Empirical Likelihood Estimation of a Diagnostic Test Likelihood Ratio

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Outline

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- An Introduction to Diagnostic Test Likelihood Ratios

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- An Empirical Likelihood Function for ρ_x

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- An Illustrative Example

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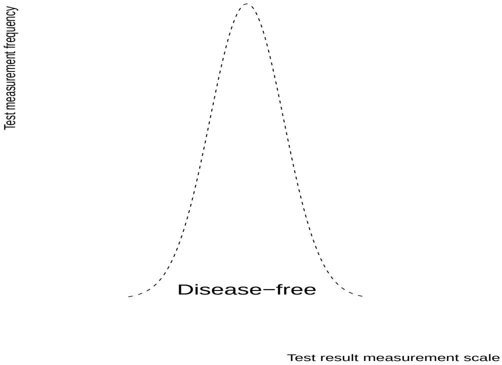
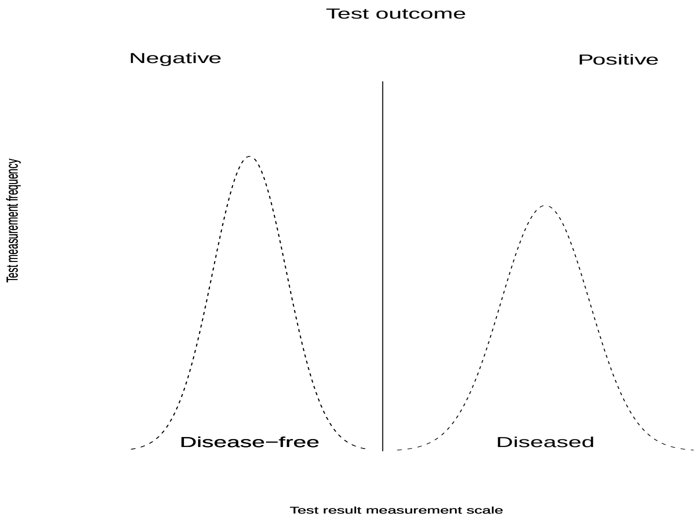
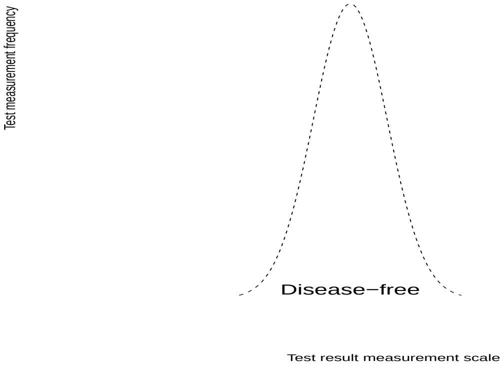
- Concluding Remarks

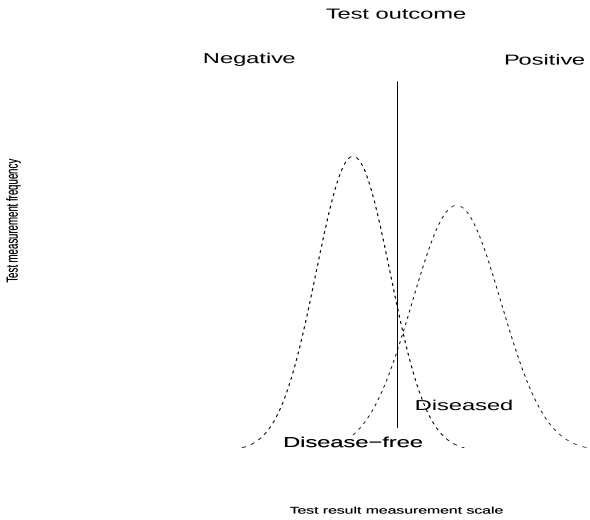
Introduction

- Assume we have two subpopulations, diseased and disease-free individuals; label the former group 1 and the latter group 2


Test measurement frequency
Disease−free
Test result measurement scale


Test outcome
Negative
Positive
Test measurement frequency
Disease−free
Diseased
Test result measurement scale


Test measurement frequency
Disease−free
Test result measurement scale


Test outcome
Negative
Positive
Test measurement frequency
Diseased
Disease−free
Test result measurement scale

- Let p_i denote the probability of a positive outcome (response) to the diagnostic test among the members of group i; we assume independence within and between both groups

