Statistica Sinica 3(1993), 233-243

EFFICIENT DESIGNS FOR ESTIMATION IN THE POWER LOGISTIC QUANTAL RESPONSE MODEL

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Abstract: A convenient three-parameter class of asymmetric dose-response models can be obtained by raising the logistic response function to the power m, for $m > 0$. For these models, called power logistic quantal response models, D-optimal two point designs for various choices of m are numerically derived. We then investigate design efficiencies and design robustness to misspecification of the three model parameters for two point designs relative to the D-optimal two point design. It turns out that if the experimenter assumes an incorrect value of m when determining a design, the loss of efficiency incurred as a result is fairly small for a wide range of m, assuming no error in the initial values of the other parameters. Moreover, the effects of poor initial values of the other parameters seem more serious when m is large than when m is small, so that special care should be taken when m is large.

Key words and phrases: Bioassay, quantal response model, D-optimal design.

1. Introduction

The typical quantal response experiment is described by a response function, called the tolerance distribution, that relates the dose level to the probability of a response. The binary response probability $p(x)$ at dose level x is modeled by a function of the form $p(x) = F(x;\theta)$, where $F(x;\theta)$ is a cumulative distribution function (CDF) with parameter vector θ. The nonsequential experimental design problem is to choose distinct dose levels $(x_1, x_2, \ldots, x_k)$ and numbers of independent binary response trials $(n_1, n_2, \ldots, n_k)$ to take at these dose levels, subject to $\sum_{i=1}^{k} n_i = n$, for n fixed. A design is said to be optimal if it optimizes a statistical inference criterion.

In this paper, we consider the experimental design problem for the case where $F(x;\theta)$ is the three parameter power logistic CDF, introduced by Prentice (1976) and studied further by Gaudard et al. (1990). The design criterion of interest is the D-optimality (Kiefer (1959)) criterion.

The power logistic model (PLM) defines the probability of response at dose level x_i by

$$p(x_i) = \left[\frac{1}{1 + e^{-\beta(x_i - \mu)}}\right]^m = p_{i,m}, \tag{1.1}$$

where $m > 0$, $\beta > 0$, and $-\infty < \mu < \infty$ are the three parameters of the model. These CDFs generalize the familiar logistic model (Johnson and Kotz (1970)). The name "power logistic" emphasizes that the PLM is the mth power of the logistic model; note that it may be written as $p_{i,m} = p_i^m$, where p_i is the logistic model's probability of a response at dose level x_i.

Since the parameter m governs the difference between the symmetric logistic model, where $m = 1$, and the asymmetric PLM, we present design robustness results and derive design efficiencies relative to misspecification of m. It is shown in Gaudard et al. (1990) that the effect of m on moments of the PLM family can be dramatic. For example, it is shown that for m less than unity both negative skewness and kurtosis increase rapidly as m gets smaller, and that the PLM has gradually increasing positive skewness and kurtosis as m increases above unity. For inference and design purposes, it is assumed that m is known, and that μ and β are unknown. As we shall see, optimal designs are fairly robust to misspecification of m.

There is a rich literature on optimal designs for quantal response models. Design considerations for the probit and logistic models are addressed from the frequentist viewpoint in Abdelbasit and Plackett (1983), Wu (1985), Tamhane (1986) and Kalish (1988). Robust estimation is considered in several of these papers, as well as in Miller and Halpern (1980). Bayesian approaches to design have also been developed (Freeman (1970), Kuo (1983), and Tsutakawa (1972, 1980)). Design issues for the PLM have received attention in Ford, Torsney and Wu (1992) and Wu (1988). However, the design robustness of the PLM with respect to model misspecification has not been studied.

As an example, consider the data set that was published in Morgan (1985, p.109, data set 11). The plot of the response proportions against dose levels shows that the density underlying the tolerance distribution is skewed, indicating that a symmetric tolerance distribution, such as the logistic, would be inappropriate for this data set. For this data set, the PLM fits much better than the logistic model. (See Gaudard et al. (1990) for details.)

Now suppose that, previous to collecting any data, an optimal design had been chosen based on the assumption that the logistic model was appropriate. The question of interest in this paper concerns the extent to which such a choice of design would cause a loss in efficiency relative to an optimal design based on the PLM. In other words, we are concerned with the robustness of the design with respect to misspecification of the underlying model, where misspecification is characterized by m. To this end, attention is focused on the loss of efficiency derived from misspecification of m, as well as from errors in the initial estimates for μ and β.

