Tests due to Pooling Data Through Preliminary Test on Biological Direct Assay

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https://doi.org/10.5109/12992

出版情報：統計数理研究. 9 (2/3), pp.25-39, 1960-10. Research Association of Statistical Sciences
バージョン：
権利関係：

TESTS DUE TO POOLING DATA THROUGH PRELIMINARY TEST ON BIOLOGICAL DIRECT ASSAY

By

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(*Received* February 8, 1960)

§ 1. Summary

This paper discusses some methods for test of a mean effect on biological direct assay on the basis of pooling of data. A need for such methods is emphasized in the experiments under a restriction of small sample size at two or several similar environments or conditions, especially on biological direct assay. The principle of pooling of data is based on a scheme of T. Kitagawa [1], B. E. B. Bennett [1] which discussed the estimation of a mean effect after preliminary test of significance. And recently H. Bozivich, T. A. Bancroft and H. D. Hartley [1] discussed the power of analysis of variance test according to the pooling scheme of data. In this paper the tests of means and percentages after the preliminary test of significance are discussed and a recommendation is given from the viewpoints of the size of the power and the power gain.

§ 2. Introduction

The principle of a direct assay is that the doses of a standard preparation and those of a test preparation, both sufficient to produce a specified responce are directly measured and a difference of their potency can be investigated by their respective critical doses. Of course the simultaneous trial method is the basis of this assay techniques, and the test preparations T can be assayed relative to a standard preparation S by simultaneous experimentation by the comparison between the observed doses of S and the observed doses of T under the same environments and conditions.

The fundamental idea of this paper is that if such a standard pattern of assay has been adopted as a routine in factory production or elsewhere, a pooling of data can be introduced, in order to reinforce the power of test under a restriction of numbers of subjects. In some circumstances we had better pool the data in repeated assay of S, and it is the purpose of this paper to formulate such a rule of pooling procedure and to clarify the consequences of the pooling procedure.

Block(Days) \ Preparation	Control	Test
1	$S_{(1)}$	T_1
2	$S_{(2)}$	T_2

When a direct assay has performed as the following (left-sided) figure, a rule of test procedure for T_2 naturally may take the following steps:

(i) *Make a statistical test on a distinction (mean or percentage) between* $S_{(1)}$ *and* $S_{(2)}$ *with a significant level* α_1.

(ii) *Then*

(a) *if the significance of the difference between* $S_{(1)}$ *and* $S_{(2)}$ *is recognized, a similar statistical test between* $S_{(2)}$ *and* T_2 *is made only in block 2 with a significant level* α_2,

(b) *otherwise, that is, if the significance of the difference is not recognized, the data of* $S_{(1)}$ *and* $S_{(2)}$ *are pooled and a similar test between* $S_{(1)+(2)}$ *and* T_2 *is made with a significant level* α_3, *where* $S_{(1)+(2)}$ *means the pooled data of* $S_{(1)}$ *and* $S_{(2)}$.

In § 3 we discuss a test on normal distribution having a common known variance, which at the same time gives us a test of percentage by means of usual normal approximation, and in § 4 we apply a t-test procedure between S and T_2, where two normal universes are assumed to have a common, but unknown variance. § 5 discusses a test of percentage by means of double dichotomies. In § 3 and § 5, some numerical considerations are given.

The author wishes his hearty thanks to Prof. T. Kitagawa for his kind suggestions and encouragement.

§ 3. u-test after preliminary u-test of significance

Let O_{N_1}: $(x_{11}, x_{12}, \cdots, x_{1N_1})$ be a random sample of N_1 from a normal universe $N(\mu_1, \sigma^2)$, which indicates the critical doses observed on S in block 1, and O_{N_2}: $(x_{21}, x_{22}, \cdots, x_{2N_2})$ be a random sample of N_2 from other normal universe $N(\mu_2, \sigma^2)$, which indicates the critical doses observed on S in block 2, and then let O_{N_3}: $(x_{31}, x_{32}, \cdots, x_{3N_3})$ be a random sample of N_3 from the third normal universe $N(\mu_3, \sigma^2)$, which indicates the critical doses observed on T_2 in block 2. These three normal universes are assumed to have a common universe variance, whose value is known to us. The difference between $S_{(1)}$ and $S_{(2)}$ may be regarded to be due to a fluctuation on blocks, which may exist or may not.

Let us suppose that we shall pool two groups of sample observations on $S_{(1)}$ and $S_{(2)}$ when the hypothesis $\mu_1=\mu_2$ cannot be rejected and then let us test the difference between T_2 and S by the pooled observations.

Our rule of test procedure is formulated as follows:

(1) *Let a statistic* u_1 *be defined by*

$$u_1=(\bar{x}_1-\bar{x}_2)\Big/\sqrt{\frac{1}{N_1}+\frac{1}{N_2}}\ \sigma, \tag{3.1}$$

where $\bar{x}_i=\sum_{j=1}^{Ni} x_{ij}/N_i$. *Let* $u(\alpha_i)$ *be the* α_i*-point of the normal distribution* $N(0, 1)$ *such that*

$$(\sqrt{2\pi})^{-1}\int_{-u(\alpha_i)}^{u(\alpha_i)} e^{-\frac{t^2}{2}}\,dt=\alpha_i, \qquad (i=1,2,3).$$

(2) *Let us introduce a test for* T_2 *defined in the following manner.*

(a) *If* $u_1 \geq u(\alpha_1)$, *then test the hypothesis* H: $\mu_2=\mu_3$ *by applying the normal test to the statistic*

$$u_2=(\bar{x}_2-\bar{x}_3)\Big/\sqrt{\frac{1}{N_2}+\frac{1}{N_3}}\,\sigma, \tag{3.2}$$

with the significance level α_2.

(b) *Otherwise, that is, if* $|u_1|<u(\alpha_1)$, *then assuming* $\mu_1=\mu_2=\mu_{12}$, *say, test the hypothesis* H: $\mu_{12}=\mu_3$ *by applying the normal test to the statistic*

$$u_3=(\bar{x}_{12}-\bar{x}_3)\Big/\sqrt{\frac{1}{N_{12}}+\frac{1}{N_3}}\,\sigma, \tag{3.3}$$

with the significance level α_3, *where* $\bar{x}_{12}=(N_1\bar{x}_1+N_2\bar{x}_2)/N_{12}$ *and* $N_{12}=N_1+N_2$.

Then the power of our test procedure are of importance in this problem, and in consequence of these considerations the values of α_1, α_2 and α_3 are proposed for the practical uses so as to keep approximately an assigned value for the power of our test.