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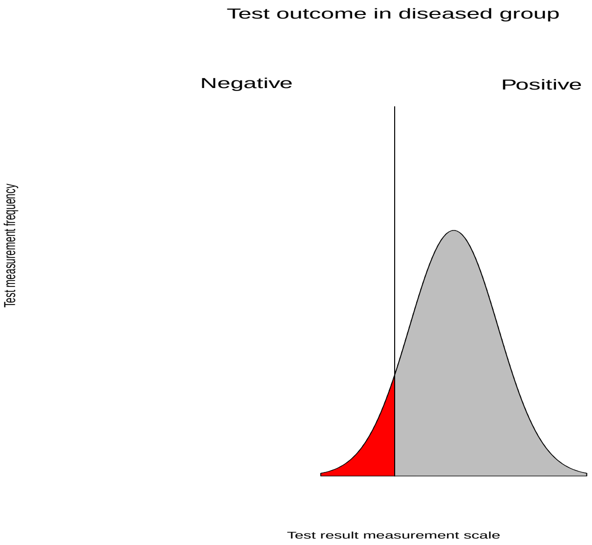
- In the terminology of diagnostic testing, p_1 is the test sensitivity, and p_2 is the probability of a false positive test error, or 1 minus the test specificity
- Since 1975, the ratios

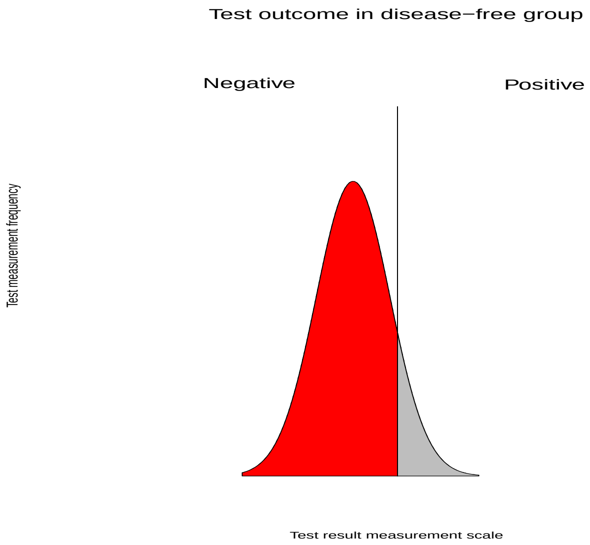
$$\rho_+ = p_1/p_2$$

and

$$\rho_- = (1 - p_1)/(1 - p_2)$$

have been of particular interest to advocates of evidence-based medicine


Test outcome in diseased group
Negative
Positive
Test measurement frequency
Test result measurement scale


Test outcome in disease−free group
Negative
Positive
Test measurement frequency
Test result measurement scale

- These functions of sensitivity and specificity have been called the "likelihood ratio of a positive test result" and the "likelihood ratio of a negative test result," as a consequence of the books by Lusted (1968) and Sackett *et al.* (1991)

