OPTIMAL DESIGNS FOR PARALLEL–LINE ASSAY

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Abstract

In this paper, the effects of model inadequacy on testing linearity, parallelism (location–shift) and parameter estimation in analysis of parallel–line assay are discussed. We propose two design criteria concerning the problem of parallel–line assay, and find the approximate optimal designs under the two design criteria from a specified class of designs.

Key words: Optimal design, Parallel–line assay, Model inadequacy.

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1. Introduction

In biological assay (or bioassay), standard statistical procedures have been used for estimating the potency of one substance relative to another by means of responses produced in biological systems. The typical problem is that of finding the amount of a new drug that is equivalent to a specified amount of an old and standard drug. In Finney (1947, 1979, 1983) some methods of quantitative estimation between drugs in terms of biological responses are discussed. More precisely, suppose that two substances S and T can produce analogous responses in appropriate biological material, and that the magnitude of response depends upon doses. Let Y_1, Y_2 represent a typical response to a dose z of S, T respectively. It is assumed that $E(Y_1) = F(z)$, where $F(z)$ is a single value function of z. By the condition of similarity, the expected response of a dose z of T follows $F(\rho z)$, where ρ is the potency of T relative to S under some conditions. The function F will have unknown parameters. Good estimators for the potency ρ and the unknown parameters are needed.

It is usually assumed that F follows a linear regression on the logarithm of dose in a certain range of interest, i.e.

$$F(z) = \beta_0 + \beta_1 \ln z = \beta_0 + \beta_1 x, \text{ where } x = \ln z.$$

Then by the condition of similarity,

$$\begin{aligned} F(\rho z) &= \beta_0 + \beta_1(\ln \rho + \ln z), \\ &= \beta_0 + \beta_1(x - \mu), \end{aligned}$$

where

$$x = \ln z, \ \mu = -\ln \rho;$$

which is equivalent to say that the two regression lines are parallel. So we need to estimate β_0, β_1, and $\mu = -\ln \rho$. Box and Draper (1959) addressed the problem that subliminal deviations from the assumed model may result in a large bias term in estimation. Validity of these estimates requires that the assumptions of linearity and parallelism of the two regression functions are satisfied. They are usually tested before doing the estimation.

In Section 2, we shall see the effect of model inadequacy in testing, especially for parallelism. In Section 3, we will review several optimal design criteria for detecting model inadequacy and propose two design criteria for the test of parallelism and parameter estimation. In Section 4, we will find the optimal designs under the two new design criteria from a specified class of designs.

Suppose that the responses $\{Y_{i1}, i = 1, \ldots, n_1\}$, $\{Y_{i2}, i = 1, \ldots, n_2\}$ are obtained independently from normal population with the same variance at dose levels $\{z_{i1}, i = 1, \ldots, n_1\}$ and $\{z_{i2}, i = 1, \ldots, n_2\}$ of S and T respectively. Let

$$x_{ij} = \ln z_{ij}, \quad i = 1, \ldots, n, \quad j = 1, 2.$$

For these responses, ρ is to be estimated. In this case, the model to be fitted is

$$Y = X\beta + \varepsilon = X_{11}\beta_1 + X_{22}\beta_2 + \varepsilon \tag{1.1}$$

where

$$\begin{aligned} Y' &= (Y_{11}, \ldots, Y_{n_1 1}, Y_{12}, \ldots, Y_{n_1 2}), \\ \varepsilon' &= (\varepsilon_{11}, \ldots, \varepsilon_{n_1 1}, \varepsilon_{12}, \ldots, \varepsilon_{n_2 2}), \\ \beta' &= (\beta_{01}, \beta_{11}, \beta_{02}, \beta_{12}), \\ X' &= \begin{pmatrix} 1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 \\ x_{11} & x_{21} & \ldots & x_{n_1 1} & 0 & 0 & \ldots & 0 \\ 0 & 0 & \ldots & 0 & 1 & 1 & \ldots & 1 \\ 0 & 0 & \ldots & 0 & x_{12} & x_{22} & \ldots & x_{n_2 2} \end{pmatrix} \\ &= \begin{pmatrix} X'_{11} & \underset{\sim}{0} \\ \underset{\sim}{0} & X'_{22} \end{pmatrix} \end{aligned}$$

under the assumption that $\varepsilon \sim N(0, \sigma^2 I)$. Let $b = (X'X)^{-1}X'Y$ be the least squares estimator of β. Then the residual sum of squares is

$$SSE = Y'(I - X(X'X)^{-1}X')Y.$$

The pure error sum of squares SSPE with n_e degrees of freedom and $E(SSPE) = n_e\sigma^2$ is obtained in the usual manner, assuming there are replicates for S and/or T.

Now well known methods of calculation then give an analysis of variance in the following Table 1.

Table 1. ANOVA for linearity and parallelism

Source	d.f.	Sum of Squares
Classes (adjusted for mean)	1	$SS(b_{02} - b_{01})$
Single slope	1	$SS(b_{11} + b_{12})$
Deviation from parallelism	1	$SS(b_{11} - b_{12})$
Deviation from linearity (Lack of fit)	$N - 4 - n_e$	
Within doses (Pure error)	n_e	
Total	$N - 1$	

Note that $SS(b_{11} - b_{12}) = (c'b)'D^{-1}(c'b)$, where $c' = (0, 1, 0, -1)$, $D = c'(X'X)^{-1}c$.

The pure mean square error $SSPE/n_e$ estimates σ^2. The usual lack of fit test for linearity is performed by using the ratio

$$F' = \frac{SSLF/(N - 4 - n_e)}{SSPE/n_e},$$

large value of F' means the assumption of linearity is rejected.

2. Model inadequacy in testing

If the postulated model is the correct model to consider, then the least square estimate $b = (X'X)^{-1}X'Y$ of β in the model $E(Y) = X\beta$ is an unbiased estimate. If it is not the correct model, then the estimate is biased. The effect of model inadequacy on testing, especially for parallelism is the main concern here. If the lack of fit test is falsely accepted, then even under the condition of similarity, the test of parallelism may reject the assumption of similarity of the two drugs with a large probability. In the following, we shall see how model inadequacy affects the test.

