Supplement to

A Limitation of the Diagnostic-Odds Ratio in Determining an Optimal Cut-off Value for a Continuous Diagnostic Test

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April 28, 2010

Abstract

This supplement considers the diagnostic odds ratio, a special summarizing function of specificity and sensitivity for a given diagnostic test which has been suggested as a measure of diagnostic discriminatory power. In the situation of a continuous diagnostic test a cut-off value has to be chosen and it is a common practice to choose the cut-off value on the basis of the maximized diagnostic odds ratio. We show that for the case of a normal distributed diseased and a normal distributed non-diseased population with equal variances the log-DOR is a convex function of the cut-off value.

Notation

We are considering the *diagnostic test accuracy* of a diagnostic test B for diagnosing the presence of a specific condition. A typical setting is as follows. The outcome of B is binary where $B = 1$ indicates the presence of the condition (test is positive) and $B = 0$ indicates the absence of the condition. Here the objective lies in determining the discriminating power of the diagnostic test in separating persons with a specific condition (diseased) from those without this condition (non-diseased). Widely, two measures of diagnostic accuracy are considered: the *sensitivity* defined as $S^+ = Pr(\text{test positive}|\text{diseased}) = (1 - \beta)$ and the *specificity* defined as $S^- = Pr(\text{test negative}|\text{non-diseased}) = (1 - \alpha)$. The sensitivity measures the capability of the diagnostic test to recognize a diseased person correctly, whereas the specificity measures the capability of diagnosing a healthy person correctly. Consequently, β is the error probability of falsely classifying a diseased person as healthy and α is the error probability of falsely classifying a healthy person as diseased. The *diagnostic odds ratio* (DOR) has been suggested and utilized frequently in the literature as a summary measure of sensitivity and specificity. The diagnostic odds ratio as a single indicator of diagnostic performance is defined as

$$D = \frac{S^+}{1 - S^+} \times \frac{S^-}{1 - S^-}. \tag{1}$$

Note that (1) can be written as the ratio of the odds $\frac{S^+}{1-S^+}$ for diagnosing a diseased person as diseased to the odds $\frac{1-S^-}{S^-}$ for diagnosing a healthy person as diseased.

Now, we suppose that the diagnostic procedure is providing a continuous outcome or an ordered categorical outcome which we denote as T. For example, a psychological test is used (potentially among other procedures) to determine a certain condition such as the presence of dementia in an elderly person. Often these diagnostic tests deliver a score and a cut-off value c is used to decide about the presence or absence of the condition. Note that T and the binary test result variable B are connected via $B = \mathbb{I}_{\{T>c\}}$, where $\mathbb{I}_S$ denotes the indicator function for a set S defined as $\mathbb{I}_S(s) = 1$ if $s \in S$ and 0 otherwise. Then, sensitivity and specificity become a function of the cut-off value c, and, consequently, also the diagnostic odds ratio

$$D8c) = \frac{S^+(c)}{1 - S^+(c)} \times \frac{S^-(c)}{1 - S^-(c)}. \tag{2}$$

The convexity result for the DOR

We now come to the general result and consider the situation that the diagnostic test T has the same variance $\sigma_D^2 = \sigma_H^2 = \sigma^2$ in the diseased and the non-diseased population. Without limitation of generality we set $\sigma^2 = 1$, $\mu_D = \mu$, $\mu_H = 0$. Hence, the following result is proved under the assumption of normality with equal variances in the two populations of healthy and diseased individuals.

Theorem 1 *Let* $\Phi(\cdot)$ *be the cumulative distribution function of the standard normal distribution. Also, let*

$$D(c) = \frac{S^+(c)}{1 - S^+(c)} \times \frac{S^-(c)}{1 - S^-(c)} = \frac{1 - \Phi(c - \mu)}{\Phi(c - \mu)} \times \frac{\Phi(c)}{1 - \Phi(c)}.$$

Then:

$$D(c) > D(\mu/2), \quad \text{for all } 0 \leq c \leq \mu, \text{ but } c \neq \mu/2, \tag{3}$$

$$\frac{d^2}{dc^2} \log D(c) > 0 \text{ for all } c \in [0, \mu]. \tag{4}$$

The theorem says that $D(\cdot)$ is actually *minimized* at $\hat{c} = \mu/2$ and that $\log D(\cdot)$ is *convex*. As a consequence, points maximizing the $D(c)$ will be on the boundary of the parameter space $[0, \mu]$, leading to useless cut-off values. In conclusion, the DOR is not useful as a criterion for maximizing discriminatory power.

