AN APPLICATION OF IT BASED METHODS FOR ANALYTICAL DECISION TO ASSES OPTIMAL FACTOR COMBINATION IN ONE MEDICAL EXPERIMENT

Milan Randjelović
Agricultural faculty University of Priština, Lešak, Kosovo and Metohia, Serbia
magis80@gmail.com
Dragan Randjelović
Academy for Criminalistic and Police Studies Belgrade,Belgrade, Serbia
dragan.randjelovic@kpa.edu.rs
Dragan Bogdanović
State University Novi Pazar, Novi Pazar, Serbia
draganbogdanovic@gmail.com

Abstract: *In many scientific disciplines, especially in biology and consequently in medical science, scientists organise experiments to affirm their hypothesis, named tests in research, or to choose the optimal available possibility in one experiment, named valuations in research. Scientists make different statistical plans which can most effectively represent complex multifactor and often multivariate experiments. Analysis of results and especially determine the optimal factor combination choice in such experiments with respondable apparatus of classical statistics known as multiple regression analysis in the case of univariate, or canonical analysis in multivarite case is very difficult. In both cases is obligatory using of variance analysis which enables study of influence of individual factors in these experiments. Because of that, especially when the case of optimal factor combination choice in one experiment is necessery, authors propose using of multi attribute methods of decision. In the paper is given one example of common, analysis of variance and ELECTRA multi attribute method, application in one medical experiment on venous leg ulcers healing.*
Key-Words: *Multi attribute analysis, Analysis of variance, Optimal factor combination choice, Medical experiment*

1. INTRODUCTION

The basic task in one experiment is considering of influence of different treatments and their combination on the unit of experimental examination. Statistical analysis of experiments is usually as analysis of variance but sometime it is necessary to solve a problem of the optimal factor combination choice what is described in [1].

1.1 ANALYSIS OF VARIANCE

Analysis of variance in notation ANOVA is a collection of statistical models (see [2]), also their associated procedures (see [3]), in which the observed variance is partitioned into components due to different explanatory variables(see [4]). The initial techniques of the analysis of variance were developed by the statistician and geneticist R. A. Fisher in the 1920s and 1930s, and is known as Fisher's ANOVA(analysis of variance). Analysis of variance gives answer on the question has any factor influence and which factor from applied in this experiment has the biggest influence on the output variable.

There are three conceptual classes of such models:

- Fixed-effects model assumes that the data came from normal populations which may differ only in their means-Model 1.
- Random-effects models assume that the data describe a hierarchy of different populations whose differences are constrained by the hierarchy-Model 2.
- Mixed effects models describe situations where both fixed and random effects are present-Model 3.

In practice, there are several types of ANOVA depending on the number of treatments and the way they are applied to the subjects in the experiment:

- One-way ANOVA is used to test for differences among two or more independent groups. Typically, however, the One-way ANOVA is used to test for differences among three or more groups, with the two-group case relegated to the t-test, which is a special case of the ANOVA.The relation between ANOVA and t is given as $F = t^2$.
- One-way ANOVA for repeated measures is used when the subjects are subjected to repeated measures; this means that the same subjects are used for each treatment. Note that this method can be subject to carryover effects.
- Factorial ANOVA is used when the experimenter wants to study the effects of two or more treatment variables. The most commonly used type of factorial ANOVA is the 2×2 – known as two by two design, where there are two independent variables and each variable has two levels or distinct values. Factorial ANOVA can also be multi-level such as 3×3, etc. or higher order such as 2×2×2, etc. but analyses with higher numbers of factors are rarely done because the

calculations are lengthy and the results are hard to interpret.

- When one wishes to test two or more independent groups subjecting the subjects to repeated measures, one may perform a factorial mixed-design ANOVA, in which one factor is independent and the other is repeated measures. This is a type of mixed effect model.
- Multivariate analysis of variance in notation MANOVA is used when there is more than one dependent variable.