Suppose the true model is

$$Y = X\beta + Z\gamma + \varepsilon, \quad (2.1)$$

where

$$Z' = \begin{pmatrix} x_{11}^2, & x_{21}^2, & \dots, & x_{n_1 1}^2, & 0, & \dots, & 0 \\ 0, & \dots, & 0, & x_{12}^2, & \dots, & x_{n_2 2}^2 \end{pmatrix} = \begin{pmatrix} Z_1, & \underset{\sim}{0} \\ \underset{\sim}{0}, & Z_2 \end{pmatrix}$$

$$\gamma' = (\beta_{21}, \beta_{22}),\ \varepsilon \sim N(0, \sigma^2 I),$$

or in an alternative form

$$Y = X(\beta + A\gamma) + Q\gamma + \varepsilon,$$

where

$$Q = Z - XA,$$

with

$$A = (X'X)^{-1}X'Z$$

being the usual bias matrix, and where $X'Q = 0$ (see Draper and Smith (1981) for such expressions). Then $b = (X'X)^{-1}X'Y$ is biased for β with $E(b) = \beta + A\gamma$. The residual sum of squares is

$$\begin{aligned} SSE &= Y'(I - X(X'X)^{-1}X')Y \\ &= \gamma'Q'Q\gamma + 2\gamma'Q'\varepsilon + \varepsilon'(I - X(X'X)^{-1}X')\varepsilon, \end{aligned}$$

and

$$E(SSE) = (n-4)\sigma^2 + \gamma'Q'Q\gamma = (n-4)\sigma^2 + \lambda\sigma^2$$

where $\lambda\sigma^2 = \gamma'Q'Q\gamma$.

So according to the analysis described earlier we will test, at level α, for lack of fit using the ratio

$$F' = \{SSLF/(N - 4 - n_e)\}/\{SSPE/n_e\}.$$

Theorem 2.1. When the true model is as in (2.1), F' is a noncentral F distribution with $(N - 4 - n_e)$ and n_e degrees of freedom and noncentrality parameter $\lambda_1 = \gamma'Q'Q\gamma/\sigma^2$. (This result can be found in most textbooks, see e.g. Draper and Smith (1981).)

Now we denote the upper tail α–percentage point of the central F variable with n_1, n_2 d.f. by $F_{n_1, n_2, \alpha}$. The null hypothesis of linearity will be falsely accepted when $F' < F_{N-4-n_e, n_e, \alpha}$ with the true model as in (2.1). So the power of the test in this case would be $P\{F' > F_{N-4-n_e,n_e,\alpha}\}$. If linearity of the regression function is accepted, as in the usual analysis, a test of parallelism will be performed. The ratio

$$F'' = \frac{(c'b)D^{-1}c'b}{SSPE/n_e}$$

will be used and parallelism of the regression lines will be rejected if

$$F'' > F_1, n_e, \alpha_2.$$

Note. We use SSPE/n_e in the denominator of F'', instead of SSE/$(N-4)$ even when linearity is accepted to avoid complexity when the true model is not really linear.

Theorem 2.2. When the true model is as in (2.1), F'' is a noncentral F with 1 and n_e degrees of freedom and noncentrality

$$\lambda_2 = (1/\sigma^2)\{(\beta + A\gamma)'cD^{-1}c'(\beta + A\gamma)\}, \text{ where } D = c'(X'X)^{-1}c.$$

Proof: Since $b = (X'X)^{-1}X'Y$ is distributed as normal with mean $\beta + A\gamma$ and variance–covariance matrix $\sigma^2(X'X)^{-1}$, then $(\sigma^2)^{-1}(c'b)'D^{-1}(c'b)$ will be distributed as noncentral χ^2 with 1 degree of freedom and with noncentrality parameter

$$\lambda_2 = (1/\sigma^2)\{(\beta + A\gamma)'cD^{-1}c'(\beta + A\gamma)\}, \text{ where } D = c'(X'X)^{-1}c.$$

Also it is easy to see that $(1/\sigma^2)SSPE$ is independent of $(\sigma^2)^{-1}(c'b)'D^{-1}(c'b)$ and is distributed as χ^2 with n_e degrees of freedom. This proves the theorem.

Corollary 2.1. When the true model is quadratic and the two regression functions for Y_1, Y_2 are parallel and the location parameter is μ, i.e.

$$\begin{aligned} EY_1 &= \beta_{01} + \beta_{11}x + \beta_2 x^2, \\ EY_2 &= \beta_{01} + \beta_{11}(x-\mu) + \beta_2(x-\mu)^2, \end{aligned} \tag{2.2}$$

then

$$\begin{aligned} \lambda_1 &= \left(\frac{\beta_2}{\sigma}\right)^2 [Z_1'(I - X_{11}(X_{11}'X_{11})^{-1}X_{11}')Z_1 + \\ &\qquad Z_2'(I - X_{22}(X_{22}'X_{22})^{-1}X_{22})Z_2], \\ &\text{and} \\ \lambda_2 &= \left(\frac{\beta_2}{\sigma}\right)^2 D^{-1}\{2\mu + (0,1)[(X_{11}'X_{11})^{-1}X_{11}'Z_1 - \\ &\qquad (X_{22}'X_{22})^{-1}X_{22}'Z_2]\}^2. \end{aligned} \tag{2.3}$$

3. Optimality Criteria

In Section 2, we have seen the effect of model inadequacy on the test of parallelism. In this section, we will review several optimal design criteria for detecting model inadequacy and propose two design criteria for the test of parallelism and parameter estimation.

In the following, the region of interest R will be defined to be $\{-1 \leq x_1 \leq 1, -1+\nu \leq x_2 \leq 1+\nu\}$. Since we can always define the region for x_1 as $[-1,1]$, ν represents our choice of the region for x_2 . We do not transform the region of x_2 to be $[-1,1]$, because we don't know the value of the location shift parameter μ, which we need to estimate. Also when we discuss the problem of design, there are actually two parts of the design. One is for x_1, the other is for x_2. Since Y_1 and Y_2 can be taken independently within the range R for x_1, x_2, and their expectations take the same parametric form, we can see easily that the optimal design ξ_2^* for x_2 is just a location shift of the optimal design ξ_1^* for x_1, i.e. $\xi_2^* = \xi_1^* + \nu$. In other words, for the distinct design points x_{i1} in ξ_1^*, $x_{i2} = x_{i1} + \nu$ with the same weight as x_{i1}.