The power of our test procedure is given by

$$Pr.\{D_1\}+Pr.\{D_2\}=\iint_{D_1} f_1(y_1,y_2)\,dy_1dy_2+\iint_{D_2} f_2(y_1,y_3)\,dy_1dy_3, \tag{3.4}$$

where we put

$$\begin{cases} f_1(y_1,y_2)=(2\pi\sigma_1\sigma_2\sqrt{1-\rho_1^2})^{-1}\exp\Big[-\dfrac{1}{2(1-\rho_1^2)}\Big\{\dfrac{(y_1-\eta_1)^2}{\sigma_1^2}-\dfrac{2\rho_1(y_1-\eta_1)(y_2-\eta_2)}{\sigma_1\sigma_2} \\ \qquad\qquad +\dfrac{(y_2-\eta_2)^2}{\sigma_2^2}\Big\}\Big], \\ f_2(y_1,y_3)=(2\pi\sigma_1\sigma_3)^{-1}\exp\Big[-\dfrac{1}{2}\Big\{\dfrac{(y_1-\eta_1)^2}{\sigma_1^2}+\dfrac{(y_3-\eta_3)^2}{\sigma_3^2}\Big\}\Big], \end{cases} \tag{3.5}$$

$$\begin{cases} y_1=\bar{x}_1-\bar{x}_2,\ y_2=\bar{x}_2-\bar{x}_3,\ y_3=\dfrac{N_1}{N_1+N_2}\bar{x}_1+\dfrac{N_2}{N_1+N_2}\bar{x}_2-\bar{x}_3, \\ \sigma_1=\sigma\sqrt{\dfrac{1}{N_1}+\dfrac{1}{N_2}},\quad \sigma_2=\sigma\sqrt{\dfrac{1}{N_2}+\dfrac{1}{N_3}},\quad \sigma_3=\sigma\sqrt{\dfrac{1}{N_1+N_2}+\dfrac{1}{N_2}}, \\ \eta_1=\mu_1-\mu_2,\ \eta_2=\mu_2-\mu_3,\ \eta_3=\dfrac{N_1}{N_1+N_2}\mu_1+\dfrac{N_2}{N_1+N_2}\mu_2-\mu_3, \end{cases} \tag{3.6}$$

$$\rho_1 = -\left\{ N_2\sqrt{\left(\frac{1}{N_1}+\frac{1}{N_2}\right)\left(\frac{1}{N_2}+\frac{1}{N_3}\right)}\right\}^{-1}, \qquad \rho_2=0$$

and

(3.7)
$$D_1: \begin{cases} \sigma\sqrt{\dfrac{1}{N_1}+\dfrac{1}{N_2}}\, u(\alpha_1)\leq y_1<\infty, \\ \sigma\sqrt{\dfrac{1}{N_2}+\dfrac{1}{N_3}}\, u(\alpha_2)\leq y_2<\infty, \end{cases}$$

$$D_2: \begin{cases} 0< y_1 <\sigma\sqrt{\dfrac{1}{N_1}+\dfrac{1}{N_2}}\, u(\alpha_1), \\ \sigma\sqrt{\dfrac{1}{N_{12}}+\dfrac{1}{N_3}}\, u(\alpha_3) <y_3 <\infty. \end{cases}$$

For the test of percentages, a condition of some normal approximation may be more or less satisfied, and as the simple normal approximation the observations $p_1=(r_1/N_1)$, $p_2=(r_2/N_2)$ and $p_3=(r_3/N_3)$ can be considered by arcsine transformation, $\sin^{-1}\sqrt{r_i/N_i}$, $(i=1, 2, 3)$, and then their variances are known to be approximately the constants, that is, $(4N_i)^{-1}$. In this situation the above results for test on normal distributions with known variance are directly applicable for that on percentages.

Now we attempt to give numerical informations about the size of power and the power gains by numerical evaluations of (3.4) by assigning some values of the pairs of $\{N_i, \alpha_i\}$, $(i=1, 2, 3)$. The power gains are used to compare our sometimes pool procedure with that of the neverpool test and are defined as follows:

(i) Assume a value of the parameter η_1 to be zero:

(ii) For this value of η_1, evaluate the size of the sometimes-pool test.

(iii) For this level of size, evaluate the power curve of the never-pool test: this power curve is then directly comparable with that of the sometimes-pool test corresponding to $\eta_1=0$.

The behaviour of the size of the power and the power gain are illustrated as a function of $(\eta_1/\sigma, \eta_2/\sigma)$ for certain values of N_1, N_2, N_3 and α_1, α_2, α_3: Fig. 1 $(N_1=N_2=N_3=4,\ \alpha_1=\alpha_2=\alpha_3=0.05)$, Fig. 2 $(N_1=N_2=N_3=4,\ \alpha_1=0.2,\ \alpha_2=\alpha_3=0.05)$, Fig. 3 $(N_1=N_2=N_3=4,\ \alpha_1=\alpha_2=\alpha_3=0.10)$; Fig. 4 $(N_1=N_2=N_3=10,\ \alpha_1=\alpha_2=\alpha_3=0.10)$.

So far as these numerical data are concerned, we can make the following observations which might be suggestive to our statistical procedure in more general situation.

(i) The size of our test procedure does not equal to the nominal level of 0.05 (or 0.10), but varies as α_1 and η_2/σ vary. It can be noted that the size of the power for the values of η_2/σ between 0 and 2 in the case of $(\eta_1=0$, and $\alpha_2=\alpha_3=0.05)$ is larger than 0.05. As η_2/σ becomes larger, the size peak tends to the left and becomes larger than the nominal pool test.

(A_1)

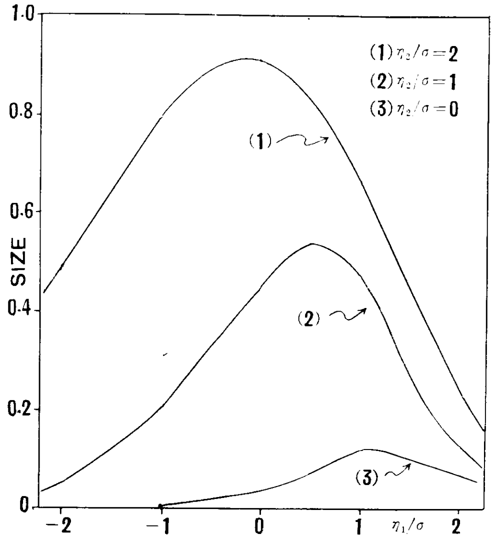

Fig. 1. (a) Size curves for $N_1=N_2=N_3=4$, $\alpha_1=\alpha_2=\alpha_3=0.05$

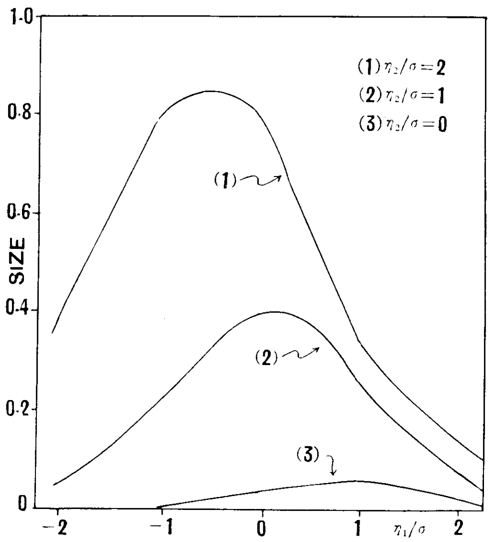

Fig. 2. (a) Size curves for $N_1=N_2=N_3=4$, $\alpha_1=0.2$, $\alpha_2=\alpha_3=0.05$