In the next section we discuss maximum likelihood estimation for β and μ,

and give the determinant of the Fisher information matrix for β and μ (for details, see Gaudard et al. (1990)). In Section 3, D-optimal two point designs for β, μ and m are obtained, their efficiencies relative to misspecification of β, μ and m are derived, and various robustness results are presented. It turns out that if the experimenter assumes an incorrect value of m when determining a design, the loss of efficiency incurred as a result is fairly small for a wide range of m, assuming no error in the initial values of the other parameters. However, if the initially assumed value of m is close to the true value of m and β is known, the efficiency is very sensitive to the assumed value of μ, while if μ is known, the efficiency is not very sensitive to the assumed value of β. Moreover, the effects of poor initial values of β and μ seem more serious when m is large than when m is small, so that special care should be taken when m is large.

2. Estimation of μ and β

If y_i is the number of responses out of the n_i trials observed at dose level x_i, the y_i, $i = 1, 2, \ldots, k$, $k \geq 2$, are k mutually independent binomial random variables, each with response probability $p_{i,m}$. The log-likelihood function is

$$\ln L = \sum_{i=1}^{k} \left[\ln \binom{n_i}{y_i} + y_i \ln(p_{i,m}) + (n_i - y_i) \ln(1 - p_{i,m}) \right]. \tag{2.1}$$

Differentiating the log likelihood function with respect to β and μ gives the likelihood equations. These equations are difficult to solve and an iterative technique, such as the Newton-Raphson process, is required.

For a given value of m, the Fisher information matrix, denoted by $I(\beta, \mu)$, for β and μ, is

$$I(\beta, \mu) = \begin{bmatrix} \beta^{-2} \sum_{i=1}^{k} n_i \Psi(u_i) u_i^2 & -\sum_{i=1}^{k} n_i \Psi(u_i) u_i \\ -\sum_{i=1}^{k} n_i \Psi(u_i) u_i & \beta^2 \sum_{i=1}^{k} n_i \Psi(u_i) \end{bmatrix} \tag{2.2}$$

where $u_i = \beta(x_i - \mu) = \text{logit}(p_{i,m}^{1/m})$ and $\Psi(u_i) = m^2 p_{i,m}(1 - p_{i,m}^{1/m})^2/(1 - p_{i,m})$, and where $\text{logit}(u) = \ln(u/(1-u))$ is the log odds function. The determinant of $I(\beta, \mu)$, is

$$D = D(\beta, \mu) = \sum_{i=1}^{k} n_i \Psi(u_i) u_i^2 \sum_{i=1}^{k} n_i \Psi(u_i) - \left(\sum_{i=1}^{k} n_i \Psi(u_i) u_i \right)^2. \tag{2.3}$$

3. Design Efficiency for Two Point D-Optimal Designs

As is well known, a D-optimal design maximizes the determinant of the Fisher information matrix. D-optimal designs for different models have been studied extensively (Silvey (1980), Abdelbasit and Plackett (1983), Jain (1987)), mainly due to their mathematical tractability, and because maximization of the determinant of the Fisher information matrix is equivalent to minimization of the volume of an asymptotic confidence ellipsoid for the parameters.

Caratheodory's theorem ensures that there is a D-optimal design for the PLM consisting of at most three points (Silvey (1980)). Analytic approaches to finding the D-optimal design are intractable, in part, because the tolerance distribution is asymmetric. When $k = 3$, (2.3) reduces to $D = n_1 n_2 \psi(u_1)\psi(u_2)(u_1 - u_2)^2 + n_1 n_3 \psi(u_1)\psi(u_3)(u_1 - u_3)^2 + n_2 n_3 \psi(u_2)\psi(u_3)(u_2 - u_3)^2$. For $m = .2, .5, 2$ and 5, we used optimum search techniques to maximize D. In all cases, the numerically obtained D-optimal design was a two point design. Moreover, the D-optimal design for the logistic model as well as for many symmetric models is a two point design. For these reasons, we proceed to study design efficiency in terms of two point designs. Note, however, that D-optimal designs for distributions with heavy tails may be three point designs (Ford, Torsney and Wu (1992), Sitter and Wu (1991)).

