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COMPARISON PROBLEMS FOR EXPERIMENTS WITH CURVE RESPONSES

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DEDICATION

David Blackwell was my dissertation professor at the University of California, and generously included me, while I was still a graduate student, as co-author on what became my first published paper. His kindness and consideration set an example I tried to follow with my students throughout my teaching career. This paper was written with my last Ph.D. student before my retirement. We dedicate it, with respect and affection, to David.

LHK

SUMMARY

We consider the problem of comparing treatment effects among two or more groups when the responses of the individuals within groups can be modeled as curves. The curves considered in this study are monotone and the principal application will be to growth curves. The method of analysis involves defining a functional of the curves, then applying standard (possibly robust) one-way ANOVA methods to its values. The functional represents a "generalized" rate of change for the curves. Specifically, the functional values are the slopes of least-squares fitted lines after the curves have been mutually straightened by a power transformation. Thus, in the case of growth curves, the groups are distinguished on the basis of group differences in growth rates. The index of the power transformation is also fitted to the data. Consequently, the small sample properties of the procedure are examined using Monte Carlo simulation.

1. INTRODUCTION

A standard experimental design in biomedical studies involves the application of two or more treatments, each to a separate treatment group, then monitoring the subjects' responses over time. The biological process will be viewed as continuous, so the subjects' responses can be modeled as curves. The

measured responses will then be sequences of (not necessarily equally spaced) points from the curves, displaced by random error.

In this paper, we focus on the special case of curves that are monotone and pass through the origin. Growth curves for entities, such as tumors, that can be viewed as having size 0 at time 0 are covered by this theory. A functional of the curves is formed by straightening the curves by a power transformation. The functional is then taken to be the slope of the straightened curves. This method is based on the empirical observation that, while the different curves may have different rates of increase or decrease, they will often be of the same general shape. Thus, a common power transformation will lead to (nearly) straight lines that differ only in their slopes. (This observation is originally due to Tukey, 1977) These slopes reflect the rates of change of the original curves, and similarities within and differences between groups are reflected in corresponding similarities and differences in the location properties of the slopes. Because of this, the problem of comparing rates of change among groups is reduced to a simple one-way analysis of variance problem for the slopes. We will demonstrate the effectiveness of the methodology by applying it to the data for the comparison of tumor growth rates in rats considered by Koziol and Maxwell(1981).

We will also demonstrate that the methodology can be extended to other types of problems by pre-transforming the data. As an example, we will apply the theory to a medical experiment for comparing the rates of removal of insulin from a perfused fluid by the hepatic cells of rats for a variety of chemical environments. Here, the original curves represent the proportion of remaining insulin as a function of time – a measurement often modeled by a logistic curve. We will introduce a family of curves for modeling this sort of data, of which the logistic curve is a member, then show that a different member of the family fits the data better. By a transformation of variables, both the fitting process and the comparison of rates will be carried out by the same methodology as used for the tumor growth rate study.

Multivariate analysis of variance has been applied to the growth rate problem by several investigators (Pottoff and Roy 1964, Rao 1965, Church 1966, Khatri 1966, Grizzle and Allen 1969, Snee and Acuff 1979). These methods are not altogether appropriate for the study of tumor growth rates, however, because they require information on each subject for the entire study period. Unfortunately, because of the death of some subjects or the remission of tumors, observations will often be missing or unusable for several subjects after a point in time that can depend both on the subject and on the size of the tumor. Where complete information is required, these subjects would have to be omitted from the study. For biomedical experiments, in which the sizes of

groups are typically rather modest, this is undesirable; it is important to be able to use the information available on all subjects, however incomplete it may be. The methodology we develop makes this possible. It will be shown that randomly censored observations lead to functional values from contaminated distributions, which tend to produce outliers. These distributions are accommodated in the analysis by the use of a robust ANOVA (Koopmans 1987).