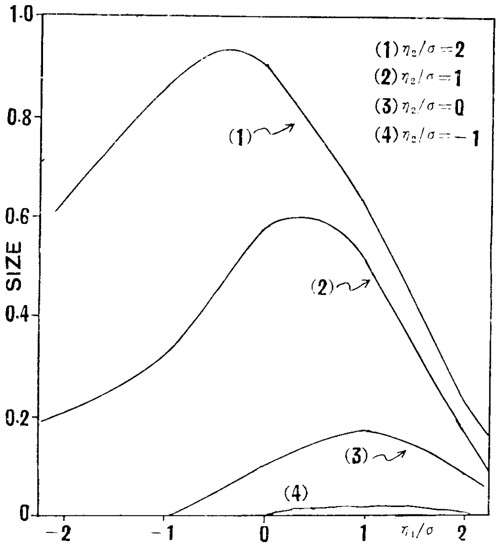

Fig. 3. (a) Size curves for $N_1=N_2=N_3=4$, $\alpha_1=\alpha_2=\alpha_3=0.10$

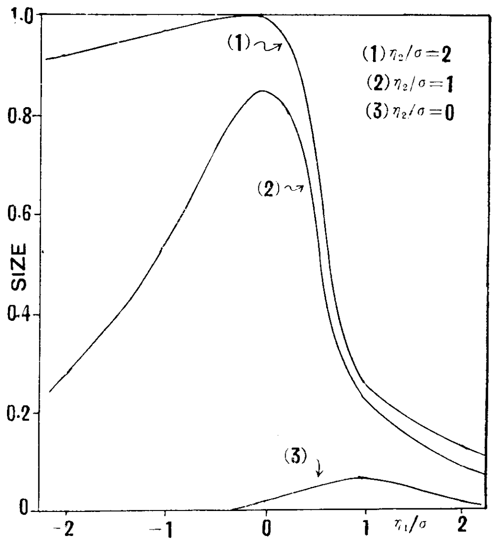

Fig. 4. (a) Size curves for $N_1=N_2=N_3=10$, $\alpha_1=\alpha_2=\alpha_3=0.10$

(A$_2$)

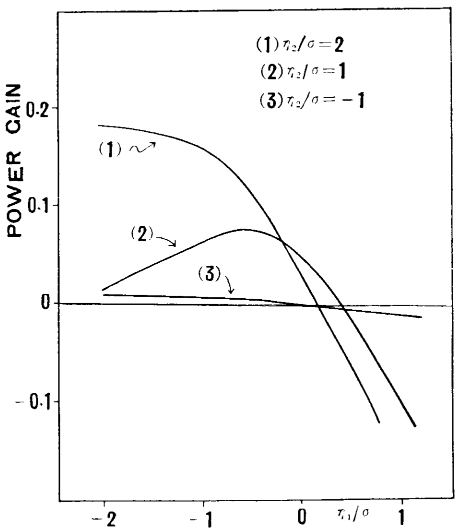

Fig. 1. (b) Power gain of the sometimes-pool procedure over teh never-pool test of the same size for $N_1=N_2=N_3=4$, $\alpha_1=\alpha_2=\alpha_3=0.05$

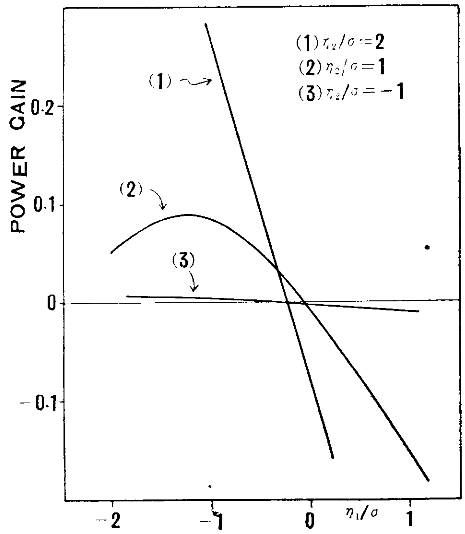

Fig. 2. (b) Power gain for $N_1=N_2=N_3=4$, $\alpha_1=0.2$, $\alpha_2=\alpha_3=0.05$

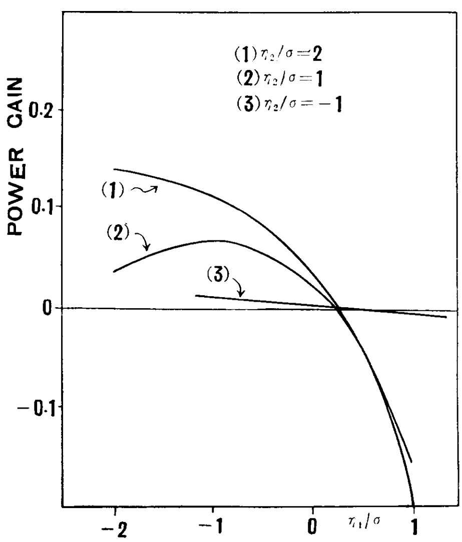

Fig. 3. (b) Power gain for $N_1=N_2=N_3=4$, $\alpha_1=\alpha_2=\alpha_3=0.10$

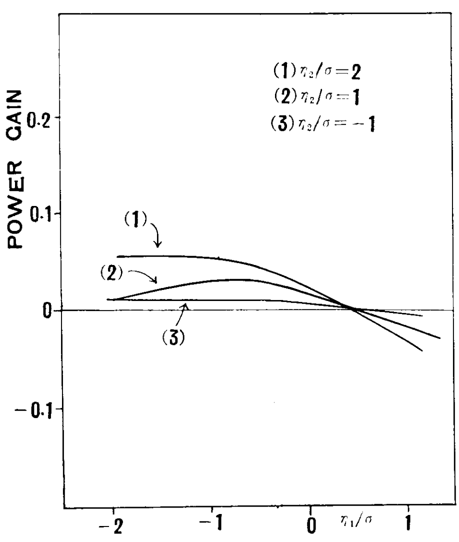

Fig. 4. (b) Power gain for $N_1=N_2=N_3=10$, $\alpha_1=\alpha_2=\alpha_3=0.10$

Moreover, the larger η_2/σ becomes, the narrower becomes the interval in which the size of the power exceeds that of the nominal pool test.

