15/26 (58)	52/69 (75)
Kjorstad et al,[30] 1980	59	16/24 (67)	24/35 (69)
Ashraf et al,[28] 1982	39	4/6 (67)	25/33 (76)
De Muylder et al,[36] 1984	100	8/18 (44)	70/82 (85)
Smales et al,[33] 1986	73	10/14 (71)	55/59 (93)
Feigen et al,[10] 1987	36	2/8 (25)	23/28 (82)
Swart et al,[35] 1989	54	7/14 (50)	30/40 (75)
Heller et al,[11] 1990	241	44/56 (79)	135/185 (73)
La Fianza et al,[12] 1990	49	8/9 (89)	37/40 (93)
Stellato et al,[34] 1992	21	4/4 (100)	14/17 (82)

The simple example



Datensatz: Scheidler, Copula: GAUSS, Constrain: NO

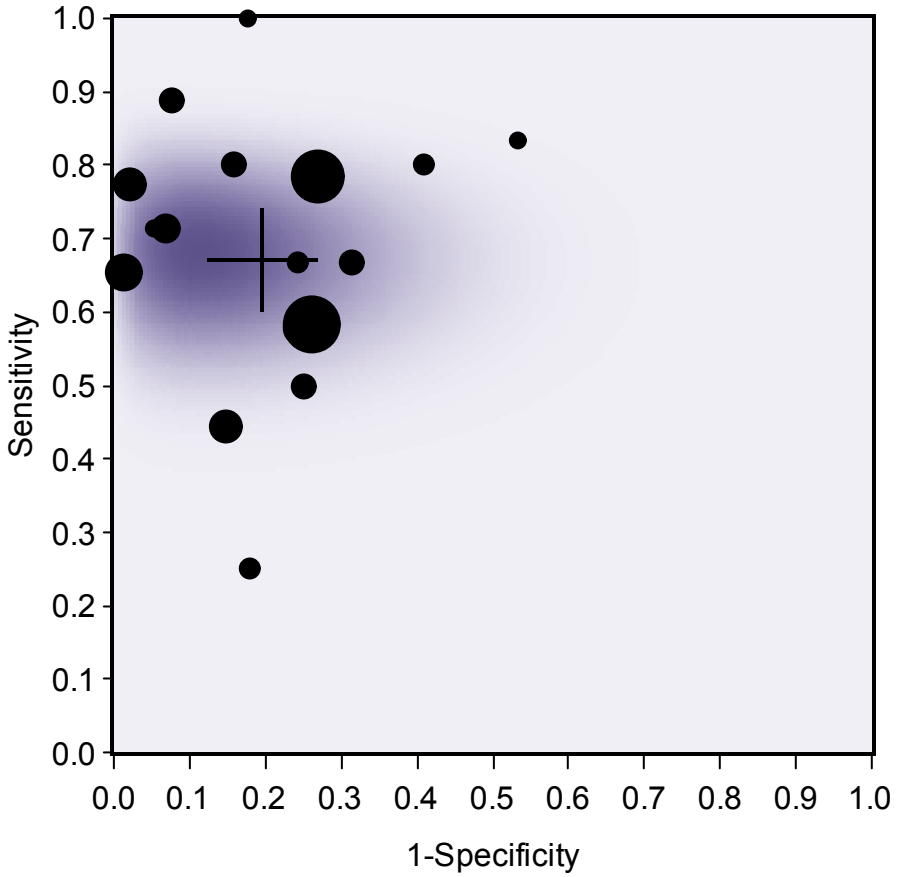
The simple example

	Sensitivity [95%-CI]	Specificity [95%-CI]	-2LogL
Gauss-Copula (Independence)	67.1% [60.0% - 74.1%]	80.7% [73.7% - 87.7%]	150.40
Gauss-Copula	67.0% [60.0% - 74.0%]	80.4% [73.1% - 87.7%]	150.30
Clayton-Copula	66.4% [58.0%, 74.7%]	80.9% [74.5%, 87.2%]	
Plackett-Copula	67.0% [60.0%, 73.9%]	80.6% [73.5%, 87.6%]	
Nelsen 4.2.16-Copula	65.2% [57.3%, 73.1%]	78.4% [69.9%, 86.9%]	
Standard Model	67.4% [59.8% - 74.2%]	83.7% [75.1% - 89.8%]	