2. THE MODEL AND SOME OF ITS CONSEQUENCES.

Our model is motivated by the random effects model given by Graybill (1975, pg. 458). Observations on all subjects are assumed to be made at times t_k, $k = 1, 2, ..., K$. If y_{ijk} is the response of the *j*th subject in the *i*th group at the *k*th time, then it is assumed that

$$y_{ijk}^{p} = \beta_{ij} t_k + \varepsilon_{ijk}$$

for $j = 1, 2, ..., n_i$ and $i = 1, 2, ..., I$. The set of random variables $\{\beta_{ij}, \varepsilon_{ijk}\}$ is assumed to be independently, normally distributed. The slopes β_{ij} have the same means, β_i, within groups, and common standard deviation σ_β, while the ε's are identically distributed with common mean 0 and standard deviation σ. The parameter p (which is not an integer multiple of 2) is the power that straightens the data.

The strategy will be to estimate p from the data and use this estimate to straighten the sample curves. The data that will then be used in the ANOVA are the least squares estimates of the random slopes.

If the parameter p were known, the estimated slopes, which have the form $\hat{\beta}_{ij} = \sum_k y_{ijk}^{p} t_k / \sum_k t_k^2 = \beta_{ij} + \sum_k t_k \varepsilon_{ijk} / \sum_k t_k^2$, would be normally distributed with mean β_i and standard deviation $\sqrt{\sigma_\beta^2 + \sigma^2 / \sum_k t_k^2}$. It follows that the appropriate test for the equality of group means, β_i, is the standard One-Way Analysis of Variance applied to the $\hat{\beta}_{ij}$'s.

We will allow the possibility that the data are randomly censored. Let T_{ij} be the time that the *j*th subject from the *i*th group is lost to the study. It is assumed that the T_{ij} are independent and identically distributed, and are

independent of the random errors, ε_{ijk}, but it is not assumed that they are independent of the random slopes, β_{ij}. Thus it is possible for, say, the rate of increase in tumor size to influence the censoring time.

Let V be a non-degenerate, positive random variable with finite 4th moment, and let Z be a standard normal variable which is independent of V. Then $W = VZ$ is said to have a contaminated normal distribution. It is easy to show (e.g. Rivest, 1981) that contaminated normal variables have kurtosis greater than 3, thus tend to have distributions with long tails (relative to normal distributions). In Appendix 1, we will show that if censoring takes place after the first observation time, t_1, with probability 1, then the estimated slopes can be written in the form $\hat{\beta}_{ij} = \beta_{ij} + \delta_{ij}$, where the δ_{ij}'s are independent random variables with 0 means and contaminated normal distributions. It follows that a robust ANOVA is appropriate to test for the equality of group means, β_i. We use the trimmed mean procedure detailed in (Koopmans, 1987) for our analyses.

It has been assumed that the power index, p, is known in the above discussion. This will not be the case in practice, of course. However, we will see, through Monte Carlo simulations, that a stable estimate of p is obtained by pooling data from all groups, and that the straightening process, thus the estimated slopes, are reasonably insensitive to modest variations in the value of p. It follows that the distribution theory based on an estimated power index is very close to that for a fixed index. Thus, using the analyses appropriate for a fixed index will lead to tests of about the correct size but with slightly reduced power.

3. ESTIMATION OF THE POWER INDEX.

A number of estimators of the power index, p, were derived and evaluated by Monte Carlo simulation (Hong, 1987). The simulations were carried out for the experimental designs of the two examples treated in this paper. For the relatively modest sample sizes of these examples, a rather simple estimator based on the coefficient of determination performed at least as well as the others, including the maximum likelihood estimator, in terms of bias, variability, and resistance to outliers. In addition, it was easier to compute. Consequently, the discussion will be limited to this estimator, which we call the maximum coefficient of determination estimator (MDE). Following the discussion of Kvalseth (1985), the coefficient of determination for measuring the simultaneous straightness of the curves for our model is taken to be

$$R^2(p) = \frac{\sum_i \sum_j \sum_k \left(\hat{\beta}_{ij} t_k\right)^2}{\sum_i \sum_j \sum_k \left(y_{ijk}^p\right)^2}$$

where $\hat{\beta}_{ij} = \sum_k t_k y_{ijk}^p / \sum_k t_k^2$. The estimated power index is the value of p that maximizes $R^2(p)$.