3.1 Optimality criteria for detecting model inadequacy

In order to discriminate between models (1.1) and (2.1) when (2.1) is true, the optimality criterion for the design of the experiment reduces to the maximization of

$$\lambda_1 = \gamma' Q' Q \gamma / \sigma^2, \tag{3.1}$$

or

$$\lambda_1 = (\gamma/\sigma)' L (\gamma/\sigma),$$

where

$$L = Z'\{I - X(X'X)^{-1}X'\}Z. \tag{3.2}$$

The choice of the design to maximize λ_1 depends, of course, on (γ/σ), which is unknown. There are several kinds of optimality criteria considered here.

(i) The maximization of $|L|$ = determinant of L as a criterion for constructing designs to detect model inadequacy was proposed by Atkinson (1972). The criterion has also received considerable attention from others such as Kiefer (1961), Atwood (1969), Studden (1980) under the heading of D_s–optimal, i.e. D–optimality for a subset of the parameters.

(ii) The Λ_1–optimality criterion proposed by Atkinson and Fedorov (1975a). Λ_1–optimality: A design $\xi_1^\star$ maximizing Λ_1 over all designs from some class of permissible designs Δ is called a Λ_1–optimal design, where Δ contains at least one design for which L has full rank, and

$$\Lambda_1 = \inf_{\gamma \in \Phi} \gamma' L \gamma; \quad \Phi = \{\gamma : \gamma' W \gamma \geq \delta > 0\}, \tag{3.3}$$

where W is positive definite which is constant for all designs. For a special choice of W and more details, see Jones and Mitchell (1978).

(iii) The Λ_2–optimality criterion proposed by Jones and Mitchell (1978). Λ_2–optimality: A design $\xi_2^\star$ maximizing Λ_2 over all designs in Δ, where

$$\Lambda_2 = \int_{\Phi_0} \gamma' L \gamma dB / \int_{\Phi_0} dB, \tag{3.4}$$

and dB is the differential to the area on the surface of the ellipsoid

$$\Phi_0 = \{\gamma : \gamma' W \gamma = \delta\}.$$

(iv) The minimum bias designs proposed by Box and Draper (1959) which are chosen to minimize J, the mean squared deviation of $\hat{Y}(x)$ from the true response $\eta(x)$, averaged over the region R of interest and normalized with respect to the number of observations and the variance, i.e.

$$J = \frac{N}{\sigma^2} \int_R E[\hat{Y}(x) - \eta(x)]^2 dx = V + B, \tag{3.5}$$

where V is the "variance error" and B is the "bias error".

(v) The D–optimal design for model (2.1).

In our case, the assumed model is of the first order over the region R, i.e. $EY_j = \beta_{0j} + \beta_{1j} x_j$, $j = 1, 2$; while the true model is of second order, i.e. $EY_j = \beta_{0j} + \beta_{1j} x_j + \beta_{2j} x_j^2$.

So when W is chosen as the special choice in Jones and Mitchell (1978), D_s-, Λ_1-, or Λ_2- optimality yields the same optimal design, i.e. placing 1/4 of the observations at each end of the two intervals I_1, I_2, and the remaining 1/2 at the centers. The second order design places 1/3 of the observations at each end and the center of the two intervals. The minimum bias design using the approach of Box and Draper (1959) places the design points at the center with certain weight and at two other points symmetrically near the ends of each interval, so that the root mean square distance of the design points from the center is approxmately .6 for each interval, i.e. $c_j = (\frac{1}{n})\sum_{i=1}^{n_j}(x_{ij} - \overline{x}_j)^2$ is approximately .36, and the fourth moment of x_j, say d_j, $d_j = (\frac{1}{n})\sum_{i=1}^{n_j}(x_{ij} - \overline{x}_j)^4$, is not small, for $j = 1, 2$.

3.2. Optimality criterion for the test of parallelism

Our concern now is whether the model is parallel (location shift). We would like to find designs which will have larger probability of accepting the parallel hypothesis when the true model is quadratic and parallel, even if we have used an inadequate simple linear model to do the test of parallelism (location shift). Now let

$$P_1 = P\{F' = \frac{SSLF/(N-4-n_e)}{SSPE/(n_e)} < F_{N-4-n_e, n_e, \alpha}|\lambda_1\} \tag{3.6}$$

which is the probability of fasely accepting the null hypothesis of linearity under α, (so large values of λ_1 are more favorable); and let

$$P_2 = P\{F'' = \frac{(c'b)D^{-1}(c'b)}{SSPE/(n_e)} > F_{1, n_e, \alpha}|\lambda_2\} \tag{3.7}$$

which is the probability of falsely rejecting the parallelism when the true model is quadratic and parallel, (so smaller values of λ_2 are more favorable). Therefore we propose to select a design that minimizes Q_1 over all designs from certain specified class, where

$$Q_1 = P_1 P_2 \tag{3.8}$$

is a measure of the chance of using an inadequate model and then incorrectly rejecting the parallelism (location shift property).

3.3 Optimality criterion for parameter estimation

If the location shift property of the model is accepted, even if we have used an inadequate model, then we need to estimate the parameters of the assumed model. Some kind of minimization concerning J is needed. We would like to give more weight for those J values which have more chance of being used. Therefore $P_1(1 - P_2)$ is treated as a weighting factor in the following criterion. The second criterion we propose is to choose a design to minimize

$$Q_2 = P_1(1 - P_2)J, \tag{3.9}$$

where P_1, P_2 are as defined above, J is as defined in (3.5), $\hat{Y}(x)$ is the least squared estimate based on model (1.1) and $\eta(x)$ is based on model (2.2).

Example 1: In this example we will use the three optimal designs for detecting model inadequacy as described in Section 3.1 to see the effects of model inadequacy on the test of parallelism and the parameter estimations. The three exact optimal designs are given in Table 2 when $N = 2n = 18$.

