SEQUENTIAL TWO SAMPLE PROBLEM IN REGRESSION (I)

Hajime Takahashi

1. INTRODUCTION

Suppose we are in a position to compare the effects of drugs A and B using patients. Let \( y_{11}, y_{12}, \ldots, y_{1m}, \ldots \) and \( y_{21}, y_{22}, \ldots, y_{2n}, \ldots \) be independent and normally distributed random variables with means \( E_{y_{1n}} = \alpha_1, E_{y_{2n}} = \alpha_2 \) (\( m, n = 1, 2, \ldots \)) and unit variance. We suppose that \( y_{1m} \) and \( y_{2n} \) represent the responses of drugs A and B, respectively. The statistical problem involving comparison of these drugs can be stated in terms of the composite hypothesis testing problem of testing \( H_0 : \alpha_1 < \alpha_2 \) against \( H_1 : \alpha_1 > \alpha_2 \). Now the usual method which seems suitable for this problem is the following: Let \( m = n \) be fixed and let us assume pairwise sampling so that we can make a sequence of new random variables \( z_i = y_{1i} - y_{2i} (i = 1, \ldots, n) \) which are independent and normally distributed with mean \( \delta = \alpha_1 - \alpha_2 \) and variance 2. Thus, after having collected the responses of 2n patients, we can calculate \( Z_n = z_1 + \ldots + z_n \) and say \( H_0 \) is true if and only if \( Z_n < 0 \), while \( H_1 \) is true if and only if \( Z_n > 0 \). This kind of test is completely good for many purposes such as scientific experimentations. But, in the case of medical trials where patients are being treated, the situation is completely different.

Let us assume the following medical experiment: patients come into a trial one by one where they are administered a drug to which we can collect their responses before the next patient enters. Then, if the absolute value of \( \delta \) is large, we may be able to tell which drug
is better before stage \( n \). Now, the problem here is whether we are supposed to continue the experiments even after having reached the conviction that drug A, for instance, is superior. Clearly we are not allowed to administer the inferior drug to the patients. But, as long as we are using the "fixed-sample" method, we have to wait until the \( 2n \) th patient is examined. Hence, there is a reason why the sequential method is superior here.

The other important problem we have to consider is the following aspect of the experiment: although the sequential method reduces the average total number of patients needed for the test, we still want to reduce the average number of patients who are administered the inferior drug. To do this first we drop the assumption that we take pair-wise sampling and, whenever a new patient comes into the trial, we decide which drug he or she is assigned based on the experiment already made. Because of this aspect of the problem, the whole analysis becomes far more difficult. Actually it brings a new problem, that is, an allocation problem, into the statistical analysis.

The answer to this problem was given first by Robbins (1952), followed by Robbins (1956), Zelen (1969) and Sobel and Weiss (1970). They use the technique called the "play the winner" rule. Later, new light was shed by Flehinger and Louis (1972), Flehinger, Louis, Robbins and Singer (1972), Robbins and Siegmund (1974) and Louis (1975), where the property of the invariant sequential test is utilized and also several allocation rules are proposed. In this paper, we will consider the two sample problem in regression utilizing the idea by Robbins and Siegmund (1974) and Louis (1975).
2. ERROR PROBABILITY AND EXPECTED SAMPLE SIZE

Let

\[ y_{1j} = \alpha_1 + \beta x_{1j} + \varepsilon_{1j}, \quad j = 1, 2, \ldots, n_1, \ldots \]
\[ y_{2j} = \alpha_2 + \beta x_{2j} + \varepsilon_{2j}, \quad j = 1, 2, \ldots, n_2, \ldots \]

where \( \varepsilon_{ij} \)'s are i.i.d. with normal mean 0 and unit variance and \( \alpha_i, \)
\( i = 1, 2 \) and \( \beta \) are unknown constants. \( x_{ij} \)'s are known and independent
of \( \varepsilon_{ij} \)'s. Now we will consider a composite hypothesis, \( H_0 : \alpha_1 < \alpha_2 \)
against \( H_1 : \alpha_1 > \alpha_2 \). Let \( \delta = \alpha_1 - \alpha_2, \quad \theta = \alpha_1 + \alpha_2 \), then the above hypothesis
is equivalent to

\[ (2-2) \quad H_0 : \delta < 0 \quad \text{vs.} \quad H_1 : \delta > 0 \]

Following Wald (1947), it suffices to consider

\[ (2-2') \quad H_{0}^* : \delta = -\delta^* \quad \text{vs.} \quad H_{1}^* : \delta = \delta^* \]

where \( \delta^* \) is some preassigned positive constant.