3.1. Derivation

For given m, the D-optimality criterion calls for maximization of (2.3), with respect to $p_{i,m}$, for $i = 1, 2, \ldots, k$ subject to $\sum n_i = n$. For $k = 2$ points, Equation (2.3) reduces to

$$D(\beta, \mu) = n_1 n_2 \Psi(u_1)\Psi(u_2)(u_1 - u_2)^2, \tag{3.1}$$

and since $n_1 + n_2 = n$, it is clear that $n_1 = n_2 = n/2$ maximizes (3.1) for any choice of $p_{1,m}$ and $p_{2,m}$. Note that we are treating n_1/n and n_2/n as continuous allocation weights. Thus, the D-optimal two point design is supported on those points $p_{1,m}$ and $p_{2,m}$ that maximize

$$\Psi(u_1)\Psi(u_2)(u_1 - u_2)^2. \tag{3.2}$$

For the given range of values of m, an examination of plots of $D(\beta, \mu)$, with $n_1 = n_2 = 1$, over the 2-dimensional plane of $(p_{1,m}, p_{2,m})$ suggests that this function has a unique maximum; this is confirmed by the theoretical results in Ford, Torsney and Wu (1992). Since maximization of (3.2) is analytically intractable, we maximized (3.2) using a Newton-Raphson optimization algorithm. The resulting values for $p_{1,m}, p_{2,m}$ are given in Table 1.

3.2. Design efficiency

We measure the efficiency of an arbitrary design at $(p_{1,m}, p_{2,m})$ relative to the optimal design at $(p^\circ_{1,m}, p^\circ_{2,m})$ by $r(p_{1,m}, p_{2,m})$, the ratio of the determinants of the Fisher information matrices evaluated at $(p_{1,m}, p_{2,m})$ and $(p^\circ_{1,m}, p^\circ_{2,m})$. Abdelbasit and Plackett (1983) report results for the special case when $m = 1$. (Note that some researchers (Minkin (1987)) prefer to use the square root of the determinant of the Fisher information matrix in computing the efficiency of two designs. Since the determinant depends on n^2, taking square roots relates the efficiency measure to the relative increase in sample size needed to obtain the same precision.) Contour plots of $r(p_{1,m}, p_{2,m})$ are given in Figure 1 for various m. Note that, when $m < 1$, the efficiency decreases more quickly in the direction of decreasing $p_{2,m}$ than in the direction of increasing $p_{1,m}$. When $m > 1$, the reverse holds.

3.3. Design robustness

Recall that the skewness of the PLM changes rapidly from the symmetry of the logistic model to high negative skewness as m decreases from 1.0. The D-optimal two point designs in Table 1 do not reflect this marked change in skewness of the tolerance curves. From $m = 1.0$ to 0.2, $(p^\circ_{1,m}, p^\circ_{2,m})$ changes only from (0.176, 0.824) to (0.206, 0.876). A similar pattern can also be seen as m increases from 1.0 to 5.0, where the PLM changes more slowly from symmetry to high positive skewness. This suggests that the D-optimality criterion is relatively robust with respect to m.

For a given value of m, optimal values $p^\circ_{1,m}$ and $p^\circ_{2,m}$ can be obtained from Table 1 or by maximizing (3.2). Suppose x°_1 and x°_2 are the actual dose levels corresponding to $p^\circ_{1,m}$ and $p^\circ_{2,m}$, respectively. Then $x^\circ_i = \mu + [\text{logit}((p^\circ_{i,m})^{1/m})]/\beta$, $i = 1, 2$. In order to implement this design to study the unknown parameters β and μ, an experimenter is in the paradoxical situation that true values of β, μ and m must be known. Thus the experimenter is forced to use initial values β_0, μ_0 and m_0, and thus the dose levels $x_{0i} = \mu_0 + [\text{logit}((p^\circ_{i,m})^{1/m_0})]/\beta_0$, $i = 1, 2$. We proceed to study the robustness of the D-optimal design relative to the initial values of β, μ and m.