The simple example

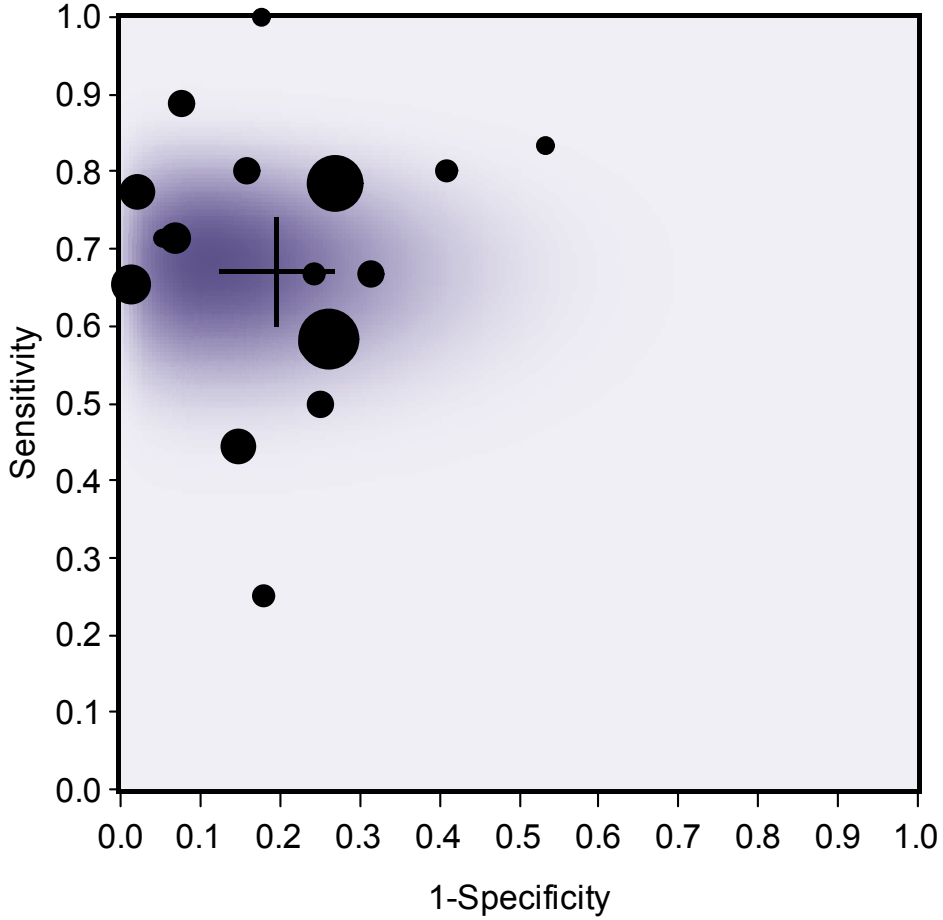
	Marg. Var. Se [95%-CI]	Marg. Var. Sp [95%-CI]	Association [95%-CI]
Gauss-Copula (Independence)	0.012 [-0.013, 0.037]	0.062 [0.011, 0.113]	0
Gauss-Copula	0.012 [-0.013, 0.037]	0.061 [0.011, 0.112]	ρ_P=0.049 [-0.271, 0.369]
Clayton-Copula	0.023 [-0.040, 0.087]	0.050 [-0.002, 0.102]	τ=-0.279 [-0.520,-0.037]
Plackett-Copula	0.012 [-0.013, 0.037]	0.061 [0.011, 0.112]	τ=0.081 [-0.316, 0.478]
Nelsen 4.2.16-Copula	0.021 [-0.013, 0.056]	0.082 [0.021, 0.143]	τ=0.212 [-0.060, 0.485]

The simple example

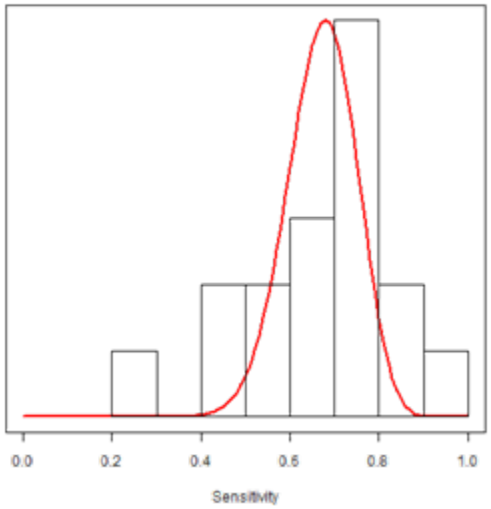


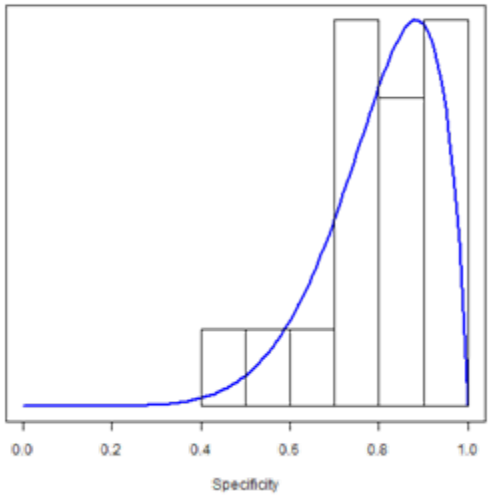
Datensatz: Scheidler, Copula: GAUSS, Constrain: NO