Since the problem is invariant with respect to the values of \( \theta \) and
\( \beta \), after having observed \( (y_{11}, x_{11}), \ldots, (y_{1n_1}, x_{1n_1}), (y_{21}, x_{21}), \ldots, (y_{2n_2}, \)
\( x_{2n_2} ) \) we put

\[ u_{1j} = y_{1j} - y_{2j} - \left( \frac{x_{1j} - x_{2j}}{x_{2j} - x_{21}} \right) (y_{2j} - y_{21}), \quad j = 1, 2, \ldots, n_1 \]
\[ u_{2j} = y_{2j} - y_{21} - \left( \frac{x_{2j} - x_{21}}{x_{22} - x_{21}} \right) (y_{22} - y_{21}), \quad j = 3, 4, \ldots, n_2 \]

\[ (2-3) \quad u_{11} = y_{11}, \quad u_{22} = y_{22} \]

Then \( E\{ u_{1j} \} = \delta \) for all \( j = 1, 2, \ldots, n_1, E\{ u_{2j} \} = 0 \) for all \( j = 3, 4, \ldots, n_2 \) and the
likelihood ratio for \( u_{11}, \ldots, u_{1n_1}, u_{23}, \ldots, u_{2n_2} \) under \( H_{0}^* \) and \( H_{1}^* \) is

\[ (2-4) \quad L_{n_1, n_2}^{(\delta^*)}(u_{11}, \ldots, u_{1n_1}, u_{23}, \ldots, u_{2n_2}) \]

\[ = \exp \{ 2\delta^* \left[ n_1 n_2 \left( \frac{n_1 + n_2}{n_1 n_2} \right) \right] \left[ y_{1} - y_{2} - b_{1} v_{2} (x_{1} - \bar{x}_{2}) \right] \} \]

where

\[ \bar{x}_{i} = \sum_{j=1}^{n_i} x_{ij}/n_i, \quad \bar{y}_{i} = \sum_{j=1}^{n_i} y_{ij}/n_i, \quad i = 1, 2 \]
SEQUENTIAL TWO SAMPLE PROBLEM IN REGRESSION (I)

\[ \bar{x} = \frac{\sum_{i=1}^{2} \sum_{j=1}^{n_i} x_{ij}}{(n_1 + n_2)} \]

\[ b_{n_1, n_2} = \frac{\sum_{i=1}^{2} \sum_{j=1}^{n_i} y_{ij} (x_{ij} - \bar{x})^2}{\sum_{i=1}^{2} \sum_{j=1}^{n_i} (x_{ij} - \bar{x})^2} \]

Let us write

\[ Z_{n_1, n_2} = \frac{n_1 n_2}{(n_1 + n_2)} \left( \bar{y}_1 - \bar{y}_2 - b_{n_1, n_2} (\bar{x}_1 - \bar{x}_2) \right) \]

Now the problems we are going to discuss in this paper are (i) the allocation rule, (ii) the termination problem, and (iii) the decision problem. Among them (ii) and (iii) are less difficult to handle and will be discussed in this section. But before we get into these, we shall state a basic assumption for the allocation rules in general.

