Efficacy-Toxicity trade-offs based on L^p norms

Technical Report UTMDABTR-003-06

John D. Cook

Department of Biostatistics and Applied Mathematics

University of Texas M. D. Anderson Cancer Center

April 18, 2006

Abstract

This report examines in detail a family of efficacy-toxicity trade-off functions simpler and more general than those originally proposed in [1]. The new trade-off functions are based on distance in L^p norm to the ideal point and were first presented in [2]. We define and illustrate these functions and demonstrate how to compute their parameters based on elicited values.

1 Desirability trade-off functions

Let x and y represent posterior mean probabilities of efficacy and response respectively. A desirability trade-off function is a function $u(x, y)$ such that $u(x, y) > u(x', y')$ if and only if a treatment with probabilities (x, y) is more desirable than a treatment with probabilities (x', y'). It follows that u must be an increasing function of x and a decreasing function of y.

The efficacy-toxicity tradeoff function given in [1] was constructed by first identifying a reference contour of the form

$$y = a + \frac{b}{x} + \frac{c}{x^2} \tag{1}$$

where x and y represent the posterior mean probabilities of efficacy and toxicity respectively. Then a family of contours was defined by translating the reference contour along the diagonal connecting (0, 1) and (1, 0). This approach had two shortcomings. First, the inverse quadratic form of equation (1) lacks flexibility. Second, there is no simple expression for the desirability trade-off for a given (x, y) point.

We construct a new family of desirability functions as follows. Let x^* and y^* be elicited points such that $(x^*, 0)$ and $(1, y^*)$ have equal desirability. For each $p > 0$, we can define the desirability of a response-toxicity pair (x, y) as $1 - r$ where

$$\left(\frac{x-1}{x^*-1}\right)^p + \left(\frac{y}{y^*}\right)^p = r^p,$$

i.e., the desirability of a point (x, y) is

$$1 - \left(\left(\frac{1-x}{1-x^*}\right)^p + \left(\frac{y}{y^*}\right)^p\right)^{1/p}. \tag{2}$$

Here r is the distance to the ideal point (1, 0) in L^p norm, with the axes scaled by x^* and y^*. If $p < 1$ the contours are concave. If $p = 1$ the contours are straight lines. If $p = 2$ the contours are ellipses. As $p \to \infty$ the contours approach rectangles.

The EffTox software (see [4]) used the the inverse quadratic method for defining trade-off contours up through version 2.8. Version 2.9 uses the L^p norm method described here.

2 Bivariate binary model

In [1], two probability models are given: one for bivariate binary outcomes, and one for trinary outcomes. In this section, we focus on the simpler bivariate binary model.

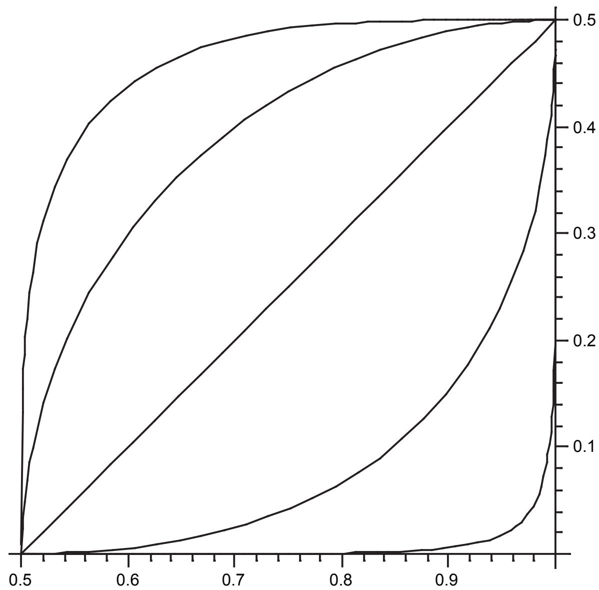

Figure 1: Curves for $r = 1$, $x^* = y^* = 1/2$ and $p = 1/4$, $1/2$, 1, 2, and 4.

In the EffTox software (see [4]), desirability trade-offs are specified by giving three points: $(x^*, 0)$, (x_1, y_1), and $(1, y^*)$. We require

$$0 < x^* < x_1 < 1$$

and

$$0 < y_1 < y^* < 1.$$

The point $(x^*, 0)$ represents acceptable response probability if toxicity were impossible. The point $(1, y^*)$ represents acceptable toxicity if efficacy were certain. These two points determine where the contour $\{(x, y) : \text{desirability} = 0\}$ intercepts the x and y axes.