Table 2. Design points for the exact designs
The number of points at x is $n(x)$

	Design	S	T
I.	$A-, D_s$–optimal	$n(\pm1) = 2,\ n(0) = 5,$	$n(\pm1+\nu) = 2, n(\nu) = 5,$
II.	Second order D–optimal	$n(\pm1) = 3,\ n(0) = 3,$	$n(\pm1+\nu) = 3, n(\nu) = 3,$
III.	Minimum bias	$n(\pm0.9) = 2,\ n(0) = 5,$	$n(\pm0.9+\nu) = 2, n(\nu) = 5.$

Then for these designs the corresponding values of P_1 and P_2 are

$$P_1 = P\{F' = \frac{SSLF/2}{SSPE/12} < F_{2,12,.05} = 3.89|\lambda_1\} \tag{3.10}$$

and

$$P_2 = P\{F'' = \frac{(c'b)D^{-1}(c'b)}{SSPE/12} > F_{1,12,.05} = 4.75|\lambda_2\} \tag{3.11}$$

with corresponding values of λ_1, λ_2.

The curve of $1 - P_1$ versus λ_1 is plotted in Figure 1 and Figure 1′. The curve of P_2 versus λ_2 is plotted in Figure 2 and Figure 2′. From the graph we can see clearly that when λ_1 is not large, say $1 < \lambda_1 < 6$, we have a chance of over .5 of making the mistake of falsely accepting linearity. Also when λ_2 is not too small, say $2 < \lambda_2 < 6$, we have a chance of over .2 of falsely rejecting the hypothesis of parallelism.

For designs which distribute the observations equally on x_1 and x_2, i.e. $n_1 = n_2 = N/2 = n$, and are symmetric about the center of the corresponding intervals for x_1, x_2, i.e. $\sum_{i=1}^{n} x_1 = 0, x_{i2} = x_{i1} + \nu, i = 1, \ldots, n$, we can easily show that under the conditions of Corollary 2.1, λ_1 and λ_2 in (2.3) can be written as follows

(3.12)
$$\lambda_1 = 2\left(\frac{\beta_2}{\sigma}\right)^2 \left\{\sum_{i=1}^{n} x_{i1}^4 - \frac{1}{n}\left(\sum_{i=1}^{n} x_{i1}^2\right)^2\right\} = 2n\left(\frac{\beta_2}{\sigma}\right)^2 \left\{c_4 - c_2^2\right\};$$

(3.13)
$$\lambda_2 = \left(\frac{\beta_2}{\sigma}\right)^2 \frac{1}{\sum_{i=1}^{n} x_{i1}^2}(2\mu - 2\nu)^2, = \left(\frac{2\beta_2}{\sigma}\right)^2 \frac{(\mu - \nu)^2}{nc_2},$$

where c_2 and c_4 are the second and fourth moment of the design for x_1. Also J can be expressed as

(3.14)
$$J = 2\left\{\left[1 + \frac{1}{3c_2}\right] + n\left(\frac{\beta_2}{\sigma}\right)^2 \left[\left(c_2 - \frac{1}{3}\right)^2 + \frac{4}{45}\right]\right\}.$$

In Table 3, under the conditions of Corollary 2.1, the values of λ_1, λ_2 and J are given for the three optimal designs in Table 2. Now let $\varsigma_1 = (\beta_2/\sigma)^2, \varsigma_2 = (2\beta_2/\sigma)^2(\mu - \nu)^2$.

Table 3. The values of λ_1, λ_2 and J for the three designs.

	Design	λ_1	λ_2	J
I.	$A-, D_s$–optimal	$(\frac{40}{9})\varsigma_1$	$\frac{1}{4}\varsigma_2$	$3.50 + (.202)(9\varsigma_1)$
II.	Second order D–optimal	$4\varsigma_1$	$\frac{1}{6}\varsigma_2$	$3.00 + (.400)(9\varsigma_1)$
III.	Minimum bias	$(2.916)\varsigma_1$	$\frac{25}{81}\varsigma_2$	$3.86 + (.179)(9\varsigma_1)$

The performance comparison of the three designs under optimality criteria Q_1, Q_2 will be discussed in Section 4.

4. Some results on optimal design

From Section 3.1 we see that the three optimal designs for detecting model inadequacy under different optimality criteria are all from the class of designs with 3 design points and are symmetric about the center of the corresponding intervals for x_1 and x_2. Therefore in this section we will find optimal designs from this class under the optimality criteria Q_1, Q_2.

More precisely, the region of interest is R and we divide the observations equally on x_1, x_2. We will find optimal designs from the class Δ where

$$\Delta = \{(\xi_1, \xi_2) | \xi_1(-x) = \xi_1(x) = p, \xi_1(0) = 1 - 2p, 0 < x \leq 1, 0 < p < 1/2,$$
$$\text{and } \xi_2 = \xi_1 + \nu, \text{ i.e. } x_{i2} = x_{i1} + \nu, i = 1, \ldots, n.\}$$

Now we express the noncentral F distribution with noncentrality parameter λ and degrees of freedom n_1, n_2 as a mixture of ratios of independent χ^2 variables, i.e. the distribution function of F can be expressed in the form

$$P(F \leq x) = \sum_{k=0}^{\infty} \frac{e^{-\lambda/2}(\lambda/2)^k}{k!} P\left(F_{n_1+2k, n_2} \leq \frac{n_1 x}{n_1 + 2k}\right). \tag{4.1}$$

For such expression, see e.g. Muirhead (1982).

Then when λ_1 and λ_2 are not too large, Q_1 and Q_2 can be written approximately in terms of λ_1 and λ_2 as

$$\begin{aligned} Q_1 &\approx \left(s_1 - \left(\frac{s_1 - s_2}{2}\right)\lambda_1\right)\left(1 - t_1 + \left(\frac{t_1 - t_2}{2}\right)\lambda_2\right), \\ &= \left(1 - \alpha - \left(\frac{1 - \alpha - s_2}{2}\right)\lambda_1\right)\left(\alpha + \left(\frac{1 - \alpha - t_2}{2}\right)\lambda_2\right) \end{aligned} \tag{4.2}$$

where

$$q_1 = F_{N-4-n_e,n_e,\alpha},$$

$$q_2 = F_{1,n_e,\alpha},$$

$$s_1 = P(F_{N-4-n_e,n_e} \le q_1) = 1-\alpha;$$

$$s_2 = P\left(F_{N-2-n_e,n_e} \le \left(\frac{N-4-n_e}{N-2-n_e}\right) q_1\right),$$

$$t_1 = P(F_{1,n_e} \le q_2) = 1-\alpha,$$

$$t_2 = P\left(F_{3,n_e} \le \left(\frac{1}{3}q_1\right)\right),$$

and

$$Q_2 \approx \left(1-\alpha-\left(\frac{1-\alpha-s_2}{2}\right)\lambda_1\right)\left(1-\alpha-\left(\frac{1-\alpha-t_2}{2}\right)\lambda_2\right)J. \tag{4.3}$$

