BU-1456-M

MINIMAL TREATMENT DESIGNS FOR ESTIMATING VARIOUS MIXING ABILITY EFFECTS

by

Walter T. Federerer

ABSTRACT

The set of all possible combinations of m items taken n at a time, i. e., m!/n!(m - n)!, is denoted as a *combinatorial.* This paper introduces the idea of a *fractional combinatorial,* which is a subset of the combinatorial selected to meet a given criterion such as minimal, optimal, balanced, etc. Combinations or mixtures of items such as cultivars, drugs, programs, nutrients, etc., are used universally in one form or another. A mixture will have a variety of effects present. In factorials, main effects and interactions are present. In combinatorials, such effects have been denoted as item effect, general mixing ability, and k-factor specific mixing ability. In the same manner as was done for fractional factorials, the experimenter often believes that k-factor mixing effects beyond a certain value of k may not exist or may be negligible. In such cases, it is desirable to have a fractional rather than a complete combinatorial. Minimal fractional combinatorials for item means, for item means plus bi-specific mixing effects, and for item means plus bi-specific mixing effects plus tri-specific mixing effects form the subject of this presentation.

Key words: Combinatorial, fractional combinatorial, mixture, mixing ability, moxing effects, top-mix.

BU-1456-M in the Technical Report Series of the Department of Biometrics, Cornell University, Ithaca, New York 14853.
September 1999.

MINIMAL TREATMENT DESIGNS FOR ESTIMATING VARIOUS MIXING ABILITY EFFECTS

1. INTRODUCTION

Minimal treatment designs (MTDs) for mixtures of n of m items have been discussed by Hall (1976), Federer and Ragahavarao (1987), and Federer (1991, Chapter 5; 1993, Chapters 6 and 7; 1998, Chapters 15 and 16). The first two references considered minimal designs for estimating general mixing ability (GMA) and specific mixing ability (SMA) for a mixture of size n of m items where n is the value of the highest order interaction or specific mixing ability effect. Other related discussion appears in Smith *et al.* (1975) and Federer *et al.* (1976). As described in the above references, a GMA effect is the effect of an item averaged over the other m - 1 items, a bi-specific mixing effect (BSMA) is the interaction effect of a pair of items, a tri-specific mixing effect (TSMA) is the interaction effect of a triplet of items, and so forth up to the kth-specific mixing effect (KSMA). When k = n is the highest specific mixing effect considered, the minimal design is all of the combinations of m items taken n at a time. The construction of MTDs when k < n is discussed to a limited extent in Federer (1998). This discussion is extended in the present paper.

Mixtures of iems is a universal phenomenon in all areas. Some examples of mixtures that have a benefical or a detrimental effect are listed below.

1. Marigold plants are grown intermingled with tomato plants and soybean plants are intermingled with cowpeas for protection from insect damage and betel plants are grown with pepper plants to protect them from a virus.
2. To improve the outcomes of heart failure in treating chronic heart failure, four treatments are used, that is, digitalis for heart stimulation, a diuretic to reduce excess fluid, ACE inhibitors to relax the blood vessels, and beta blockers to block the stress hormone adrenaline and reduce the heart workload.
3. The combination of Tagamet HB for heartburn and Coumadin for blood clotting can interact to cause both internal and external bleeding.

4. Aspirin can cancel the effect of Vasotec to control high blood pressure.
5. Moderate to heavy alcohol users should not take Extra Strength Tylenol as liver failure often results.
6. Several drugs are used to form the "cocktail" treatment for AIDS.