1.2 OPTIMAL FACTOR COMBINATION CHOICE

Considering the optimal factor combination choice in one multifactor and multivariate experiment towards the aim of this experiment is invention of the minimum or maximum answer dependent variables in this experiment. In the case of univariate experiments we may write for dependent variable y_i which is called the response surface

$$y_i=F(x_{1i},x_{2i},x_{3i},\ldots,x_{pi})+e_i ,$$

where i=1,2,…,n represents the n observation in the multi factorial experiment and x_{pi} represents the level of p-th factor in the i-th observation and residual e_i measures the experimental error of the i-th observation . When the mathematical form of function F isn't known, this function can be approximated satisfactorily, for example by a polynomial, different degree, in the independent variables x_{pi}.

Since the fitting of a polynomial can be treated as a particular case of multiple linear regression, we shall use the calculations required to fit a multiple linear regression of y_i on the k variables x_{pi} where i=1,2,…,n and p=1,2,…,k in the form

$y_i=\beta_0 + \beta_1x_{1i}+ \beta_2x_{2i}+ \beta_3x_{3i}+\ldots+ \beta_kx_{ki}+e_i$.

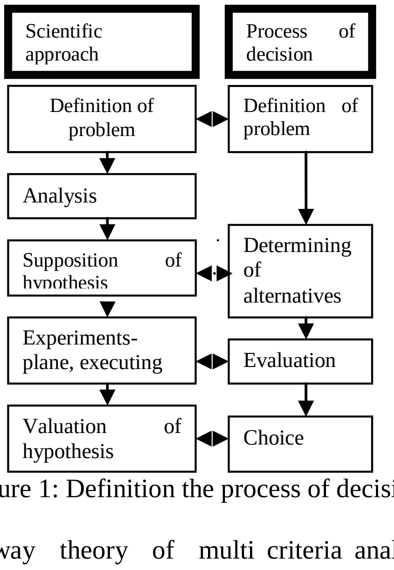

Figure 1: Definition the process of decision

In other way theory of multi criteria analysis gives possibility that we can make in easier way analysis of experiments results. This possibility follows if we use the apparatus of operational research and have already presented general definition of French mathematicians Descartes in XVII century for Scientific approach and process of decision (see Figure 1).

An application of multi criteria analysis in the optimal factor combination choice on the basis of one experiment results is possible because of that in this experiments exist:

- More criteria – functions of aim for decision which are defined with defined explicit attributes
- More and that finite number of discreet alternatives
- One finite solution

2. MATHEMATICAL APPARATUS FOR OPTIMAL FACTOR COMBINATION CHOICE

Mathematical apparatus for analysis of results of one experiments towards the aim of optimal factor combination choice can be in univariate case:

* statistical analysis of multiple linear regression,
* multi attribute decision methods and

and in multivariate case canonic correlation analysis.

Becase of that the multiple linear regression is very known method we give only short introduction for it, also we don't consider multivariate case. Practically we explain seriously multi attribute decision methods in this paper.

2.1 MULTIPLE LINEAR REGRESSION

Method for examining the influence of more different independent variables .for example $x_{1i},x_{2i},x_{3i},\ldots,x_{pi}$ on one dependent variable for example y is called multiple regression and can be given in the form

$y=a + b_1x_1+ b_2x_2+ b_3x_3+\ldots+ b_px_p$.

where b_i i=1,2,…,p are partial coefficients of regression. In the case of fixed values independent variables x when we have and experimental error in each from fully n observation we can present multiple regression in the form

$y_i=\beta_0 + \beta_1x_{1i}+ \beta_2x_{2i}+ \beta_3x_{3i}+\ldots+ \beta_kx_{ki}+e_i$.

The calculation of parameters a,b1,b2,b3,…,b_p

we can make with the method of smallest quadrates with minimization of expression

$$\sum_{i=1}^{n}(y_i - a - b_1x_{1i} - b_2x_{2i} - \cdots - b_px_{pi})^2 .$$

Practically, algebraic algorithm for solving arising system of equation is rarely in use than known Gaussian method of multiplication all the more so this method is already used in calculation for regression valuation and therefore we consider this method. With differentiation in relation on a,b1,b2,b3,…,b_p and with exchange in notation b_0=a we obtain next normal equation which must be solved to receive parameters:

$b_0(00)+b_1(01)+\ldots+b_p(0p)=(0y)$

$b_0(10)+b_1(11)+\ldots+b_p(1p)=(1y)$

…

$b_0(p0)+b_1(p1)+\ldots+b_p(pp)=(py)$, where (jk)=(kj)= $\sum_{i=1}^{n} x_{ji}x_{ki}$ is the sum of products of j-th and k-th variables x_j and y_k, (jj)= $\sum_{i=1}^{n}(x_{ji})^2$ is the sum of squares j-th

column of variable x_i, (jy)= $\sum_{i=1}^{n} x_{ji} yi$ is the sum of products j-th column of variable x_j and of variable y.
The matrix of independent variables x and vector y are the initial basis for calculation sum of squaresand products of variables and can be given with Table 1.