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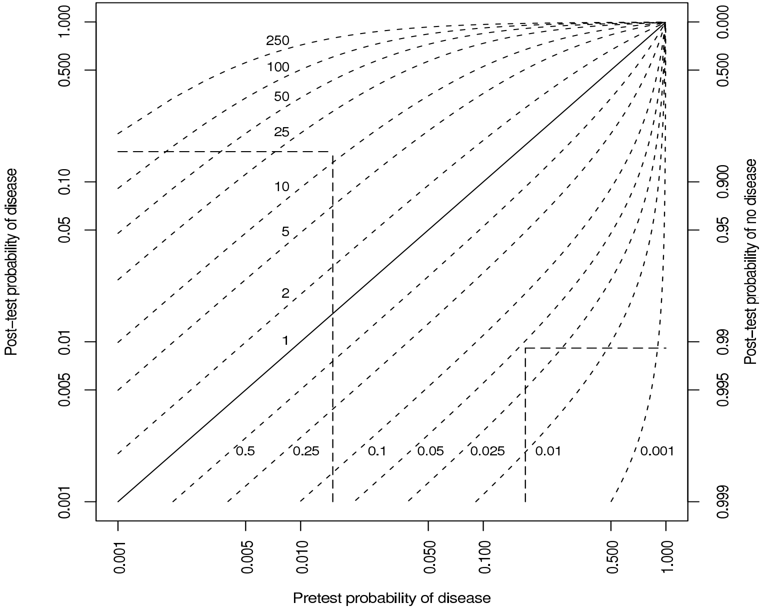
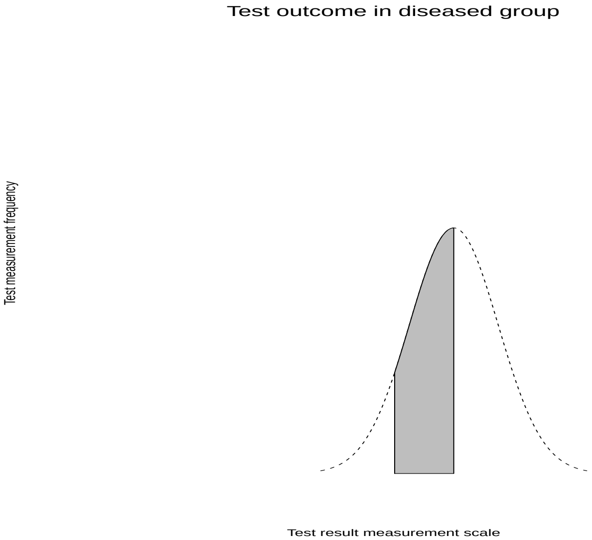
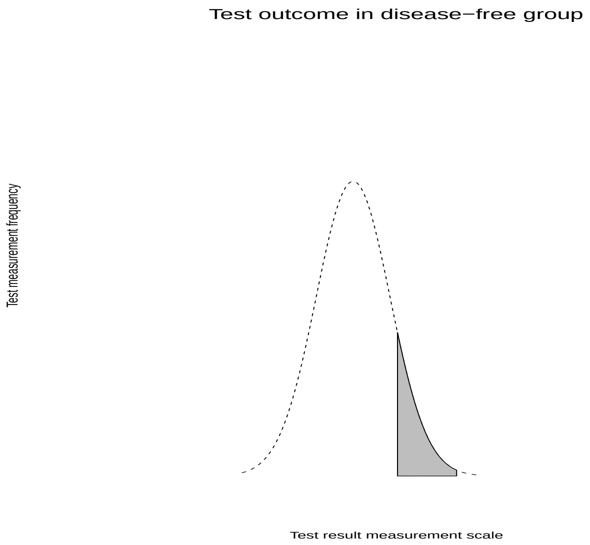
- $$\begin{aligned} & \frac{\Pr(\text{disease}|\text{positive test})}{\Pr(\text{no disease}|\text{positive test})} \\ & = \frac{\Pr(\text{positive test}|\text{disease})}{\Pr(\text{positive test}|\text{no disease})} \times \frac{\Pr(\text{disease})}{\Pr(\text{no disease})} \\ & = \rho_+ \frac{\Pr(\text{disease})}{\Pr(\text{no disease})} \end{aligned}$$


Post–test probability of disease
1.000
0.500
0.10
0.05
0.01
0.005
0.001
250
100
50
25
10
5
2
1
0.5
0.25
0.1
0.05
0.025
0.01
0.001
0.000
0.500
0.900
0.95
0.99
0.995
0.999
Post–test probability of no disease
0.001
0.005
0.010
0.050
0.100
0.500
1.000
Pretest probability of disease

- Suppose the test result is classified into $K > 2$ categories, e.g., for iron-deficiency anemia, Guyatt *et al.* (1992) report

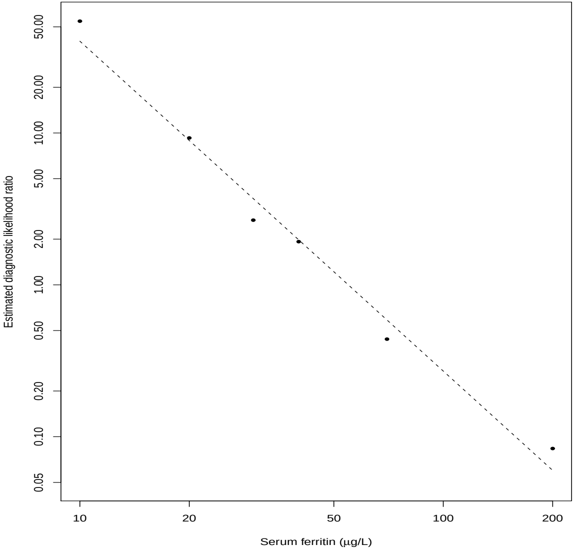
	Serum ferritin concentration (μgm/L)					
Group	[0, 15)	[15, 25)	[25, 35)	[35, 45)	[45, 100)	≥ 100
Diseased	474	117	58	36	76	48
Disease-free	20	29	50	43	398	1320


