# University of Texas, MD Anderson Cancer Center

UT MD Anderson Cancer Center Department of Biostatistics
Working Paper Series

# Efficacy-Toxicity trade-offs based on Lp norms

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## 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 Lp 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.

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

# Technical Report UTMDABTR-003-06

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April 18, 2006; revised June 20, 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 toxicity 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

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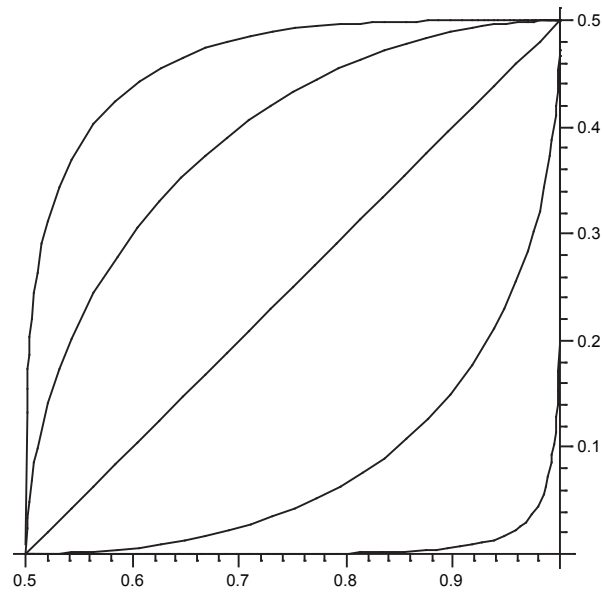
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Figure 1: Curves for $r = 1$, $x^* = y^* = 1/2$ and $p = 1/4$, $1/2$, $1$, $2$, and $4$.

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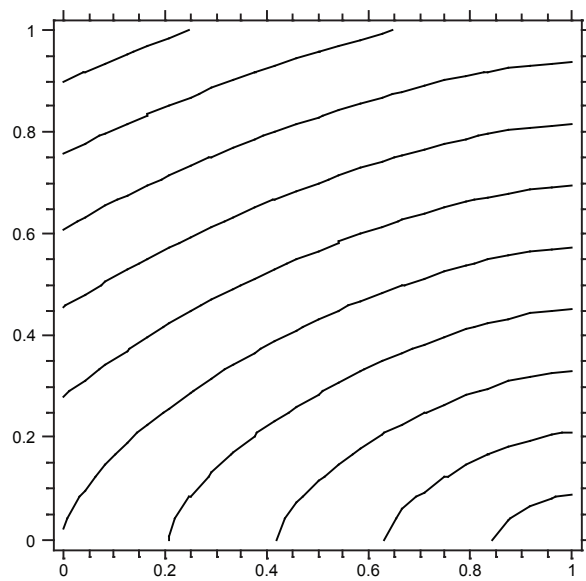
$$f(p) \equiv \alpha^p + \beta^p$$

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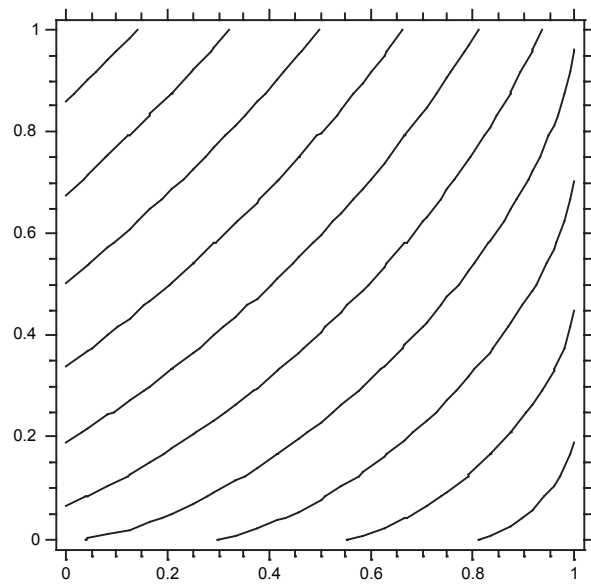Figure 2: Convex contours filling the unit square for $x^* = 0.2$, $y^* = 0.4$, and $p = 1.5$.

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

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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 $x + y \leq 1$.
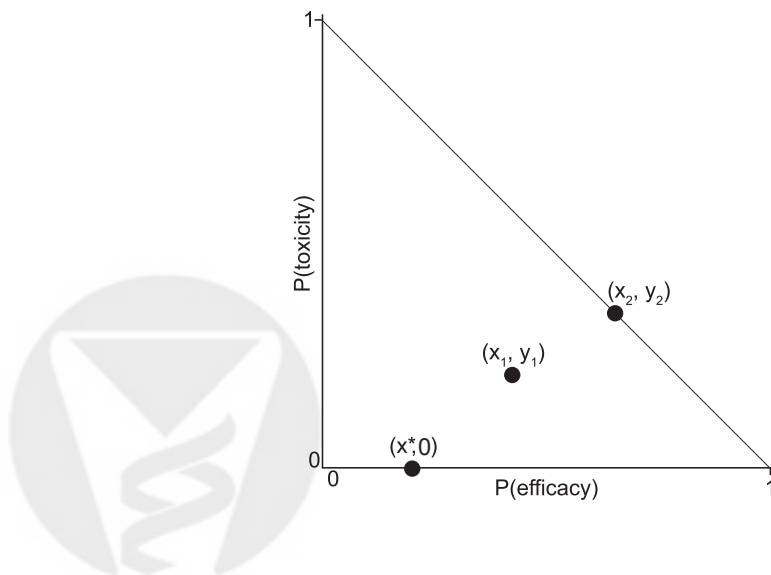


Figure 4: Efficacy-toxicity trade-offs for trinary model

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As before, we define the desirability of a point $(x, y)$ as the $L^p$ distance to the ideal point $(1, 0)$, 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 $\alpha$, $\beta$, $\gamma$, and $\delta$ 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 $\alpha$, $\gamma$, and $\delta$ to be their former values divided by $\beta$. 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 $g(0) = 0$. $\diamond$

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**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

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

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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 $y^*$.                                                                          $\diamondsuit$

# 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/

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