For clarity, we emphasize the dependence of $D(\beta, \mu)$ on m by writing it as $D(\beta, \mu, m)$. Let $R(\beta_0, \mu_0, m_0)$ denote the ratio of $D(\beta, \mu, m)$ evaluated at (x_{01}, x_{02}) to the maximum value of $D(\beta, \mu, m)$. Then $R(\beta_0, \mu_0, m_0)$ measures the robustness of the D-optimal design to initial values of β, μ and m. Values of $R(\beta_0, \mu_0, m_0)$ resulting from a numerical study for various values of m between 0.2 and 5.0 and for various ratios β/β_0 and differences $\beta(\mu - \mu_0)$ are given in Table 2.

The most striking consequence of Table 2 is that, if the experimenter incorrectly assumes that $m_0 = 1$ (the logistic model) when designing the experiment, the minimum value of $R(\beta, \mu, m_0)$ for $.5 \leq m \leq 1.5$ is 82.6%, achieved when

$m = .5$. Note that this presumes that the experimenter's initial values of β and μ are correct. Thus, the optimal design based on the logistic model is robust to a fairly wide range of m, assuming no error in the initial values for β and μ.

We draw the following general conclusions from our numerical study. Assuming that μ is known and that m_0 is close to m, the ratio $R(\beta_0, \mu, m_0)$ is not very sensitive to misspecification of β, suggesting that the initial value for β need not be extremely precise. If β is known, however, $R(\beta, \mu_0, m_0)$ is very sensitive to the difference between μ and μ_0, suggesting that a good initial value for μ is critical. The most severe loss in robustness occurs when β is overestimated and μ is underestimated. The effects of poor initial values of both β and μ seem more serious when m is large than when m is small, so that special care should be taken when m is large.

Table 1. D-optimal two point designs for various m

m	$p^{\circ}_{1,m}$	$p^{\circ}_{2,m}$
0.2	0.2058	0.8760
0.4	0.2289	0.8543
0.5	0.2214	0.8475
0.6	0.2213	0.8414
0.8	0.1919	0.8316
1.0	0.1760	0.8240
1.2	0.1635	0.8179
1.5	0.1491	0.8111
2.0	0.1327	0.8031
2.5	0.1218	0.7976
3.0	0.1141	0.7937
4.0	0.1039	0.7884
5.0	0.0975	0.7849

Table 2. Relative efficiencies (%) for the D-optimality criterion relative to initial values of β, μ and m

$\beta(\mu-\mu_0)=-1.5$				m			
β/β_0	m_0	0.2	0.5	1	1.5	2	5
0.6	0.2	66.1	90.2	60.0	27.0	9.8	0.0
0.6	0.5	18.7	40.5	67.1	85.3	95.2	55.2
0.6	1.0	6.8	15.7	29.4	42.8	55.1	88.9
0.6	2.0	2.7	6.6	13.0	20.0	27.4	66.4
0.6	5.0	0.9	2.2	4.6	7.3	10.4	32.7
1.0	0.2	69.1	46.7	7.5	0.7	0.1	0.0
1.0	0.5	35.5	67.2	85.6	80.8	65.0	3.9
1.0	1.0	13.1	29.5	51.6	69.7	82.9	75.3
1.0	2.0	3.9	9.3	18.2	27.8	37.6	85.9
1.0	5.0	0.7	1.6	3.4	5.6	8.0	27.5
1.4	0.2	60.1	18.0	0.6	0.0	0.0	0.0
1.4	0.5	36.3	56.6	49.1	29.7	14.8	0.0
1.4	1.0	15.3	32.4	51.1	61.4	64.2	23.1
1.4	2.0	3.7	8.7	16.9	25.4	33.9	68.6
1.4	5.0	0.3	0.8	1.7	2.8	4.1	14.9
$\beta(\mu-\mu_0)=-0.5$				m			
β/β_0	m_0	0.2	0.5	1	1.5	2	5
0.6	0.2	85.7	91.4	37.1	9.7	2.0	0.0
0.6	0.5	37.3	70.1	88.9	84.0	67.9	4.2
0.6	1.0	19.3	40.6	63.9	76.9	80.9	31.5
0.6	2.0	10.2	22.9	40.1	54.4	65.2	63.5
0.6	5.0	4.3	10.2	19.4	28.8	38.0	71.6
1.0	0.2	95.7	48.4	4.5	0.2	0.0	0.0
1.0	0.5	60.6	95.4	85.1	53.4	27.7	0.1
1.0	1.0	33.1	65.9	93.0	98.7	90.4	13.1
1.0	2.0	14.5	32.3	56.2	75.4	89.0	76.7
1.0	5.0	3.6	8.6	16.9	26.0	35.4	83.9
1.4	0.2	86.7	19.0	0.4	0.0	0.0	0.0
1.4	0.5	61.6	78.0	44.3	16.7	5.1	0.0
1.4	1.0	34.3	63.1	76.3	67.7	50.8	1.9
1.4	2.0	13.2	29.1	49.4	64.2	73.3	49.3
1.4	5.0	1.9	4.7	9.4	14.6	20.4	55.1
$\beta(\mu-\mu_0)=0$				m			
β/β_0	m_0	0.2	0.5	1	1.5	2	5
0.6	0.2	86.7	80.0	24.4	4.7	0.7	0.0
0.6	0.5	43.5	74.2	78.1	59.8	38.4	0.5
0.6	1.0	26.3	51.5	70.7	73.1	65.3	8.1
0.6	2.0	16.1	34.2	54.3	66.0	70.4	30.1
0.6	5.0	8.1	18.3	32.8	45.4	55.5	63.3
1.0	0.2	100.0	43.0	2.9	0.1	0.0	0.0
1.0	0.5	70.9	100.0	71.6	35.1	14.0	0.0
1.0	1.0	44.9	82.6	100.0	89.3	67.8	2.8
1.0	2.0	23.7	50.2	79.1	95.2	100.0	37.7
1.0	5.0	7.4	17.2	32.3	47.1	60.9	100.0
1.4	0.2	92.3	17.0	0.2	0.0	0.0	0.0
1.4	0.5	75.3	84.7	38.0	11.0	2.6	0.0
1.4	1.0	46.5	78.5	79.9	58.3	35.5	0.3
1.4	2.0	21.7	45.1	68.9	80.0	80.7	22.4
1.4	5.0	4.2	9.9	19.1	28.7	38.3	77.8