The simple example



Datensatz: Scheidler, Copula: GAUSS, Constrain: NO





The tricky example

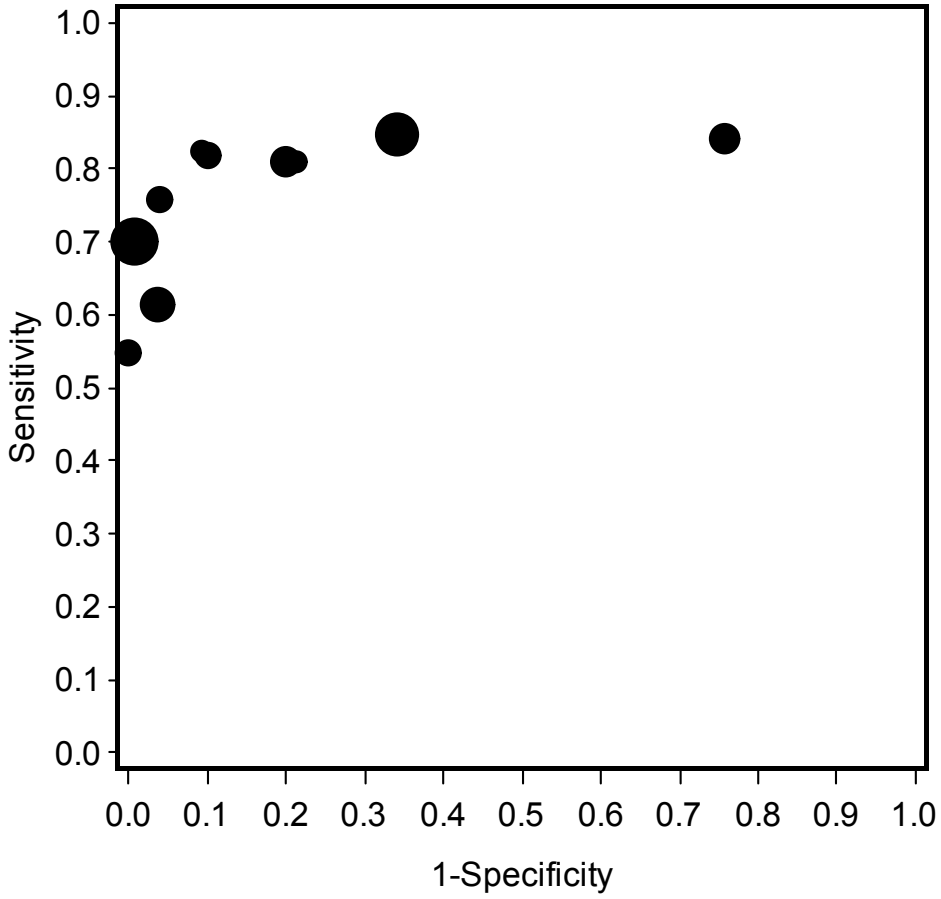
From: Glas et al. Tumor markers in the diagnosis of primary bladder cancer. A systematic review.

Aim: Validation of telomerase (urinary tumor marker) for primary bladder cancer

Gold standard: Cytoscopy and/or histopathology

	% True Pos.	% False Pos.	% False Neg.	% True Neg.
Telomerase:				
Ito et al[10]	1	8	25	76
Rahat et al[11]	3	4	11	81
Kavaler et al[12]	16	16	31	85
Yoshida et al[13]	3	10	80	62
Ramakumar et al[24]	1	17	137	70
Landman et al[25]	6	9	24	81
Kinoshita et al[26]	0	19	12	55
Gelmini et al[28]	2	6	18	82
Cheng et al[43]	3	3	29	82
Cassel et al[49]	22	7	7	84