(ii) Referring to the size curve for a preliminary test carried out at the 0.05 level, the peak is usually high. Clearly, a preliminary test carried out at this level will in many cases admit an unacceptable size disturbance. Therefore, with the intention of size control for the nominal level of 0.05, that is, in order to decrease the peak of the size or to narrow the interval which exceeds the power of the never-pool test, we may propose a statistical procedure taking 0.20 as the value of α_1 with $\alpha_2=\alpha_3=0.05$.

(iii) From the point of the power gain, if we can assume that $0.5\geq\eta_1/\sigma \geq -2$, we may find a large power gain by choosing the level $\alpha_1=0.20$. However, under the assumption $0.5<\eta_1/\sigma$, the power gain is less than the never-pool test. And if we have nothing to assume, we may propose a borderline test.

(iv) The larger $N(=N_i)$ becomes, the smaller the power gain is obtained.

§ 4. *t*-test after preliminary *t*-test of significance

Let O_{N_1}: $(x_{11}, x_{12}, \cdots, x_{1N_1})$, O_{N_2}: $(x_{21}, x_{22}, \quad , x_{2N_2})$ and O_{N_3}: $(x_{31}, x_{32}, \cdots, x_{3N_3})$ be random sample from normal universe $N(\mu_1, \sigma_2)$, $N(\mu_2, \sigma^2)$ and $N(\mu_3, \sigma^2)$, respectively, with the same meaning as in § 3. In this section, the three normal universes are assumed to have a common but unknown variance σ^2. The universe means μ_1, μ_2 and μ_3 are not necessarily assumed to be equal.

In this case, our rule of test procedure is defined as follows.

(i) *Let $\bar{x}_1, \bar{x}_2$ and $\bar{x}_3$ be sample means and let s_1^2, s_2^2 and s_3^2 be sample variances respectively.*

(ii) *Let a statistic t_1 be defined by*

$$t_1=(\bar{x}_1-\bar{x}_2)\Big/\left(\frac{1}{N_1}+\frac{1}{N_2}\right)^{\frac{1}{2}}\left(\frac{(N_1-1)s_1^2+(N_2-1)s_2^2}{N_1+N_2-2}\right)^{\frac{1}{2}}, \tag{4.1}$$

where $\bar{x}_i=\sum_{j=1}^{Ni} x_{ij}/N_i$, $s_i^2=\sum_{j=1}^{Ni}(x_{ij}-\bar{x}_{i.})^2/(N_i-1)$,

and let $t_\phi(\alpha_i)$ be a significance value of t-distribution with the ϕ degrees of freedom and the significance level α_i, $(i=1, 2, 3)$.

(iii) *Let us introduce a test for T_2 defined in the following manner:*

(a) *If $|t_1|>t_{N_1+N_2-2}(\alpha_1)$, then test the hypothesis H: $\mu_2=\mu_3$ by applying the t-test to the statistic*

$$t_2=(\bar{x}_2-\bar{x}_3)\Big/\left(\frac{1}{N_2}+\frac{1}{N_3}\right)^{\frac{1}{2}}\left(\frac{(N_2-1)s_1^2+(N_3-1)s_3^2}{N_2+N_3-2}\right)^{\frac{1}{2}}, \tag{4.2}$$

with the significance level α_2.

(b) *Otherwise, that is, if $|t_1|\leq t_{N_1+N_2-2}(\alpha_1)$, then assuming $\mu_1=\mu_2=\mu_{12}$, say, test the hypothesis H: $\mu_{12}=\mu_3$ by applying the t-test to the* *statistic*

$$t_3=(\bar{x}_{12}-\bar{x}_3)\Big/\left(\frac{1}{N_{12}}+\frac{1}{N_3}\right)^{\frac{1}{2}}\left(\frac{(N_{12}-2)s_{12}^2+(N_3-1)s_3^2}{N_{12}+N_3-2}\right)^{\frac{1}{2}}, \tag{4.3}$$

with the significance level α_3, *where*

$$\begin{aligned}\bar{x}_{12}&=(N_1\bar{x}_1+N_2\bar{x}_2)/(N_1+N_2),\\ s_{12}^2&=\{(N_1-1)s_1^2+(N_2-1)s_2^2\}/(N_1+N_2-2).\end{aligned} \tag{4.4}$$

Now our problem is to obtain the power of the test given by the above test procedure, as in § 3, and this problem can be reduced the determination of the value of α_1, α_2 and α_3 for the practical uses so as to keep approximately an assigned value of the power of test.

The power is denoted as follows.

$$\begin{aligned}Pr.\{D_1\}+Pr.\{D_2\}=&Pr.\{|t_1|>t_{N_1+N_2-2}(\alpha_1),|t_2|>t_{N_2+N_3-2}(\alpha_2)\}\\ &+Pr.\{|t_1|\leq t_{N_1+N_2-2}(\alpha_1),|t_3|>t_{N_{12}+N_3-2}(\alpha_3)\}.\end{aligned} \tag{4.5}$$

Now let us put, for the moment,

$$\begin{aligned}&y_1=\bar{x}_1-\bar{x}_2, \qquad y_2=\bar{x}_2-\bar{x}_3,\\ &n_i=N_i-1\end{aligned} \tag{4.6}$$

and

$$W_1=\frac{n_1s_1^2+n_2s_2^2}{\sigma^2}, \qquad W_2=\frac{n_2s_2^2+n_3s_3^2}{\sigma^2}, \qquad W_3=\frac{n_3s_3^2}{\sigma^2}. \tag{4.7}$$

Then the joint elementary probability of (W_1, W_2, W_3) is shown by

$$\begin{aligned}&G(W_1, W_2, W_3)\ dW_1\,dW_2\,dW_3\\ &=\frac{2^{-(n_1+n_2+n_3)/2}}{\Gamma\left(\frac{n_1}{2}\right)\Gamma\left(\frac{n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}(W_1-W_3)^{\frac{n_1}{2}-1}(W_2-W_3)^{\frac{n_2}{2}-1}W_3^{\frac{n_3}{2}-1}e^{-\frac{W_1+W_2-W_3}{2}}\\ &\qquad\cdot dW_1dW_2dW_3\end{aligned} \tag{4.8}$$

and we obtain the probability of (W_1, W_2), integrating out W_3, as follows.

