Application of jackknife procedures to inter-experiment comparisons of parameter estimates for the Michaelis–Menten equation

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The jackknife procedure is introduced as a means of making comparisons among Michaelis–Menten parameter estimates for six different experimental conditions. In addition to providing a solution to the general inter-experimental comparison problem, the jackknife procedure will provide valid parameter estimates even when some of the assumptions usually required for statistical analysis are violated, e.g., the random errors are not normally distributed and the variances are not homogeneous. Other recent variations of the jackknife have also been introduced and briefly investigated: (i) the linear jackknife, which is more efficient computationally, and (ii) the weighted jackknife, which reduces the influence of design points (substrate concentrations) that have an excessive influence on the precision of parameter estimates.

The literature on parameter estimation for Michaelis–Menten enzyme-kinetic data is extensive, originating in the 1930s and continuing to the present, with three recent extensive review papers by Henderson (1978), Cleland (1979) and Atkins & Nimmo (1980). The progress achieved mirrors developments in computational capabilities and advances in statistical methodology. In addition, inter-experimental comparisons of these parameters are often required to distinguish among various steady-state or inhibition kinetic mechanisms. There is, however, little in the literature to facilitate the objective comparison of these parameters. Henderson (1978), Nimmo & Atkins (1979) and Porter & Trager (1977) provide means for comparing parameter estimates restricted to only two experiments. All too often, for comparisons between more than two experiments, investigators must rely on subjective methods, such as a graphical approach, to determine the effect of an experimental variable on the Michaelis–Menten parameters. In the present paper we describe the application of the jackknife procedure for comparing parameter estimates for any number of different experimental conditions. Another advantage of the jackknife procedure, even for estimating parameters for a single experiment, is its validity robustness, i.e., the parameter estimates obtained are somewhat free of error distribution and variance homogeneity assumptions.

Cornish-Bowden & Wong (1978) and others consider that the main disadvantage of the jackknife is the amount of computation required. A recent

variant of the regular jackknife, referred to as the 'linear jackknife' (Fox *et al.*, 1980), preserves the regular jackknife's advantages and is computationally more efficient. In addition, Hinkley (1977) has developed a weighting procedure for the regular jackknife (a weighted jackknife) that incorporates design factors in the estimation procedure and reduces the influence of high leverage points, i.e., a few substrate concentrations that are well removed from most of the remaining points. A weighted linear jackknife (Fox *et al.*, 1980) should then provide further assistance in obtaining valid estimates and confidence intervals while not becoming computationally burdensome.

The present paper will briefly review the regular jackknife procedure and introduce the linear-jackknife and the weighted-linear-jackknife procedures in the context of the inter-experimental comparisons of Michaelis–Menten parameters for the data of G. T. Miwa & A. Y. H. Lu (1981). All three jackknife procedures have been applied and compared for these data in which the parameters were compared under six different experimental conditions.

Theory

The jackknife procedure was introduced by Quenouille (1956) as a method for eliminating bias in estimating parameters. Tukey (1958) proposed that the jackknife be used for robust interval estimation. Mosteller & Tukey (1977) provide a clear, non-mathematical exposition, with examples

using the jackknife, whereas Miller (1974) presents an excellent review of the statistical literature dealing with the jackknife. Cornish-Bowden & Wong (1978) obtained such promising results with the jackknife that they have suggested that it "should be seriously considered as a general technique for analysis of enzyme kinetic results."

A non-linear model representation of the Michaelis-Menten equation is as follows:

$$v_i = \frac{V[S]_i}{K_m + [S]_i} + e_i; \quad i = 1, 2, \dots, n \quad (1)$$

where v (the reaction velocity) and $[S]$ (the substrate concentration) are observed, V (maximum reaction velocity) and K_m (Michaelis constant) are the parameters to be estimated, the e 's are the random error components and n denotes the sample size.