Numerical investigation of the coefficient of determination shows it to be a smooth function of p. Consequently, the estimated power index can be obtained using a rather simple maximization algorithm. The method used for the computations reported in this paper was, essentially, the golden section search method described in (Press, Flannery, et al, 1986). This algorithm was incorporated in the program used for the simulations described in the next section.

4. SIMULATION RESULTS

A 3 group simulation study was carried out as follows. Independent, normally distributed variables ε_{ijk} and β_{ij} were generated for the sample sizes and parameter values given in the following table. The ε_{ijk}'s have mean 0 and standard deviation σ, while the β_{ij}'s have mean β_i and standard deviation σ_β. The time points, t_k, were taken to be 8, 10, 12, 14, 16, 18, and 20.

These values were then combined according to the expression

$$y_{ijk} = \left(\beta_{ij} t_k + \varepsilon_{ijk}\right)^{1/p}$$

to obtain "raw" observations for the simulation with power index p= 1/3. Once these observations were generated, the power index required to straighten the curves was estimated and the estimated slopes were calculated. The one-way ANOVA was then applied to these slopes, yielding an F statistic for testing the equality-of-slopes null hypothesis. This process was repeated 1000 times for significance level calculations, and 200 times for power calculations. The estimated significance levels and power values are the proportions of generated F values that exceed the critical value from a table of the F distribution for the appropriate degrees of freedom.

σ	σ_β	β_1	β_2	β_3	$n_i = 3$	$n_i = 6$	$n_i = 12$
.45	.02	.37	.37	.37	.049	.042	.041
.10	.02	.37	.37	.37	.054	.045	.054
.45	.02	1.00	1.00	1.00	.051	.054	.050
.45	.01	1.00	1.00	1.00	.046	.052	.047

Estimated Significance Levels for the Test of Equal Means when the Fixed Exponent Test Has Significance Level 5%. The Computations are Made for a Selection of Parameter Values and Sample Sizes.

There appears to be no significant differences between the given significance level of 5% and the values obtained from the estimation process.

Power values were also computed using the known index, p. These quantities are given, for comparison, in the following table along with the estimated powers from the simulation.

σ	σ_β	β_1	β_2	β_3	$n_i = 3$	$n_i = 6$	$n_i = 12$
.50	.045	.382	.375	.344	.127(.14)	.188(.25)	.454(.45)
.45	.020	.384	.378	.356	.177(.20)	.347(.52)	.771(.87)
.20	.020	.384	.378	.356	.237(.20)	.477(.52)	.861(.87)
.45	.040	.500	.450	.400	.497(.55)	.899(.945)	1.00(1.0)

Estimated and Computed (in parentheses) Powers for the Tests of Equal Slopes for Selected Parameter Values and Sample Sizes.

Although the power values appear to be somewhat lower for the estimation process, only one value differs significantly from the computed power. Consequently, at least within the scope of this rather limited simulation study, the conjecture that estimating the power index has little effect on the test characteristics is borne out.

5. AN APPLICATION

The nonparametric analysis of a particular set of tumor growth data was made by Koziol and Maxwell, 1981. The data, repeated from their study in Appendix 2, represent tumor sizes at selected times for 3 groups of rats subjected to different immunotherapies.

Censoring due to the deaths of subjects, and nonstandard growth patterns caused by the remission of tumors, are distinctive features of the data. Both phenomena will lead to possible outliers in the estimated slope data, hence it will be highly desirable to use a robust method of ANOVA in this problem.

The estimated power index for the data is 0.305. The fact that this quantity is near 1/3 suggests that a linear dimension of tumor volume has a growth rate that is nearly a linear function of time. A schematic diagram of the estimated slopes is given in Figure 1.