Denote all possible combinations as a *combinatorial*.. Then a subset of the combinatorial will be called a *fractional combinatorial*, in the manner used for factorials and fractional factorials. A MTD is the minimum number of mixtures required to obtain solutions for the order of effects specified, resulting in a saturated design whenever possible. A scientific challenge here is to develop theory for fractional combinatorials to the extent that it has been done for fractional factorials. Fractional combinatorials (FCs) will be used when the it is desired to estimate GMA, BSMA, and up to KSMA for $k < n$, the mixture size. For example, an investigator might be interested in GMA and BSMA effects and wishes to use a minimal design for mixtures of size $n = 3$. The question is which $m(m - 1)/3$ combinations out of the $m(m - 1)(m - 2)/6$ mixtures of size $n = 3$ should be selected in order to have a minimal as well as a variance optimal design. Since the total number of mixtures for m even moderately large can become large, minimal fractional combinatorials (MFCs) are desired. In order for the MFC to have optimal properties, pairwise balance, triplet balance, etc. are desired. The so-called t-designs have this property. The application of t-design theory to optimizing MFCs is an unresolved problem.

In the following section, MTDs for estimating GMA effects are discussed for mixtures of n of m items when responses are available for each item in the mixture. The mixture size may vary from $n = 2$ to $n = m$. In the third section, MTDs are obtained for the case when individual responses for the n items in a mixture are *not* available but only the response for the mixture is available. In section four, MTDs are discussed for GMA plus BSMA effects for various mixture sizes and for the case when an individual response is available for each item in the mixture. These FCs will contain at least $m(m - 1)/3$ mixtures. The case where the individual responses are not available but only the mixture total response is considered in section five. MTDs for GMA, BSMA, and TSMA effects when individual item responses are available are discussed in section six. The case where the individual item responses are not available is discussed in section seven. The last section contains some comments and discussion.

2. MTD FOR GMA EFFECTS-INDIVIDUAL RESPONSES AVAILABLE

A minimal treatment design for GMA effects is the one described in Federer (1998, Chapter 15). This MTD is composed of

one mixture of all m items

and

each of the m items included as a single (sole) entry

to produce a MTD of m + 1 items. A response model equation for this design may be

$$Y_{mgh} = \mu_{mh} + \varepsilon_{mgh} = (\mu_m + \tau_h + \delta_h + \varepsilon_{mgh})/(n = m) \quad (1)$$

and

$$Y_{sgh} = \mu_{sh} + \varepsilon_{sgh} = \mu_s + \tau_h + \varepsilon_{sgh} \quad (2)$$

where Y_{mgh} and Y_{sgh} are the ghth responses for the hth item in a mixture and as a sole item, respectively, μ_x , x = m or s, is a general mean effect, μ_{xh} is the hth item mean, τ_h is the hth item effect as a sole entry, δ_h is the GMA effect of item h, ε_{xgh} is a random error effect distributed with mean zero and variance σ^2. The divisor n in equation (1) is needed when the amount of space or material is 1/nth of that used for the sole entry (See Federer, 1993, 1998). If the amount of the item in the mixture is the same as in the sole item, the factor 1/n would be omitted in equation (1). If the amount is somewhere in-between, the factor would need to be adjusted accordingly to make the effects in (1) and (2) comparable.

In plant breeding programs a system denoted as top-crossing is used to assess the general combining abilities of m lines (items). The m items are crossed (mixed) with a standard cultivar (item). The lines are evaluated for their sole line effects plus their general combining (mixing) abilities. This is denoted as a *cultivar* effect in the top-cross. These top-crosses are evaluated in varietal yield trials. Only those with high cultivar effects are further tested for specific combining ability (SCA or BSMA) effects. A line with a high cultivar effect and a high SCA is desired. The idea of top-crossing may be utilized for m drugs, m products, m programs, m curricula, etc. (See Federer, 1998, Chapter 19). Using a standard item, each of the m items is mixed with the standard to form m mixtures of size n = 2. We designate these mixtures as *top-mixes*. The treatment design is

m top-mixes with the standard item

and

a sole entry for each of the m items

to make 2m treatments. If only an *item effect* = sole effect plus GMA effect is desired, the m soles may be omitted. Response model equations (1) and (2) may be used here as well.