$$\begin{aligned}H(W_1, W_2)dW_1dW_2=&Pr.\{W_1>W_2\}\left[\int_0^{W_2}G(W_1, W_2,W_3)dW_3\right]dW_2dW_1\\ &+Pr.\{W_1\leq W_2\}\left[\int_0^{W_1}G(W_1, W_2, W_3)dW_3\right]dW_2dW_1\\ =&A\frac{2^{-\frac{n_1+n_2+n_3}{2}}}{\Gamma\left(\frac{n_1}{2}\right)\Gamma\left(\frac{n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}\sum_i^{\frac{n_1}{2}-1}\sum_j^{\frac{n_2}{2}-1}\sum_r^{\frac{n_3}{2}-1+i+j}(-1)^{i+j+r}\binom{\frac{n_1}{2}-1}{i}\binom{\frac{n_2}{2}-1}{j}\frac{2^{r+1}\left(\frac{n_3}{2}-1+i+j\right)!}{\left(\frac{n_3}{2}-1+i+j-r\right)!}\end{aligned} \tag{4.9}$$

$$\cdot W_1^{\frac{n_1}{2}-1-i} W_2^{\frac{n_2+n_3}{2}-2+i-r} e^{-\frac{W_1}{2}} dW_2\, dW_1 + (1-A)\frac{2^{-\frac{n_1+n_2+n_3}{2}}}{\Gamma\left(\frac{n_1}{2}\right)\Gamma\left(\frac{n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}\sum_i\sum_j\sum_r (-1)^{i+j+r}$$

$$\cdot\binom{\frac{n_1}{2}-1}{i}\binom{\frac{n_2}{2}-1}{j}\frac{2^{r+1}\left(\frac{n_3}{2}-1+i+j\right)!}{\left(\frac{n_3}{2}-1+i+j-r\right)!} W_1^{\frac{n_1+n_3}{2}-2+j-r} W_2^{\frac{n_2}{2}+1-j} e^{-\frac{W_3}{2}} dW_2 dW_1\ ,$$

where

$$(4.10)\qquad A = Pr.\left\{\frac{n_1 s_1^2}{\sigma^2}\Big/\frac{n_3 s_3^2}{\sigma^2}>1\right\} = \int_{n_3/n_1}^{\infty} h_{n_1,n_3}\ (F)\ dF.$$

But the joint probability of (y_1, y_2) is shown by

$$(4.11)\quad f(y_1, y_2)dy_1dy_2 = (2\pi\sigma_1\sigma_2\sqrt{1-\rho^2})^{-1}\exp\Big[-\frac{1}{2(1-\rho^2)}$$

$$\cdot\left\{\frac{(y_1-\eta_1)^2}{\sigma_1^2}-\frac{2\rho(y_1-\eta_1)(y_2-\eta_2)}{\sigma_1\sigma_2}+\frac{(y_2-\eta_2)^2}{\sigma_2^2}\right\}\Big]\ dy_1\ dy_2\ ,$$

where

$$(4.12)\qquad \sigma_1=\sigma\sqrt{\frac{1}{N_1}+\frac{1}{N_2}}\ ,\quad \sigma_2=\sigma\sqrt{\frac{1}{N_2}+\frac{1}{N_3}}\ ,\ \eta_1=\mu_1-\mu_2,\ \eta_2=\mu_2-\mu_3,$$

$$\rho = -\left\{n_2\sqrt{\left(\frac{1}{N_1}+\frac{1}{N_2}\right)\left(\frac{1}{N_2}+\frac{1}{N_3}\right)}\right\}^{-1}.$$

Consequently, the joint probability of (W_1, W_2, y_1, y_2) is obtained by

$$(4.13)\qquad H(W_1, W_2)f(y_1, y_2)dW_1dW_2dy_1dy_2\ ,$$

and further let us transform (W_1, W_2, y_1, y_2) into (T_1, T_2) by

$$(4.14)\qquad T_1=y_1/\sqrt{W_1}\sigma_1,\ T_2=y_2/\sqrt{W_2}\sigma_2\ .$$

As a result, throughout the troublesome calculations, the first term of the power is expressed by the following function,

$$(4.15)\quad Pr.\{D_1\} = A\frac{\exp\left\{\frac{-1}{2(1-\rho^2)}\left(\frac{\eta_1^2}{\sigma_1^2}-2\rho\frac{\eta_1\eta_2}{\sigma_1\sigma_2}+\frac{\eta_2^2}{\sigma_2^2}\right)\right\}}{\pi\,\Gamma\left(\frac{n_1}{2}\right)\Gamma\left(\frac{n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}\sum_{i=0}^{\frac{n_1}{2}-1}\sum_{j=0}^{\frac{n_2}{2}-1}\sum_{r=0}^{\frac{n_3}{2}-1+i+j}(-1)^{i+j+r}$$

$$\cdot\binom{\frac{n_1}{2}-1}{i}\binom{\frac{n_2}{2}-1}{j}\binom{\frac{n_3}{2}-1+i+j}{r}r!\sum_{a=0}^{\infty}\sum_{b=0}^{\infty}\sum_{c=0}^{\infty}2^{\frac{a+b+2c}{2}}(1-\rho^2)^{\frac{n_1+n_2+n_3}{2}-\frac{a+b}{2}-r-\frac{1}{2}}$$

$$\cdot\frac{\left(\frac{\eta_1}{\sigma_1}-\rho\frac{\eta_2}{\sigma_2}\right)^a\left(\frac{\eta_2}{\sigma_2}-\rho\frac{\eta_1}{\sigma_1}\right)^b\rho^c}{a!\ b!\ c!}\left\{\Gamma\left(\frac{n_1}{2}-i-\frac{a+c+1}{2}\right)\Gamma\left(\frac{n_2+n_3}{2}+i-r+\frac{b+c-1}{2}\right)\right.$$

$$\cdot\iint_{D_1}\left(\frac{1}{T_2^2}\right)^{\frac{n_2+n_3}{2}+i-r-\frac{1}{2}}\left(\frac{1}{T_1^2}\right)^{\frac{n_1}{2}-i+\frac{1}{2}}\left(\frac{T_1^2}{(1-\rho^2)+T_1^2}\right)^{\frac{n_1}{2}-i+\frac{a+c+1}{2}}dT_1dT_2+\Gamma\left(\frac{n_1+n_3}{2}+j-r+\frac{a+c-1}{2}\right)$$

$$\left.\cdot\Gamma\left(\frac{n_2}{2}-j+\frac{b+c+1}{2}\right)\iint_{D_1}\left(\frac{1}{T_1^2}\right)^{\frac{n_1+n_3}{2}+j-r-\frac{1}{2}}\left(\frac{1}{T_2^2}\right)^{\frac{n_2}{2}-j+\frac{1}{2}}\left(\frac{T_2^2}{(1-\rho^2)+T_2^2}\right)^{\frac{n_2}{2}-j+\frac{b+c+1}{2}}dT_1dT_2\right\},$$

where D_1 shows the domain of (T_1, T_2) such that

$$(4.16)\qquad \frac{\sqrt{n_1n_2}}{n_1+n_2}t_{N_1+N_2-2}(\alpha_1)\leq T_1<\infty,\quad \frac{\sqrt{n_2n_3}}{n_2+n_3}t_{N_2+N_3-2}(\alpha_2)\leq T_2<\infty.$$