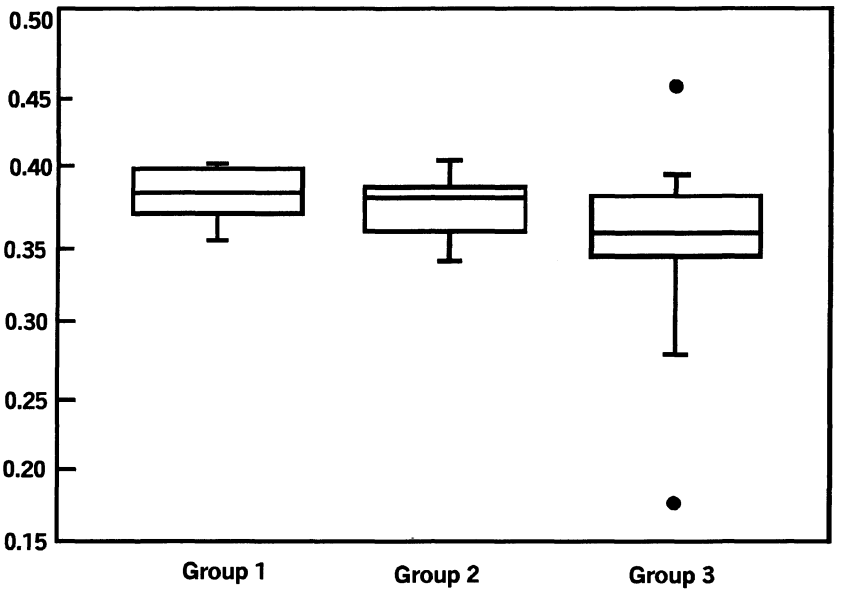

Figure 1. Schematic Diagram of Tumor Growth Rates for Three Groups of Rats

A trimmed mean ANOVA (Koopmans, 1987) with a 20% trimming fraction yields a *P*–value of 0.0772 for the test of equal slope means. The *P*–value achieved by the Koziol–Maxwell method for this data was 0.160. Moreover, by applying a 10% Fisher Least Significant Difference analysis to the data (Miller, 1966, or Koopmans, 1987), we can conclude that group 3 has a significantly smaller mean tumor growth rate than do the other two groups. These two groups are indistinguishable at the 10% level, suggesting that treatment regimen 3 is superior to the others.

6. AN APPLICATION BASED ON THE USE OF TRANSFORMATIONS

A physician from the University of New Mexico School of Medicine undertook an experiment to study the effects of various chemical environments on the rate of removal of insulin by hepatic cells from a fluid perfused through rats' livers. Seven chemical environments were established and a varying number of trials, each involving a single rat, was run for each environment. We will designate the groups of rats exposed to these environments as groups 1 through 7.

A perfusate with a known amount of insulin was introduced into the circulation system at time 0 and then fluid was removed for testing at times 5, 10, 15, 20, 30, 45, 60, 75, and 90 minutes. A substance was added to the withdrawn fluid to precipitate out the degraded insulin by-products, and the concentration of remaining insulin at each time was then determined by subtraction. These concentrations, in percents, are given in Appendix 2.

A commonly used model for this kind of data (in decimal, rather than percent form) is the following logistic model :

$$r(t) = \frac{1}{1 + e^{bt}}$$

Note that this function has value 1, or 100%, at t = 0. This model can also be represented in terms of the logistic transformation as

$$\log\left[\frac{1 - r(t)}{r(t)}\right] = bt$$

This expression has a useful interpretation from the viewpoint of this paper. It suggests that, after carrying out the transformation $f(x) = (1 - x)/x$, the logarithm, which is the power transformation with index $p = 0$, has

straightened the curve, *f(r(t))*, and produced a line through the origin. Moreover, the parameter that determines the rate of change of the original function is simply the slope of this line. Since this rate of change is the feature we are after, the slope is, again, the appropriate functional to use to distinguish between groups.

Because the perfusion system in this problem is a recirculating one, it is not clear that the logistic model is appropriate. However, it is an easy step from this interpretation to the extension of the logistic model to a two-parameter family of models defined by the equation

$$f_p\left[\frac{1-r(t)}{r(t)}\right] = bt$$

where f_p is the power transformation with index p. Our method then allows us to fit the appropriate member of this family to the data and obtain the estimated slopes by the simple expedient of pre-transforming the data with the transform $f(x) = (1-x)/x$ before carrying out the straightening process.