Table 1: Matrix of independent variables x and vector y

X				*y*
x_{01}	x_{11}	∘∘∘	x_{p1}	y_1
x_{02}	x_{12}	∘∘∘	x_{p2}	y_2
∘∘∘	∘∘∘	∘∘∘	∘∘∘	∘∘∘
x_{0n}	x_{1n}	∘∘∘	x_{pn}	y_n

From this matrix and vector we form sums of square and product of variables x and products of x and y which form system of normal equation as in Table 2.

Table 2: Sums of square and product of variables x and products of x and y

jk=x'x				jy=x'y
00	01	∘∘∘	0p	0y
10	11	∘∘∘	1p	1y
∘∘∘	∘∘∘	∘∘∘	∘∘∘	∘∘∘
p0	p1	∘∘∘	pp	py

With inversion of matrix x'x (see [6],[7]) we obtain Gauss' multipliers given in Table 3.

Table 3: Gauss multipliers

$C_{jk} = C_{kj}$ = x'x			
C_{00}	C_{01}	∘∘∘	C_{0p}
C_{10}	C_{11}	∘∘∘	C_{1p}
∘∘∘	∘∘∘	∘∘∘ .	∘∘∘
C_{p0}	C_{p1}	∘∘∘	C_{pp}

Partial coefficients of regression are:

$$b_i = \sum_{i=1}^{p} (C_{jk})(jy)$$

i.e. the sum of products of k-th column C_{ij} with the column (jy). When the independent variables are mutually orthogonal normal equations are particularly easy to solve therefore in this case all sums of products (jk) vanish (j≠k) and the normal equations for b_i reduces to: $(jj)b_j=(jy)$
Also and the multiplier in inverse matrix becomes values $C_{jj}/(jj)$ and $C_{jk}=0$.

2.2 MULTI ATTRIBUTE DECISION

Multi criteria decision methods are grouped in two basis groups:

- multi target methods
- multi attribute methods

and in each of these two basis groups we have a few methods which are explained in [5]. The subject of interest in this paper is multi attribute methods. In this group we have two different subgroup of methods:

- subgroup without heaviness coefficients which typical represent is data envelopment analysis (DEA) method , described in [6], and
- the methods with heaviness coefficients for considered units which well known represent of this group are Elimination et choice translating reality (ELECTRE) method and preference ranking organization method for enrichment evaluations (PROMETHEE) method in the subgroup of standard heaviness coefficients determining and Analytical hierarchical process(AHP)method in the subgroup for objective heaviness coefficients determining.

As we have noticed the multiple factor experiments, which are usually object of considering ones experiment therefore they give possibility for greater precision and also considering of interaction and where practically each treatment consists of one combination of values of each factor the application of multi attribute methods and that one concrete from enumerated method is possible so that it is easy to make the table of criteria which are in columns of this table and alternatives which are rows in this table with values from executed experiments take the values of factor combinations.
With the application of method of mathematical programming, which is in the basis of multi attribute methods, today we can produce also information support in the form of suitable software package. Multi attribute methods can be given with next mathematical model:
Max $\{f_1(x), f_2(x),\dots, f_n(x), n\geq 2\}$
by restriction x∈A=$[a_1, a_2,\dots, a_m,]$, where is:
n-number of criteria(attributes) j=1,2,…,n
m-number of alternatives(actions) i=1,2,…,m
f_j – criteria(attributes) j=1,2,…,n
a_i –alternatives(actions) i=1,2,…,m
A – set of all alternatives(actions).
Also are known values f_{ij} of each considered criteria f_j which are received with each from possible alternatives a_i :
$f_{ij} = f_j\ (a_i)\ \ \forall (i,j)$; i=1,2,…,m; j=1,2,…,n.
Usually the model of some multi criteria method is given with suitable matrix of attributes values for individual alternative like in Table 4.