Table 2. Continued

$\beta(\mu-\mu_0)=0.5$		m					
β/β_0	m_0	0.2	0.5	1	1.5	2	5
0.6	0.2	80.4	63.3	14.1	1.9	0.2	0.0
0.6	0.5	45.1	68.4	57.5	34.1	16.7	0.0
0.6	1.0	31.1	55.5	63.9	54.3	39.2	1.1
0.6	2.0	21.9	43.1	59.8	62.7	56.8	7.8
0.6	5.0	13.2	28.3	46.0	57.6	63.4	33.8
1.0	0.2	95.7	34.6	1.7	0.0	0.0	0.0
1.0	0.5	76.4	95.2	53.2	19.8	5.9	0.0
1.0	1.0	55.2	92.3	93.0	67.4	40.8	0.4
1.0	2.0	34.6	68.2	94.6	98.6	88.7	11.3
1.0	5.0	13.6	30.6	53.6	72.6	86.7	81.2
1.4	0.2	89.9	13.8	0.1	0.0	0.0	0.0
1.4	0.5	86.6	85.7	29.7	6.5	1.1	0.0
1.4	1.0	59.5	91.0	76.3	44.6	21.4	0.0
1.4	2.0	32.4	63.0	84.6	84.8	72.8	6.7
1.4	5.0	8.3	19.0	34.8	49.3	61.7	79.9

$\beta(\mu-\mu_0)=1.5$		m					
β/β_0	m_0	0.2	0.5	1	1.5	2	5
0.6	0.2	55.9	30.7	3.4	0.2	0.0	0.0
0.6	0.5	35.5	40.5	19.3	6.0	1.5	0.0
0.6	1.0	29.5	41.1	29.4	14.6	5.9	0.0
0.6	2.0	26.0	41.5	38.8	26.1	14.6	0.1
0.6	5.0	21.9	40.0	48.4	43.6	33.6	1.5
1.0	0.2	70.0	17.1	0.4	0.0	0.0	0.0
1.0	0.5	68.2	63.2	19.7	3.9	0.6	0.0
1.0	1.0	62.1	81.7	51.6	22.0	7.6	0.0
1.0	2.0	52.1	85.4	83.0	57.8	33.6	0.2
1.0	5.0	32.6	64.6	90.8	96.1	87.9	12.7
1.4	0.2	67.6	6.9	0.0	0.0	0.0	0.0
1.4	0.5	90.4	66.5	12.9	1.5	0.1	0.0
1.4	1.0	79.9	96.9	51.1	17.8	5.0	0.0
1.4	2.0	57.3	93.5	89.3	60.7	34.3	0.2
1.4	5.0	24.1	50.2	76.5	88.7	89.3	24.7