We may solve for p so that the zero desirability contour goes through the point (x_1, y_1). To see this, define $\alpha = (1 - x_1)/(1 - x^*)$ and $\beta = y_1/y^*$. Note that $0 < \alpha, \beta < 1$. Define

$$f(p) \equiv \alpha^p + \beta^p$$

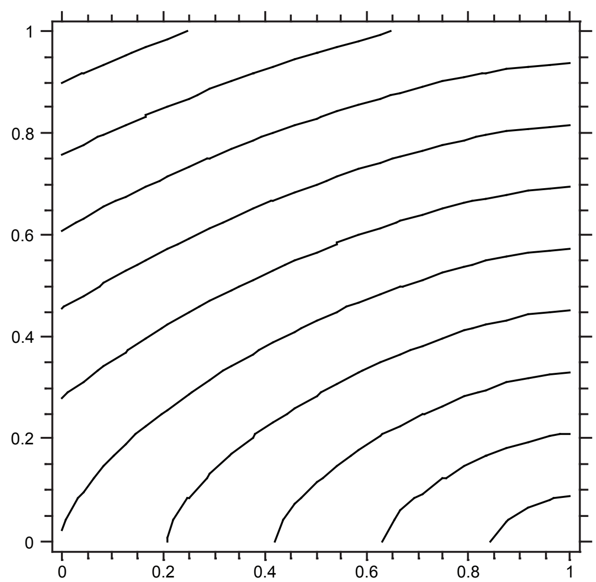

Figure 2: Convex contours filling the unit square for $x^* = 0.3$, $y^* = 0.4$, and $p = 1.5$.

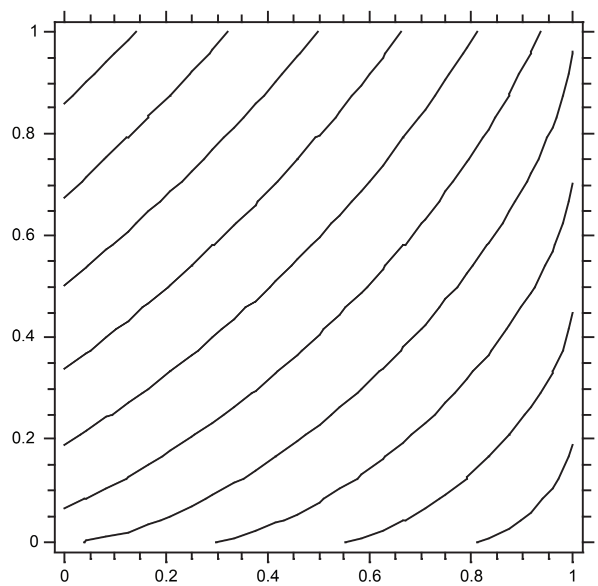

Figure 3: Concave contours filling the unit square for $x^* = 0.4$, $y^* = 0.6$, and $p = 0.7$.

and solve for p such that $f(p) = 1$. The function $f(p)$ is monotone decreasing and continuous on $[0, \infty)$. We have $f(0) = 2$ and $\lim_{p \to \infty} f(p) = 0$ and so there exists a unique solution to $f(p) = 1$.

Note the L^p contours always fit the three elicited points exactly. The inverse quadratic contours did not; the method solved for the parameters that minimized the error in the fit

3 Trinary trade-offs

The trinary model allows three outcomes: efficacy, toxicity, or neither. The space of probabilities to consider is a triangle rather than a square: since efficacy and toxicity are mutually exclusive under this model, we must have $x + y \leq 1$.

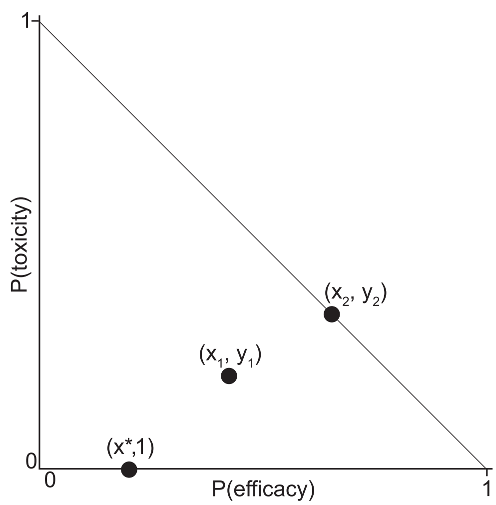

Figure 4: Efficacy-toxicity trade-offs for trinary model

As before, we define the desirability of a point (x, y) as the L^p distance to the ideal point (0, 1), given by equation (2). For convenience, we define our desirability functions on the entire unit square, even though points above the diagonal line $x + y = 1$ no longer represent meaningful probabilities.