If only GMA effects are of interest and if it is immaterial which item is used as a partner, then a MTD may be constructed by dividing the m items into v = (m/n to the next largest integer) mixtures, where n is the mixture size. Denote the number of mixtures as v. To illustrate, consider these v mixtures of size 2 for m = 4 to 9.

m=4	m=5	m=6	m=7	m=8	m=9
1,2	1,2	1,2	1,2	1,2	1,2
3,4	3,4	3,4	3,4	3,4	3,4
	1,5	5,6	5,6	5,6	5,6
			1,7	7,8	7,8
					1,9

where the mixture is denoted as x,y.

For n= 3, the v mixtures are:

m=4	m=5	m=6	m=7	m=8	m=9
1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3
2,3,4	3,4,5	4,5,6	4,5,6	4,5,6	4,5,6
			5,6,7	6,7,8	7,8,9

The above mixtures plus the m sole items produce a TD with m + v treatments. Response model equations (1) and (2) may be used to obtain solutions for GMA effects. If only item effects are desired, then the m sole items may be omitted.

Rather than replicate mixtures in the above designs, the v mixtures should be reconstituted to achieve as much pairwise balance as possible for the m items. Balanced incomplete block designs (BIBDs) for m = b incomplete blocks of size k = n with n = r replicates of each item are also known as Youden designs. A Youden design is a selected subset of the rows of an m by m Latin square where the columns are the incomplete blocks. Rows of a Youden may be deleted in such a manner that keeps the resulting design as near-pairwise-balanced as possible.

3. MTD FOR GMA EFFECTS - MIXTURE TOTALS ONLY AVAILABLE

A minimal treatment design for estimating item effect (sole plus GMA effect), for mixtures of size n is obtained by taking n rows from a Latin square arrangement (See Federer, 1998, Table 16.2). Whenever possible, a Youden or near-Youden design should be selected to obtain the v mixtures. If GMA effects rather than item effects are desired, then it will be necessary to add the m sole items to the above mixture or incomplete block design. This results in a TD of 2m treatments. These designs have been discussed by Raghavarao and Federer (1979) and Federer (1991, Chapter 5) in the context of sample surveys and obtaining answers to embarrassing or incriminating questions.

Instead of using the above designs to obtain the mixtures, supplemented block designs as described by Raghavarao and Federer (1979), Federer (1998), and Raghavarao and Rao (1999) may be used. The standard item replaces the sensitive question in these designs. A number of these supplemented designs appear in Table 16.3 of Federer (1998) and in Raghavarao and Rao (1999).

A PBIBD or BIBD for m items in m mixtures is constructed. Then, the standard treatment is added to each of the m mixtures plus one mixture of all m items plus the standard item. This makes m + 1 mixtures. Since only item effects are obtainable from this design, it is necessary to add m sole treatments making a total of 2m + 1 treatments in the TD, to obtain the GMA effects.

4. MTD FOR ESTIMATING GMA AND BSMA EFFECTS - INDIVIDUAL RESPONSES AVAILABLE

For m items, there are m GMA effects and m(m - 1) BSMA effects for which solutions are needed. When individual responses are available, the two-factor interaction effect is obtained for *each* member of the pair ij, i. e., it is possible to determine the contribution to the interaction from each item. This is different from the usual two-factor interaction in factorial experiments. Applying the restriction that the sum of the BSMA effects for each item is zero, m(m - 1) responses are necessary in order to obtain solutions for all item means and BSMA effects. The sum of the GMA effects is not required to sum to zero as all GMA could be positive or negative in their effect. The m(m - 1) degrees of freedom will have m allocated to the item means and m(m - 1) - m = m(m - 2) degrees of freedom associated with the BSMA effects. If sole crops are included, then solutions for GMA and BSMA effects may be obtained. In order to obtain solutions for the item means and the BSMA effects, one need only to obtain solutions for the $m(m - 1)$ pair ij means. Then the sum of the means over j for item i results in the ith item mean which is the overall mean plus the sole effect plus the GMA effect. This is because the sum of the BSMA effects for each i is taken to be zero.