**Assumption A.** If after having observed \((y_{1i}, x_{1i}), \ldots, (y_{n_1, x_{n_1}})\) and \((y_{2i}, x_{2i}), \ldots, (y_{2n_2}, x_{2n_2})\), we decide to continue sampling, then the allocation rule which tells us which drug is assigned to the next patient is measurable with respect to the sigma-field generated by \(u_{ij}\)'s, i.e.,

\[ F_{n_1, n_2} = \sigma(u_{ij}, j=1, \ldots, n_i, i=1, 2) \]

We call an allocation rule measurable if it satisfies Assumption A. Let \(a\) be a given positive constant and let us define a 2-dimensional stopping time

\[ [N_1, N_2] = \text{first} (n_1, n_2) \text{ such that } |Z_{n_1, n_2}| \geq a \]

and say

\begin{align*}
&\text{reject } H_0^* \quad \text{iff } Z_{n_1, n_2} \geq a \\
&\text{reject } H_1^* \quad \text{iff } Z_{n_1, n_2} \leq -a
\end{align*}

For the termination rule and decision rule above, we have the following basic result which is valid for all measurable allocation rules.

\[ P_*(\text{reject } H_1^*) = \sum_{F_{n_1, n_2}} dP_* \]
\[ \sum' \int_{E_{n_1 n_2}} \frac{dP_{(n_1, n_2)}}{dP_{-\delta \cdot \{ \text{reject } H_1^* \}}} \leq e^{-2\alpha \delta^*} \sum' \int_{E_{n_1 n_2}} dP_{-\delta^*} \]

\[ \leq e^{-2\alpha \delta^*} \sum' P_{-\delta^*} \{ \text{reject } H_1^* \} = e^{-2\alpha \delta^*} [1 - P_{\delta^*} \{ \text{reject } H_1^* \}] \]

where

\[ E_{n_1 n_2} = \{ (N_1, N_2) = (n_1, n_2), Z_{n_1 n_2} \leq -a \} \]

and the summation \( \sum' \) is over all the pairs \((n_1, n_2)\), \(n_1, n_2 = 1, 2, \ldots, \)

\( P_{\pm \delta^*} \) denotes the restriction of \( P_{\pm \delta} \) to the sigma-field \( F_{n_1 n_2} \).

Hence, we have in general for any \( \delta > 0 \)

\[ (2-11) \quad P_{\delta} \{ \text{error} \} \leq (1 + e^{2\alpha \delta^*})^{-1} \]

Now for all \( \delta > 0 \)

\[ (2-12) \quad E[Z_{n_1 n_2} | \delta, x_{ij}, j = 1, \ldots, n_i, i = 1, 2] = \frac{n_1 n_2}{n_1 + n_2} C_{n_1 n_2} \delta \]

and

\[ (2-13) \quad \text{Var}[Z_{n_1 n_2} | \delta, x_{ij}, j = 1, \ldots, n_i, i = 1, 2] = \frac{n_1 n_2}{n_1 + n_2} C_{n_1 n_2} \]

where

\[ (2-14) \quad C_{n_1 n_2} = \frac{\sum_{i=1}^{2} \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i)^2}{\sum_{i=1}^{2} \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i)^2} \]

In order to discuss expected sample size we need

\[ \text{Lemma 2-1} \quad \text{For given } x_{ij}'s \text{ and } \delta \text{ the 2-dimensional stochastic sequence} \]

\[ (2-15) \quad \{ Z_{n_1 n_2} - \frac{n_1 n_2}{n_1 + n_2} C_{n_1 n_2} \delta, F_{n_1 n_2}, n_1, n_2 \geq 1, \max(n_1, n_2) \geq 3 \} \]

is a 2-dimensional martingale.

Proof of Lemma 2-1 will be given in part II of this paper.

Hence, if we apply a measurable allocation rule, (2-15) becomes a 1-dimensional martingale. By Doob's (1953) martingale system theorem for all \( \delta > 0 \) and given \( x_{ij}'s \), we thus have

\[ (2-16) \quad E_{\delta}(Z_{n_1 n_2} - \frac{N_1 N_2}{N_1 + N_2} C_{n_1 n_2} \delta) = 0 \]
under some regularity conditions on \((N_1, N_2)\) and the allocation rule. Therefore,

\[
E_\delta\left( \frac{N_1N_2}{N_1+N_2} C_{N_1N_2} \right) = \frac{1}{\delta} E\left[ Z_{N_1N_2} \right] = \frac{a}{\delta} \left( \frac{\epsilon^{2\delta a} - 1}{\epsilon^{2\delta a} + 1} \right)
\]