Now we substitute the values of λ_1 and λ_2 in terms of the second and fourth moment of the design ξ_1 into Q_1 and Q_2, where λ_1 and λ_2 are as in (3.12) and (3.13). We obtain

$$Q_1 \approx (1-\alpha-nb_1(c_4-c_2^2))(\alpha+b_2/(nc_2)),$$

and

$$Q_2 \approx 2(1-\alpha-nb_1(c_4-c_2^2))(1-\alpha-b_2/(nc_2))$$
$$\cdot\left\{\left(1+\frac{1}{3c_2}\right)+n\left(\frac{\beta_2}{\sigma}\right)^2\left[\left(c_2-\frac{1}{3}\right)^2+\frac{4}{45}\right]\right\}.$$

where

$$b_1 = (1-\alpha-s_2)\left(\frac{\beta_2}{\sigma}\right)^2,$$

$$b_2 = \left(\frac{1-\alpha-t_2}{2}\right)\left(\frac{2\beta_2}{\sigma}\right)^2(\mu-\nu)^2.$$

Since b_1 and b_2 are both greater than zero, it can easily be shown that we should choose designs such that $c_4 = c_2$ in order to minimize Q_1 and Q_2. Therefore the design points for x_1 should be at $-1, 0, 1$. Now we only need to find the optimal values of c_2 to minimize Q_1 and Q_2 respectively, which can be found fairly easy now. In Example 2, we will find the optimal designs under the design criteria Q_1, Q_2 when $N = 2n = 18$.

Example 2. Let $N = 2n = 18, (\beta_2/\sigma) = 1,\ (\mu - \nu) = 1/2$, and $\alpha = 0.05$. Since the designs for x_1 are on 3 design points, then $n_e = 12$, $q_1 = F_{2,12,.05} = 3.89$, and $q_2 = F_{1,12,.05} = 4.75$,

$$s_2 = P(F_{4,12} \leq 1.95) = 0.833312,$$
$$t_2 = P(F_{3,12} \leq 1.58) = 0.754391;$$

and

$$b_1 = (.95 - .83) = .12,$$
$$b_2 = (.95 - .75)/2 = .10.$$

i.e.

$$Q_1 \approx (.95 - 1.08(c_2 - c_2^2))(.05 + .10/(9c_2)),$$
$$Q_2 \approx 2(.95 - 1.08(c_2 - c_2^2))(.95 - .10/(9c_2)) \left\{ \left(1 + \frac{1}{3c_2} + 9 \left[\left(c_2 - \frac{1}{3} \right)^2 + \frac{4}{45} \right] \right) \right\}.$$

The graphs of Q_1 and Q_2 versus c_2 are plotted in Figure 3, 4, for $0.1 < c_2 < 1$ (we assume λ_2 is not too large). It can easily be shown that Q_1 is minimized when $c_2 = .633$, and Q_2 is minimized when $c_2 = .463$. Note that the minimizing c_2 for both Q_1 and Q_2 are within the range .444 and .666, which correspond to the c_2 values of the $A-, D_s$–optimal design and the second order D–optimal design respectively. The values of Q_1, Q_2 in terms of c_2 for the three optimal designs in Section 3 are also indicated in Figure 3, 4 respectively.

In Example 2, $\beta_2/\sigma = 1$ represents the case that the quadratic coefficient β_2 is of about the same size as the standard deviation σ of random error. $(\mu - \nu) = 1/2$ means the interval where the observations Y_2 can be taken, are misplaced for about 1/2 away from the true location shift distance, here 1/2 is a relative measure compared to the total length 2 of the two intervals. If $(\mu - \nu) = 0$, then the test of parallelism (location shift) is the same for both linear and quadratic models, and there is no problem in rejecting parallelism with large probability. Therefore it is important for us to choose a reasonable range for x_2 in order to minimize the effect of model inadequacy on the test of parallelism.

For other values of β_2/σ and $(\mu - \nu)$, the optimal designs under Q_1 or Q_2 will have c_2 values following a certain pattern. When $(\mu - \nu) = 1/2$, and the size of β_2/σ is larger than 1, then the optimal c_2 values under Q_1 or Q_2 are smaller than the two c_2 values in

Example 2 respectively. When $\beta_2/\sigma = 1$ and $(\mu - \nu)$ is larger than 1/2, the optimal c_2 values under Q_1 or Q_2 are larger than the two c_2 values in Example 2. When β_2/σ gets larger and $(\mu - \nu)$ gets smaller or vice versa, then the optimal c_2 values depend on the comparative size of β_2/σ to $(\mu - \nu)$. Most of the time, we do not have a unified answer concerning the two criteria. Therefore we will have to choose a criterion which is more important, or a compromise between these two criteria.

The minimum bias design does not perform well in both Q_1, Q_2 criteria. The reason is that it is not performing well in testing model inadequacy and in testing the parallelism.

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Figure 1. The probability of rejecting linearity when the true model is quadratic for N = 18, $\alpha = 0.05$.