A MTD may be formed by taking the mixtures of size $n = m - 1$ and using the m combinations formed by taking $m - 1$ rows of a Latin square, resulting in the $m(m - 1)$ responses needed to obtain solutions for the item means and the BSMA effects. Adding the m sole treatments to this MTD allows solutions for the GMA effects.

For mixtures of size n equal to two, $m(m - 1)/2$ mixtures of all combinations of m items taken two at a time, will be required for a MTD. Since two responses are obtained from each mixture, the required $m(m - 1)$ responses are obtained.

If the mixture size is three and if the BSMA effect is unaffected by mixture size, then at least $m(m - 1)/3$ mixtures are needed to obtain the $m(m - 1)$ responses. A response model equation for mixtures of size three for item h in the presence of items i and j, or h(ij), is

$$Y_{mgh(ij)} = [\mu_{mh(ij)} + \varepsilon_{mgh(ij)}$$

$$= (\mu_m + \tau_h + \delta_h + 2(\gamma_{h(i)} + \gamma_{h(j)} + \varepsilon_{mgh(ij)})]/(n = 3) \qquad (3)$$

where $\gamma_{h(i)}$ and $\gamma_{h(j)}$ are the BSMA effects for item h with item i and with item j, respectively. The 2/3 is needed to put these BSMA effects on the same basis as $n = 2$ (See Federer, 1993, 1998).

For $m = 4$ to 15, the numbers of combinations N equal to m items taken n at a time for $n = 3$, 4, and 5 are given in Table 1. Also, given in Table 1 are the values of $v = m(m - 1)/n$ to indicate the fractions of N needed to obtain solutions for the ij pair means or the item means and the BSMA effects. These $m(m - 1)/n$ mixtures must be selected in such a manner as to have a connected incomplete block design for $m - 1$ items for each $i = 1, 2, \dots, m$. For $n = 3$ and an incomplete block design for blocks of size 2, inverses of circulant design matrices only of odd order, m even, exist. For $m = 4$, a MTD of $v = 4$ mixtures (columns) is

1	1	1	2
2	2	3	3
3	4	4	4

For each item, a balanced incomplete block design is formed for v = 3, $k = 2$, $r = 2$, and $\lambda = 1$. Since all ij pairs are included, this design is connected for item means and BSMA effects or the $m(m - 1)$ pair ij means.

For $m = 5$, at least seven mixtures of size $n = 3$ are required to obtain the $m(m - 1) = 20$ responses. A connected design was not found for $v = 7$ but was for the following $v = 8$ mixtures

1	1	1	1	2	2	2	3
2	2	3	4	3	3	3	4
3	4	4	5	5	4	5	5

For $m = 6$, ten mixtures of size $n = 3$ should suffice. However, the minimal design found had eleven mixtures and is

1	1	1	1	1	2	2	2	3	3	3
2	3	4	5	2	3	4	5	4	5	4
3	4	5	6	6	4	5	6	6	6	5

For mixtures of size $n = 4$, the fractional combinatorial requires $v = m(m - 1)/ 4$ at least in order to obtain solutions for the ij pair means. If $m = 5$, five mixtures are required and form the MTD described at the beginning of this section. If $m = 6$, at least eight of the 15 possible combinations are required. Consider the following FCD

1	1	1	1	1	2	2	3
2	2	2	3	3	3	3	4
4	3	4	4	5	4	5	5
5	6	6	5	6	5	6	6

This design is a MTD.

For $n = 5$ and $m = 7$, consider the following FCD

1	1	1	1	1	1	2	2	3
2	3	4	5	6	7	3	4	4
3	4	5	6	7	2	4	5	5
4	5	6	7	2	3	5	6	6
5	6	7	2	3	4	6	7	7

The minimum number of mixtures required is v = 9. Forty five responses are obtained but only 7(6) = 42 are needed. Therefore the above is a MTD.