Since \(C_{N_1N_2} \leq 1\) a.s. we have

\[
\text{Lemma 2-2. For all } \delta,
\]

\[
E_\delta\left( \frac{N_1N_2}{N_1+N_2} \right) \geq \frac{a}{|\delta|} \left( \frac{\epsilon^{2\delta a} - 1}{\epsilon^{2\delta a} + 1} \right)
\]

where \(\geq\) means approximate inequality disregarding the overshoot.

3. ALLOCATION RULES

In order to find an optimal (in some sense) allocation rule, let us first assume \(\beta = 0\). Because the main difference between the simple two sample problem and the regression case is, as is clear from the previous section, the "norming factor" \(C_{N_1N_2}\) which is always less than or equal to 1. Let us consider the role of \(C_{N_1N_2}\) a little further. Since

\[
C_{N_1N_2} = \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} (x_{ij} - \bar{x}_i)^2 / \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} (x_{ij} - \bar{x}_i)^2
\]

it is a test statistic for detecting the difference of means \(Ex_{1j}\) and \(Ex_{2j}\).

Thus, if all \(x\)'s come from the same population, the value of \(C_{N_1N_2}\) must be very close to 1.

Hence, without loss of generality, we may assume that \(\delta = 0\).

Following Robbins and Siegmund (1974), let

\[
u_{1j} = y_{1j} - y_{21}, \quad j = 1, 2, \ldots, n_1, \ldots
\]

\[
u_{2j} = y_{2j} - y_{21}, \quad j = 2, 3, \ldots, n_2, \ldots
\]

Then the likelihood ratio under \(H_0^*\) and \(H_1^*\) defined by (2-2') becomes

\[
L_{N_1N_2} = \exp \left( 2\delta^* \left( \frac{n_1n_2}{n_1+n_2} \right) (y_1 - y_2) \right)
\]
where \( \bar{y}_i \) are defined by (2-5).

Putting

\[
Z_{n_1 n_2} = \frac{n_1 n_2}{n_1 + n_2} (\bar{y}_1 - \bar{y}_2)
\]

\[
F_{n_1 n_2} = \sigma (u_{11}, \ldots, u_{1n_1}, u_{21}, \ldots, u_{2n_2})
\]

we will define stopping time \((N_1, N_2)\) as in (2-8).

Now we state a basic lemma due to Robbins and Siegmund (1974).

**Lemma 3-1.** Let \( W(t) \) be a Brownian motion process with drift \( \delta \) and variance 1 per unit time such that \( W(0) = 0 \). Then, for any sequence of pairs \((n_1, n_2)\) of positive integers which is non-decreasing in each coordinate, the random sequences \( \{Z_{n_1 n_2}\} \) and \( \{W \left( \frac{n_1 n_2}{n_1 + n_2} \right) \} \) have the same joint distribution.

Since the behavior of \( Z_{n_1 n_2} \) is characterized only by \( n_1 n_2/(n_1 + n_2) \) and \( \delta \), the stopping rule does not depend on the allocation rule. This fact suggests to us the following: we observe Brownian motion \( W(t) \) up to the stage \( t = t_0 \) (say), and then we find \( n_1^*(t_0) \) and \( n_2^*(t_0) \) which minimize the risk we are going to specify.