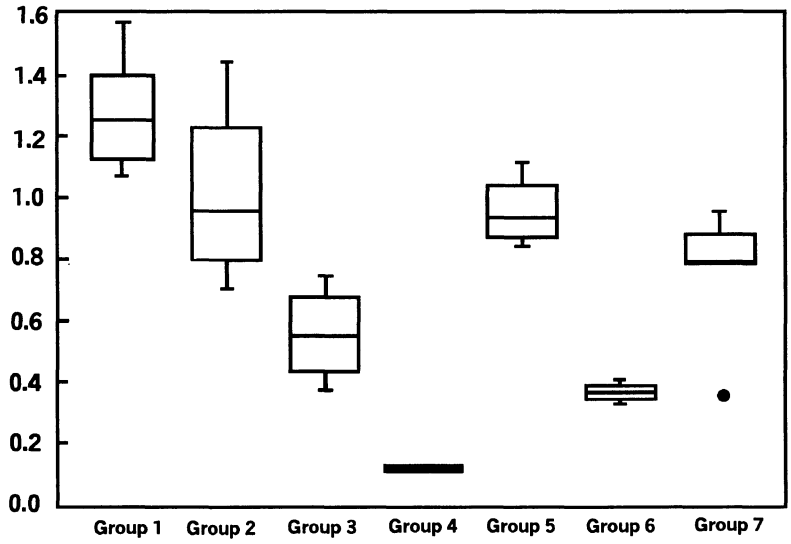

Figure 2. Schematic Diagram of Slopes for Insulin Perfusion Data

For the perfusion data, our procedure produced an estimated power index of 0.881, which (solving for $r(t)$) suggests that the model

$$r(t) = \frac{1}{1+(bt)^{1.135}}$$

fits the data better than does the logistic model. A schematic diagram of the estimated slopes for the 7 groups is given in Figure 2.

An outlier appears in group 7, and the data display unequal variation from group to group. Group 4, consisting of two observations, was a control group in which the effect of the apparatus alone was being tested. It is apparent from Figure 2 that the apparatus had minimal influence on the experiment and this group was eliminated before testing the differences among the remaining groups. An ANOVA was carried out based on 10% trimmed means. The *P*-value for this test was less than 0.00001, indicating considerable differences among means for the 6 remaining chemical environments. Fisher's Least Significant Difference Method at the 5% significance level produced the groupings

{group 3, group 6} < {group 2, group 5, group 7} < {group 1}

Thus, chemical environments 3 and 6 had the least influence on the rate of insulin removal, environments 2, 5, and 7 a greater influence, and environment 1 the greatest influence. Differences within groups are indistinguishable at the 5% level.

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APPENDIX 1 – Some Distribution Theory.

In this appendix we show that if the curves produced by the individuals in the various groups are randomly censored, then the estimated slopes have heavy-tailed distributions. Specifically, it is assumed that if T_{ij} represents the censoring time for the *j*th individual in group *i*, then the T_{ij}'s are independent for all *i* and *j*, and each T_{ij} exceeds the first observation time t_1, with probability 1. It is also assumed that, whereas the T_{ij}'s may depend on the random slopes β_{ij}, they are independent of the random errors ε_{ijk}. This property is also shared by the indicator variables V_{ijk} which have the value 1 if $T_{ij} > t_k$ and are 0 otherwise.

Now, if $\hat{\beta}_{ij}$ is the estimated slope for the *j*th individual in the *i*th group, then we will show that $\delta_{ij} = \hat{\beta}_{ij} - \beta_{ij}$ has a contaminated normal distribution, and that $E(\hat{\beta}_{ij}) = \beta_i$ and $Var(\hat{\beta}_{ij}) = \sigma_\beta^2 + \sigma^2 E(1/\sum V_{ijk} t_k^2)$. (All sums are over the index, *k*)