5. MTD FOR ESTIMATING GMA AND BSMA EFFECTS - INDIVIDUAL RESPONSES NOT AVAILABLE

When individual responses are not available, then it will not be possible to obtain solutions for the BSMA effect for each member of the pair. Instead, only the sum of these effects, the usual idea for interaction, will be available. Then, $m(m - 1)/2$ responses are required to obtain solutions for the $m(m - 1) / 2$ pair ij means. For n = 2, all possible mixtures of m items taken two at a time will be required. For m = 6 and n=3, consider the following design

1	1	1	1	1	2	2	2	3	3
2	3	4	5	6	3	4	5	4	5
3	4	5	6	2	4	5	6	5	6

Fifteen pair means are to be estimated from these ten mixtures of size n = 3. Using mixtures of size n = 2 would have required 15 mixtures, or five more mixtures. For n = 4 and m = 6, consider the following design with eight mixtures

1	1	1	1	2	2	2	3
2	3	4	5	3	4	5	4
3	4	5	6	4	5	6	5
4	5	6	2	5	6	3	6

6. MTD FOR ESTIMATING GMA, BSMA, and TSMA EFFECTS - INDIVIDUAL RESPONSES AVAILABLE

An individual response for item h in a mixture with items i, j, and k has several effects. A response model equation for n = 4 is taken to be

$$Y_{gh(ijk)} = (\mu + \tau_h + \delta_h + 2[\gamma_{h(i)} + \gamma_{h(j)} + \gamma_{h(k)}] +$$

$$3[\beta_{h(ij)} + \beta_{h(ik)} + \beta_{h(jk)}] + \varepsilon_{ghijk})/\ 4$$

Three BSMA effects, $\gamma_{h(i)}$, $\gamma_{h(j)}$, and $\gamma_{h(k)}$, and three TSMA effects, $\beta_{h(ij)}$, $\beta_{h(ik)}$, and$\beta_{h(jk)}$, are present in the response for item h in the mixture hijk (See Federer, 1993 and 1998, for more detail).

As Hall (1976) and Federer and Raghavarao (1987) have shown, the MTD for estimating item means, BSA effects, and TSMA effects when $n = 3$, is $m! / 3!(m - 3)!$ mixtures. For any one item, the remaining $m - 1$ treatments form a BIBD with $v = m - 1$, $k = 2$, $r = m - 2$, and $\lambda = 1$. This relationship holds for each of the m items.

For $n = 4$ and for a given item, it is sufficient that the other $m - 1$ items form a BIBD with $v = m - 1$, $k = 3$, $r = (m - 2)(m - 3) / 2$, and $\lambda = m - 3$. For $n = 5$, it is sufficient that the the other $m - 1$ items form a BIBD with $v = m - 1$, $k = 4$, $r = (m - 2)(m - 3)(m - 4) / 6$, and $\lambda = (m - 3)(m - 4) / 2$. Note that these are sufficient, not necessary, conditions. It is necessary that a connected incomplete block design be selected for the $m - 1$ other items for each of the m items. An illustrative example is given in Table 15.7 and Example 15.3 of Federer (1998). The numbers of mixtures required for a MTD for $m = 6$ to 15 are given in Table 2.

MTDs for $n = m - 1$ and $m - 2$ have not been investigated but they appear possibilities for reducing the number of mixtures and still allowing estimation of the effects of this section.

7. MTD FOR ESTIMATING GMA, BSMA, and TSMA EFFECTS - INDIVIDUAL RESPONSES NOT AVAILABLE

When individual responses are not available but only mixture totals are, $m(m - 1)(m - 2) / 6$ mixture totals are required to obtain solutions for the item means, the BSMA effects, and the TSMA effects. If the mixture size is three, $v = m(m - 1)(m - 2) / 6$ mixtures. If the mixture size is four, then a fraction of $4 / (m - 3)$, $m > 6$, of $m! / 4! (m - 4)!$ combinations would form a MTD. For $n = 5$, the fraction of $m! / 5! (m - 5)!$ to form a MTD would be $20 / (m - 3)(m - 4)$ for $m > 7$. For $n = 6$, the fraction of $m! / 6! (m - 6)!$ would be $120 / (m - 3)(m - 4)(m - 5)$ for $m > 8$.