Before we go the proof of the main result of Theorem 1 let us introduce some notation and assumptions.

The random variable T *is distributed according to a general distribution function* $\Phi_\mu(\cdot)$, *with mean* μ, *fixed variance (say, equal to* 1*), and symmetric about the mean. For simplicity, we write* $\Phi(\cdot)$ *when* $\mu = 0$. *Clearly,* $\Phi_\mu(\cdot) = \Phi(\cdot - \mu)$. *Let* $\phi(\cdot)$ *be the derivative of* $\Phi(\cdot)$.

Note that $\Phi(\cdot)$ is not restricted to the normal case yet. Define

$$g(c) = \frac{\Phi(c)}{1 - \Phi(c)}, \qquad \text{and} \qquad D(c) = \frac{g(c)}{g(c-\mu)}.$$

Note that $g(c)$ corresponds to $S^-/(1 - S^-)$ in (1) and $g(c - \mu)$ to $(1 - S^+)/S^+$ in (1).

From the symmetry property, $g(c)g(-c) = 1$, and therefore

$$D(c) = g(c)g(\mu - c).$$

Theorem 1 can be written in the equivalent form

$$\ln g(c) + \log g(\mu - c) > 2 \log g(\mu/2), \qquad \text{for all } 0 \leq c \leq \mu, \text{ but } c \neq \mu/2.$$

Proof of Theorem 1

Let us compute and define

$$\frac{d}{dc} \log g(c) = \frac{\phi(c)}{\Phi(c)\,[1 - \Phi(c)]} =: h(c).$$

Then

$$\frac{d}{dc} \log g(\mu - c) = -h(\mu - c),$$

and therefore

$$\frac{d}{dc} \log D(c) = h(c) - h(\mu - c), \qquad \text{and} \qquad \frac{d^2}{dc^2} \log D(c) = h'(c) + h'(\mu - c)$$

where $h' = dh/dc$. In particular, we see that $\frac{d}{dc} \log D(\mu/2) = 0$.

In the following we show that

$$h'(\cdot) > 0 \qquad \text{on} \quad [0, \mu], \tag{5}$$

which will imply two things: a) $\frac{d}{dc} \log D(\cdot)$ is strictly increasing on $[0, \mu]$ and therefore it has only one stationary point on this interval; and b) the stationary point $c = \mu/2$ is a minimum and the theorem holds.

By elementary algebra

$$h'(c) = \frac{\phi(c)}{\Phi(c)\,[1 - \Phi(c)]} \left[\frac{\phi'(c)}{\phi(c)} - \phi(c) \frac{1 - 2\Phi(c)}{\Phi(c)\,[1 - \Phi(c)]} \right].$$

Case 1 : the density $\phi(\cdot)$ is nondecreasing on $[0, \mu]$. Then

$$\frac{\phi'(c)}{\phi(c)} - \phi(c) \frac{1 - 2\Phi(c)}{\Phi(c)\,[1 - \Phi(c)]} > 0, \qquad \forall c \in [0, \mu], \tag{6}$$

because, by the symmetry property, $1 - 2\Phi(c) < 0$ for $c > 0$. This case is of little practical interest, but to obtain the result of the theorem in its most general form we try to use as few assumptions as possible.

Case 2 : the density $\phi(\cdot)$ is decreasing on $[0, \mu]$. In particular, this case is met in the standard Gaussian case. Once again, to get (5), we have to show (6). Let us assume that for all $c \in [0, \mu]$, we have

$$c \geq -\frac{\phi'(c)}{\phi(c)}. \tag{7}$$

Note that (7) is in particular satisfied in the Gaussian case where we have equality. If (7) is satisfied, then (6) is implied by the following inequality

$$2 - \frac{1}{\Phi(c)} > c\frac{1 - \Phi(c)}{\phi(c)}, \qquad \forall c \in [0, \mu], \tag{8}$$

which is proved in the Lemma 1 further below for the Gaussian case. Then the proof is complete also for this case.

Case 3 : the density $\phi(\cdot)$ is nondecreasing on some interval $[0, c]$ and decreasing on $[c, \mu]$ (or decreasing and nondecreasing on the respective intervals). In this case it suffices to combine the arguments used for Cases 1 and 2 which ends the proof.