Regular jackknife procedure

The regular jackknife procedure requires $(n+1)$ non-linear least-squares estimates of V and K_m . Estimates are obtained by using all n data points ($\hat{V}_0, \hat{K}_{m,0}$), as well as being calculated from the $(n-1)$ data points with the i th observation deleted ($\hat{V}_{-i}, \hat{K}_{m,-i}$). Pseudo-values for the parameter estimates are defined as:

$$J_i(\hat{V}) = n\hat{V}_0 - (n-1)\hat{V}_{-i} \quad (2a)$$

$$J_i(\hat{K}_m) = n\hat{K}_{m,0} - (n-1)\hat{K}_{m,-i} \quad (2b)$$

The jackknife estimates $[J(\hat{V}_0), J(\hat{K}_{m,0})]$ of (V, K_m) are then the mean of the pseudo-values, i.e.:

$$J(\hat{V}_0) = \frac{1}{n} \sum_{i=1}^n J_i(\hat{V}) \quad (3a)$$

$$J(\hat{K}_{m,0}) = \frac{1}{n} \sum_{i=1}^n J_i(\hat{K}_m) \quad (3b)$$

with the estimated variances:

$$S^2[J(\hat{V}_0)] = \frac{1}{n(n-1)} \sum_{i=1}^n [J_i(\hat{V}) - J(\hat{V}_0)]^2 \quad (4a)$$

$$S^2[J(\hat{K}_{m,0})] = \frac{1}{n(n-1)} \sum_{i=1}^n [J_i(\hat{K}_m) - J(\hat{K}_{m,0})]^2 \quad (4b)$$

Rather than omit a single observation at a time, groups of observations can also be deleted, as in Cornish-Bowden & Wong (1978). The pseudo-values can be used to set approximate confidence intervals by using Student's t -distribution with

$(n-1)$ degrees of freedom (for single-observation deletion).

The linear jackknife

Whereas the regular jackknife procedure requires $(n+1)$ iterative non-linear least-squares fits with n data points, an alternative method, the linear jackknife, developed by Fox *et al.* (1980), requires only one least-squares fit. The least-squares estimates of V and K_m when the i th point is deleted are obtained by finding the values $\hat{V}_{-i}$ and $\hat{K}_{m,-i}$, which minimize the following sums of squares:

$$\sum_{j=1, j \neq i}^n \left(v_j - \frac{V[S]_j}{K_m + [S]_j} \right)^2 \quad (5)$$

The linear-jackknife method is based on approximating expression (5) by a Taylor series expansion up to linear terms. Although the Michaelis-Menten equation is a non-linear function, it may be adequately represented as a linear function in a small region about $\hat{V}_0, \hat{K}_{m,0}$ and this allows computational simplifications. Fox *et al.* (1980) present general expressions for the linear-jackknife pseudo-values by using matrix notation. For the special case of the Michaelis-Menten equation, these linear-jackknife pseudo-values are presented in the Appendix (eqns. A1.a and A1.b) and are of the following form:

$$LJ_i(\hat{V}) = \hat{V}_0 + P(V) \quad (6a)$$

$$LJ_i(\hat{K}_m) = \hat{K}_{m,0} + P(K_m) \quad (6b)$$

The P 's are a measure of an observation's influence on the parameter estimates $\hat{V}_0, \hat{K}_{m,0}$. These expressions only require the determination of $\hat{V}_0, \hat{K}_{m,0}$ and not $\hat{V}_i, \hat{K}_{m,-i}$. Thus only one least-squares fit is needed.