Let us introduce the following loss structure. For given positive numbers \( \gamma_1 \) and \( \gamma_2 \), we define a risk function

\[
R_i = \gamma_1 \times \text{[expected number allocated to the inferior population]} + \gamma_2 \times \text{[average total sample number]}
\]

Assume that \( \delta \) has a priori distribution,

\[
P \{ \delta = \delta^* \} = \frac{1}{2} = P \{ \delta = -\delta^* \}.
\]

34
Then,

\[ \pi = \pi_{n_1 n_2} = P(\delta = \delta^* | F_{n_1 n_2}) = \frac{L_{n_1 n_2}}{1 + L_{n_1 n_2}} \]

At the stage \((n_1, n_2)\) such that \(n_1 n_2 / (n_1 + n_2) = t_0\) for a given \(t_0\) the risk minimizing pair \((n_1^*(t_0), n_2^*(t_0))\) at \(t_0\) is defined to be the one which minimizes

\[ R_{n_1 n_2} = \pi_{n_1 n_2} \{ \gamma_1 n_2 + \gamma_2 (n_1 + n_2) \} + (1 - \pi_{n_1 n_2}) \{ \gamma_1 n_1 + \gamma_2 (n_1 + n_2) \} \]

among all pairs \((n_1, n_2)\) such that \(n_1 n_2 / (n_1 + n_2) = t_0\). By solving this minimization problem we have

\[ n_1^*(t_0) = \left\lfloor \sqrt{\frac{\pi \gamma_1 + \gamma_2}{(1 - \pi) \gamma_1 + \gamma_2} + 1} \right\rfloor t_0 \]

\[ n_2^*(t_0) = \left\lfloor \sqrt{\frac{(1 - \pi) \gamma_1 + \gamma_2}{\pi \gamma_1 + \gamma_2} + 1} \right\rfloor t_0 \]

Now, after having observed \(y_i, \ldots, y_{i+n_1}, y_{n_1+1}, \ldots, y_{2n_2}\), we have observed

\[ \{ W(s), s = k_1 k_2/(k_1 + k_2), k_1 \leq n_1, \ k_2 \leq n_2 \} \]

If \(|Z_{n_1 n_2}| < a\), we would take the next sample. Here, it is reasonable to take \(y_1, n_1 + 1\) next if \(n_2^*(t_0) < n_2\). Thus, we have an

**Allocation Rule.** Take \(y_1, n_1 + 1\) next if and only if

\[ |Z_{n_1 n_2}| < a \text{ and } n_2^*(t_0) \leq n_2 \]

Since \(n_1 n_2 / (n_1 + n_2) = n_1^*(t_0) n_2^*(t_0) / (n_1^*(t_0) + n_2^*(t_0))\), the second inequality in (3-10) is equivalent to

\[ \frac{n_1}{n_1 + n_2} \leq \frac{n_1^*(t_0)}{n_1^*(t_0) + n_2^*(t_0)} \]

Let us present several examples.

**Example 1.** A trivial one is to put \(\gamma_1 = 0, \ \gamma_2 = 1\). Then, it is clear from (3-9) and (3-11) that we have an alternating sampling rule.
Example 2. Let, for some $r>1$, $r_1=r-1$ and $r_2=1$. Then
\begin{align}
n_1(t_0) &= \left(\sqrt{rL_{n_1n_2} + 1} + \sqrt{r + L_{n_1n_2}}\right) t_0 \\
n_2(t_0) &= \left(\sqrt{r + L_{n_1n_2}} + \sqrt{rL_{n_1n_2} + 1}\right) t_0
\end{align}
Thus,
\begin{align}
n_1^*(t_0) &= \left(\sqrt{rL_{n_1n_2} + 1} + \sqrt{r + L_{n_1n_2}}\right) t_0 \\
n_2^*(t_0) &= \left(\sqrt{r + L_{n_1n_2}} + \sqrt{rL_{n_1n_2} + 1}\right) t_0
\end{align}

Example 3. Let $r_1=1$, $r_2=0$. Then
\begin{align}
n_1^*(t_0) &= \left(\sqrt{L_{n_1n_2}} + 1\right) t_0 \\
n_2^*(t_0) &= \left(\sqrt{L_{n_1n_2}} + 1\right) t_0
\end{align}
\begin{align}
n_1^*(t_0) &= \left(\sqrt{L_{n_1n_2}} + 1\right) t_0 \\
n_2^*(t_0) &= \left(\sqrt{L_{n_1n_2}} + 1\right) t_0
\end{align}

Hence, take $y_1, n_1+1$ if
\begin{align}
n_1^2/n_2^2 \leq L_{n_1n_2} = \exp\left(2\delta Z_{n_1n_2}\right)
\end{align}

The argument here is essentially the same as Louis (1975). From now on we are going to use the allocation rule given by (3-15). We now present the following theorem.

