Ratios:
A short guide to
confidence limits and proper use

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Abstract

Researchers often calculate ratios of measured quantities. Specifying confidence limits for ratios is difficult and the appropriate methods are often unknown. Appropriate methods are described (Fieller, Taylor, special bootstrap methods). For the Fieller method a simple geometrical interpretation is given. Monte Carlo simulations show when these methods are appropriate and that the most frequently used methods (index method and zero-variance method) can lead to large liberal deviations from the desired confidence level. It is discussed when we can use standard regression or measurement error models and when we have to resort to specific models for heteroscedastic data. Finally, an old warning is repeated that we should be aware of the problems of spurious correlations if we use ratios.
In a number of situations, researchers are interested in the ratio of two measured quantities. For example, in bioassay researchers are interested in the potency of a drug relative to a standard drug (Finney, 1978). Similarly, whenever we calculate “percentage change” or “relative change” we calculate a ratio (Miller, 1986). Another example is inverse prediction in regression analysis. Assume researchers fit the linear model: \( y_i = \alpha + \beta x_i + \epsilon_i \) (with \( i = 1, \ldots, n \)) and then want to predict at which \( x_0 \) to expect a certain \( y_0 \) value. This calculates as \( x_0 = (y_0 - \hat{\alpha}) / \hat{\beta} \) which is again a ratio of the random parameter estimates \( \hat{\alpha} \) and \( \hat{\beta} \). Inverse prediction is often used in calibration procedures (cf. Kendall, Stuart, & Ord, 1991; Miller, 1986; Buonaccorsi, 2001).

Similar situations arise in psychology and in the neurosciences. Ratios of measured quantities have been calculated in the investigation of perceived speed (Hammett, Thompson, & Bedingham, 2000), perceived slant (Proffitt, Bhalla, Gossweiler, & Jonathan, 1995), distance perception (Emde, Schwarz, Gomez, Budelli, & Grant, 1998; Proffitt, Stefanucci, Banton, & Epstein, 2003), visual discrimination performance (Watson & Robson, 1981), human motor control (Carrier, Heglund, & Earls, 1994; Serrien et al., 2002; Serrien & Wiesendanger, 2001; Turrell, Li, & Wing, 2001), psychological and biological bases of stress, drug addiction, and emotion (Lees & Neufeld, 1999; Maes, Christophe, Bosmans, Lin, & Neels, 2000; Thomas, Beurrier, Bonci, & Malenka, 2001; Yamawaki, Tschanz, & Feick, 2004).

Specifying confidence limits for ratios is a well–known problem in statistics with a number of unusual properties. The classic solution to this problem is called “Fieller’s theorem” (Fieller, 1940, see also Fieller, 1944, 1954; Read, 1983; Buonaccorsi, 2001) and is routinely used in a number of areas (e.g., in bioassay and health economics, cf. Finney, 1978; Briggs, O’Brien, & Blackhouse, 2002). Quite surprisingly, however, this issue seems to be largely unknown in psychology and the cognitive neurosciences. For example, none of the above cited studies used Fieller’s method. Most studies unquestioningly used a method which I will call the “index” method and which turns out to require very specific assumptions about the distribution of numerator and denominator of the ratio. If these assumptions are not met, the method can lead to confidence limits with much too small coverage. Other studies used another ad–hoc method (the “zero–variance” method), which is even more problematic.

The index method is closely related to the use of indices which are determined on a per observation basis and then processed further as if they
were normal observations. Examples are the body mass index (body weight divided by height squared) or income per capita (total personal income divided by total population). Indices are quite frequently used in medicine and in econometrics and have been in the focus of a long and heated controversy about spurious correlations (Pearson, 1897; Neyman, 1979; Kronmal, 1993), such that some caution is in order here. I will sketch the main problems and remedies.

Before discussing the details of the different methods, let me describe the unusual problems posed by ratios. The main problem arises from the fact that the function $y/x$ has a singularity at $x = 0$. Therefore, if the denominator is noisy and “too close” to zero the estimate for the ratio goes astray. This problem is so serious that the probability distribution of the ratio shows unusual behavior. For example, there neither exists the expected value nor the variance for the ratio if the denominator is normally distributed. We can only specify “pseudo” values for the expected value and the variance in cases where the denominator is “far” from zero.

A further example for the unusual behavior of ratios is the Cauchy distribution. This occurs if, in addition to a normally distributed denominator, the numerator is also normally distributed (and both are independent and have an expected value of zero). The probability–density of the Cauchy distribution looks like that of a normal distribution, but with heavier tails. Neither the expected value nor the variance exist for this distribution. Even worse, if we calculate the mean of independent, identically Cauchy–distributed variables we find that the mean follows the same Cauchy distribution as each of the individual variables. That is, the mean is no more informative than any of the individual values (e.g., Johnson & Katz, 1970). This is in strong contrast to the “typical” behavior of random variables for which expected value and variance exist. Typically, calculating the mean of independent, identically distributed (i.i.d.) random variables leads to a decrease of the variance and therefore allows us to use the mean as a better estimate for the expected value.

Given this unusual behavior, it does not seem surprising that we need special methods to deal with ratios. I will discuss these methods in four parts:

The first part ("The standard case") discusses confidence limits for ratios if numerator and denominator are normally distributed. In this part, I give a simple geometric description of the Fieller method, a discussion of alternatives to Fieller’s method, and of recent developments in the area of the
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bootstrap which allows to relax the assumption of normality. Also, I show in
simulations under which conditions the often used index and zero–variance
methods fail and to which extent this is relevant for the interpretation of
existing studies. For this a number of sample studies are described and the
variability of numerator and denominator in these studies is compared to the
results of the simulations. (Details about the studies can be found in the
supplementary material provided with this article). A short summary with
recommendations is given at the end of this part.

The second part (“When can we use regression methods?”) views ratios
as the special case of a linear model with zero intercept, such that the ratio
corresponds to the slope. Also, we assume in this part homoscedastic data.
That is, the variability of the numerator is assumed to be constant over the
range of observations of the denominator. Linear models allow us to deal with
more complex situations as, for example, the comparison of ratios. I discuss
when we can use standard regression methods and when we have to use
the more complicated measurement error models and show the relationship
between Fieller method and measurement error models.

The third part (“When can we use indices?”) discusses which models
are needed to justify the use of indices and of the index method. We will
see that these models require a special form of heteroscedastic data with the
numerator having larger variability at larger values of the denominator.

The fourth part (“Beware: Spurious correlations and faulty ratio stan-
daards”) discusses the century–old problem of spurious correlations and faulty
ratio standards. Although these problems could appear with any of the meth-
ods discussed in the first three parts of the article, they are typically discussed
in the context of indices. We will see that the central question is whether
we are justified in assuming that the intercept of a linear model is zero (such
that the ratio corresponds to the slope of the model) or whether we have to
assume a non–zero intercept.

At the end of the article, an overall summary is given which allows the
practitioner to quickly decide which method is appropriate for the situation
at hand.
The standard case

Notation, assumptions, and point-estimate

Let $X, Y$ be random variables with expected values $E(X)$ and $E(Y)$ and the ratio of interest: $\rho := E(Y)/E(X)$. Very often, we encounter the case of $N$ paired measurements $(x_i, y_i)$ with $i = 1 \ldots N$ (assumed to be i.i.d.). When discussing the alternatives to Fieller’s method, we will see that some of these methods are restricted to paired measurements. For simplicity, I will restrict most of the discussion to this important case (for generalizations of the Fieller method to independent samples with unequal variances see Wu & Jiang, 2001; Lee & Lin, 2004).

Unbiased estimators for the expected values are the sample means $\bar{x}$ and $\bar{y}$. Their variances and covariances are estimated by the usual estimators:

\[
\hat{\sigma}^2_X = \frac{1}{N} \frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{x})^2
\]
\[
\hat{\sigma}^2_Y = \text{analogue to } \hat{\sigma}^2_X
\]
\[
\hat{\sigma}_{X,Y} = \frac{1}{N} \frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{x})(y_i - \bar{y})
\]

The coefficients of variation (CV) for the individual values are: $CV_X := \sigma_X / E(X)$ and $CV_Y := \sigma_Y / E(Y)$. The CVs for the sample means are $CV_{\bar{X}} := \sigma_{\bar{X}} / E(\bar{X})$ and $CV_{\bar{Y}} := \sigma_{\bar{Y}} / E(\bar{Y})$.

We assume that $(\bar{X}, \bar{Y})$ is (approximately or exactly) distributed as bivariate normal. Note, that due to the central limit theorem it is often a good approximation to assume the sample means to be normally distributed even if the individual values are not. For the bootstrap methods it is possible to relax the assumption of normality, see the discussion there. For generalizations of the Fieller method to non-normal distributions, as for example the Gamma, Poisson, or Weibull distributions, see Cox (1967) and Wu, Wong, and Ng (2005). An intuitive point-estimate for the ratio of interest is:

\[
\hat{\rho} = \frac{\bar{y}}{\bar{x}}
\]

This estimator is often used in conjunction with the different methods to determine confidence limits, as described below (an exception is the index
method). As we are dealing with a ratio, this estimator shows unusual behavior: First, neither expected value nor variance exist and the probability distribution is complex (cf. Marsaglia, 1965 and Hinkley, 1969, 1970). In cases where the denominator has a small CV we can specify “pseudo” values for expected value and variance. We do this by truncating the distribution such that the denominator cannot get close to zero. Second, the estimator is biased. This can be seen by performing a second order Taylor expansion on the ratio. Certain corrections have been proposed (Beale, 1962; Tin, 1965; Durbin, 1959; Rao, 1981; Dalabehera & Sahoo, 1995) but in practical situations they do not seem to perform much better than the estimator in Equation (2) (Miller, 1986), such that they will not be discussed here. Both problems are attenuated with larger sample sizes because then the CV of the denominator gets smaller.

**Fieller method**

The central statistics of the Fieller method (Fieller, 1940, see also Fieller, 1944, 1954; Read, 1983; Buonaccorsi, 2001) can be derived as follows: Because the difference of normal variables is also normally distributed, the term \( \bar{y} - \rho \bar{x} \) is normally distributed. Dividing this term by the appropriate estimator of the standard deviation gives us the statistics:

\[
T_0 = \frac{\bar{y} - \rho \bar{x}}{\sqrt{\hat{\sigma}_Y^2 - 2 \rho \hat{\sigma}_{X,Y} + \rho^2 \hat{\sigma}_X^2}}
\]

which follows approximately or exactly a Student–t–distribution with \( df \) degrees of freedom.