Weighted linear jackknife

It is well known that, in regression analysis (linear and non-linear), certain design points (substrate concentrations here) will, *a priori*, have greater influence on the resulting fit than other design points (Hoaglin & Welsch, 1978). Hinkley (1977) has developed a weighting scheme that can be used with the jackknife and which is useful for unbalanced data, i.e., when a few of the design points (substrate concentrations) are well removed from the remaining points. The basic idea is similar to that employed in weighted least-squares, where velocity results from substrate concentrations with large variability are given less weight in estimating the resulting parameters. Here, the concern is that a few observations obtained at 'extreme' substrate concentrations can have an overly influential effect on the resulting parameter estimates and their estimated variability. Thus a measure of the distance of

a single design point from the centre of the design is calculated ($\hat{W}_i$), and observations obtained at substrate concentrations far from the centre of the design (large values of $\hat{W}_i$) are given a smaller weight ($1 - \hat{W}_i$) in the final parameter estimates than those closer to the centre of the design.

Fox *et al.* (1980) have also adapted this weighting procedure to the non-linear case, the weighted linear jackknife, and present general expressions for the pseudo-values. These results are presented for the special case of the Michaelis–Menten equation in the Appendix (eqns. A2.). One notes that they differ from the unweighted linear jackknife (eqns. A1.a and A1.b) by only a factor of $(1 - \hat{W}_i)$ in the second term, i.e., the perturbations, P 's, in eqns. (6a and 6b), are multiplied by a weighting term. Since the weighted perturbation terms sum to zero, the weighted linear-jackknife estimates are the same as the non-linear least-squares estimates; however, the precision of the estimates will differ.

Inter-experimental comparisons

The pseudo-values can be used as if they were independent, identically distributed estimates of the unknown parameters, and hence standard statistical procedures can be applied to make inter-experimental comparisons. Various statistical designs can be used, depending on how the experiments differ, e.g., a one-way analysis of variance design for changes in only one factor, factorial designs for several factors changing simultaneously, noise-reducing designs, such as randomized block or latin-square designs, etc. In addition, tests for interactions of experimental factors, trend tests for factors with quantitative levels, or comparisons of various linear functions of conditions using multiple-comparison procedures can all be obtained.

These inter-experimental comparisons can be made with any of the three jackknife procedures presented by employing the appropriate pseudo-values, i.e.: eqns. (2a) and (2b), regular jackknife; eqns. (A1.a) and (A1.b), linear jackknife; and eqns. (A2.a) and (A2.b) (in the Appendix), weighted linear jackknife.

Transformations

Mosteller & Tukey (1977) suggest that it is desirable to avoid situations where the sampling distribution of the estimated parameters (i) has one or more straggling tails, and/or (ii) is markedly unsymmetrical. Jackknifing the logarithm of K_m and V is in this spirit. In addition, Cornish-Bowden & Wong (1978) have had good success in using a logarithmic transformation, and they note also that it avoids meaningless negative parameter estimates from entering the calculations.

To apply a logarithmic transformation, one calculates pseudo-values by using $\log(\hat{V}_0)$,

$\log(\hat{K}_{m,0})$, $\log(\hat{V}_{-i})$, and $\log(\hat{K}_{m,-i})$ instead of $\hat{V}_0$, $\hat{K}_{m,0}$, $\hat{V}_{-i}$ and $\hat{K}_{m,-i}$, and then proceed as in the usual manner. For the regular jackknife, refer to eqns. (2a) and (2b), and for the unweighted and weighted linear jackknife, refer to eqns. (A3.a) and (A3.b) in the Appendix. It should be noted, however, that when transformations are used, the weighted linear-jackknife estimate may not be the same as the non-linear least-squares estimate.

Computer programs

All the computations needed have been easily generated on a computer and are readily available for the regular, linear or weighted-linear jackknife. The computer programs and their use have been described by Capizzi & Oppenheimer (1981) and are based on the data management, graphics and statistical package SAS (Statistical Analysis System) (Helwig & Council, 1979). The linear- and weighted-linear-jackknife programs use a matrix procedure of SAS that is similar to using the BASIC or APL computer language.