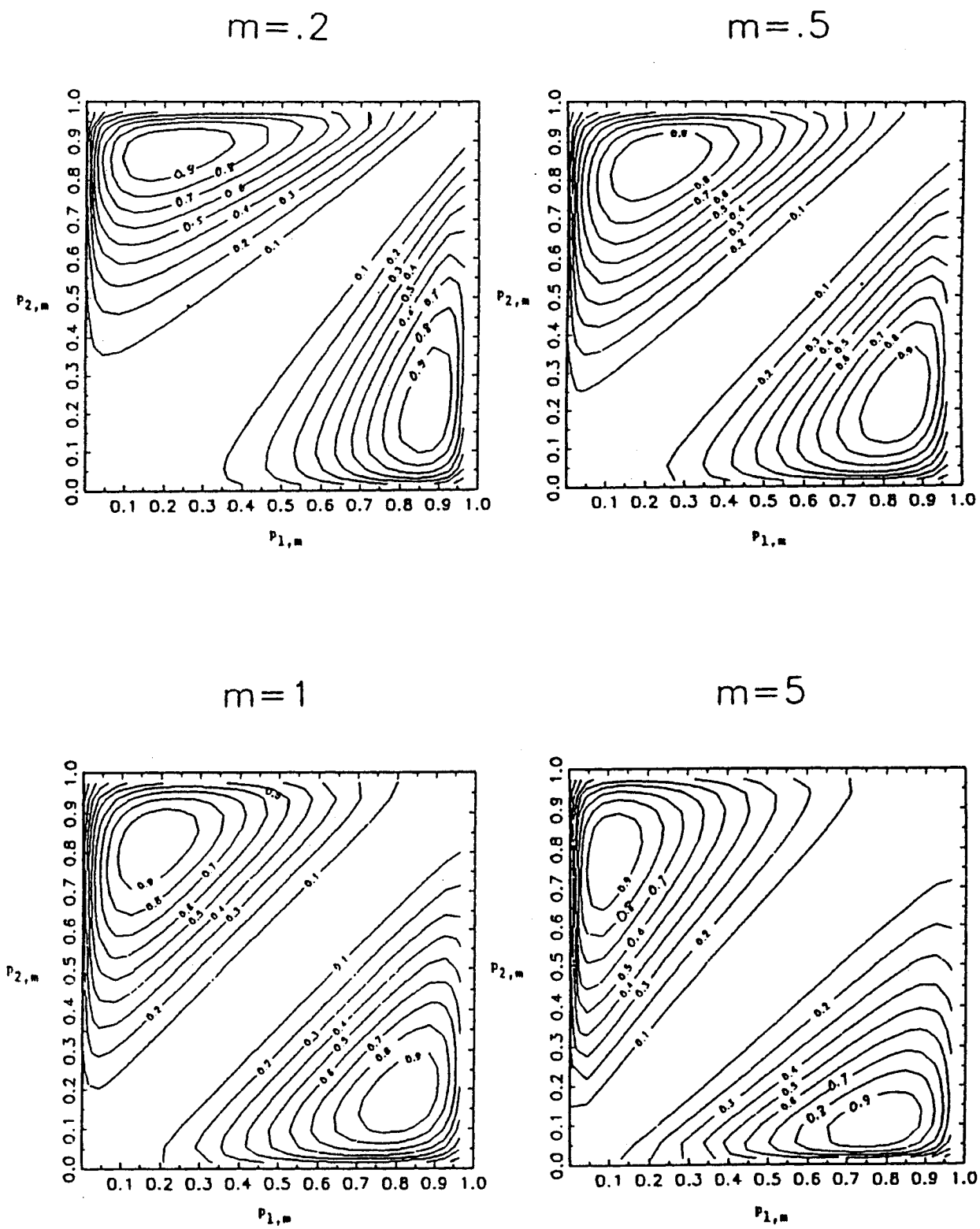

Figure 1. Contour plot of $r(p_{1,m}, p_{2,m})$ for $m = 0.2, 0.5, 1.0$ and 5.0

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(Received November 1989; accepted May 1992)