In most cases this relationship is only approximate and the t–distribution corresponds to the normal distribution (with \( df = \infty \)). The relationship is exact if the following conditions are met: (a) \( (\bar{X}, \bar{Y}) \) is exactly normally distributed (b) the variance–covariance matrix is known up to a proportionality constant: \( \sigma^2 \) (c) the proportionality constant is estimated by the estimator \( \hat{\sigma}^2 \) independent of \( (\bar{X}, \bar{Y}) \), such that \( \frac{df \hat{\sigma}^2}{\sigma^2} \) is distributed as chi–square with \( df \) degrees of freedom. In this case, the t–distribution has \( df \) degrees of freedom (cf. Buonaccorsi, 2001).

To obtain confidence limits for \( \rho \), we calculate the set of \( \rho \) values for which the corresponding \( T_0 \) values lie within the \( (1 - \alpha) \) quantiles of the t–distribution (denoted by \( t_q \) in the following). This results in a quadratic
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equation, the solution of which gives us three cases: (a) If the denominator $\bar{x}$ is significantly different from zero at significance level $\alpha$ (that is, if $\bar{x}^2/\hat{\sigma}^2_X > \frac{t^2}{\alpha}$), we obtain a normal confidence interval with the limits $l_1$ and $l_2$ ("bounded case"):

$$l_{1/2} = \frac{(\bar{x} \bar{y} - t_\alpha^2 \hat{\sigma}_{X,Y}) \pm \sqrt{(\bar{x} \bar{y} - t_\alpha^2 \hat{\sigma}_{X,Y})^2 - (\bar{x}^2 - t_\alpha^2 \hat{\sigma}^2_X)(\bar{y}^2 - t_\alpha^2 \hat{\sigma}^2_Y)}}{\bar{x}^2 - t_\alpha^2 \hat{\sigma}^2_X} \quad (4)$$

If the denominator $\bar{x}$ is not significantly different from zero, we first need to calculate:

$$t^2_{unbounded} = \frac{\bar{x}^2}{\hat{\sigma}^2_X} + \frac{(\bar{y} \hat{\sigma}^2_Y - \bar{x} \hat{\sigma}_{X,Y})^2}{\hat{\sigma}^2_X(\hat{\sigma}^2_X \hat{\sigma}^2_Y - \hat{\sigma}^2_{X,Y}^2)} \quad (5)$$

With this we can discriminate between: (b) If $t^2_{unbounded} > t_\alpha^2$, we obtain a confidence set which excludes only the values between $l_1$ and $l_2$, but all other values are included ("unbounded/exclusive" case). (c) If $t^2_{unbounded} < t_\alpha^2$, the confidence set does not exclude any value at all ("unbounded" case).

This might seem as quite a complex behavior, but it is possible to present these results in a simple, geometrical fashion which is equivalent to Fieller’s method (von Luxburg & Franz, 2004; Guiard, 1989; see also Milliken, 1982). For this, we depict $X$ at the abscissa and $Y$ at the ordinate of a coordinate system and draw a line from the origin to the estimates ($\bar{x}, \bar{y}$); as is shown in Figure 1a. The slope of this line corresponds to the ratio ($\frac{\bar{y}}{\bar{x}}$) and is graphically represented by the intersection of the line with a vertical line at $X = 1$. Now we need to determine the confidence limits for the ratio.

Because all points which lie inside the gray wedge project onto the same interval, all we need to do is to adjust the size of this wedge such that the appropriate confidence level for the ratio is achieved. von Luxburg and Franz (2004) showed that the wedge forms tangents to an ellipse centered at ($\bar{x}, \bar{y}$). The projection of the ellipse onto the abscissa corresponds to the marginal confidence interval of $\bar{x}$, the projection onto the ordinate corresponds to the marginal confidence interval of $\bar{y}$ and the shape of the ellipse is determined by the covariance $\hat{\sigma}_{X,Y}$.

Using this geometrical method, we can assess the qualitative behavior of the Fieller confidence limits. If the denominator ($\bar{x}$) is significantly different
from zero at a significance level of $\alpha$, then the ellipse does not touch the $y$–axis and we get normal, bounded confidence intervals (Figure 1a). Now assume the denominator is not significantly different from zero such that the ellipse touches the $y$–axis. In this case the result of the projection of the wedge onto the $X = 1$ line is unbounded: We either get a confidence set which exclude only a small part of all possible values (unbounded/exclusive case, see Figure 1b; the arrows indicate that the confidence set is unbounded), or a confidence set which does not exclude any value at all (unbounded case, Figure 1c).

Unbounded confidence sets are certainly a puzzling result and some remarks are necessary here: (a) for practical applications, we usually want bounded confidence intervals. A necessary and sufficient condition for this is that the $(1 - \alpha)$ confidence interval of the denominator does not contain zero (which is equivalent to the denominator being significantly different from zero at a significance level of $\alpha$). (b) if the denominator is not significantly different from zero, then its confidence interval allows values arbitrarily close to zero. In consequence, the ratio can assume arbitrarily large (or small) values and the confidence sets are unbounded. This implies that at the given confidence level we learned only little from our experimental data (in the unbounded/exclusive case), or nothing at all (in the unbounded case). While this might be a discomforting result, it is a simple consequence of the ratio we are interested in and there is no way to force a different outcome. In fact, different researchers (Gleser & Hwang, 1987; Koschat, 1987; Hwang, 1995) have shown that any method which is not able to generate unbounded confidence limits for a ratio can lead to arbitrary large deviations from the intended confidence level (which I will call the “Gleser–Hwang theorem”). We will see that this theorem limits almost all of the alternatives to the Fieller method, except for a special bootstrap method (the Hwang–bootstrap method) and for the case that the true ratio is bounded away from zero.

Note, that the unbounded confidence sets contribute to the overall performance of the method. That is, if in a certain situation there are on average, say 10% unbounded confidence sets, these will count as being including the true ratio. For a discussion of the conditional confidence level, given that the Fieller confidence limits are bounded, see Buonaccorsi and Iyer (1984). This leads to an interesting problem: If we assume that we report a measured ratio only if it has bounded confidence intervals, then we effectively use the conditional confidence level. This can, however, be arbitrarily low (this follows from the Gleser–Hwang theorem because this conditional pro-
procedure will never generate unbounded confidence limits; see also Neyman, 1954, Tsao, 1998, and Read, 1983). One solution was proposed by Tsao and Hwang (1998) who suggest to estimate the confidence as 1 in the unbounded case and as $1 - \alpha$ in the other cases (see also Kiefer, 1977).

**Alternative approaches**

In this section I give an overview of alternatives to Fieller’s method as discussed in the statistical literature or employed by previous studies. (I will not discuss Bayesian approaches here, because they are based on a different notion of confidence limits and a full treatment would go beyond the scope of this article. For application of Bayesian approaches to ratios see Mandallaz & Mau, 1981; Buonaccorsi & Gatsonis, 1988; Raftery & Schweder, 1993).

**Taylor method**

The Taylor method (sometimes also called delta–method) calculates a linear approximation for the sample estimates:

$$\frac{\bar{y}}{\bar{x}} \approx \rho \left(1 - \frac{\bar{x}}{E(X)} + \frac{\bar{y}}{E(Y)} \right)$$  \hspace{1cm} (6)

Because the approximation is linear, it is easy to calculate confidence limits for this function if we again assume that $(X, Y)$ is bivariate normally distributed. The approximate confidence limits (denoted by $l_1$ and $l_2$) are symmetric relative to the sample estimates $(\bar{x}, \bar{y})$ and will never be unbounded:

$$l_{1/2} = \hat{\rho} \pm t_q |\hat{\rho}| \sqrt{\frac{\hat{\sigma}_X^2}{\bar{x}^2} + \frac{\hat{\sigma}_Y^2}{\bar{y}^2} - 2 \frac{\hat{\sigma}_{X,Y}}{\bar{x} \bar{y}}}$$  \hspace{1cm} (7)

The Taylor approximation has virtues because the linear function is mathematically easy to handle. However, the approximation will fail for the “problematic” cases, when the denominator is close to zero (this is to be expected by the Gleser–Hwang theorem because the Taylor limits are never unbounded). But, if the denominator has a small CV the Taylor method provides a serious alternative to the Fieller method. We will see in the simulations that the Taylor method is a very good approximation in these cases (cf. Cox, 1990; Polsky, Glick, Willke, & Schulman, 1997; Gardiner, Huebner, Jetton, & Bradley, 2001).
Bootstrap methods

The bootstrap (Efron, 1979; Efron & Tibshirani, 1993) is a general purpose method which allows to determine confidence limits in an easy and consistent way, even for very complicated statistics. It uses the measured sample as a basis for re-sampling with the goal to create an approximation to the population distribution. For our ratio problem with \( N \) paired measurements, bootstrap methods would draw a large number of samples (with replacement) from the set of the measured values \((x_i, y_i)\). Each sample has the same size as the original sample and we would calculate for each sample the ratio \( \frac{y}{x} \). The distribution of these re-sampled ratios (the “empirical distribution”) is the basis for the calculation of the confidence intervals. In the simplest case, the confidence intervals are the \((1 - \alpha)\) percentiles of the empirical distribution (“percentile method”). Other methods perform certain corrections, most notably the widely used \( BC_a \) method (“bias corrected and accelerated”).

These standard bootstrap methods can provide an alternative to approximate solutions as the Taylor method, especially in cases where \((X, Y)\) is not normally distributed (Chaudhary & Stearns, 1996; Polsky et al., 1997; Briggs, Mooney, & Wonderling, 1999; Briggs et al., 2002).

However, standard bootstrap methods face two problems when dealing with ratios: (a) Bootstrap confidence limits can be erroneous if the variance of the statistic does not exist as in the case of ratios (Athreya, 1987; Knight, 1989). (b) Because bootstrap confidence limits cannot result in unbounded confidence limits the Gleser–Hwang theorem applies such that there can be arbitrary large deviations from the intended confidence level for ratios. We will see in the simulations that this problem occurs if the denominator is close to zero.