Experimental data

A set of experiments were run to determine the effect of the lipid phosphatidylcholine on the enzyme kinetics for the cytochrome *P*-450-catalysed *N*-demethylation of benzphetamine (G. T. Miwa & A. Y. H. Lu, 1981). Substrate concentrations ($[S]$) were varied (0.05, 0.1, 0.2, 0.5 and 1.0 mM), and duplicate initial rates for each substrate concentration were determined (v) in min^{-1} (a total of ten data points per experiment). The experiment was repeated for six different lipid concentrations ($[\text{phosphatidylcholine}] = 0, 2, 5, 10, 20, 30 \mu\text{g/ml}$). The purpose of the experiment was to determine if the phosphatidylcholine concentration selectively affected the V parameter (asymptote), but not the K_m parameter (Michaelis constant) for this enzyme reaction.

The objectives of the data-analysis problem are as follows:

(i) For each lipid concentration the estimates, standard errors of the estimates, and confidence intervals for the unknown parameters V and K_m were required.

(ii) A procedure was needed to determine whether V or K_m , obtained for the various lipid concentrations, were the same or not.

Results

Objective (i)

Four analytical procedures have been considered: (i) asymptotic normal-theory least squares (N); (ii) the regular jackknife (J); (iii) the linear jackknife (LJ); and (iv) the weighted linear jack-

Table 1. Comparison of four parameter-estimation procedures

For each of the six experiments, estimates of V and K_m are presented along with the estimated standard error and 95% confidence interval for: (N) least-squares asymptotic normal theory; (J) the regular jackknife; (LJ) unweighted linear jackknife; and (LJW) weighted linear jackknife. Abbreviation used: [PC], phosphatidylcholine concentration.

[PC] ($\mu\text{g/ml}$)	Theory	$V(\text{min}^{-1})$			$K_m(\text{mM})$		
		Estimate	Standard error*	95% Confidence interval	Estimate	Standard error	95% Confidence interval
0	N	8.84	0.61	(7.43, 10.26)	0.067	0.019	(0.024, 0.111)
	J	8.96	1.03	(6.91, 11.61)	0.070	0.024	(0.032, 0.153)
	LJ	8.78	0.93	(6.91, 11.15)	0.068	0.019	(0.036, 0.129)
	LJW	8.87	0.75	(7.32, 10.75)	0.069	0.016	(0.041, 0.115)
2	N	26.71	2.46	(21.03, 32.39)	0.099	0.032	(0.027, 0.171)
	J	27.38	4.29	(19.20, 39.04)	0.109	0.053	(0.037, 0.324)
	LJ	26.35	3.42	(19.64, 35.35)	0.101	0.037	(0.045, 0.230)
	LJW	26.84	2.73	(21.32, 33.78)	0.103	0.030	(0.053, 0.200)
5	N	49.79	3.89	(40.82, 58.76)	0.101	0.028	(0.037, 0.165)
	J	50.96	6.72	(37.82, 68.68)	0.109	0.038	(0.049, 0.242)
	LJ	49.07	5.70	(37.74, 63.81)	0.101	0.028	(0.054, 0.187)
	LJW	49.98	4.55	(40.67, 61.42)	0.104	0.023	(0.063, 0.169)
10	N	54.49	2.74	(48.17, 60.81)	0.070	0.014	(0.038, 0.102)
	J	55.00	4.31	(46.06, 65.67)	0.072	0.016	(0.044, 0.119)
	LJ	54.15	4.08	(45.67, 64.21)	0.070	0.014	(0.045, 0.109)
	LJW	54.58	3.32	(47.56, 62.63)	0.071	0.011	(0.050, 0.101)
20	N	53.73	2.90	(47.04, 60.42)	0.057	0.013	(0.027, 0.087)
	J	54.20	4.58	(44.77, 65.62)	0.059	0.014	(0.034, 0.101)
	LJ	53.45	4.40	(44.37, 64.38)	0.057	0.012	(0.035, 0.093)
	LJW	53.84	3.62	(46.23, 62.70)	0.058	0.010	(0.039, 0.086)
30	N	52.06	1.72	(48.09, 56.03)	0.048	0.0074	(0.031, 0.065)
	J	52.24	2.46	(46.97, 58.11)	0.049	0.0070	(0.035, 0.067)
	LJ	51.94	2.43	(46.72, 57.74)	0.048	0.0067	(0.035, 0.066)
	LJW	52.10	2.02	(47.72, 56.88)	0.048	0.0055	(0.037, 0.063)