Table 4:Matrix of attributes values-individual alternative

	max f_1	*max f_2*	∘∘∘	*max f_n*
a_1	f_{11}	f_{12}	∘∘∘	f_{1n}
a_2	f_{21}	f_{22}	∘∘∘	f_{2n}
∘∘∘	∘∘∘	∘∘∘	∘∘∘	∘∘∘
a_m	f_{m1}	f_{m2}	∘∘∘	f_{mn}

Criteria type of minimization can be translated in criteria type of maximization for example with multiplication of their values with -1. For example, method ELECTRE is based on the fact:
When is alternative a better then alternative b for majority criteria and in addition don't exist criteria for which is alternative a strict worse then alternative b we can say ,without risc, alternative a is better then b i.e. alternative a surpassed alternative b.
The base of algorithm of decision for ELECTRE method form two conditions:

- condition of agreement defined trough desired level of agreement P and real index of agreement c(a,b)
- condition of disagreement defined trough desired level of disagreement Q and real index of disagreement d(a,b)

Indexes of agreement and disagreement express quantitative indexes of agreement or disagreement that the alternative a can be ranged before alternative b in the sense of all criteria
simultaneously.
Index of agreement is the relation of the sum of
relative importance of each criteria which give that the alternative a is better or equals in relation with alternative b and total sum of relative importance w_j criteria K_j in the sense which we make range

$$c(a,b) = \frac{\sum_{j \in J_1} w_j}{\sum_{j=1}^{n} w_j} \cdot 100(\%)$$

where J_1 is the set of all criteria trough which is alternative a better then alternative b or equals. Indexes of agreement (they are n(n-1)) take values from 0 to 1 end we notice they in matrix of agreement C_{nxn}.
Index of disagreement is defined like maximum normalized interval of disagreement i.e. relation of the maximum of intervals for criteria where is alternative a worse then b and maximum interval of valuation for each criteria

$$d(a,b) = \begin{cases} 0, for I_2 = \varnothing \\ \dfrac{\max_j r(a,b)}{\max_j R_j}, contrary. \end{cases}$$

r(|a,b)-difference of valuations criteria values for alternatives a and alternatives b for individual criteria,
R_j – maximum span of valuations for each criteria
(max a_j -min a_j)
I_2 – set of each criteria for which is alternative a worse then alternative b.
With the choice the biggest range of agreement(p=1) and the least range of disagreement(q=0) we separate only alternatives which are better for each criteria simultaneously.
The range is determined on the basis of relation index agreement and disagreement for even comparison i.e.

- a is better then b if c(a,b)≥p and d(a,b)≤q
- b is better then a if c(b,a)≥p and d(b,a)≤q
- in other cases alternatives a and b are incomparable