Hwang (1995) showed that these problems can be overcome by a special bootstrap method which does not perform the bootstrap on the ratio directly, but on \( T_0 \) in Equation (3). The method first uses the bootstrap to determine the \((1 - \alpha)\) quantiles of \( T_0 \) and then proceeds as the Fieller method does (i.e., solves the quadratic equation). Depending on the result of the quadratic equation, this method can produce unbounded confidence limits and is therefore the only alternative to Fieller’s method which is not limited by the Gleser–Hwang theorem. We will see in the simulations that the Hwang–bootstrap method performs as well as the Fieller method if the sample sizes are large enough. In addition, Hwang (1995) showed that for non-normal distributions with non-zero skewness, the Hwang–bootstrap method...
is superior to Fieller’s method: The Fieller method is only first order correct, with the coverage converging as $O(1/\sqrt{N})$ against the desired coverage, while the Hwang–bootstrap method is second order correct, converging as $O(1/N)$ (see also Hall, 1986, 1988 for first/second order correctness). While this qualifies the Hwang–bootstrap method as an excellent alternative to the Fieller method, it should also be clear that the standard bootstrap methods will not always fail. The Hwang–bootstrap is, however, more general and it is therefore safer to use this method than the standard bootstrap methods.

**Index method**

This method can only be applied to the special case of $N$ paired measurements. The idea is to determine the ratio for each of the $N$ subjects individually:

$$ r_i = \frac{y_i}{x_i} $$

(8)

From these individual ratios (or “indices”) the mean $\overline{r_i}$ and standard error are calculated. Assuming that the mean is approximately normally distributed, confidence limits are calculated.

The index method is used very often (almost all of the example studies in the supplementary material provided with this article used this method). We can justify the method in the context of a linear model if the denominator is bounded away from zero and if the data have a specific heteroscedastic structure, such that the the numerator has larger variability at larger values of the denominator. This model will be discussed in the section “When can we use indices?”.

Because the method is used so often and because it seems unlikely that the data in all these cases show the specific heteroscedastic structure (the studies typically do not report having tested for this), I will first discuss what happens if the method is applied to bivariate normal data. We will see that in this case the method can lead to large deviations from the desired confidence level. Also, if the mean ratio $\overline{r_i}$ is used as point–estimate for $\rho$ it shows systematic biases and can be much more variable than the ratio of the means $\overline{y}/\overline{x}$. 


Zero–variance method

Some studies (e.g., Glover & Dixon, 2001a, 2001b, 2002a, 2002b; Haffenden, Schiff, & Goodale, 2001; Danckert, Nadder, Haffenden, Schiff, & Goodale, 2002) estimated the variability of the ratio by dividing the individual numerator–value of each subject by the overall mean of the denominator (calculated across all subjects):

\[ r_i := \frac{y_i}{\bar{x}} \]  

From these individual ratios the mean and standard error were calculated. It is easy to show that this procedure is equivalent to dividing the mean of the numerator and its standard error by \( \bar{x} \), such that we get as estimates for the mean ratio \( \hat{\rho} = \frac{\bar{y}}{\bar{x}} \) and its standard error: \( \hat{\sigma}_{\hat{\rho}} = \frac{\hat{\sigma}_y}{\bar{x}} \). An inspection of the formulas shows that this procedure does not take into account the variability of the denominator. Clearly, this is problematic. To justify this approach, we would have to assume that the measured denominator corresponded to the true value of the denominator in the population such that the variability of the denominator were zero (for this reason, I call this approach the zero–variance approach). In consequence, the zero–variance approach will often underestimate the variability of the ratio and will therefore result in liberal statistical tests.

A numerical example

Before investigating the methods systematically, I will give a simple example. The example is taken from a study by Pang, Gao, and Wu (2002), the only study I found to provide enough detail to calculate the confidence limits using most of the different methods (because the sample sizes were small, the bootstrap would not make sense here and is omitted). The study reported four different ratios (which I denote with “P1”, “P2”, “P3”, “P4”) using the index method. For more details about the data see the supplementary material provided with this article. Also, as a tutorial example, raw data and results are given for one of the ratios in Table 1, such that it is possible to reconstruct the calculations.

| Insert Table 1 & Figure 2 about here |

Figure 2 a.–d. shows the 95% confidence limits according to each of the methods. There are large differences: In some cases, all alternatives to the
Fieller method lead to a much smaller width of the confidence intervals than the Fieller method. For example, in case “P1” the Fieller method gives an upper limit of 498, while all other methods estimate upper limits below 10. The discrepancy occurs because the denominator is just about significantly different from zero. If there were slightly more variability in the denominator, then it would not be significantly different from zero and the Fieller limits would be unbounded. This can be seen if we use the geometric construction method for the Fieller limits (Figures 2e. and f.). In case “P1” the ellipse almost touches the y–axis (which would result in unbounded limits).

The discrepancy suggests that the coverage of the alternative methods is smaller than intended. We will see in the simulations that this is indeed often the case. Of course, the alternative methods are not always as bad as in case “P1”. This can be seen in case “P2” where all methods lead to similar results.

Simulations
We saw that the alternatives to Fieller’s method likely can lead to a much smaller coverage than intended. But how general is this problem? I will present the results of Monte Carlo simulations which used known distributions of $(X, Y)$. All methods were applied to the simulated data, and the percentage of simulation runs in which the confidence limits contained the true values was determined. For a 95% confidence level, we expect that the confidence limits contain the true value in 95% of the simulation runs, while in 5% the confidence limits should not contain the true value (i.e., be significantly different from the true value). A liberal construction method will lead to a higher percentage of significant results, while a conservative construction method will lead to a lower percentage.

Methods
Each simulation is described in terms of the sample size $N$ of the paired measurements and the CVs of numerator and denominator. For simplicity the correlation is assumed to be zero, such that we explore a 3–dimensional parameter–space $(CV_X, CV_Y, N)$. This space is covered across typical ranges in the Figures 3 and 4. The use of the CVs allows us to compare the results of different studies with the simulations (see the data points which are plotted on top of the Figures 3 and 4). More details on these studies are given in the
supplementary material provided with this article. Note that the simulations are based on a correlation of zero which will not be the case in the example studies. However, further simulations showed that the results are essentially identical for a wide range of correlation coefficients (−.99 . . . +.99), such that this choice is not critical.

The random number generation for the normally distributed numerator and denominator was performed using an algorithm described by Kinderman and Ramage (1976) as implemented in the free data analysis language R (R Development Core Team, 2004). 95% confidence limits were calculated according to each of the methods, and the coverage of the true ratio $\rho$ was determined.

As “standard” bootstrap method I used the $BC_a$ method as described in Davison and Hinkley (1997) and implemented in the R–boot package (the S original was implemented by Angelo Canty, the R–port by Brian Ripley). Results for the percentile method were similar to the $BC_a$ method and are therefore not shown. The number of bootstrap replications was always $B = 2000$. For the Hwang–bootstrap method, I performed a $BC_a$ bootstrap on $T_0$ in Equation (3). Because the Hwang–bootstrap method is relatively new, I describe it in more detail here: We have a sample of paired measurements $(x_i, y_i)$ with $i = 1 \ldots N$ and want to bootstrap $T_0 = T_0(\bar{x}, \bar{y}, \rho)$ in Equation (3). For this, we generate $B$ bootstrap–samples. Each bootstrap–sample consists of $N$ pairs drawn with replacement from the original sample $(x_i, y_i)$. For each bootstrap–sample, we calculate the means $(\bar{x}^*, \bar{y}^*)$. Following Hwang (1995, p. 163/164 and p. 170), we use these bootstrap means to determine the empirical distribution of $T_0^* = T_0(\bar{x}^*, \bar{y}^*, \hat{\rho})$. Based on this empirical–distribution we determine the quantiles of $T_0^*$ and then proceed as with the Fieller method. Note, that the Hwang–bootstrap method (as well as the Fieller method) is not restricted to paired measurements, but can also be adapted to the case of independent observations (Fieller, 1954; Hwang, 1995; Lee & Lin, 2004). In this case, the denominator of $T_0$ will be different to reflect the different estimate for the standard deviation of $\bar{y} - \rho\bar{x}$.

For the index method, additional calculations were performed using trimmed means and Winsorized standard deviations as described by Tukey and McLaughlin (1963). Trimming was always 25% (cf. Rosenberger & Grasko, 1983).
Results & Discussion

Figure 3 shows the results of the simulations for small sample sizes \( (N = 20) \). The empirical confidence levels of the Fieller method are not shown because they are always close to 95%. The Hwang–bootstrap method performs equally well, while most other methods are only accurate if the CV of the denominator is small. The zero–variance method fails if the CV of the denominator is larger than that of the numerator. This leads to large deviations from the desired confidence level even in cases where the denominator has a small CV. Therefore we should not use the zero–variance method.

In Figure 3 all other methods are accurate if the denominator is typically significantly different from zero (this is left of the solid, vertical line). We might be tempted to infer from this that as soon as the denominator is significantly different from zero, all these methods are accurate. However, this is not the case for the index method, as can be seen if we increase the sample size.

Figure 4 shows the results for larger sample sizes \( (N = 500) \). The area where the denominator is typically significant (again: left of the vertical solid line) is now larger and stretches further to the right. Accordingly, the area where the bootstrap \( (BC_a) \) and Taylor methods are accurate also stretches further to the right.

For the index method, however, this area moved to the left. That is, by increasing the sample size we lose accuracy in this method. This problem occurs right in the area where most of the example studies are located (as indicated by the points plotted on top of the Figures 3 and 4). A closer look shows that there is a band of correct confidence levels for denominator CVs of about 1. We will see that left of this band the index method usually overestimates the value of \( \rho \) and right of this band the index method underestimates it. These biases lead to the deviations from the desired confidence level.

This can be seen in Figure 5 which shows the results of 40 simulations as error–bar plots. The simulations were performed left of the band (point “A”), in the band (point “B”), and right of the band (point “C”). We expect
about 2 significant deviations from the true ratio (given 95% confidence limits and 40 simulation runs) and this is what we find for Fieller method, both bootstrap methods, and the Taylor method. This is not surprising because we are for all these methods in unproblematic areas where the denominator is typically significant (because the results were similar, only the results for the Fieller method are shown; significant deviations are denoted by exclamation marks in the lower part of the figure).