Similarly the second term of the power is obtained from the joint distribution of $(W_1\ W_3, y_1, y_3)$, that is,

$$(4.17)\qquad H(W_1, W_3)\,f(y_1, y_3)\,dW_1\,dW_3\,dy_1\,dy_3=\frac{2^{-\left(\frac{n_1+n_2+n_3}{2}+1\right)}}{\pi\sigma_1\sigma_3\Gamma\left(\frac{n_1+n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}(W_3-W_1)^{\frac{n_3}{2}-1}$$

$$\cdot W_1^{\frac{n_1+n_2}{2}-1}\exp\left[-\frac{1}{2}\left\{W_3+\frac{(y_1-\eta_1)^2}{\sigma_1^2}+\frac{(y_3-\eta_3)^2}{\sigma_3^2}\right\}\right]dW_1\,dW_3\,dy_1\,dy_3\ ,$$

where we put

$$(4.18)\qquad y_1=\bar{x}_1-\bar{x}_3,\quad y_3=\frac{N_1}{N_1+N_2}\bar{x}_1+\frac{N_2}{N_1+N_2}\bar{x}_2-\bar{x}_3\ ,$$

$$\sigma_1=\sqrt{\frac{1}{N_1}+\frac{1}{N_2}}\ \sigma,\quad \sigma_3=\sqrt{\frac{1}{N_2+N_3}+\frac{1}{N_1}}\ \sigma,\quad \rho_2\equiv\rho(y_1, y_3)=0,$$

$$\eta_1=\mu_1-\mu_2,\quad \eta_3=\frac{N_1}{N_1+N_2}\mu_1+\frac{N_2}{N_1+N_2}\mu_2-\mu_3\ .$$

Now let us transform (W_1, W_3, y_1, y_3) into the following (T_1, T_3)

$$(4.19)\qquad T_1=y_1/\sqrt{W_1}\sigma_1,\qquad T_3=y_3/\sqrt{W_3}\sigma_3\ ,$$

and then we obtain the following power function.

$$(4.20)\qquad Pr.\{D_2\}=\frac{2^{-\left(\frac{n_1+n_2+n_3}{2}+1\right)}}{\pi\Gamma\left(\frac{n_1+n_2}{2}\right)\Gamma\left(\frac{n_3}{2}\right)}\sum_{i=0}^{\frac{n_3}{2}-1}(-1)^i\iint_{D_2}W_1^{\frac{n_1+n_2-1}{2}+i}\ W_3^{\frac{n_3-1}{2}-i}$$

$$\cdot\exp\Big[-\frac{1}{2}\Big\{W_3+\Big(T_1W_1^{1/2}-\frac{\eta_1}{\sigma_1}\Big)^2+\Big(T_3W_3^{1/2}-\frac{\eta_3}{\sigma_3}\Big)^2\Big\}\Big]dT_1\,dT_3\,dW_1\,dW_3\ ,$$

where D_2 shows the interval

$$\text{(4.21)}\quad\begin{cases}0<T_1<\dfrac{\sqrt{n_1n_2}}{n_1+n_2}\,t_{N_1+N_2-2}\,(\alpha_1),\quad \dfrac{\sqrt{n_3(n_1+n_2)}}{n_1+n_2+n_3}\,t_{N_{12}+N_3-2}(\alpha_3)\leq T_3<\infty\ .\\ 0<W_1<\infty,\ 0<W_3<\infty.\end{cases}$$

The power defined by the formula (4.5) can now be written in terms of the right hand-sides of (4.15) and (4.20), and a paper of the author is being prepared which will give the numerical tables with various (η_1/σ_1), (η_2/σ_2) and N_1, N_2, N_3 using magnetic drum data-processing machine, where we may apply the Monte Carlo method with some considerations to the formula (4.5).

§ 5. Other test for percentages after preliminary test for percentages

In simultaneous trials, whether they may be measured by attributes or not, a method of double dichotomies may be considered as one of the most reasonable procedures. That is, our consideration in this section is summarized as follows.

Let P_S and P_T be the means of two binomial populations which denote the lethal (or effective) percentages of standard preparation and that of the test preparation respectively. Then a difference of the toxicity (or the effectiveness, etc.) between two preparations, S and T, may be obtained usually by P_T-P_S or by P_T/P_S. But the size itself of P_T-P_S or P_T/P_S to be used in comparing with two preparations is under the strong influence of actual sizes of the absolute values of percentages P_S and P_T, and it is much more so in practical situation where the observations obtained by a routine assay method may suffer from some block variations (days, places of a laboratory and so on). Consequently another function of P_S and P_T is better sought for to be used in our present formulation.

Now let (a_i, b_i) be a pair of results in i-th simultaneous trial $(i=1, 2, \cdots, N)$ and let us consider only the pairs $(0,1)$ and $(1,0)$, where a and b are the outcomes of the observations from the assay of standard preparation and test preparation and 1 and 0 denote a death and a survival of subject, respectively. Then the probability that $(a, b)=(1, 0)$ is equal to $P_S\cdot(1-P_T)$ and the probability that $(a, b)=(0,1)$ is equal to $P_T(1-P_S)$. Hence, knowing that (a, b) is equal to one of the pairs $(0,1)$ and $(1,0)$, the conditional probability that it is equal to $(0,1)$ is given by $P=(1-P_S)P_T/\{P_S(1-P_T)+P_T(1-P_S)\}$ and the conditional probability that it is equal to $(1,0)$ is $1-P=P_S(1-P_T)/\{P_S(1-P_T)+P_T(1-P_S)\}$. And in order to devise a proper test for testing the hypothesis that $P_T\geq P_S$, we shall state what risks of making wrong decisions we are willing to tolerate. The toxicity of test preparation may be measured by a ratio (the odds) $k_2=P_2/(1-P_2)$ of lethals to survivals and test preparation may be regarded the more toxic, the larger the value of k_2 becomes. The relative superiority of test preparation over standard preparation can reasonably be measured by a ratio of k_2 to $k_1(=P_1/(1-P_1))$, that is, $u=P_2(1-P_1)/P_1(1-P_2)$. If $u=1$, the toxicity of two preparations is equally and if $u>1$, test preparation is more toxic than another, and further, if $u<1$, standard preparation is more toxic than another.