* Since a logarithmic (base 10) transformation was used for the jackknife results, estimated back-transformed results are reported as follows:

$$\text{Standard error}(v) = [10^{\log(v)}] \{ \text{standard error } [\log J(\hat{v}_d)] \} (\log_e 10)$$

Table 2. Comparison of parameter estimates for V and K_m across the six experiments*

Comparisons are made with Duncan's New Multiple Range Test. Estimates having a letter in common are not statistically significantly different at the $P = 0.05$ level. The comparisons are made for (i) the regular jackknife, (ii) the linear unweighted, and (iii) the linear weighted jackknife.

[PC] ($\mu\text{g/ml}$)	$V(\text{min}^{-1})$		
	Regular jackknife	Linear unweighted	Linear weighted
30	52.24 A	52.94 A	52.10 A
20	54.20 A	53.45 A	53.84 A
10	55.00 A	54.15 A	54.58 A
5	50.96 A	49.07 A	49.98 A
2	27.38 B	26.35 B	26.84 B
0	8.96 C	8.78 C	8.87 C
Estimate of variability in logarithmic units ...	0.0222	0.0176	0.0100
[PC] ($\mu\text{g/ml}$)	$K_m(\text{mM})$		
	Regular jackknife	Linear unweighted	Linear weighted
30	0.049 A	0.048 A	0.048 B
20	0.059 A	0.507 A	0.058 A B
10	0.072 A	0.070 A	0.071 A B
5	0.109 A	0.101 A	0.104 A
2	0.109 A	0.101 A	0.103 A
0	0.070 A	0.068 A	0.069 A B
Estimate of variability in logarithmic units ...	0.1885	0.1231	0.0709

* The analysis was done in the $\log_{10}$ scale, but back-transformed (10^x) means are reported. Variability is measured on the logarithmic scale.

knife (LJW). All the jackknife procedures (ii–iv) employed a logarithmic transformation. Estimates of the parameters V and K_m , corresponding estimated standard errors and 95% confidence intervals for the experimental data are presented in Table 1 for each of the four procedures. No dramatic differences are observed in the results. The regular jackknife estimate of V and K_m is always the largest of the four, but the discrepancies are not sizeable. The lengths of the confidence intervals for the regular jackknife and the linear jackknife tend to be comparable, as do those for the normal theory and weighted linear jackknife. The lengths of the former are larger than the latter, this difference becoming small as [phosphatidylcholine] gets larger.

Objective (ii)

The pseudo-values have been evaluated by using a one-way fixed-effects analysis-of-variance model with experiment as the factor of interest. If an overall statistically significant experiment effect was observed, all pairwise comparisons were made by using Duncan's New Multiple Range Test (Steel & Torrie, 1960). The results are presented in Table 2. The estimated values of V have the following statistically

significant ($P < 0.05$) ordering ([PC] = phosphatidylcholine concentration; values are in $\mu\text{g/ml}$):