For the index method, however, we can see two things: (a) The results are much more variable than with the other methods. This is due to the fact that the index method uses the individual ratios $y_i/x_i$ as the basis for calculating the estimator. For some of these individual ratios, the denominator will “hit” the problematic region around zero and this will lead to huge deviations in either positive or negative direction. The other methods do not have this problem because they first reduce the variability of the denominator by calculating its mean. (b) There is first a tendency to overestimate the ratio $\rho$ (point “A”), then the estimate is noisy but balanced (point “B”), and finally there is a systematic underestimation (point “C”).

Note, that the biases cannot be eliminated by using trimmed means and winsorized standard deviations. Trimming excludes systematically a certain percentage of the most extreme values from the statistics (Tukey & McLaughlin, 1963; Dixon & Tukey, 1968; Rosenberger & Grasko, 1983). Further simulations showed that trimming does indeed reduce the huge variability of the point estimator, but does not reduce the bias and therefore does not lead to better confidence limits, as can be seen in the corresponding panels in Figures 3 and 4.

In summary, the index method can fail badly if applied to bivariate normal data even in situations in which the denominator is significantly different from zero. In these situations, the Taylor and standard bootstrap methods both perform gracefully, while they fail if the denominator is not significantly different from zero. The zero–variance method fails if the denominator has larger variability than the numerator, while Hwang–bootstrap and Fieller methods never fail.
Recommendations for the standard case

Based on the previous discussion we can issue the following recommendations for the “standard” case that the means of numerator and denominator are approximately normally distributed (cf. Table 2): Fieller method and Hwang–bootstrap method can generally be used, with the Hwang–bootstrap method having advantages if there are deviations from normality. If the denominator is clearly significantly different from zero ($CV_X < 1/3$ if 95% confidence limits are intended), we can also use Taylor and the standard bootstrap methods. Note, that with sample sizes smaller than $N = 15$ the bootstrap methods (including the Hwang–bootstrap) lead to slightly smaller coverage than intended (for sake of brevity these simulations are not shown).

Index method and zero–variance method are problematic and should not be used. This does not mean that studies which used the index or zero–variance methods necessarily need to be wrong. For both method there are areas in the Figures 3 and 4 where these methods lead to the intended confidence level. For the index methods this is the case if the CV of the denominator is so small that the individual denominator values will hardly ever get close to zero (for 95% confidence limits this corresponds to $CV_X < 1$ and $CV_X < 0.03$ for $N = 20$ and $N = 500$, respectively). For the zero–variance method this is the case if the CV of the numerator exceeds the CV of the denominator. Also note that the index method can be appropriate if the data show a specific form of heteroscedasticity, see the section “When can we use indices?”.

When can we use regression methods?

We can view a ratio as the slope of a linear relationship with zero intercept. Therefore the question arises whether we could use standard regression methods to estimate the ratio and its confidence limits — which would be easier and more flexible than the methods discussed so far. And indeed, this is sometimes possible. However, we have to be careful about the assumptions we make. We will see that the most critical question is whether there is error in the measurement of the regressor (corresponding to the denominator of the ratio). Depending on this, we might have to use the more complex
measurement error models instead of standard regression models. In the first part of this section I will describe under which conditions we can choose regression models and in the second part I will describe situations which can be dealt with by regression methods.

**Measurement error models vs. standard regression**

To give an overview, I will describe the linear model in a form which allows for measurement error in the response as well as in the regressor (cf. Madansky, 1959; Fuller, 1987; Schaalje & Butts, 1993; Buonaccorsi, 1994, 1995; Cheng & Van Ness, 1999). Consider a regression model on true values:

\[ v_i = \alpha + \beta u_i + e_i \]  

(10)

with \((u_i, v_i)\) being the true values of the paired measurements \((x_i, y_i)\). The error \(e_i\) is often called “error in the equation” and assumed to be i.i.d. with zero mean and constant variance. To specify the model, we also need to know whether the \(u_i\) are random (the structural case) or whether they are fixed (the functional case, cf. Kendall, 1951, 1952; Dolby, 1976).

Often, there is measurement error (or “error in the variables”), such that the observed values \((x_i, y_i)\) do not correspond to the true values \((u_i, v_i)\). Typically, the errors are assumed to be additive:

\[
\begin{align*}
x_i &= u_i + c_i \\
y_i &= v_i + d_i
\end{align*}
\]

(11)

with the measurement errors \(c_i\) and \(d_i\) each assumed to be i.i.d. with expected values zero and all being uncorrelated with the \(u_i\) and the \(e_i\) of Equation (10). Using this model we can discuss the standard regression model, as well as measurement error models.

First, assume that the true values can be observed exactly such that \(x_i = u_i\) and \(y_i = v_i\) (i.e., \(c_i\) and \(d_i\) are zero and with zero variance). This results in the model:

\[ y_i = \alpha + \beta x_i + e_i \]  

(12)

This is the classic regression situation and we can use standard regression methods in both, the structural as well as the functional cases (e.g, Madansky, 1959; Sampson, 1974).
Second, assume that there is measurement error in the response $v_i$ (i.e., $d_i$ has non-zero variance), while we still can observe the regressor exactly such that $x_i = u_i$. This results in the model:

$$y_i = \alpha + \beta x_i + e_i + d_i$$  \hspace{1cm} (13)

This model is similar to the classic regression model of Equation (12) and indeed we can use standard regression methods if we assume that $d_i$ has constant variance. However, the estimation of the parameters can be improved if we have information about the measurement error, which is typically obtained by repeated measures on the same subject. With this information, it is also possible to account for non-equal variances of $d_i$ (Buonaccorsi, 1994, 1995), as well as for non-additive errors (Buonaccorsi, 1989, 1996).

Third, assume that the true values cannot be observed exactly (i.e., $c_i$ and $d_i$ have non-zero variance). In this case we have to use measurement error models. There is a large variety of different models. Standard textbooks are Fuller (1987) and Cheng and Van Ness (1999). Here, I will sketch two variants: (a) a “classic” structural errors-in-variables model. This model is interesting because it shows the typical issues related to measurement error models as well as the connection to the Fieller method. (b) the “Berkson model of a control experiment”, which offers an alternative solution if we have control over $x_i$ and which allows us to use standard regression methods.

For the “classic” structural errors-in-variables model assume that there is no “error in equation” (i.e., $e_i$ is zero with zero variance) and that the measurement errors $c_i$ are uncorrelated with the measurement errors $d_i$. Also, assume that the true values $u_i$ and the measurement errors are normally distributed. These assumptions create a bivariate normal distribution for the pair of observable variables $(x_i, y_i)$. The model has three important properties: (i) If we ignored the measurement error and used a standard regression procedure, this would lead to a downward bias in the estimate for the slope $\beta$. This bias is often called “attenuation” or “regression dilution” (cf. Spearman, 1904; Schmidt & Hunter, 1996; DeShon, 1998; Frost & Thompson, 2000; Charles, 2005). The importance of this issue can be seen by the fact that attenuation was a key argument in a recent discussion on semantic priming in Psychology (Greenwald, Draine, & Abrams, 1996; Draine & Greenwald, 1998; Dosher, 1998; Klauser, Draine, & Greenwald, 1998; Miller, 2000; Klauser, Draine, & Greenwald, 2000). Note, however, that attenuation is only a problem if we estimate $\alpha$ or $\beta$. If we only want to predict $y$ given a
certain \( x \) then we can use standard regression procedures. Also, if the measurement errors are correlated it is possible that there is not attenuation but that the slope is overestimated by standard regression procedures (Schaalje & Butts, 1993). (ii) The model is nonidentifiable as long as we don’t have additional information about the error–variances such that we cannot obtain a unique solution (cf. Reiersol, 1950; Madansky, 1959). This additional information can, for example, be the ratio of the variances of the measurement errors \( c_i \) and \( d_i \) which could be estimated by repeated measure methods. (iii) If the intercept is zero, the nonidentifiability problem disappears and the appropriate solution is the Fieller method. This shows the connection between measurement error models and Fieller method.

In the “Berkson model of a control experiment” we assume that we have control over \( x_i \), even though we cannot measure the corresponding true values accurately. This enables us to observe \( y_i \) at fixed, predefined \( x_i \)–values. If we assume that the measurement errors \( c_i \) have zero mean, then we get a model which is quite different from the classic measurement error model: While in the classic measurement error model the true values \( u_i \) and the measurement errors \( c_i \) are uncorrelated, now the \( u_i \) and the \( c_i \) are perfectly negatively correlated. Berkson (1950) showed that in this case we can use standard regression methods (see also Madansky, 1959; Fuller, 1987; Cheng & Van Ness, 1999). For a discussion of this model in the context of repeated measure designs with multiple subjects, see Buonaccorsi and Lin (2002).

In summary, we can use standard regression methods if: (a) we can measure the \( x_i \) very accurately. (b) we do not estimate \( \alpha \) or \( \beta \), but only want to predict \( y \), given a certain \( x \). (c) we have control over \( x_i \), even though we cannot measure the corresponding true value accurately (“Berkson model of a controlled experiment”).

**Application of regression methods to ratios**

With regression models the situation is simpler and we can apply standard methods as are described in most textbooks. This easily allows us to estimate \( \alpha \), \( \beta \) and the corresponding confidence intervals. If we assume the intercept \( \alpha \) to be zero, then \( \beta \) corresponds to our ratio of interest. Regression methods can, if applicable, also help us with more complicated situations. For example, if we want to compare two or more ratios obtained in different groups we can use the analysis of covariance (ANCOVA). For this we set up the model:

\[
y_{gi} = \beta y x_{gi} + e_{gi}
\]
with \( x_{gi}, \ y_{gi} \) being the values obtained in group \( g = 1...m \) for participant \( i = 1...n; \) \( \beta_g \) the ratios of interest and \( e_{gi} \) the errors. Standard ANCOVA methods then allow to decide whether the ratios are different (Miller, 1986).