Therefore this method may be considered immediately as a testing method concerning a difference between the means of two binomial distributions without a condition of normal approximation, Wald [1].

Now let us consider three binomial distributions and let P_i $(i=1, 2, 3)$ be an unknown parameter showing the probability of a success (death, effectiveness, etc) in a single trial of the i-th binomial population. Our problem is to test the hypothesis $P_2=P_3$ finally on the basis of the odds-ratio u defined by the observations of the same number N on each population, Now our rule for the procedure is formulated as follows.

(i) *Let v_1 and v_2 be defined by*

$$(5.1)\qquad \begin{cases} v_1=1/2, \\ v_2=u_2/(1+u_2)=P_2(1-P_1)/\{P_2(1-P_1)+P_1(1-P_2)\}. \end{cases}$$

(ii) *Let l be a number of the favourable pairs between $S_{(1)}$ and $S_{(2)}$ in each sequence of N and let m be a number of pairs that show us the effectiveness of $S_{(2)}$ against $S_{(1)}$ in l pairs. Then the number m is compared with a number k_1 (or k_2), where k_1 (or k_2) satisfies the following relation:*

$$(5.2)\qquad \sum_{i=k_1}^{l}\binom{l}{i}\left(\frac{1}{2}\right)^l \leq\alpha_1, \text{ for the alternative hypothesis } P_2>P_1,$$

or

$$\sum_{i=0}^{k_2}\binom{l}{i}\left(\frac{1}{2}\right)^l \leq\alpha_1, \text{ for the alternative hypothesis } P_2<P_1.$$

(iii) *Now let us introduce a test for T_2 defined in the following manner.*

(a) *If $m\geq k_1$ (or $m\leq k_2$), we define v_1' and v_2' by*

$$(5.3)\qquad \begin{cases} v_1'=1/2 \\ v_2'=P_3(1-P_2)/\{P_3(1-P_2)+P_2(1-P_3)\}, \end{cases}$$

and the following test procedure is carried out finally.

Let l' be a number of the favourable pairs betewen $S_{(2)}$ and T_2 in each sequence of N and let m' be a number of pairs that show us the effectiveness of T_2 against $S_{(2)}$ in l' pairs. Then the number m' is compared with *a number k_1' (or k_2'), where k_1' (or k_2') satisfies the following relation.*

(5.4)
$$\sum_{i=k_1'}^{l'} \binom{l'}{i}\left(\frac{1}{2}\right)^{l'} \leq \alpha_2, \quad \textit{for the alternative hypothesis } P_3 > P_2,$$

or

$$\sum_{i=0}^{k_2'} \binom{l'}{i}\left(\frac{1}{2}\right)^{l'} \leq \alpha_2, \quad \textit{for the alternative hypothesis } P_3 < P_2.$$

(b) *If $m < k_1$ (or $m > k_2$), we define v_1'' and v_2'' by*

(5.5)
$$\begin{cases} v_1'' = 1/2, \\ v_2'' = \{P_3(1-P_1)+P_3(1-P_2)\} / \{P_1(1-P_3)+P_2(1-P_3)+P_3(1-P_1) \\ \qquad +P_3(1-P_2)\}, \end{cases}$$

and the following test procedure is carried out finally.

Let l'' be $l'+l_1$ and let m'' be $m'+m_1$, where l' and m' are defined by (a) *and let l_1 be defined by a number of the favourable pairs between T_2 and $S_{(1)}$ in each sequence of N, and let m_1 be a number of pairs that show us the effectiveness of T_2 against S in l_1 pairs. Then the number m'' is compared with a number k_1'' (or k_2'') where k_1'' (or k_2'') satisfies the following relation.*

(5.6)
$$\sum_{i=k_1''}^{l''} \binom{l''}{i}\left(\frac{1}{2}\right)^{l''} \leq \alpha_3, \quad (P_3 > P_2)$$

or

$$\sum_{i=0}^{k_2''} \binom{l''}{i}\left(\frac{1}{2}\right)^{l''} \leq \alpha_3, \quad (P_3 < P_2).$$

Now we assume under the consideration of numerical calculation that a correlation of $\{P_1(1-P_3)+P_3(1-P_1)\}$ and $\{P_3(1-P_2)+P_2(1-P_3)\}$may and now shall be neglected on the basis of the fact that this correlation is approximately given by $P_2(1-P_2)/N$ for moderate large value of N, e.g., it becomes 0.0125 in case that $N=20$ and $P_2=0.5$, and 0.0045 in case that $N=20$ and $P_2=0.9$.

Then the power according to our test procedure is shown as follows approximately:

(5.7)
$$\sum_{i=k_1}^{l} \binom{l}{i} v_2^i(1-v_2)^{l-i} \sum_{j=k_1'}^{l'} \binom{l'}{j} v_2'^j (1-v_2')^{l'-j}$$
$$+\sum_{i=0}^{k_1-1} \binom{l}{i} v_2^i(1-v_2)^{l-i} \sum_{j=k_1''}^{l''} \binom{l''}{j} v_2''^j (1-v_2'')^{l''-j}.$$

Now in case of testing a lethal ratio for test preparation, where the hypothesis that $P_3=P_2$ is tested against an alternative hypothesis that $P_3>P_2$ and our successive procedure of this test is defined by using k_2 first and then by using k_1' or k_1'' secondly, the behaviour of the size of the power and the power gain are given in Fig. 5 ($\alpha_1=\alpha_2=\alpha_3=0.05$) and in Fig. 6 ($\alpha_1=0.20$, $\alpha_2=\alpha_3=0.05$), for $N=20$ and for each (P_1, P_2, P_3) of all the combinations of 30%, 50% and 70%.

In these figures, we note that each number of the favourable pairs depends on a combination of each value of (P_1, P_2, P_3) and the nominal level of 0.05 is not given on the basis of each percentagetest, but is defined on the basis of odds ratio test. From a general view of these figures, we may obtain some resonable explanations as in § 3. That is to say, we may prefer to take about 20% as α_1 with an intension of size control and from the view-point of the power gain. Here we need to introduce some assumptions in regard to a distance between P_1 and P_3.