3 MAIN RESULTS

The authors of this paper propose an application of multi attribute methods beside obligatory using the method of analysis of variance for asses optimal factor combination in medical experiment and that concrete ELECTRA method in the way which is present in next several lines of this section (see also [7]). From this reason authors consider application of F-test analysis of variance and proposed ELECTRA multi attribute method on one example for solving a problem of the venous leg ulcers healing using the results of the study which was organised on Clinic for Vascular Surgery, Clinical Centre Nis, Vascular Department, Nis, Serbia.
In the ELECTRA method we make the beginning matrix which is given like table of criteria which are in columns of this table and alternatives, i.e combination of factors, which are rows in this table with values from obtained results from executed experiments which take the middle value of one factor combination and for all that last row take values of heaviness coefficients of this criteria. Sum of values this heaviness coefficients is normalized on value 1.
It is known that exist a methods for exact determining the heaviness coefficients of applied criteria, which are unfortunately also very dificult.
Therefore , without generalization we understood that the heaviness coefficients for applied criteria are equal for a group of output and a group of input criteria.
For the group of input criteria author proposes using of F parameters computed using the method of analysis of variance, which are obviously already used to consider the results of one experiment in the sense of affirmation supposed hypothesis, in the way that the values of heaviness coefficients of criteria can take whichever values, which sum is obviously identical one, if this F parameters have not a significant values for each input criteria. In this way with connection the methods analysis of variance and multi attribute decision method we obtain the new procedure which evident enables an easier and efficacious way for considering a results of experiment.
It is known that venous leg ulcers (VLU) have a huge social and economic impact. An estimated 1.5% of European adults will suffer a venous ulcer at some point in their lives. Despite the widespread use of bandaging with high pressure in the treatment of this condition, recurrence rates range between 25% to 70%. Numerous studies have suggested that the compression system should provide sub-bandage pressure values in the range from 35 mm Hg to 45 mm Hg in order to achieve the best possible healing results.
STUDY: An open, randomized, prospective, single-center study was performed in order to determine the healing rates of VLU when treated with different compression systems and different sub-bandage pressure values. One hundred thirty-one patients (72 women, 59 men; mean age, 59-years-old) with VLU (ulcer surface >3 cm(2); duration >3 months) were randomized into three groups: group A - 42 patients who were treated using an open-toed, elastic, class III compression device knitted in tubular form (Tubulcus, Laboratoires Innothera, Arcueil, France); group B - 46 patients treated with the multi-component bandaging system comprised of Tubulcus and one elastic bandage (15 cm wide and 5 cm long with 200% stretch, Niva, Novi Sad, Serbia); and group C - forty-three patients treated with the multi-component bandaging system comprised of Tubulcus and two elastic bandages. Pressure measurements were taken with the Kikuhime device (TT MediTrade, Soro, Denmark) at the B1 measuring point in the supine, sitting, and standing positions under the three different compression systems.

3.1 APPLICATION OF ANALYSIS OF VARIANCE

The authors of this paper made standard statystical analysis of variance and that Thamane’s post hoc test from ANOVA (*p* values) and F-test.
The median resting values in the supine and standing positions in examined study groups were as follows:

group A - 36.2 mm Hg and 43.9 mm Hg; group B - 53.9 mm Hg and 68.2 mm Hg; group C - 74.0 mm Hg and 87.4 mm Hg. The healing rate during the 26-week treatment period was 25% (13/42) in group A, 67.4% (31/46) in group B, and 74.4% (32/43) in group C. The success of compression treatment in group A was strongly associated with the small ulcer surface (<5 cm(2)) and smaller calf circumference (CC; <38 cm).

On the other hand, compliance in group A was good. In groups B and C, compliance was poor in patients with small CC, but the healing rate was high, especially in patients with large ulcers and a large CC (>43 cm).

The authors of this paper made conclusion: The results obtained in this study indicate that better healing results are achieved with two or multi-component compression systems than with single-component compression systems and that a compression system should be individually determined for each patient according to individual characteristics of the leg and CC. Target sub-bandage pressure value (B1 measuring point in the sitting position) of the compression system needed for the ulcer healing could be determined according to a simple formula, what is described in details in [8].

Table 5:Results of F test

Comparing by	F	*p*
All characteristics	14,435	<0,001
Size of the ulcer	40,311	<0,001
Calf circumference	11,101	0,001
Sub-bandage pressure	15,535	<0,001

Table 6:Mean healing time by size of the ulcer, calf circumference and sub-bandage pressure

Size of the ulcer *(cm²)*	Calf circumference *(cm)*	Sub-bandage pressure in the supine and standing positions *(mm Hg)*	N	Mean healing time *(week)*	Group number
≤14	≤38	36.2 and 43.9	13	14,62	1
		53.9 and 68.2	12	6,75	2
		74.0 and 87.4	11	7,73	3
	>38	36.2 and 43.9	11	21,91	4
		53.9 and 68.2	12	15,00	5
		74.0 and 87.4	10	8,40	6
>14	≤38	36.2 and 43.9	8	26,00	7
		53.9 and 68.2	10	20,90	8
		74.0 and 87.4	10	12,30	9
	>38	36.2 and 43.9	10	26,00	10
		53.9 and 68.2	12	23,75	11
		74.0 and 87.4	12	18,08	12

Table 7:Results of Tamhane's post hoc test from ANOVA (*p* values)