Note, however, that even in situations in which we can use regression methods we sometimes need Fieller’s method. This is the case if we want to calculate ratios of the parameters estimated by regression methods, as for example in the inverse prediction described in the Introduction. Another classic example is the slope ratio assay (Finney, 1978). Here, researchers first calculate an ANCOVA as described in Equation (14), but then are interested in the ratio of two \( \beta_g \) estimates (typically indicating the effectiveness of a drug relative to a standard drug). Again, they need Fieller’s method for this ratio of regression parameters. In general, it is possible to calculate Fieller confidence limits for linear combinations of parameters of general linear models (Zerbe, 1978), generalized linear models (Cox, 1990), and mixed–effects models (Young, Zerbe, & Hay, 1997). For examples of such applications see Buonaccorsi and Iyer (1984) and Sykes (2000).

Ratios of estimated parameters can also occur in the context of nonlinear regression models (e.g., Bates & Watts, 1988) and nonlinear mixed effects models (e.g., Davidian & Giltinan, 1995; Vonesh & Chinchilli, 1997; Pinheiro & Bates, 2002). These models are designed to deal with general nonlinear problems and therefore can also deal with ratios. In addition, the nonlinear mixed effects models can handle repeated measure data, as are frequent in psychological and biological research. Typically, these models perform a linear approximation at the point of the estimated parameters and therefore can fail in a similar way as the Taylor method discussed in this article. But, if the denominator of the ratios have small CVs, these models will provide an elegant solution such that it can be beneficial to reformulate a statistical problem in terms of a nonlinear model (see also Cox, 1990).

### When can we use indices?

Linear models as described in the previous section assume that the residual errors are constant over the range of observations (“homoscedastic”). Sometimes this is clearly not the case (the errors are “heteroscedastic”). Two classes of models can improve this situation and lead to an interest in indices. Both models use standard regression methods, such that as soon as the models are specified the specification of confidence limits for the ratio of
interest pose no additional problems. For simplicity of presentation, I will assume in the following that the denominator of the ratios is bounded away from zero such that it cannot attain values close to zero. This is often the case in situations in which indices are used (cf. Belsley, 1972). Without this assumption we cannot justify the use of indices. Also, I assume that the regressor can be measured with negligible error, such that we don’t need to use measurement error models.

First, consider the case that we want to fit a structural regression model to our data:

$$y_i = \alpha + \beta x_i + e_{1,i}$$  \hspace{1cm} (15)

Assume that the residual errors $e_{1,i}$ are heteroscedastic. This can lead to serious deviations from the desired confidence level if we used standard regression methods to determine confidence limits for $\alpha$ and $\beta$. Often it is possible to correct for the heteroscedasticity by using weighted least squares analysis (e.g., Miller, 1986). Sometimes, it turns out that the errors are proportional to the absolute size of $x_i$ such that the $y_i$ spread out with larger $x_i$. In this case, we can use a special variant of weighted least–squares analysis and divide the whole equation by $x_i$ (Kuh & Meyer, 1955; Firebaugh & Gibbs, 1985; Kronmal, 1993):

$$\frac{y_i}{x_i} = \alpha \frac{1}{x_i} + \beta + e_{2,i}$$  \hspace{1cm} (16)

If now the assumptions of regression models are met, most notably that the new error term $e_{2,i} = e_{1,i}/x_i$ is homoscedastic and normally distributed, then we can determine confidence limits using standard regression methods (with $y_i/x_i$ and $1/x_i$ being response and regressor, respectively). Note, that although this method uses indices, it estimates the same parameters $\alpha$ and $\beta$ as the standard linear model in Equation (15) (Firebaugh & Gibbs, 1985). It is also possible to have more than one regressor; an example is given in the next section (“Beware: Spurious correlations and faulty ratio standards”) in Equation (25). These models are often used in econometrics, where the ratios are often called “deflated variables” and the denominator “deflator”. For a discussion of non–random denominators see Belsley (1972) and for a discussion of the case with measurement error in the denominator see Casson (1973).

Using this model we can also justify the index method, if we assume that
α in Equation (16) is zero:

\[
\frac{y_i}{x_i} = \beta + e_i
\]  

(17)

with β being the ratio of interest and e_i being the error, typically assumed to be i.i.d. as normal. Note the specific heteroscedastic structure we have to assume to justify this method.

Second, consider an allometric or power function model (Kleiber, 1947; Sholl, 1948; Nevill, Ramsbottom, & Williams, 1992; Nevill & Holder, 1994, 1995a; Dreyer & Puzio, 2001):

\[
y_i = \beta x_i^\gamma e_i
\]  

(18)

With \((x_i, y_i)\) being the observed values, \(\beta\) and \(\gamma\) the parameters, and \(e_i\) the error term. Sometimes the parameters can be estimated by log–transformation to a log–linear model. This results in:

\[
\log(y_i) = \log(\beta) + \gamma \log(x_i) + \log(e_i)
\]

(19)

If the assumptions of regression models are met for the log-linear model, most notably that \(\log(e_i)\) is homoscedastic and normally distributed, then we can use standard regression methods on Equation (19) to determine the confidence limits of \(\log(\beta)\) and \(\gamma\).

Allometric models can also incorporate more than two variables. A good example is given by Nevill et al. (1992) who showed that for recreational runners the 5–km run speed \(z_i\) is well predicted by an index of maximum oxygen uptake \(y_i\) and body mass \(x_i\). For this, they used the allometric model:

\[
z_i = \beta y_i^{\gamma_1} x_i^{\gamma_2} e_i
\]

(20)

and fitted it with log–linear regression. As result, they obtained the fit:

\[
z_i = 84.3 \frac{y_i^{1.01}}{x_i^{1.03}}
\]

(21)

Because the exponents are close to one, the fit contains essentially an index, such that in this case the use of an index seems warranted. Also, the model turned out to be superior to linear models and it seems biologically plausible that performance is affected by oxygen uptake relative to body mass. (For
a further discussion of allometric models and the relation to indices see also Nevill & Holder, 1995a, 1995b; Kronmal, 1993, 1995).

In summary, there are two models which make accepted use of index variables: The linear model with correction for heteroscedasticity by division and the allometric model. Both models assume that the denominator is bounded away from zero and heteroscedastic structures of the data, with the $y_i$ spreading out in a fan–like fashion with larger $x_i$ values.

**Beware: Spurious correlations and faulty ratio standards**

Spurious correlations are a famous and much discussed problem (e.g., Pearson, 1897; Kronmal, 1993; McShane, 1995; Nevill & Holder, 1995b; Kronmal, 1995). We will see that spurious correlations can occur if numerator and denominator of a ratio are linearly related with non–zero intercept and inappropriate methods are used, typically involving indices.

Consider that we are interested in the relationship between two measurements $y_i$ and $z_i$, but want to “correct” for the effect of a third variable $x_i$. A famous, hypothetical example was given by Neyman (1952): A researcher relates the number of babies to the number of storks in a number of different counties. Because larger counties inhabit more women and consequently more babies (and more storks), the researcher wants to correct for the number of women. Table 3 gives a simplified version of the data.

First, consider the accepted way to do the correction: For this we use partial regression analysis and set up a restricted model and a full model:

$$y_i = \alpha_{rest} + \beta_{rest} x_i + e_{1,i} \quad (22)$$

$$y_i = \alpha_{full} + \beta_{full} x_i + \gamma z_i + e_{2,i} \quad (23)$$

With $y_i$ being the number of babies, $x_i$ the number of women, and $z_i$ the number of storks; $x_i$ and $z_i$ assumed to be random and measured with negligible error. We can think of partial regression as a two–step process: We first fit the restricted model (22). This model is designed to linearly predict the babies ($y_i$) based on the number of women ($x_i$). In the second step, we determine how much the fit is improved if we use the full model (23) which also
includes the number of storks \((z_i)\). (If \(z\) were a factor, we would replace \(\gamma z_i\) by parameters indicating the effects at the different factor levels. This would correspond to an ANCOVA; cf. Maxwell, Delaney, & Manheimer, 1985). Visual inspection of the example data in Table 3 shows that the number of babies is almost perfectly predicted by the number of women, such that the addition of the storks does not improve the fit significantly. Therefore, we conclude that number of storks has no influence on the number of babies.

This standard partial regression analysis assumes again that the errors \(e_{1,i}\) and \(e_{2,i}\) are homoscedastic. If the errors are heteroscedastic and scale with the size of \(x_i\), we can apply the correction discussed in the section “When can we use indices?” and divide both equations by \(x_i\). This results in:

\[
\frac{y_i}{x_i} = \alpha_{\text{rest}} \frac{1}{x_i} + \beta_{\text{rest}} + e_{3,i} \\
\frac{y_i}{x_i} = \alpha_{\text{full}} \frac{1}{x_i} + \beta_{\text{full}} + \gamma \frac{z_i}{x_i} + e_{4,i}
\]

(24)

(25)

If now the errors are homoscedastic, we can proceed as before with the standard regression methods. Note, that these corrected models estimate the same parameters \(\alpha_{\text{rest}}, \alpha_{\text{full}}, \beta_{\text{rest}},\) and \(\beta_{\text{full}}\) as the models (22) and (23) (Firebaugh & Gibbs, 1985).

Now, consider the problematic way to do the correction: Here, we simply divide the number of babies \((y_i)\) and storks \((z_i)\) by the number of women \((x_i)\) and then investigate the linear relationship between these individual ratios. This results in:

\[
\frac{y_i}{x_i} = \beta_{\text{full}} + \gamma \frac{z_i}{x_i} + e_{5,i}
\]

(26)

Typically, \(\gamma\) is tested against zero. This corresponds to a comparison of the full model (26) with the restricted model:

\[
\frac{y_i}{x_i} = \beta_{\text{rest}} + e_{6,i}
\]

(27)

Comparing these models to the partial regression models with correction for heteroscedasticity in the Equations (24) and (25) shows that the models are equivalent if we assume that \(\alpha_{\text{rest}}\) and \(\alpha_{\text{full}}\) in Equations (24) and (25) are zero. Because \(\alpha_{\text{rest}}\) and \(\alpha_{\text{full}}\) correspond to the intercepts in Equations (22) and (23) this means that we assume the intercepts of the linear relationships between \(y_i\) and \(x_i\) to be zero. This assumption of zero intercept is at the core
of the debate about spurious correlations (Kuh & Meyer, 1955; Firebaugh, 1988). The problem is that if the intercepts deviate from zero then the correction does not work properly.