Test outcome in diseased group
Test measurement frequency
Test result measurement scale


Test outcome in disease−free group
Test measurement frequency
Test result measurement scale

- By analogy with the case of $K = 2$ categories the corresponding table of estimated DLRs for each of the serum ferritin test result categories would be

	Serum ferritin concentration (μgm/L)					
Group	[0, 15)	[15, 25)	[25, 35)	[35, 45)	[45, 100)	$\geq$ 100
Estimated DLR	54.5	9.3	2.7	1.9	0.4	0.1



Estimated diagnostic likelihood ratio
50.00
20.00
10.00
5.00
2.00
1.00
0.50
0.20
0.10
0.05
10
20
50
100
200
Serum ferritin (µg/L)

- If we push the envelope for multiple categories to the limit, then the corresponding DLR for each category becomes

$$\lim_{h \to 0+} \frac{\mathcal{F}_1(x) - \mathcal{F}_1(x+h)}{\mathcal{F}_2(x) - \mathcal{F}_2(x+h)} = \frac{f_1(x)}{f_2(x)} = \rho_x$$

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- Since each probability density function can be conveniently expressed in terms of the corresponding hazard function, i.e.,

$$f_i(x) = h_i(x) \exp\left\{ - \int_0^x h_i(s)\ ds \right\}$$

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- Formulate the estimation problem using the two-sample time-to-response framework of Kaplan-Meier (1958)

An Empirical Likelihood Function for ρ_x

- Denote the ordered, distinct response measurements in the two samples by

$$\begin{array}{rl} \text{Diseased} & x_{11} < x_{12} < \cdots < x_{1n} \\ \text{Disease-free} & x_{21} < x_{22} < \cdots < x_{2m} \end{array}$$

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- Define d_{ij} and r_{ij}, the respective event and the risk sets in sample i at response measurement x_{ij}.
- The nonparametric log-likelihood function for $\mathbf{h} = \{h_{ij}\}$, based on these data, is

$$\begin{aligned} \ell(\mathbf{h}) &= \sum_{j=1}^{n} \{d_{1j} \log h_{1j} + (r_{1j} - d_{1j}) \log(1 - h_{1j})\} \\ &\quad + \sum_{k=1}^{m} \{d_{2k} \log h_{2k} + (r_{2k} - d_{2k}) \log(1 - h_{2k})\} \end{aligned}$$

- Let t denote a fixed value of the response measurement; represent the corresponding value of the DLR at $x = t$ by ρ_t (but suppress the dependence on t subsequently); then

$$\log \rho_t = \log h_1(t) - \int_0^t h_1(s)\ ds - \log h_2(t) + \int_0^t h_2(s)\ ds\ ,$$

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- Due to the discrete nature of the empirical log-likelihood function, fixing the value of ρ_t means we want to hold fixed the quantity

$$\log \rho_t = \log h_{1t} - \sum^{(t)} (1 - h_{1j}) - \log h_{2t} + \sum^{(t)} (1 - h_{2k})$$

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- Then $\ell(\rho_t)$, the profile log-likelihood for ρ_t, can be obtained by evaluating the constrained MLEs, $\tilde{h}_{ij}$, that maximize

$$
\begin{aligned}
\ell_\xi(\rho_t) \quad = \quad & \ell + \xi\{\log h_{1t} - \sum^{(t)} \log(1 - h_{1j}) \\
& - \log h_{2t} + \sum^{(t)} \log(1 - h_{2k}) - \log \rho_t\}
\end{aligned}
$$

where ξ is a Lagrange multiplier

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- The score equations for $\mathbf{h} = \{h_{ir}\}$ that lead to the constrained MLEs, $\tilde{\mathbf{h}} = \{\tilde{h}_{ir}\}$, are