8. DISCUSSION

In some situations it is posssible that responses for some items in a mixture are available but for others, individual responses are not available. For example, blood pressure measurements may be available for a blood pressure medication but the individual responses for using vitamins A, B, and C are not. Statistical designs and analyses need to be developed for this situation.

In some cases, one or more standard items are to be included in mixtures with a number of other items. Minimal treatment designs for this situation for various mixing effects is another area requiring deveopment.

Designs requiring a variety of mixture sizes are required in certain situations, for example, consider m = 4 items in mixtures of size n = 3. In order to obtain solutions for the item means, the BSMA effects, and TSMA effects, mixtures of sizes 2 and 3 will be required. If the QSMA effect is also desired, another mixture of size n = 4 will be needed.

9. LITERATURE CITED

Federer, W. T. (1991). *Statistics and Society*. Marcel Dekker, Inc., New York, Basel, and Hong Kong, Chapter 5.

Federer, W. T. (1993). *Statistical Design and Analysis for Intercropping Experiments: Volume I. Two Crops.* Springer-Verlag, New York, Berlin, and Heidelberg, xx + 298 pp., Chapters 6 and 7.

Federer, W. T. (1998). *Statistical Design and Analysis for Intercropping Experiments: Volume II. Three or More Crops.* Springer-Verlag, New York, Berlin, and Heidelberg, xxiv + 262 pp., Chapters 15 and 16.

Federer, W. T., A. Hedayat, C. C. Lowe, and D. Raghavarao (1976). Application of statistical design theory to crop estimation with special reference to legumes and mixtures of cultivars. Agronomy J. 68:914-919.

Federer, W. T. and D. Raghavarao (1987). Response models and minimal designs for mixtures of n of m items useful for intercropping and other investigations. Biometrika 74:571-577.

Hall, D. G. (1976). Mixing designs: A general model, simplifications, and some minimal designs. M. S. Thesis, Cornell University, Ithaca, New York.

Raghavarao, D. and G. N. Rao (1999). Design and analysis of intercropping experiments when the intercrops are in different classes. Unpublished paper, Deptartment of Statistics, Temple University.

Smith, L. L., W. T. Federer, and D. Raghavarao (1975). A comparison of three techniques for eliciting truthful answers to sensitive questions. Proc., American Statistical Association, Social Statistics Section, pp. 447-452.

Table 1. Number of mixtures and number in MTD for various values of m items in mixtures of size n for item means and BSMA effects.

	n = 3		n = 4		n = 5	
m	N	v	N	v	N	v
4	4	4	-	-	-	-
5	10	20/3	5	5	-	-
6	20	10	15	30/4	6	6
7	35	14	35	42/4	21	42/5
8	56	56/3	70	14	56	56/5
9	84	24	126	18	126	72/5
10	120	30	210	90/4	252	18
11	165	110/3	330	110/4	462	22
12	220	44	495	33	792	132/5
13	286	52	715	39	1287	156/5
14	364	182/3	1001	91/2	2002	182/5
15	455	70	1365	105/2	3003	42

N = m! / n! (m - n)!   v = m (m - 1) / n

Table 2. Number of mixtures and number in MTD for various values of m items in mixtures of size n for item means, BSMA effects, and TSMA effects.

	n = 4		n = 5		n = 6	
m	N	v	N	v	N	v
6	15	15	-	-	-	-
7	35	105/4	21	21	-	-
8	70	42	56	168/5	28	28
9	126	62	126	252/5	84	42
10	210	90	252	72	210	60
11	330	450/4	462	99	462	165/2
12	495	165	792	132	924	110
13	715	429/2	1287	858/5	1716	143
14	1001	273	2002	1092/5	3003	154
15	1365	1365/4	3003	273	4005	455/2

N = m! / n! (m - n)!   v = m (m - 1) (m - 2) / 2n