$$([PC] = 0) < ([PC] = 2) < ([PC] = 5) = ([PC] = 10) = ([PC] = 20) = ([PC] = 30)$$

and these results were obtained with all three jackknifing procedures. For the K_m values, no statistically significant differences were obtained with the regular or the linear jackknife. However, the weighted-linear-jackknife procedure indicated that the estimated K_m value for [phosphatidylcholine] = $30 \mu\text{g/ml}$ ($0.048 \mu\text{g/ml}$) is statistically significantly less than the estimated K_m values at [phosphatidylcholine] = 2 and $5 \mu\text{g/ml}$ (0.103 , $0.104 \mu\text{g/ml}$). One notes that this discrepancy between procedures is not due to differences in the magnitudes of the estimated K_m values, but in the estimates of experimental variability. The estimated within-experiment variance (pooled over all six experiments) for the weighted linear jackknife was 58% ($0.0709/0.1231$) of that for the linear jackknife, and 38% ($0.0709/0.1885$) of that for the regular jackknife. A similar situation exists for the V

values, but this did not result in disparate results among the three procedures.

The use of the logarithmic transformation had an additional beneficial effect by helping to stabilize the variances needed for the analysis-of-variance model.

Discussion

We have introduced the jackknife procedure as a means for handling the general inter-experimental comparison problem. Henderson's (1978) review paper discusses the dearth of published material on tests for the significance of the difference between the parameter estimates for two experiments. The methods he presents require the untenable assumption that the parameter estimates follow a normal distribution. Nimmo & Atkins (1979) consider that this approach can give erroneous results and prefer a non-parametric approach. Porter & Trager (1977) discuss a different non-parametric procedure, in connection with the direct linear plot, but this is applicable only for comparing across two experiments. At present, the jackknife procedure is the only available method for comparing across more than two experiments.

Since a drawback to the use of the jackknife procedure is the amount of computation required, we have also applied the linear jackknife that is computationally more efficient. The linear jackknife should not be thought of as an approximation to the regular jackknife, but instead as one of several similar methods of obtaining approximate confidence intervals. Although similar results have been obtained by using the linear and regular jackknife, this may not hold for all non-linear models, and may be a result of the regular nature of the Michaelis-Menten equation.

Study-design considerations are also an important factor in parameter estimation. For example, although Cornish-Bowden *et al.* (1978) reported good results for the direct linear plot when compared with non-linear least squares for moderate sample sizes, Kohberger (1980) found that the direct linear plot did not perform well and should not be used for harmonic spacing of the data (substrate concentration). The weighted jackknife incorporates design factors in the estimation procedure and reduces the influence of high leverage points. In our example the weighted jackknife greatly reduced the estimated measure of random variation, resulting in the ability to detect (statistically) smaller differences in parameter estimates. Further investigation is needed to assess which procedure provides the most valid estimate of variation.

As Cornish-Bowden & Wong (1978) point out, the jackknife procedure has much to offer, even for the case of parameter estimation for a single experiment. For example, in applying normal-

theory-least squares, the standard errors and confidence intervals reported in Table 1 are asymptotic results, and some concern is required about whether the sample size is sufficiently large (Gallant, 1975; Duncan, 1978). For our data with ten observations, it was not clear *a priori* that normal-theory least squares would give valid results. In addition, normal-theory least squares may be sensitive to the usual assumptions made for the random error component (e) in eqn. (1), i.e. normality and homogeneity of variance.

Storer *et al.* (1975) consider that every experiment and assay may have its own particular error structure and each series of experiments should be treated as a separate problem with respect to weighting, etc. These uncertainties underline the appeal of methods, such as the jackknife procedure, that are relatively insensitive to the way in which the random errors are distributed. In addition, Hinkley's (1977) use of robust regression procedures, as well as trimmed means, on the pseudo-values can provide additional protection against violations of underlying assumptions.

The jackknife procedure is quite versatile and flexible, and can readily be applied to diverse complex enzyme-kinetic models with several parameters (Herzfeld & Schlesinger, 1975). With an appropriate study design, the jackknife can also readily test the fit of a single model or compare several competitive models (Dammkoehler, 1966). Concern about computational issues is no longer a factor with the development of the linear jackknife (Fox *et al.*, 1980) and the availability of computer programs to automatically perform the jackknife operations (Capizzi & Oppenheimer, 1981). Further study is needed on the results of applying the linear and weighted linear form of the jackknife to a variety of enzyme-kinetic problems.