We determine the parameters for our desirability function from three elicited points of equal desirability as before. However, now the three points are $(x^*, 0)$, (x_1, y_1), and (x_2, y_2) where (x_2, y_2) is on the hypotenuse of our probability triangle, *i.e.* $x_2 + y_2 = 1$. We still define our desirability in terms of equation (2) which involves y^*. Now y^* is an analytical parameter we solve for rather than a meaningful probability in our model. We will show how to find y^* and p so that the three elicited points have equal desirability.

Lemma 1 *Let α, β, γ, and δ satisfy*

$$\alpha > \gamma,\ \delta > \beta > 0.$$

Then there is a $p > 0$ such that

$$\alpha^p + \beta^p = \gamma^p + \delta^p \tag{3}$$

provided $\alpha < \gamma\delta$.

Proof Without loss of generality, we may assume $\beta = 1$. Otherwise, redefine α, γ, and δ to be their former values divided by β. Define

$$g(p) = \alpha^p + 1 - \gamma^p - \delta^p$$

for $p \geq 0$. Note that $\lim_{p \to \infty} g(p) = \infty$. If g is ever negative, g must be zero somewhere and hence equation (3) has a solution.

Taking the derivative from the right,

$$g'(0) = \log(\alpha) - \log(\gamma) - \log(\delta).$$

If $\alpha < \gamma\delta$, $g'(0) < 0$ and $g(p)$ must be negative for sufficiently small positive values of p since $g(0) = 0$. $\diamondsuit$

Claim 1 *If*

$$0 < x^* < x_1 < x_2 < 1,$$

$$0 < y_1 < y_2,$$

and

$$x_2 + y_2 = 1$$

then there exist $p > 0$ and $y^* > y_2$ such that the curve

$$\left(\frac{x-1}{x^*-1}\right)^p + \left(\frac{y}{y^*}\right)^p = 1$$

passes through the three points $(x^*, 0)$, (x_1, y_1), and (x_2, y_2).

Proof Such p and y^* exist if we can solve

$$\left(\frac{1-x_1}{1-x^*}\right)^p + \left(\frac{y_1}{y^*}\right) = \left(\frac{1-x_2}{1-x^*}\right)^p + \left(\frac{y_2}{y^*}\right) = 1.$$

Let $a = 1 - x^*$, $b = 1 - x_1$, $c = 1 - x_2 = y_2$, and $d = y_1$. Then our problem becomes solving

$$\left(\frac{b}{a}\right)^p + \left(\frac{d}{y^*}\right)^p = \left(\frac{c}{a}\right)^p + \left(\frac{c}{y^*}\right)^p = 1$$

or

$$\left(\frac{1}{y^*}\right)^p = \left(\frac{1}{d}\right)^p - \left(\frac{b}{ad}\right)^p = \left(\frac{1}{c}\right)^p - \left(\frac{1}{a}\right)^p.$$

This will follow if we can solve

$$(ac)^p + (cd)^p = (ad)^p + (bc)^p.$$

The order assumptions on the x's and y's imply

$$a > b > c > d$$

and thus

$$ac > ad,\ bc > dc.$$

The lemma above then says we can indeed find the value of p we're looking for. Then knowing p we can solve

$$\left(\frac{1}{y^*}\right)^p = \left(\frac{1}{d}\right)^p - \left(\frac{b}{ad}\right)^p$$

for y^*. ♢

References

[1] Peter F. Thall and John D. Cook. Dose-Finding Based on Efficacy-Toxicity Trade-Offs. Biometrics 60, p684-693, September 2004.

[2] Peter F. Thall and John D. Cook. Adaptive dose-finding based on efficacy-toxicity trade-offs. Encyclopedia of Biopharmaceutical Statistics, 2nd Edition. Chein-Chung Chow editor. In press.

[3] Peter F. Thall, John D. Cook, and Eli Estey. Adaptive dose selection using efficacy-toxicity trade-offs: illustrations and practical considerations. To appear in Journal of Biopharmaceutical Statistics.

[4] MDACC Department of Biostatistics and Applied Mathematics software download site. http://biostatistics.mdanderson.org/SoftwareDownload/

This report and other MDACC biostatistics technical reports are available at http://tinyurl.com/743xv.