The proof is based on the following least squares representation for $\hat{\beta}_{ij}$ with censoring:

$$\hat{\beta}_{ij} = \sum y_{ijk}^p V_{ijk} t_k / \sum V_{ijk} t_k^2$$

$$= \sum (\beta_{ij} t_k + \varepsilon_{ijk}) V_{ijk} t_k / \sum V_{ijk} t_k^2$$

$$= \beta_{ij} + \sum \varepsilon_{ijk} V_{ijk} t_k / \sum V_{ijk} t_k^2$$

We obtain from this expression the representation

$$\delta_{ij} = \sum X_{ijk} \varepsilon'_{ijk} ,$$

where $\varepsilon'_{ijk} = \varepsilon_{ijk} / \sigma$. The ε'_{ijk}'s are independent standard normal variables, and

$$X_{ijk} = \sigma V_{ijk} t_k / \sum V_{ijk} t_k^2 .$$

Now, a result of Rivest (1981) shows that the distribution of δ_{ij} is the same as the distribution of the random variable $\varepsilon'_{ij1}U_{ij}$, where $U_{ij} = \sqrt{\sum X_{ijk}^2}$. But, since U_{ij} is a positive random variable with finite 4th moment, the result of Rivest quoted in Section 2 establishes that δ_{ij} has a contaminated normal distribution.

By the above least squares expression for β_{ij}, and the independence of X_{ijk} and ε'_{ijk}, it is clear that $\hat{\beta}_{ij}$ has the same expectation as β_{ij}. Consequently, only the expression for the variance of this variable remains to be established.

Write $Var(\hat{\beta}_{ij)} = Var(\beta_{ij}) + Var(\delta_{ij}) + 2Cov(\beta_{ij}, \delta_{ij})$. By Rivest's result, $Var(\delta_{ij}) = Var(\varepsilon'^2_{ij1}U_{ij}^2) = E(\varepsilon'^2_{ij1})E(U_{ij}^2)$. But a simple computation establishes that

$$U_{ij}^2 = \sigma^2 / \sum V_{ijk} t_k^2 .$$

Consequently,

$$Var(\delta_{ij}) = \sigma^2 E(1 / \sum V_{ijk} t_k^2) .$$

Finally,

$$\begin{aligned} Cov(\beta_{ij}, \delta_{ij}) &= \sum Cov(\beta_{ij}, X_{ijk}\varepsilon'_{ijk}) \\ &= \sum (E(\beta_{ij} X_{ijk}\varepsilon'_{ijk}) - E(\beta_{ij})E(X_{ijk}\varepsilon'_{ijk})) \\ &= \sum \left[(E(\beta_{ij} X_{ijk}) \cdot 0 - E(\beta_{ij})E(X_{ijk}) \cdot 0) \right] \\ &= 0 . \end{aligned}$$

Thus, since $Var(\beta_{ij}) = \sigma_\beta^2$, the result is established.

APPENDIX 2 – Data Tables.

Table 1. Tumor growth data (in mm^3)