In our stork example, this can be seen in Table 3: The birth-rate $y_i/x_i$ is highly and significantly correlated with the stork-rate $z_i/x_i$, such that based on this problematic analysis we would conclude that there is a strong dependence. This dependence, however, is only “spurious” and is generated by the fact that the intercepts in the Equations (22) and (23) are not zero (if we extrapolate the data, there are $y_0 \approx 10$ babies at $x_0 = 0$ women).

Now, one might argue that there is indeed theoretical reason to assume that the intercept should be zero: Obviously, if there are no women, there cannot be any babies (McShane, 1995, but see: Kronmal, 1995). However, this zero–point can easily be obtained if the data are non–linear beyond the range of observations. An every–day example would be the fuel–efficiency of cars. For longer distances, the fuel consumed is linear to the distance traveled. For short distances, however, this linearity breaks down because here cars need an disproportionate large amount of fuel. Therefore, we would be wrong if we compared the fuel efficiency (expressed as a ratio: miles per gallon or liters per 100 kilometers) of one car that was used for short distances with that of another car that was used for long distances.

Of course, the assumption of zero intercept is not always wrong. But, given all the potential problems involved if it is violated it should be carefully tested or there should be serious theoretical reasons to assume a linear model with zero intercept. There are ample examples of studies which likely fell prey to spurious correlations (cf. Kuh & Meyer, 1955; Kronmal, 1993). Also note that the problematic method described above relies on a second strong assumption, namely the assumption of heteroscedasticity with the errors scaling with the size of $x_i$. This should also be tested. A good example of a careful model–test which also considered the potential heteroscedasticity of the data is the study of Nevill et al. (1992) on the ratio of maximum oxygen uptake and body mass in recreational runners (see the section “When can we use indices?”).

A problem closely related to spurious correlations is the problems of faulty ratio standards. If ratios are used to define a medical standard for the “normal” or average human, and if the data have non–zero intercept, then this standard can lead to serious biases. For example, Tanner (1949) showed that stroke volume of the heart is linearly related to body weight with positive, non–zero intercept. Because, however, the average ratio was used as stan-
standard, the average lightweight person was automatically above the standard and the average heavy person was automatically below the standard. Tanner (1949) gives a large number of further illustrative examples and concludes that many patients classified as having deviant values “may have been suffering from no more formidable a disease than statistical artefact” (p. 3).

In summary, spurious correlations and faulty ratio standards can occur if we use ratios on data which are linearly related, but with non–zero intercept. In the literature, this problem is typically discussed together with the use of indices, but it is not restricted to indices. The use of indices only adds the additional assumption of heteroscedasticity with the errors scaling with the size of the denominator.

**Summary and Conclusions**

Ratios of measured quantities pose unusual statistical problems. When dealing with ratios we should first clarify whether we are justified in using a ratio, that is whether the numerator can safely be assumed to be a linear function of the denominator with zero intercept. Otherwise we should better use a linear model with non–zero intercept; see the section “Beware: Spurious correlations and faulty ratio standards”. If a ratio is appropriate, we can use the methods summarized in Table 2 and describe in the section “The standard case”.

Sometimes, we can simplify the calculations by using standard regression methods. This is typically the case if the denominator can be measured with negligible error; see the section “When can we use regression methods?”. Regression methods can help us also in more complicated cases in which, for example, we want to compare ratios or have repeated measure data. If it turns out that the residuals are heteroscedastic and if the denominator is bounded away from zero, index method or allometric models can be potential remedies, see the section “When can we use indices?”.

This shows that the wide use of the index method (illustrated by the example studies provided with this article) rests on very specific and likely often problematic assumptions. The simulations in the section “The standard case” show that the index method can lead to large deviations from the desired confidence level if these assumptions are not met. Also, the point estimate closely associated with this method (i.e., the mean ratio) can lead to systematic biases and much more variable estimates than the ratio of the
means. Therefore we should not use the index method as long as there is no indication for the specific heteroscedastic structure assumed by this method. A simple, straightforward alternative for cases in which one might be tempted to use the index method (i.e., if the denominator is bounded away from zero) is the Taylor method. For this, all the researcher needs to do is to use Equation (7) instead of the index method. Of course, all the other methods described in Table 2 would also be viable alternatives (most notably, standard bootstrap methods if there are deviations from normality). If, however, the denominator is not bounded away from zero, we best use either the Fieller method or the Hwang–bootstrap method.
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Figure Legends

Figure 1: Qualitative behavior and geometric construction of the Fieller confidence limits for $\rho$. The confidence limits (indicated by the thick, solid vertical lines) can be constructed using a wedge which forms tangents to an ellipse centered at $(\bar{x}, \bar{y})$. The size of this ellipse is such that its projection onto the abscissa corresponds to the marginal confidence interval of $E(X)$, the projection onto the ordinate corresponds to the marginal confidence interval of $E(Y)$ and the shape of the ellipse is determined by the covariance $\hat{\sigma}_{X,Y}$. If the denominator is significantly different from zero at a significance level of $\alpha$, then the ellipse will not touch the ordinate and the $(1 - \alpha)$ confidence limits will be bounded (left panel). If the denominator is not significantly different from zero, the ellipse will touch the ordinate and the confidence limits will be unbounded (middle and right panel, the arrows indicate infinity). In the unbounded/exclusive case, we still can exclude a small interval (the dashed vertical line in the middle panel) while in the unbounded case, we can not exclude any value at all (right panel).

Figure 2: a.–d. Comparison of the 95% confidence limits for the example data from Pang et al. (2002), as calculated by the Fieller, Taylor, index and zero–variance methods. The study reported four different ratios in four different conditions (denoted here by “P1”, “P2”, “P3”, “P4”). For P1, the upper Fieller limit is 498 (which is beyond the upper limit of the y–scale). e.–f. The geometrical construction method applied to the conditions P1 and P2. At P1 the construction ellipse just about touches the y–axis, which leads to an almost infinite upper Fieller limit. If the ellipse touched the y–axis, we would get unbounded/exclusive Fieller limits.

Figure 3: Empiric confidence levels of the different methods for small sample sizes ($N = 20$). The empiric confidence levels of the Fieller method are not shown, because they are of course always close to the expected 95%. The empiric confidence levels are color–coded. For example, light gray corresponds to an empiric confidence level between 90% and 99%. Left of the solid vertical line the denominator is typically significantly different from zero. (This is achieved by depicting $CV_X = \frac{\sigma_X}{E(X)} = 0.5$ which corresponds to $CV_X = \frac{\sigma_X}{E(X)} = 2.2$ at the abscissa). The dotted
diagonal line indicates equal CVs of numerator and denominator. In each panel the CVs that were reported in a number of example studies are plotted as single data points (see also the supplementary material provided with this article). At the CVs indicated with “A”, “B”, “C”, and “D” further simulations were run, see Figure 5.

**Figure 4:** Empiric confidence levels for $N = 500$. As in Figure 3, the denominator is typically significantly different from zero left of the solid vertical line. (This is achieved by depicting $CV_X = \frac{\sigma_X}{E(X)} = 0.5$ which corresponds to $CV_X = \frac{\sigma_X}{E(X)} = 11.2$ at the abscissa). For further detail, see Figure 3.

**Figure 5:** Results of simulations at the points “A” “B” and “C” (as are shown in the Figures 3 and 4). Each plot shows the results of 40 simulation runs, ordered by the magnitude of the estimated ratio ($\frac{Y}{X}$). In each run $N = 500$ subjects are simulated and analyzed using the Fieller and index methods (the results of Hwang–bootstrap, Taylor, and bootstrap $BC_a$ were practically identical to the results of the Fieller method and are therefore not shown). For 95% confidence limits, we expect that about 2 of the 40 simulation runs are significantly different from the true value (as indicated by the exclamation marks in the bottom of each plot). For the points “B” and “C” the rightmost panel shows the results of the index method at a larger scale. Despite this larger scale, the estimated ratio of one simulation was still beyond the scope of the scale. This values is indicated numerically (42). The results at point “D” are similar to the results at point “C” and are therefore not shown.
a. bounded

b. unbounded/exclusive

c. unbounded

Figure 1
Figure 2
Empiric confidence levels

N = 20

Coefficient of variation for denominator: $\sigma_X/\mu_X$

Coefficient of variation for numerator: $\sigma_Y/\mu_Y$

Bootstrap (Hwang) | Bootstrap (BCa)

Taylor | Index method

Index + trimmed mean | Zero variance method

Figure 3
Empiric confidence levels

N = 500

Coefficient of variation for denominator: $\sigma_X / \mu_X$
Coefficient of variation for numerator: $\sigma_Y / \mu_Y$

Zero variance method
Taylor
Index method
Index + trimmed mean
Bootstrap (Hwang)
Bootstrap (BCa)

Figure 4
Figure 5
Table 1: Results of the example calculation for point “P1” in Figure 2

| method        | lower limit | estimate | upper limit |
|---------------|-------------|----------|-------------|
| Fieller       | -0.02       | 1.88     | 498.75      |
| Taylor        | -1.88       | 1.88     | 5.64        |
| Index         | -1.81       | 2.29     | 6.39        |
| Zero–variance | -0.03       | 1.88     | 3.79        |

Note. Pang et al. (2002) measured the following pairs of values: \( y_i = (4.87, 8.30, 11.66) \) and \( x_i = (6.34, 4.02, 2.88) \). Calculated are 95% confidence limits, based on the quantiles of the Student–t–distribution \( t_q(df = 2) = \pm 4.3027 \). For further details see the supplementary material provided with this article.
Table 2: Standard methods to calculate confidence limits for ratios

| distribution of \((X,Y)\) | further restrictions | adequate method           |
|---------------------------|----------------------|---------------------------|
| bivariate normal          |                      | Fieller                   |
| bivariate normal          | \(CV_X < 1/3\)       | Taylor                    |
| not necessarily normal    | \(N > 15\)           | Hwang–bootstrap           |
| not necessarily normal    | \(N > 15; CV_X < 1/3\)| Standard bootstrap        |

**Note.** The restrictions are meant as rules of thumb and apply to the case that we are interested in 95% confidence limits.
Table 3: Hypothetical example for spurious correlations

| county | women \( (x_i) \) | babies \( (y_i) \) | storks \( (z_i) \) | birth–rate \( \left( \frac{y_i}{x_i} \right) \) | stork–rate \( \left( \frac{z_i}{x_i} \right) \) |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1      | 1               | 15.8            | 3.2             | 15.8            | 3.2             |
| 2      | 2               | 20.2            | 4.1             | 10.1            | 2.1             |
| 3      | 3               | 25.4            | 5.6             | 8.5             | 1.9             |
| 4      | 4               | 30.1            | 6.3             | 7.5             | 1.6             |

**Note.** Women are \( x10000 \).
Supplementary material: Details about the cited studies

This supplement gives a short description of the studies for which the CVs are shown in the Figures 3 and 4. The exact values for numerator and denominator variability and the sample sizes are also shown in Table 4. If specified, I describe the method which was used to calculate confidence limits (or SEM, which are typically interpreted as 68% confidence limits).