Lemma 1 *Let $\Phi(\cdot)$ and $\phi(\cdot)$ denote the distribution function and the density of the standard normal law. Then, for all $c > 0$*

$$2 - \frac{1}{\Phi(c)} > c\frac{1 - \Phi(c)}{\phi(c)}.$$

Proof. We shall prove the equivalent inequality $\psi(c) > 0$ for all $c > 0$, where

$$\psi(c) = [2\Phi(c) - 1]\,\phi(c) + c\Phi(c)\,[\Phi(c) - 1]\,.$$

Notice that $\psi(0) = 0$. Moreover, since in the Gaussian case

$$\lim_{c\to\infty} c[1 - \Phi(c)] = 0,$$

we also have $\psi(\infty) = 0$. Compute the derivative

$$\begin{aligned}\psi'(c) &= 2\phi^2(c) + [2\Phi(c) - 1]\{\phi'(c) + c\phi(c)\} - \Phi(c)[1 - \Phi(c)] \\ &= 2\phi^2(c) - \Phi(c)[1 - \Phi(c)]\end{aligned}$$

where for the last equality we use the property $\phi'(c) + c\phi(c) = 0$. Let us notice that the statement $\psi'(c) > 0$ for all $c > 0$ does not hold. However, $\psi'(\infty) = 0$ and

$$\phi(0) > \frac{1}{2\sqrt{2}},$$

which implies $\psi'(0) > 0$. Since $\psi(0) = \psi(\infty) = 0$, in order to show $\psi(c) > 0$ for all $c > 0$ it suffices to show that the derivative of $\psi(\cdot)$ is strictly positive on some interval $(0, a)$ and negative on (a, ∞), where $a > 0$. This means that $\psi'(\cdot)$ has the sign

$$+ \quad 0 \quad - \tag{9}$$

on $(0, \infty)$. Compute

$$\psi''(c) = \phi(c)[4\phi'(c) - 1 + 2\Phi(c)] = \phi(c)[-4c\phi(c) - 1 + 2\Phi(c)],$$

where for the last equality we used again the fact that we are in the Gaussian case and thus $\phi'(c) = -c\phi(c)$. Notice that $\psi''(0) = \psi''(\infty) = 0$ (since $c\phi^2(c) \to 0$ when $c \to \infty$ and $\Phi(0) = 1/2$). Unfortunately, we cannot rapidly say $\psi''(\cdot) < 0$ and close the proof. However, if we show that the sign of the second derivative $\psi''(\cdot)$ is

$$- \quad 0 \quad + \tag{10}$$

on $(0,\infty)$ (that is, $\psi''(\cdot)$ has only one root on $(0,\infty)$), then given that $\psi'(0) > 0$ and $\psi'(\infty) = 0$, one deduces the variation (9) for $\psi'(\cdot)$. Since $\phi(\cdot) > 0$, to prove the variation (10) for $\psi''(\cdot)$, it suffices to prove that the sign of the function $\gamma(c) = -4c\phi(c) - 1 + 2\Phi(c)$ is

$$- \quad 0 \quad + \tag{11}$$

on $(0,\infty)$. Notice that $\gamma(0) = 0$ and $\gamma(\infty) = 1$ (since $c\phi(c) \to 0$ when $c \to \infty$). Now,

$$\gamma'(c) = -4\phi(c) - 4c\phi'(c) + 2\phi(c) = 2\phi(c)\left[2c^2 - 1\right].$$

The function $\gamma'(c)$ is strictly negative on $(0, 1/\sqrt{2})$, vanishes at $c = 1/\sqrt{2}$, and is strictly positive for $c > 1/\sqrt{2}$. This means that when c moves from 0 to ∞, the function $\gamma(\cdot)$ starts from zero, strictly decreases, reaches a minimum level at $c = 1/\sqrt{2}$ (which is necessarily negative since $\gamma(0) = 0$ and $\gamma(\cdot)$ is strictly decreasing from $c = 0$ to $c = 1/\sqrt{2}$) and strictly increases for all values $c > 1/\sqrt{2}$ and approaches the limit value $\gamma(\infty) = 1$. In such a case, the sign of the function $\gamma(\cdot)$ on $(0,\infty)$ is necessarily like in (11). This completes the proof.