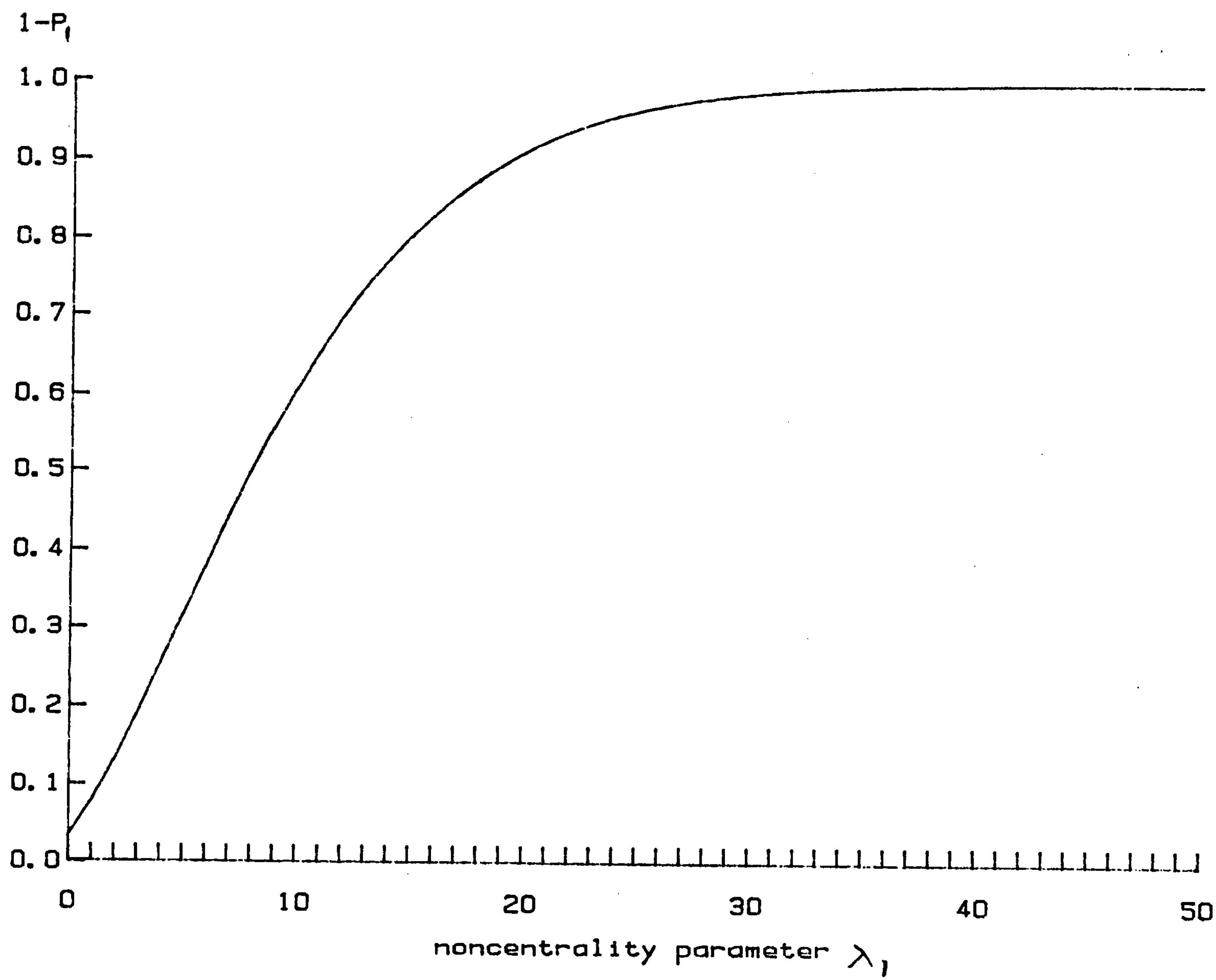

Figure 1. The probability of rejecting linearity when the true model is quadratic for N = 18, $\alpha = 0.05$.

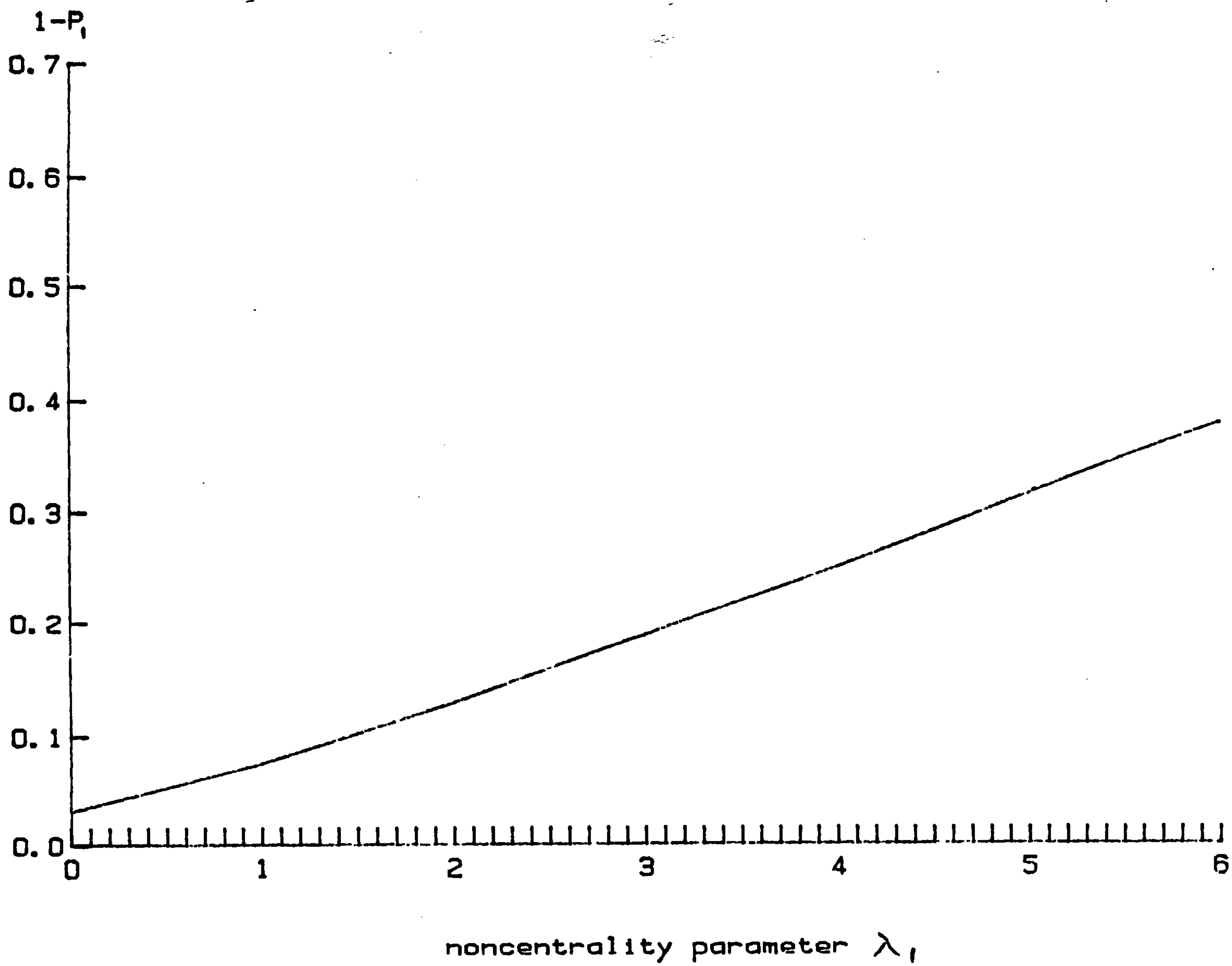

Figure 2. The probability of rejecting parallelism when the true model is quadratic and parallel for N = 18, $\alpha = 0.05$.