**Capuron et al., 2003:** Data are from Table 1, p. 909. The data describe the ratio of Kynurenine (KYN) to Tryptophan (TRP) during interferon (IFN–α) therapy: KYN/TRP. Method used: Index method (p. 908) Background: TRP degradation into KYN by the enzyme, indoleamine-2,3-dioxygenase, during immune activation may contribute to development of depressive symptoms during IFN–α therapy. 26 patients with malignant melanoma had received IFN–α treatment and received in parallel either an antidepressant (paroxetine) or placebo. Conditions: Antidepressant free patients vs. paroxetine–treated patients, measured at treatment initiation, weeks 2, 4, and 12.

**Franz, 2003:** Data are from Table 2, p. 219 and from my own records. The data describe the effect of an illusionary change of object–size relative to the effect of a physical change of object–size at different times of a reach to grasp movement. The ratio (illusion–effect)/(physical–size–effect) was calculated for each time–point. The study is also discussed in Franz (2004) and Franz, Scharnowski, and Gegenfurtner (2005), where also re-calculations using the correct Fieller–method are given. Method used: Index method. Background: The planning/control model of action (Glover & Dixon, 2001a; Glover, 2004, 2002) assumes that grasping is sensitive to certain illusionary changes of object–size only in early stages of the movement (planning), but not in later stages (control). In consequence, the relative effects of these illusions should decrement during a grasping movement. Conditions: Grasp aperture measured at start of movement (t = 0%), at the time of the maximum grip aperture (t = 100%), and at intermediate times (t = 25%, t = 50%, t = 75%).

**Maes et al., 2000:** Data are from Table 1, p. 912. The data describe the $\omega_6/\omega_3$ polyunsaturated fatty acids (PUFAs) ratios. Method used: Index
method on z–transformed scores (p. 912). **Background:** Psychological stress in humans induces the production of proinflammatory cytokines. An imbalance of ω6 to ω3 PUFAs in the peripheral blood causes an overproduction of proinflammatory cytokines. The study examined whether an imbalance in ω6 to ω3 PUFAs in human blood predicts a greater production of proinflammatory cytokines in response to psychological stress. **Conditions:** ω6/ω3 ratios a few weeks before (PRE) and after (POST) as well as one day before (STRESS) a difficult oral examination. Participants were also divided into groups with low/high fatty acid status.

**Marsland, Henderson, Chambers, & Baum, 2002:** Data are from Table 1, p. 867. Data describe the ratio of T–helper (CD4+) cells to T–suppressor/cytotoxic (CD8+) cells: CD4+/CD8+. **Method used:** Not described. **Background:** To explore the stability of immune reactivity in humans, the study assessed lymphocyte responses to a speech task and a mental arithmetic task. Dependent measure was (beside others) the ratio of CD4+ to CD8+ cells. **Conditions:** Mental arithmetic task, Speech task, Baseline performances.

**Metzger et al., 2002:** Data are from Table 2, p. 54. Data describe the amplitude of P50 event–related brain potentials in response to two auditory clicks (i.e., second click amplitude/first click amplitude) **Method used:** Index method. **Background:** Individuals with post traumatic stress disorder (PTSD) have been found to show several event–related brain potential abnormalities including P50 suppression. Female Vietnam nurse veterans with and without current PTSD completed P50 paired–click tasks: Two clicks were presented and the amplitude of the P50 for each of the clicks was determined. **Conditions:** Current PTSD versus never PTSD.

**Müller, Rau, Brody, Elbert, & Heinle, 1995:** Data are from Table 1, p. 74. Data describe the relationship of low density lipoprotein (LDL) cholesterol to high density lipoprotein (HDL) cholesterol: LDL/HDL. **Method used:** Not described. **Background:** The relationship between habitual anger coping styles, especially anger expression in a socially assertive manner and serum lipid concentrations was assessed. The LDL/HDL ratio was analyzed because it provides a predictor for coronary heart disease. **Conditions:** Two groups: male versus female.
Olincy et al., 2000: Data are from Table 2, p. 972. Data describe the amplitude of P50 event–related brain potentials in response to two auditory clicks (i.e., test P50 amplitude/conditioning P50 amplitude). Method used: Index method (p. 972) Background: Attention-deficit/hyperactivity disorder (ADHD) and schizophrenia are both conceptualized as disorders of attention. Failure to inhibit the P50 auditory event–evoked response, extensively studied in schizophrenia, could also occur in ADHD patients, if these two illnesses have common underlying neurobiological substrates. The study examined the inhibition of the P50 auditory event–evoked potential in unmedicated adults with ADHD, schizophrenic outpatients, and normal control subjects. Auditory stimuli were presented in a paired stimulus, conditioning–testing paradigm. The ratio of the test to the conditioning response amplitudes were observed. Conditions: Three groups: unmedicated adults with ADHD, schizophrenic outpatients, and normal control subjects.

Pang et al., 2002: Because this study gave excellent details about the data, I could use it as an example in this article. For simplicity (and because we are only interested in the statistical properties of the data), I used the following aliases for the conditions:

| alias | cell  | parameter                              | source         |
|-------|-------|----------------------------------------|----------------|
| P1    | OFF   | $\Delta_{gCL}/\Delta_{gC}(NR)$        | Table 1, p. 24 |
| P2    | ON    | $\Delta_{gCL}/\Delta_{gC}(NR)$        | Table 1, p. 24 |
| P3    | OFF   | $Q_C(P + S + I)/Q_C(NR)$              | Table 2, p. 25 |
| P4    | ON    | $Q_C(P + S + I)/Q_C(NR)$              | Table 2, p. 25 |

Also, for simplicity, I used the absolute values in the cases P3 and P4 (values are negative in the original study). Background: Pang et al. (2002) investigated the relative contributions of bipolar and amacrine cell input to light responses of 3 and 5 retinal ganglion cells. Two of the ratios describe the light–evoked changes in chloride conductance relative to the cation conductance $\Delta_{gCL}/\Delta_{gC}(NR)$ in normal Ringer’s (NR) solution, the other two ratios describe the light–evoked charge transfer in picrotoxin + strychnine + Imidazole-4-acidic acid (P+S+I) relative to NR: $Q_C(P + S + I)/Q_C(NR)$. Method used: Index method. Note: In the calculation of the variances, Pang et al. divided sometimes by $N$, (describing the sample variability) and sometimes by $N - 1$ (estimating the population variability). For consistency, I always used $N - 1$ in my calculations. Background: Light-evoked
postsynaptic currents (lePSCs) were recorded from ON, OFF and ON-OFF ganglion cells in dark-adapted salamander retinal slices under voltage clamp conditions, and the cell morphology was examined using Lucifer yellow fluorescence with confocal microscopy. The charge transfer of lePSCs in NR and in P+S+I was compared.

**Richter, Hinton, Meissner, & Scheller, 1995:** Data are from Table 1, p. 133/134. Data represent salivary [K+]/[Na+] ratios. **Method used:** Index method with log-transformed data (p. 137). **Background:** It was hypothesized that choice reaction-time testing would cause salivary [K+]/[Na+] to increase. Relative contributions of [K+] and [Na+] to ratio changes were investigated in 23 hypertensives and 10 hospital staff. Changes in post-rest and post-test ionic concentrations and [K+]/[Na+] were investigated. **Conditions:** 5 conditions: day 1 (relaxed), day 2 (pre-test), unpaced RT task, paced RT task, post-test (rest); Two groups: Hypertensives and control group.

**Schumann et al., 1998:** Data are from Table 2, p. 1374. They represent the ratio of cerebral blood flow (CBF) to cerebral blood volume (CBV), as measured by PET: CBF/CBV. **Method used:** Index method and non-parametric tests (p. 1371). **Background:** Local cerebral perfusion pressure (CPP), a crucial parameter that should allow a better assessment of the haemodynamic compromise in cerebrovascular diseases, is not currently measurable by non-invasive means. Experimental and clinical studies have suggested that the regional ratio of cerebral blood flow to cerebral blood volume (CBF/CBV), as measured by PET, represents an index of local CPP in focal ischaemia. The study was designed to evaluate further the reliability of the CBF/CBV ratio during manipulations of CPP by deliberately varying mean arterial pressure (MAP) in the anesthetized baboon. Cortical CBF, CBV, cerebral metabolic rate for oxygen and oxygen extraction fraction were measured by PET in 10 anesthetized baboons. **Conditions:** Five baboons (Group A) underwent four PET examinations at different levels of MAP: base line, moderate hypotension, minor hypotension, profound hypotension. Five other baboons (Group B) were subjected to hypertension and were compared with their base line state.
Serrien & Wiesendanger, 2001: Data are from Table 1, p. 419. Data present the ratio of grip force to load force during grasping: grip–force/load–force. Method used: Not described. Background: The study examined interlimb interactions of grasping forces during a bimanual manipulative assignment that required the execution of a drawer–opening task with the left hand and an object–holding task with the right hand. The grip/load–force ratio of the bimanual task was compared with the unimanual performance in order to investigate the coordinative constraint between grip and load force. Conditions: Unimanual versus bimanual; object holding versus drawer opening.

Sloan et al., 1994: Data are from Table 2, p. 93. Data present the ratio of low (LF) to high (HF) frequency bands of heart period variability (HPV): LF/HF. Method used: Mixed effect regression model on log–transformed data (p. 92). Background: The study investigated changes in cardiac autonomic control during psychological stress in ambulatory subjects. 24–h electrocardiographic recordings of 33 healthy subjects were analyzed for heart period variability responses associated with periodic diary entries measuring physical position, negative affect, and time of day. A total of 362 diary entries were made during the 24–h sessions, each in response to a device which signaled on an average of once per hour. HPV was analyzed in the frequency domain, yielding estimates of spectral power in low and high frequency bands, as well as the LF/HF ratio. Conditions: Standing, sitting, reclining positions.