Group	Mouse	Day										
		7	11	12	13	14	15	17	18	19	20	21
1	1	35.3	157.1	122.5	217.6	340.3	379.0	556.6	661.3	634.8		
	2	10.0	152.2	129.6	176.6	213.9	317.9	356.4	580.0	415.2	400.0	520.1
	3	27.0	122.4	196.1	196.1	332.2	388.9	469.3	397.1	505.4	541.5	
	4	55.0	95.0	205.9	205.9	270.0	307.3	405.1	726.0	950.4	661.5	798.0
	5	24.6	168.8	135.3	196.0	340.2	340.4	507.3	767.2	820.0	937.5	
	6	12.6	85.0	70.1	225.1	225.1	289.0	317.9	529.1	653.4	687.7	750.2
	7	35.2	129.8	180.0	274.7	420.1	340.3	507.3	634.8	714.3	777.6	912.6
	8	29.8	157.0	126.8	202.5	225.0	307.2	320.1				
	9	70.0	129.7	196.0	205.8	375.7	419.1	421.2	573.4	701.8		
	10	29.5	156.9	176.7	225.0	289.0	372.6	379.2	529.2	573.3	560.1	520.0
2	1	48.6	115.3	90.8	176.5	317.9	421.2	529.2	388.8	629.0		
	2	66.7	289.0	215.6	268.8	388.8	487.4	551.3	767.1	677.6	846.4	634.9
	3	24.5	143.7	115.0	90.7	194.3	559.6	629.3	573.3	540.0		
	4	14.4	84.7	135.2	191.2	176.4	356.4	397.1	551.4	605.0	480.0	634.8
	5	10.8	70.0	80.0	118.3	156.8	215.6	268.8	346.8	551.3	946.4	440.0
	6	11.3	15.0	205.8	289.0	346.8	529.2	629.2	551.3	714.2	772.6	806.4
	7	18.0	56.7	115.3	96.8	177.5	268.8	320.0	372.8	487.4	573.3	683.6
	8	60.0	166,6	166.7	324.0	420.0	440.0	634.8	500.0	289.0	560.0	748.8
	9	29.4	152.1	122.4	186.3	186.3	274.7	485.1	397.0			
	10	41.1	186.2	176.6	274.6	361.0	379.1	440.0	415.2			
3	1	12.5	108.0	96.8	186.2	202.5	213.8	379.1	379.0	433.2	379.0	500.0
	2	23.4	129.0	176.5	196.6	320.0	397.1	500.0	687.7	767.1	806.4	937.5
	3	22.2	65.0	176.4	191.3	213.8	274.6	405.0	520.0	796.6	978.7	864.0
	4	11.2	52.9	70.0	129.6	152.1	303.5	415.0	440.0	556.7	812.5	1014.0
	5	66.6	147.0	260.1	420.0	460.0	653.4	806.4				
	6	11.4	115.2	65.1	32.0	10.8	3.2	1.4	0.0	0.0	0.0	0.0
	7	22.1	55.0	115.2	55.0	93.6	118.8	118.3	230.4	217.6	243.2	217.6
	8	40.5	156.8	65.0	84.7	191.2	291.5	400.0				
	9	32.0	44.6	108.9	258.8	247.5	405.0	372.6	388.0	451.3	580.0	573.3
	10	10.0	118.3	166.6	176.4	186.2	340.2	361.0	556.6	556.6	268.8	346.8

Table 2. Insulin perfusion data (in %)

Group	Rat	Observation Time(Min.)								
		5	10	15	20	30	45	60	75	90
1	1	91	73	73	72	58	41	30	31	30
	2	90	83	82	63	49	36	33	34	32
	3	90	73	76	67	57	40	42	44	43
	4	83	89	96	82	74	64	44	38	36
	5	96	93	90	76	63	45	40	33	29
	6	76	88	89	78	69	55	43	35	31
	7	94	94	82	68	56	45	40	35	36
	8	93	98	81	79	63	55	42	38	37
	9	95	91	87	71	65	46	40	36	30
	10	95	81	79	65	55	46	40	38	36
	11	89	88	84	68	64	49	38	41	34
2	1	92	95	99	92	72	63	59	51	49
	2	92	88	74	71	59	48	48	46	40
	3	92	74	68	61	55	44	31	33	35
	4	93	91	84	73	68	48	48	50	45
	5	92	92	88	89	86	72	65	60	59
3	1	92	98	91	90	84	67	60	48	44
	2	93	94	97	80	74	70	63	55	54
	3	93	93	94	90	81	74	73	65	54
	4	93	93	94	97	91	83	78	70	61
4	1	89	89	93	99	91	98	90	92	89
	2	95	92	92	92	97	94	97	90	90
5	1	92	82	74	66	58	51	47	43	47
	2	93	88	81	75	63	53	42	43	35
	3	92	80	86	93	72	62	55	46	38
	4	92	98	87	78	68	56	51	47	47
6	1	92	96	93	90	78	83	70	67	65
	2	94	99	89	87	91	92	81	71	65
	3	97	94	89	83	88	85	74	70	68
	4	95	90	89	89	85	83	77	74	63
7	1	79	89	96	91	92	80	83	68	64
	2	98	97	96	89	91	72	58	45	35
	3	95	89	89	83	66	61	52	42	39
	4	99	93	92	91	83	65	57	46	44
	5	86	91	91	87	68	68	57	50	42