		Group										
		1	2	3	4	5	6	7	8	9	10	11
Group	2	0,292										
	3	0,901	1,000									
	4	0,831	**0,001**	**0,008**								
	5	1,000	0,426	0,918	0,959							
	6	0,854	1,000	1,000	**0,004**	0,901						
	7	**0,016**	**<0,001**	**<0,001**	0,997	0,066	**<0,001**					
	8	0,873	**<0,001**	**0,006**	1,000	0,984	**0,001**	0,482				
	9	1,000	0,998	1,000	0,594	1,000	1,000	0,052	0,679			
	10	**0,016**	**<0,001**	**<0,001**	0,997	0,066	**<0,001**	.	0,482	0,052		
	11	0,092	**<0,001**	**0,001**	1,000	0,292	**<0,001**	0,734	1,000	0,147	0,734	
	12	1,000	**0,001**	0,063	1,000	1,000	**0,016**	**0,033**	1,000	0,998	**0,033**	0,361

Table 8: Linear regression analysis

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3	3462.424	1154.141	62.43649	2.04E-05
Residual	9	249.5481	27.72757		
Total	12	3711.972			

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	0	#N/A	#N/A	#N/A
Size of the ulcer *(cm²)*/X1	0	0	65535	#NUM!
Calf circumference *(cm)*/X2	0.985858	0.171927	5.734179	0.000282
Sub-bandage pressure *(mmHg)/X3*	-0.29872	0.092443	-3.23146	0.010298

With statystical analysis of multiple linear regression, using Excel data analysis option, we obtain results whch are given in Table 8. Output multiple linear regression gives us relation between normalized input (independent) and only one output (depended)factor :

$$Y= 0 + 0X1 + 0.985858X2 - 0.29872X3$$

We can calculate that the optimal factor combination are in repetition 2, 3, 6 i 9 from the reason that all input factor should have biger values and the output factor mean healing time should have smaller values.

3.2 APPLICATION OF ELECTRA METHOD

Table 9: Beginning matrix for ELECTRA method

Elektra - C:\DOCUME~1\DRAGAN\DESKTOP\VKOSOF~1\PROGRAMI\ELECTRA\BUGARS...

File Korak About

B.K 4 B.A 12

	f1	f2	f3	f4
a2	0.5	0.5	54	7
a3	0.5	0.5	74	8
a4	0.5	1	36	22
a5	0.5	1	54	15
a6	0.5	1	74	8
a7	1	0.5	36	26
a8	1	0.5	54	21
a9	1	0.5	74	12
a10	1	1	36	26
a11	1	1	54	24
a12	1	1	74	18
	0.3	0.075	0.125	0.5

Unos polazne matrice odlucivanja i tezinskih koeficijenata

Let us solve considered example with procedure proposed in this paper with ELECTRA method, made in Faculty of organization sciences Belgrade, Serbia, multi attribute decision and with heaviness coefficients for criteria i.e factors which values are proportionally with their corespondable values obtained from F –test of analysis of variance. Between groups of input and output factors heaviness coefficients have equal value (Table9.).

Table 10**:** Results of experiment obtained with ELECTRA method

a1 dominant over: a4 a7 a10	a7 non dominant
a2 dominant over: a1 a4 a5 a7 a8 a10 a11	a8 dominant over: a4 a7 a10 a11
a3 dominant over: a1 a4 a5 a7 a8 a10 a11	a9 dominat over: : a1 a4 a5 a7 a8 a10 a11 a12
a4 non dominant	a10 dominat over: : a7
a5 dominant over: a1 a4 a7 a10	a11 dominat over: : a7 a10
a6 dominant over : a1 a3 a4 a5 a7 a8 a10 a11	a12 dominat over: : a4 a7 a8 a10 a11

Obtained results indicates that the best action are a6 and a9 what is identical as we use the method of linear regression.

4. CONCLUSION

Because of that the application of the classical statistic mathematical apparatus is difficult for result analysis of different multifactor anyhow multivariate experiments, especially in solving a problem of the optimal factor configuration choice, authors propose one application the mathematical apparatus of multi attribute analysis. Evidently this procedure can process these results in one easier, efficacious and universal way.

Proposed application multi attribute decision methods is based on one connection between analysis of variance and selected multi attribute decision method.

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