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APPENDIX

Algebraic expressions for the linear and weighted linear jackknife for the Michaelis–Menten equation

Pseudo-values

Fox *et al.* (1980) present general expressions for the pseudo-values by using matrix notation. What follows is an algebraic representation for the specific case of the Michaelis–Menten equation.

Define

$$\text{Sum}(p) = \sum_{j=1}^n \frac{[S]_j^p}{(\hat{K}_{m,0} + [S]_j)^p}$$

$$D = \hat{V}_0^2 [\text{Sum}(2) \text{Sum}(4) - \text{Sum}^2(3)]$$

$$\hat{W}_i = \frac{\hat{V}_0^2}{D} \frac{[S]_i^2}{(\hat{K}_{m,0} + [S]_i)^2} \left[\text{Sum}(4) - \frac{2 \text{Sum}(3)}{(\hat{K}_{m,0} + [S]_i)} + \frac{\text{Sum}(2)}{(\hat{K}_{m,0} + [S]_i)^2} \right]$$

= a measure of the distance of the i th design point (substrate concentration) from the centre of the design

$$r_i = v_i - \frac{\hat{V}_0 [S]_i}{(\hat{K}_{m,0} + [S]_i)}$$

= i th residual, i.e., the deviation of the i th predicted value from the observed response

$$B(V) = \left[\frac{\hat{V}_0^2 [S]_i}{\hat{K}_{m,0} + [S]_i} \right] \text{Sum}(4) - \left[\frac{\hat{V}_0^2 [S]_i}{(\hat{K}_{m,0} + [S]_i)^2} \right] \text{Sum}(3)$$

$$B(K_m) = \left[\frac{\hat{V}_0 [S]_i}{(\hat{K}_{m,0} + [S]_i)} \right] \text{Sum}(3) - \left[\frac{\hat{V}_0 [S]_i}{(\hat{K}_{m,0} + [S]_i)^2} \right] \text{Sum}(2)$$

Linear-jackknife pseudo-values

$$LJ_i(\hat{V}) = \hat{V}_0 + \frac{n}{D} \frac{r_i}{1 - \hat{W}_i} B(V) \quad (\text{A1.a})$$

$$LJ_i(\hat{K}_m) = \hat{K}_{m,0} + \frac{n}{D} \frac{r_i}{1 - \hat{W}_i} B(K_m) \quad (\text{A1.b})$$

The weighted linear jackknife differs only in that the second term in eqns. (A1.a) and (A1.b), i.e., the B 's, are multiplied by $(1 - \hat{W}_i)$ as follows:

Weighted-linear-jackknife pseudo-values

$$LJW_i(\hat{V}) = \hat{V}_0 + \frac{n}{D} r_i B(V) \quad (\text{A2.a})$$

$$LJW_i(\hat{K}_m) = \hat{K}_{m,0} + \frac{n}{D} r_i B(K_m) \quad (\text{A2.b})$$

Expressions needed to apply transformations

In order to apply a transformation, we require expressions that will represent $\hat{V}_i$ and $\hat{K}_{m,-i}$ in terms of $\hat{V}_0$ and $\hat{K}_{m,0}$. Note that the above pseudo-values can be obtained by using these relationships.

$$\hat{V}_{-i} = \hat{V}_0 - \frac{r_i}{1 - \hat{W}_i} B(V) \quad (\text{A3.a})$$

$$\hat{K}_{m,-i} = \hat{K}_{m,0} - \frac{r_i}{1 - \hat{W}_i} B(K_m) \quad (\text{A3.b})$$

This result applies to the linear jackknife; a similar expression for the weighted linear jackknife results by multiplying the B 's by $(1 - \hat{W}_i)$.

References

Fox, T., Hinkley, D. & Larntz, K. (1980) *Technometrics* **22**, 29–33