Willemsen, Carroll, Ring, & Drayson, 2002: Data are from Table 1, p. 225. Data describe the ratio of T–helper (CD4+) cells to T–suppressor/cytotoxic (CD8+) cells: CD4+/CD8+. Method used: Not specified. Background: To examine gender differences in immune reactions to stress and relationships between immune and cardiovascular reactivity, measures of cellular and mucosal immunity and cardiovascular activity were recorded in 77 men and 78 women at rest and in response to active (mental arithmetic) and passive (cold pressor) stress tasks. Conditions: Two groups: Men versus Women; mental arithmetic, rest, and cold pressor.
| study/simulation | condition         | N  | y  | x  | y/x | plot |
|------------------|-------------------|----|----|----|-----|------|
| Capuron 03       | antidep-free init | 15 | 1.6| 0.5| 35.9| 8.4  |
| Capuron 03       | antidep-free week 2| 15 | 3.7| 1.4| 30.4| 10.5 |
| Capuron 03       | antidep-free week 4| 15 | 2.8| 1.1| 30.7| 11.1 |
| Capuron 03       | antidep-free week 12| 15 | 2.8| 0.8| 38  | 6.7  |
| Capuron 03       | Paroxetine init.  | 11 | 1.3| 0.5| 33.5| 9.2  |
| Capuron 03       | Paroxetine week 2 | 11 | 3.5| 1.3| 30.8| 10.8 |
| Capuron 03       | Paroxetine week 4 | 11 | 2.8| 0.9| 31.4| 7.3  |
| Capuron 03       | Paroxetine week 12| 11 | 2.9| 0.9| 32.7| 8.0  |
| Franz 03         | t=0               | 26 | 0.226| 0.612| 0.011| 0.062| 2.708| 5.636| y    |
| Franz 03         | t=25              | 26 | 0.333| 1.16| 0.292| 0.219| 3.483| 3.750| y    |
| Franz 03         | t=50              | 26 | 0.974| 1.443| 0.765| 0.315| 1.482| 0.412| y    |
| Franz 03         | t=75              | 26 | 1.278| 1.8 | 1.04 | 0.302| 1.408| 0.290| n    |
| Maes 03          | Low (PRE)         | 17 | 28.97| 3.41| 2.82 | 0.87 | 0.118| 0.309| y    |
| Maes 03          | Low (STRESS)      | 17 | 29.85| 3.2 | 3.15 | 1.26 | 0.074| 0.400| n    |
| Maes 03          | Low (POST)        | 17 | 29.95| 3.1 | 3.1  | 1.55 | 0.231| 0.500| n    |
| Maes 03          | High (PRE)        | 10 | 33.93| 0.93| 5.45 | 0.64 | 0.027| 0.117| n    |
| Maes 03          | High (STRESS)     | 10 | 33.25| 2.9 | 5.67 | 1.33 | 0.087| 0.235| y    |
| Maes 03          | High (POST)       | 10 | 32.92| 1.4 | 5.49 | 1.25 | 0.043| 0.228| y    |
| Marsland 02      | Arithmetic Baseline| 31 | 705 | 314| 388 | 175 | 0.445| 0.451| n    |
| Marsland 02      | Arithmetic Task   | 31 | 699 | 302| 393 | 173 | 0.432| 0.440| n    |
| Marsland 02      | Speech Baseline   | 31 | 719 | 314| 396 | 168 | 0.437| 0.424| n    |
| Marsland 02      | Speech Task       | 31 | 736 | 314| 449 | 210 | 0.427| 0.468| n    |
| Metzger 02       | P50 current       | 24 | 1.78 | 1.72| 4.52 | 2.52 | 0.966| 0.558| y    |
| Metzger 02       | P50 never         | 24 | 1.74 | 1.58| 4.98 | 2.33 | 0.908| 0.468| y    |
| Müller 95        | Males             | 53 | 188.85| 34.65| 54.98| 12.22| 0.183| 0.222| n    |
| Müller 95        | Females           | 33 | 115.58| 39.34| 57.61| 22.78| 0.340| 0.395| y    |
| Olincy 00        | Schizophrenia     | 16 | 2.53 | 1.58| 1.53 | 0.85 | 0.625| 0.556| y    |
| Olincy 00        | ADHD              | 16 | 2.08 | 1.21| 0.66 | 0.88 | 0.582| 1.333| y    |
| Olincy 00        | Normal            | 16 | 2.61 | 1.57| 0.5  | 0.65 | 0.602| 1.300| y    |
| Pang 02          | P1                | 5  | 278 | 105| 48  | 36  | 0.378| 0.750| y    |
| Pang 02          | P2                | 5  | 283 | 105| 48  | 36  | 0.378| 0.750| y    |
| Richter 95       | Hypertensive day 1| 23 | 18.1 | 8.8 | 6.2  | 3.3  | 0.486| 0.532| n    |
| Richter 95       | Hypertensive day 2| 23 | 25.7 | 12.1| 6.4  | 3.7  | 0.471| 0.578| n    |
| Richter 95       | Hypertensive unpaced RT | 23 | 34.7 | 15.5| 7   | 4.5  | 0.447| 0.629| y    |
| Richter 95       | Hypertensive paced RT | 23 | 36.2 | 14.6| 6.8  | 3.3  | 0.403| 0.485| n    |
| Richter 95       | Hypertensive rest | 23 | 29.8 | 11.4| 6.2  | 2.8  | 0.383| 0.452| n    |
| Richter 95       | Normals day 1     | 10 | 34.2 | 8.7 | 8.2  | 1.7  | 0.254| 0.207| n    |
| Richter 95       | Normals day 2     | 10 | 41.7 | 11.8| 6.5  | 1.1  | 0.283| 0.169| n    |
| Richter 95       | Normals unpaced RT| 10 | 53.8 | 23.6| 7.5  | 2    | 0.439| 0.267| n    |
| Richter 95       | Normals paced RT  | 10 | 50.7 | 21.7| 7.3  | 2.2  | 0.428| 0.301| n    |
| Richter 95       | Normals rest      | 10 | 46.4 | 12.2| 7    | 1.5  | 0.263| 0.214| n    |
| Schumann 98      | Hypotension Baseline| 5  | 31.1 | 3.9 | 3.15 | 0.71 | 0.125| 0.225| y    |
| Schumann 98      | Moderate Hypotension| 5  | 27.5 | 4  | 3.61 | 1.09 | 0.145| 0.302| y    |
| Schumann 98      | Minor Hypotension | 5  | 24.7 | 3.5 | 3.2  | 0.5  | 0.142| 0.156| y    |
| Schumann 98      | Profound Hypotension| 5  | 19.7 | 4.9 | 3.63 | 0.55 | 0.249| 0.152| y    |
| Schumann 98      | Baseline Hypotension| 5  | 27.5 | 2  | 2.72 | 0.22 | 0.073| 0.081| y    |
| Schumann 98      | Hypertension      | 5  | 36.1 | 2.4 | 2.84 | 0.11 | 0.066| 0.039| y    |
| Serrien 01       | Onset Drawer U    | 6  | 20.31| 4.52| 13.92| 3.34 | 0.223| 0.240| n    |
| Serrien 01       | Onset Drawer B    | 6  | 21.34| 3.84| 14.52| 3.5  | 0.180| 0.241| n    |
| Serrien 01       | Impact Drawer U   | 6  | 23.72| 4.35| 15.24| 3.25 | 0.183| 0.213| n    |
Table 4 (continued)

| study/simulation | condition                   | N  | y       | $\sigma_y$ | x       | $\sigma_x$ | $\sigma_y/y$ | $\sigma_x/x$ | plot |
|------------------|-----------------------------|----|---------|------------|---------|------------|--------------|--------------|------|
| Serrien 01       | Static Object U             | 6  | 10.44   | 0.9        | 8.01    | 0.02       | 0.088        | 0.002        | n    |
| Serrien 01       | Onset Object B              | 6  | 11.82   | 1.15       | 8.02    | 0.02       | 0.097        | 0.002        | n    |
| Serrien 01       | Impact Object B             | 6  | 12.4    | 1.25       | 8.01    | 0.01       | 0.101        | 0.001        | n    |
| Sloan 94         | Standing                    | 96 | 1210.4  | 984.2      | 243.6   | 619.82     | 0.813        | 2.544        | y    |
| Sloan 94         | Sitting                     | 191| 1354.5  | 973.5      | 518.5   | 613.07     | 0.719        | 1.182        | y    |
| Sloan 94         | Reclining                   | 28 | 1392.8  | 1205.93    | 559.8   | 759.38     | 0.866        | 1.357        | y    |
| Willemsen 02     | Men Rest                    | 78 | 626     | 170        | 419     | 154        | 0.272        | 0.368        | n    |
| Willemsen 02     | Men Artihmetik              | 78 | 589     | 143        | 423     | 154        | 0.243        | 0.364        | n    |
| Willemsen 02     | Men Cold pressor            | 78 | 560     | 144        | 405     | 154        | 0.257        | 0.380        | n    |
| Willemsen 02     | Women Rest                  | 79 | 722     | 230        | 446     | 155        | 0.319        | 0.348        | y    |
| Willemsen 02     | Women Artihmetik            | 79 | 694     | 203        | 473     | 184        | 0.293        | 0.389        | n    |
| Willemsen 02     | Women Cold pressor          | 79 | 691     | 211        | 448     | 171        | 0.305        | 0.382        | n    |
| Point A          | -                           | 500| 1       | 0.1        | 1       | 0.15       | 0.100        | 0.150        | y    |
| Point B          | -                           | 500| 1       | 0.1        | 1       | 0.75       | 0.100        | 0.750        | y    |
| Point C          | -                           | 500| 1       | 0.1        | 1       | 3          | 0.100        | 3.000        | y    |
| Point D          | -                           | 500| 1       | 1.5        | 1       | 3          | 1.500        | 3.000        | y    |

Note: The column “plot” indicates whether the data point is plotted in the Figures 3 and 4.