Theorem 3-1. Let $\delta>0$ be arbitrary. If the allocation rule (3-15) is applied, then
\begin{align}
E_{\delta}(N_2) &\sim \frac{a}{\delta} (1 + e^{-a\delta^*}) \sim \frac{a}{\delta} \\
as \delta \to \infty.
\end{align}
\begin{align}
E_{\delta}(N_1) &\sim \frac{a}{\delta} (1 + e^{a\delta^*})
\end{align}

The rigorous proof will be given in part II of this paper. But, heuristically, it can be derived easily from (3-14). Assume $\delta>0$ and let $a \to \infty$. Since $N_1N_2/(N_1+N_2) \sim \frac{a}{\delta}$ and $L_{n_1n_2} \sim e^{-2a\delta^*}$, (3-16) and (3-17)
follow from (3-14).

Now, going back to the regression case, let us use the sampling rule analogous to (3-15). First rewrite $n_1^2/n_2^2$ as follows:

\[
(3-18) \quad \frac{n_1^2}{n_2^2} = \left( \frac{n_1^2}{(n_1 + n_2 + 1)(n_1 + n_2)} \right) \left( \frac{n_2^2}{(n_1 + n_2 + 1)(n_1 + n_2)} \right) 
\]

\[
= \frac{n_1(n_2 + 1)}{(n_1 + n_2 + 1)n_2} - \frac{n_1n_2}{(n_1 + n_2)} 
\]

Thus, in the regression case the allocation rule (3-15) can be stated as follows: after having observed $(y_{11}, x_{11}), \ldots, (y_{1n_1}, x_{1n_1}), (y_{21}, x_{21}), \ldots, (y_{2n_2}, x_{2n_2})$ and $x$ which can be either $x_{1,n_1+1}$ or $x_{2,n_2+1}$ and if we decide to keep sampling, take the $(y_{1,n_1+1}, x_{1,n_1+1})$ pair next if and only if

\[
(3-19) \quad \frac{n_1(n_2 + 1)}{(n_1 + n_2 + 1)n_2} \left( \frac{C_{n_1n_2+1}^{n_1n_2}}{n_1 + n_2} - \frac{C_{n_1n_2}^{n_1n_2}}{n_1 + n_2} \right) \leq \exp \left\{ \frac{2e - Z_{n_1n_2}^*}{Z_{n_1n_2}^*} \right\} 
\]

where $Z_{n_1n_2}^*$ and $C_{n_1n_2}^*$ are defined in (2-6) and (2-14) respectively. Simulated results of the allocation rules (3-15) and (3-19) together with (3-16) and (3-17) are shown in Table I below.

4. SIMULATION RESULTS AND REMARKS

The following table gives 1000 run Monte Carlo approximations to $E(N_{i,j}^*)$, where $j$ denotes the number of concomitant variables and $i$ tells the populations, together with the numerical approximations from asymptotic results given in Theorem 3-1 of the previous section.
Table I.

<table>
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<tr>
<th>( \delta )</th>
<th>((3-17))</th>
<th>(E(N_1^{(0)}))</th>
<th>(E(N_1^{(1)}))</th>
<th>((3-16))</th>
<th>(E(N_2^{(0)}))</th>
<th>(E(N_2^{(1)}))</th>
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<td>88.02</td>
<td>—</td>
<td>86.05</td>
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<tr>
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</table>

Here the sampling rules \((3-15)\) and \((3-19)\) are used for simple and regression cases respectively. Also we set \(\delta^* = .25\) and \(a = 6\) to get the error probability \(.05\) when \(\delta = .25\).

In part II of this paper the case where more than one independent variables come into the model will be discussed. And the applications to some economic model together with the proofs of Lemma 2-1 and Theorem 3-1 will be given.

References


Hajime Takahashi
Columbia University and
Hitotsubashi University
D. C. 3.