$$\begin{aligned}
\partial\ell_\xi/\partial h_{1j} &= d_{1j}/h_{1j} - (r_{1j} - d_{1j} - \xi)/(1 - h_{1j}) = 0\ , \\
&\quad \text{if } x_{1j} < t\ , \\
&= (d_{1t} + \xi)/h_{1t} - (r_{1t} - d_{1t})/(1 - h_{1t}) = 0 \\
&\quad \text{if } x_{1j} = t \\
&= d_{1j}/h_{1j} - (r_{1j} - d_{1j})/(1 - h_{1j}) = 0 \\
&\quad \text{if } x_{1j} > t
\end{aligned}$$

$$
\begin{aligned}
\partial \ell_\xi / \partial h_{2k} &= d_{2k}/h_{2k} - (r_{2k} - d_{2k} + \xi)/(1 - h_{2k}) = 0 \\
&\qquad \text{if } \; x_{2k} < t \\
&= (d_{2t} - \xi)/h_{2t} - (r_{2t} - d_{2t})/(1 - h_{2t}) = 0 \\
&\qquad \text{if } \; x_{2k} = t \\
&= d_{2k}/h_{2k} - (r_{2k} - d_{2k})/(1 - h_{2k}) = 0 \\
&\qquad \text{if } \; x_{2k} > t
\end{aligned}
$$

i.e.,

$$
\begin{aligned}
\tilde{h}_{1j} &= d_{1j}/(r_{1j} - \xi) \,, && \text{if } \; x_{1j} < t \\
&= (d_{1t} + \xi)/(r_{1t} + \xi) \,, && \text{if } \; x_{1t} = t \\
&= d_{1j}/r_{1j} \,, && \text{if } \; x_{1j} > t
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$$

$$
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\tilde{h}_{2k} &= d_{2k}/(r_{2k} + \xi) \,, && \text{if } \; x_{2k} < t \\
&= (d_{2k} - \xi)/(r_{2k} - \xi) \,, && \text{if } \; x_{2k} = t \\
&= d_{2k}/r_{2k} \,, && \text{if } \; x_{2k} > t
\end{aligned}
$$

- It follows that the LRS for $\log \rho_t$, and hence for ρ_t, is equal to

$$
\begin{aligned}
& 2\{\ell(\hat{\mathbf{h}}) - \ell(\tilde{\mathbf{h}})\} \\
= \;& 2\sum^{[t]} \left[d_{1j} \log(\hat{h}_{1j}/\tilde{h}_{1j}) + (r_{1j} - d_{1j}) \log \left\{ \frac{1 - \hat{h}_{1j}}{1 - \tilde{h}_{1j}} \right\} \right] \\
& + 2\sum^{[t]} \left[d_{2k} \log(\hat{h}_{2k}/\tilde{h}_{2k}) + (r_{2k} - d_{2k}) \log \left\{ \frac{1 - \hat{h}_{2k}}{1 - \tilde{h}_{2k}} \right\} \right] \\
= \;& 2\sum^{(t)} \left[r_{1j} \log \left(1 - \frac{\xi}{r_{1j}}\right) - (r_{1j} - d_{1j}) \log \left\{ 1 - \frac{\xi}{r_{1j} - d_{1j}} \right\} \right] \\
& + 2\sum^{(t)} \left[r_{2k} \log \left(1 + \frac{\xi}{r_{2k}}\right) - (r_{2k} - d_{2k}) \log \left\{ 1 + \frac{\xi}{r_{2k} - d_{2k}} \right\} \right] \\
& + 2\Big[r_{1t} \log \left(1 + \frac{\xi}{r_{1t}}\right) - d_{1t} \log \left(1 + \frac{\xi}{d_{1t}}\right) \\
& \qquad + r_{2t} \log \left(1 - \frac{\xi}{r_{2t}}\right) - d_{2t} \log \left(1 - \frac{\xi}{d_{2t}}\right) \Big] ,
\end{aligned}
$$

- A $100(1-\alpha)\%$ CI for ρ_t is found by solving the inequality

$$-2r(\rho_t) \leq c^*_{1,\alpha}$$

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- In practice, solve the equation

$$-2r(\rho_t) = c^*_{1,\alpha}$$

  for the two zeros, $\xi_- < 0$ and $\xi_+ > 0$; use these values to calculate the corresponding lower and upper confidence bounds for ρ_t