The tricky example



Datensatz: Telomerase, Copula: GAUSS, Constrain: NO

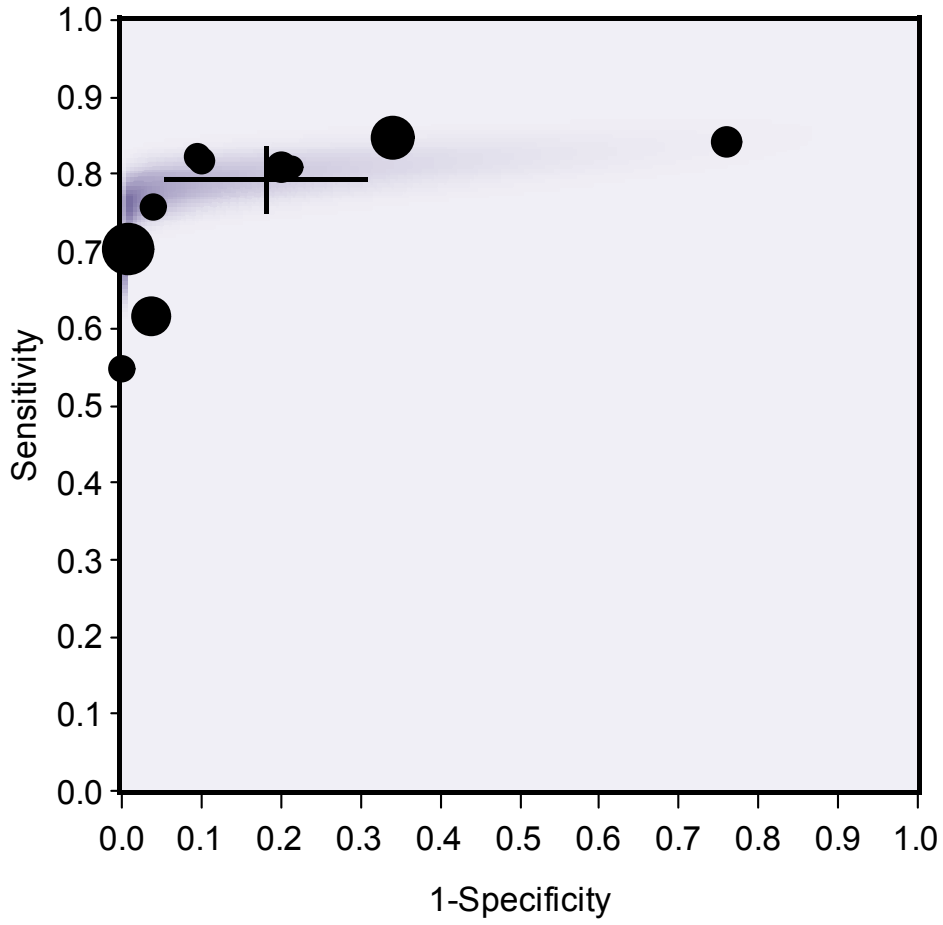
The tricky example

	Sensitivity [95%-CI]	Specificity [95%-CI]	-2LogL
Gauss-Copula (Independence)	75.8% [68.9%, 82.7%]	81.0% [67.0%, 95.1%]	92.30
Gauss-Copula	79.4% [75.1%, 83.7%]	81.9% [69.0%, 94.7%]	79.09
Clayton-Copula	--	--	
Plackett-Copula	77.6% [72.6%, 82.6%]	86.5% [74.7%, 98.3%]	
Nelsen 4.2.16-Copula	75.7% [71.3%, 80.2%]	87.7% [79.2%, 96.2%]	
Standard model (PROC NLMIXED)	--	--	
Standard model (MCMC, Paul et al.)	76.7% [69.8%, 82.6%]	90.9% [73.7%, 97.8%]	
Original analysis (Glas et al.)	75% [71%, 79%]	86% [71%, 94%]	

The tricky example

	Marg. Var. Se [95%-CI]	Marg. Var. Sp [95%-CI]	Association [95%-CI]
Gauss-Copula (Independence)	0.015 [-0.011, 0.041]	0.157 [0.036, 0.277]	0
Gauss-Copula	0.0001 [-0.0074, 0.0076]	0.147 [0.048, 0.245]	ρ_P=-0.711 [-0.954, -0.469]
Clayton-Copula	--	--	--
Plackett-Copula	0.009 [-0.005, 0.025]	0.200 [0.073, 0.326]	τ=-0.854 [-1.027, -0.681]
Nelsen 4.2.16-Copula	0.016 [-0.0006, 0.033]	0.235 [0.130, 0.339]	τ=-0.720 [-0.926, -0.514]
Standard-Modell (MCMC, Paul et al.)			$\rho_{P(logits)}$=-0.88 [-0.99, -0.18]
Original analysis (Glas et al.)			$\rho_{P(logits)}$=-0.73

The tricky example



Datensatz: Telomerase, Copula: GAUSS, Constrain: NO

Future plans

- Comparison of our model and the standard model by simulation
- What is a good measure for goodness-of-fit?
- Is the mean actual the best estimator of sensitivity and specificity (mode, median, …)?
- Confidence ellipsoids of sensitivity and specificity
- Meta regression
- Apply beta-binomial/copula methodology on other situations (e.g. intervention studies)
- Check statistical theory

References

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