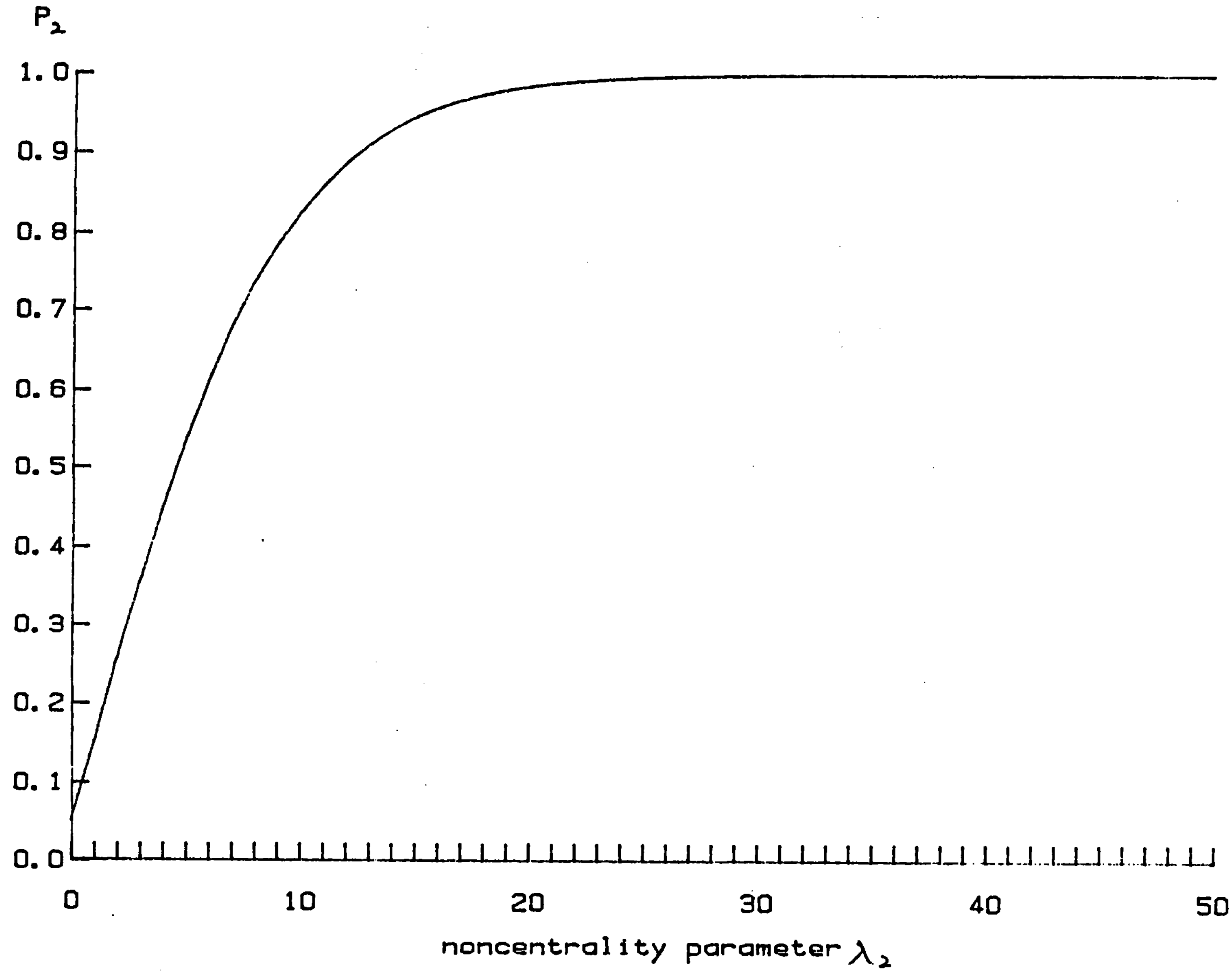

Figure 2′ The probability of rejecting parallelism when the true model is quadratic and parallel for $N = 18$, $\alpha = 0.05$.