(B1)

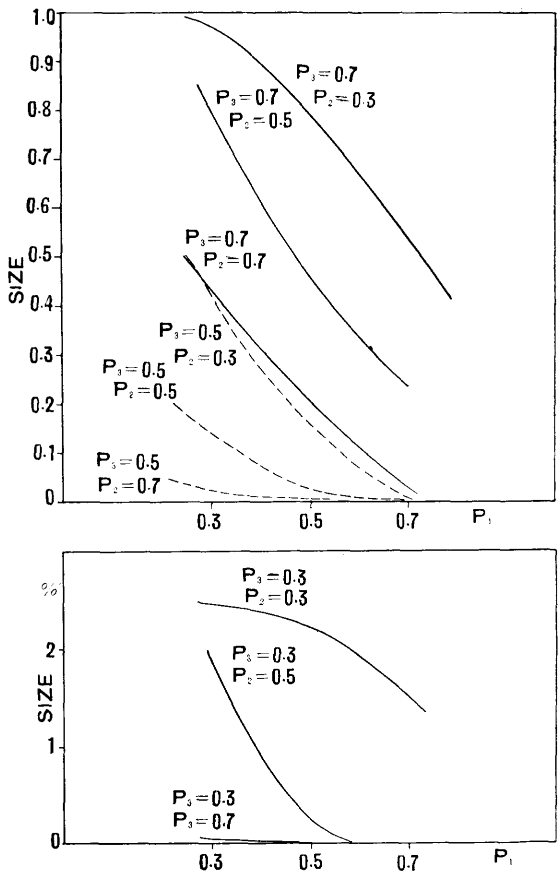

Fig. 5. (a) Size curves for $N=20$, $\alpha_1=\alpha_2=\alpha_3=0.05$

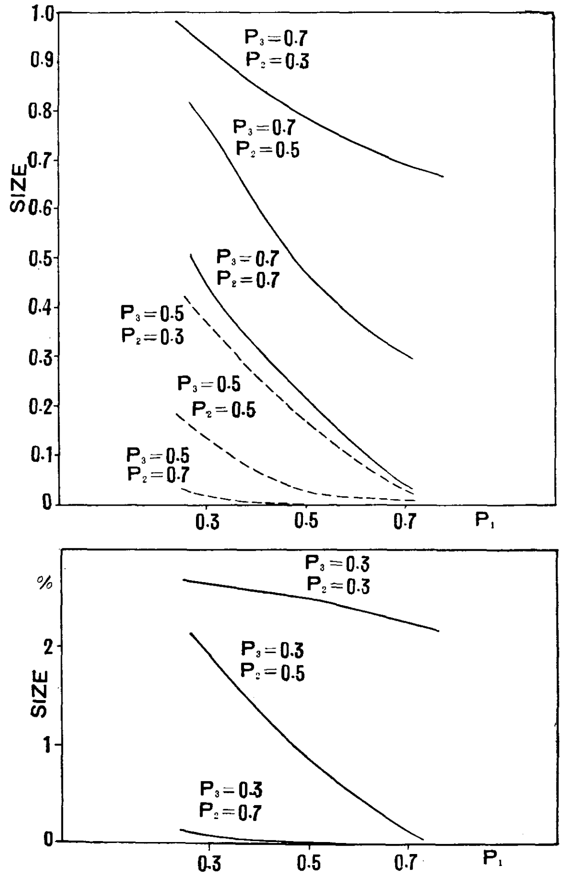

Fig. 6. (a) Size curves for $N=20$, $\alpha_1=0.20$, $\alpha_2=\alpha_3=0.05$

(B$_2$)

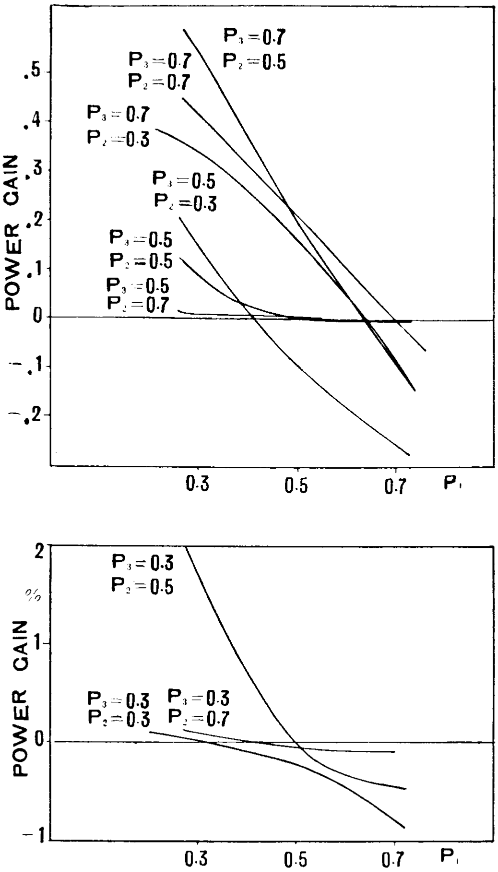

Fig. 5. (b) Power gainfor $N=20$, $\alpha_1=\alpha_2=\alpha_3=0.05$

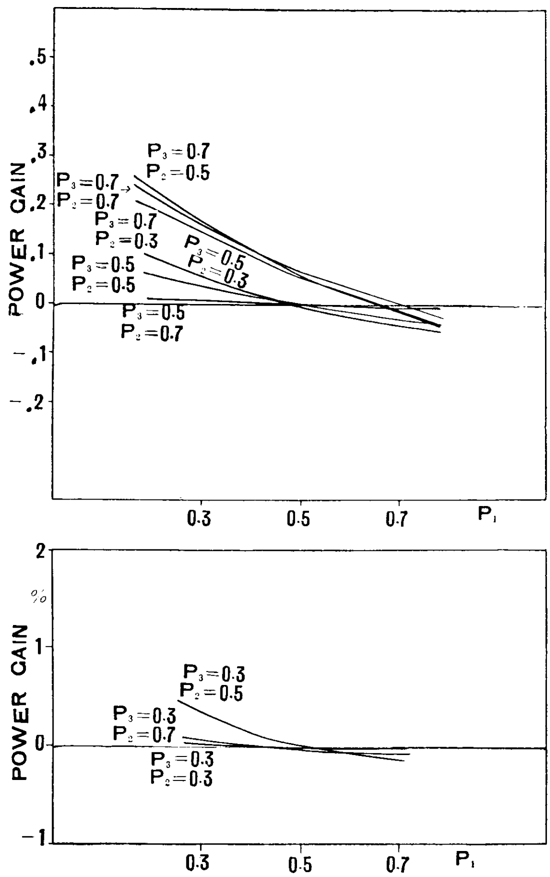

Fig. 6. (b) Power gain for $N=20$, $\alpha_1=0.20$, $\alpha_2=\alpha_3=0.05$

In conclusion, if we can assume a situation $P_3>P_1$, we may propose to take our sometimes pooling procedure taking 20% as α_1, and otherwise if we can assume a situation $P_3<P_1$, a never-pool test should be recommended to be used, and when we have nothing to assume, we may propose a borderline test.

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