- Via linear and quadratic expansions of various log functions, we can show the LRS is approximately equal to

$$\frac{(\log \hat{\rho}_t - \log \tilde{\rho}_t)^2}{V_t} \,,$$

where

$$\begin{aligned} V_t &= \sum^{(t)} \{1/(r_{1j} - d_{1j}) - 1/r_{1j}\} + (1/d_{1t} - 1/r_{1t}) \\ &\quad + \sum^{(t)} \{1/(r_{2k} - d_{2j}) - 1/r_{2k}\} + (1/d_{2t} - 1/r_{2t}) \end{aligned}$$

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- This corresponds to the usual form of a Wald statistic, based on the MLE, used to test a hypothesis concerning log relative risk, i.e., $\log\rho_t$

An Illustrative Example

- Wieand *et al.* (1989) report results of CA 19-9 (cancer antigen) diagnostic test measurements. A total of 141 measurements were recorded, 51 from disease-free individuals (with pancreatitis) and 90 from subjects with confirmed pancreatic cancer.

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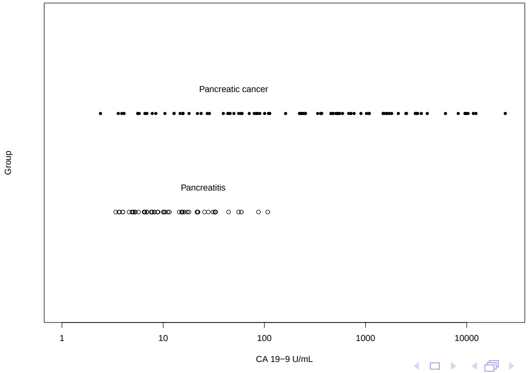

- If we fix the value of t at 21.8 U/mL

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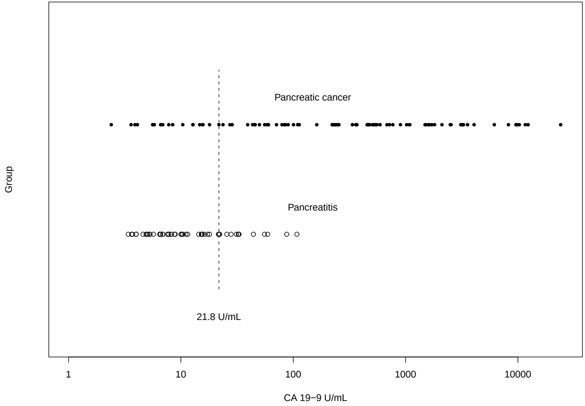
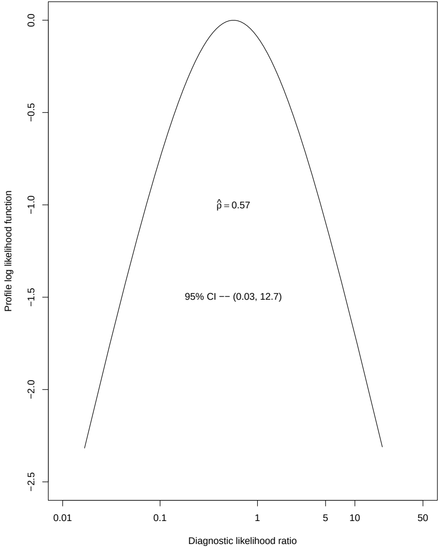


the resulting profile log-likelihood is



Concluding Remarks

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- Empirical likelihood has the advantage that it is range-preserving, data-driven, and easy to construct; no variance estimate is required, and the resulting point or interval estimate is transformation-invariant

Concluding Remarks

- In the absence of any distributional assumptions, empirical likelihood provides a convenient basis on which to estimate the DLR, ρ_x, for a continuous-scale test measurement
- Empirical likelihood has the advantage that it is range-preserving, data-driven, and easy to construct; no variance estimate is required, and the resulting point or interval estimate is transformation-invariant
- Sensible estimates can only be derived at test measurements that are duplicated in both samples; additional assumptions, such as smoothness, should alleviate this drawback

Good medicine does not consist in the indiscriminate application of laboratory examinations to a patient, but rather in having so clear a comprehension of the probabilities of a case as to know what tests may be of value . . . it should be the duty of every hospital to see that no house officer receives his diploma unless he has demonstrated . . . a knowledge of how to use the results in the study of his patient.

Dr. George W. Peabody (1922)

References

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