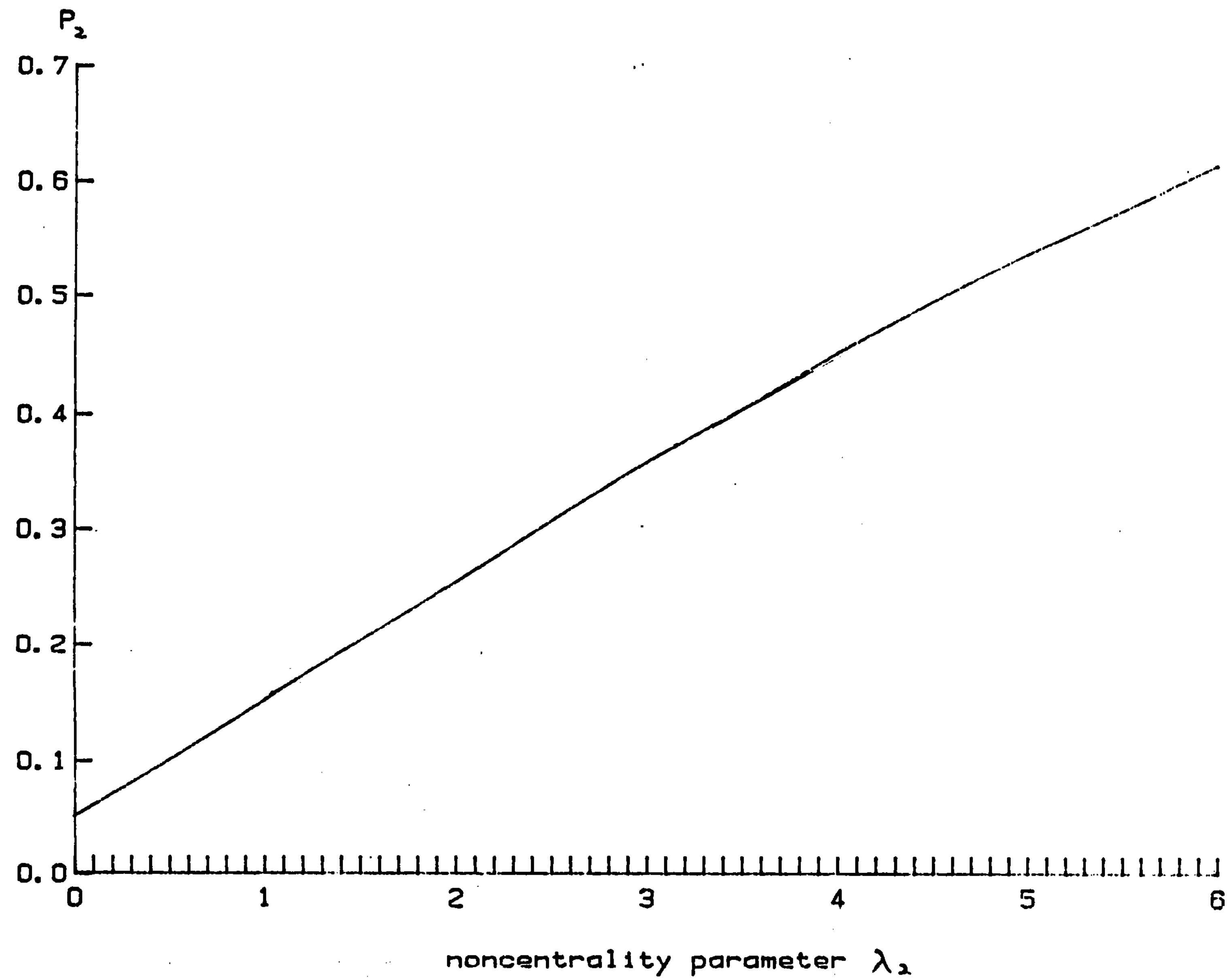

Figure 3. The value of Q_1 versus c_2 when $(\beta_2/\sigma) = 1$, and $\mu - \nu = 1/2$.

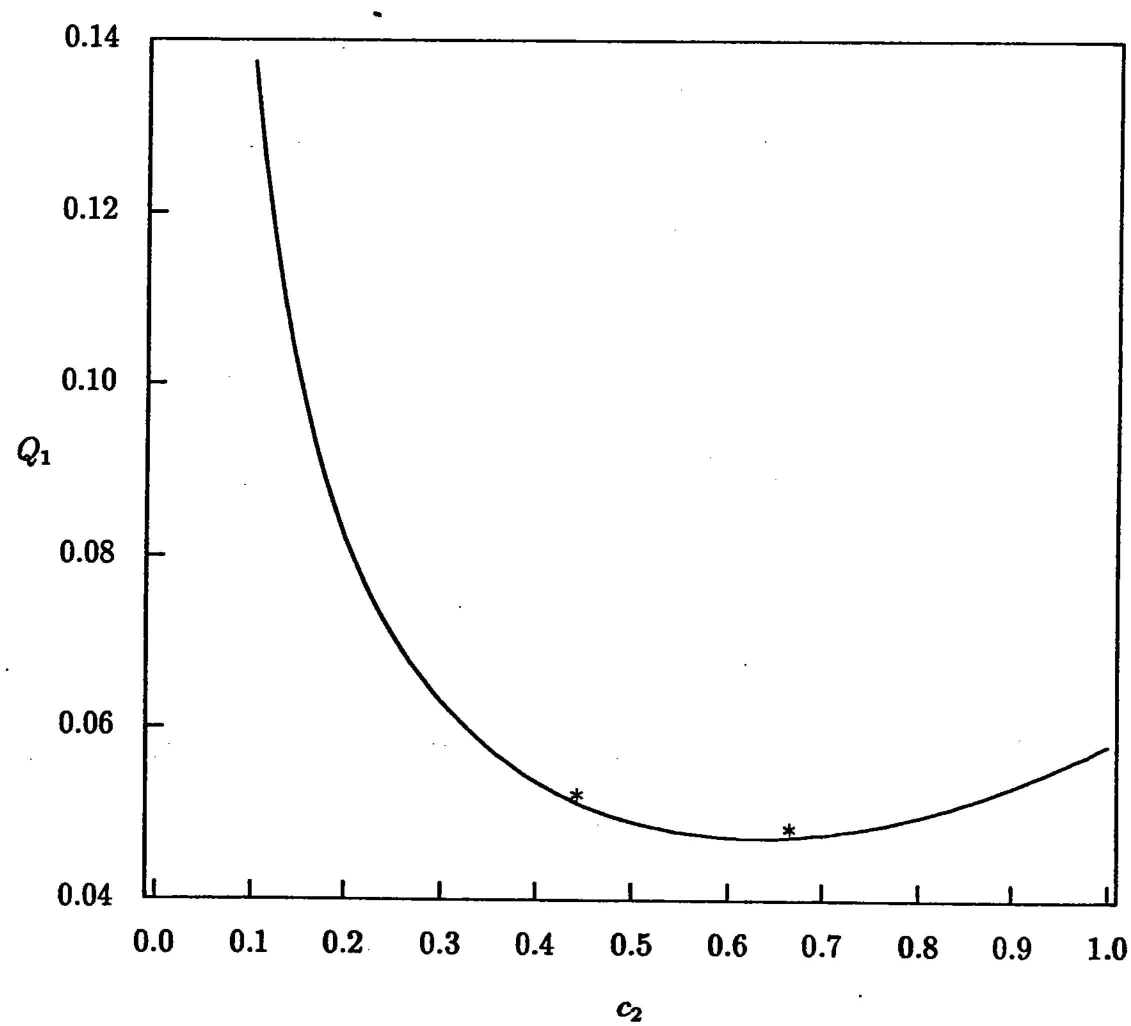

Figure 4. The value of Q_2 versus c_2 when $(\beta_2/\sigma) = 1$, and $\mu - \nu = 1/2$.