



Modeling Patient Progression when Observations are Autocorrelated

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Abstract

Purpose: The standard trend analysis for data arising in clinical health care work considers a linear regression model on time with independent errors and estimates the trend parameter through least squares. We discuss why the independence assumption may be misguided.

Methods: We suggest a trend model with autocorrelated errors that combines independent measurement errors and autoregressive trend persistence, and we estimate the trend parameter through generalized least squares. We investigate the consequences of ignoring autocorrelation on the efficiency of the least squares trend estimate and on the false rejection probability when no trend is present.

Results: While there will always be inefficiency in the least squares estimate when errors are correlated, we find that the efficiency loss – especially for moderate sample sizes – is small. Concerning the false rejection probability when no trend is present, we find evidence of spurious regression when autocorrelations in series of length 25 and 50 are ignored.

Conclusions: In the typical clinic situation with a very moderate number of observations, the consequences of ignoring the autocorrelation are negligible.

Translational Relevance: Clinicians assess patient progression on short-time records of consecutive measurements and need simple statistical tools to analyze the information. Clinical decisions are usually based on trend estimates that assume independent observations. While there are good reasons for successive observations to be correlated, this study shows that for short-time records the autocorrelations can be safely ignored.

Keywords: Trend Detection; Time Series Analysis; ARMA(1,1) Model; Estimation Efficiency; Spurious Regression

Introduction

The linear trend model for assessing patient progression

Ledolter and Kardon [1] describe how clinicians study the progression (that is, changes over time) of functional and structural ophthalmic characteristics such as OCT retinal nerve fiber layer and ganglion cell layer thickness, and visual field test sensitivity at given test locations and mean deviation and pattern standard deviation summaries. For each patient, n consecutive measurements

Y_t are obtained at times $Time_1 < Time_2 < \dots < Time_n$. Times are typically expressed in years, and there is no requirement that times are spaced equally. Times are often expressed relative to the time of the initial visit. For example, $Time_1 = 0$, $Time_2 = 0.5$, $Time_3 = 1.0$, $Time_4 = 1.25$, ..., $Time_8 = 4.14$ express that eight observations are available – at the start of the study, after six months, after 12 months, after 15 months, ... and after 4 years and $365(0.14) = 51$ days since the start of the study.

Typically a linear trend regression model is considered for the progression of the observations Y_t (sometimes, their log-transforms are used),

$$Y_t = \alpha + \beta Time_t + \varepsilon_t. \quad \dots\dots(1)$$

The intercept α reflects the expected level at the beginning of the study. The slope β reflects the expected change in measurement for a unit-change in time (which, in our illustration, is one year). The model makes an assumption of linearity; the mean change over the first year is the same as the mean change in the second year, and so on. It also assumes that measurement errors ε_t are independent, homoscedastic (that is, with constant variance σ^2), and normally distributed. Least squares estimates are optimal under these assumptions. The least squares estimates of the slope and intercept are given by

$$\hat{\beta} = \frac{\sum_{t=1}^n (Time_t - \overline{Time}) Y_t}{\sum_{t=1}^n (Time_t - \overline{Time})^2} \text{ and } \hat{\alpha} = \bar{Y} - \hat{\beta} \overline{Time} \quad \dots\dots(2)$$

where $\bar{Y} = (1/n) \sum_{t=1}^n Y_t$ and $\overline{Time} = (1/n) \sum_{t=1}^n Time_t$. Standard errors of the least squares estimates are given by

$$\sigma(\hat{\beta}) = \frac{\sigma}{\sqrt{\sum_{t=1}^n (Time_t - \overline{Time})^2}} \text{ and } \sigma(\hat{\alpha}) = \sigma \sqrt{\frac{1}{n} + \frac{(\overline{Time})^2}{\sum_{t=1}^n (Time_t - \overline{Time})^2}} \quad \dots\dots(3)$$

The error standard deviation σ is replaced by its estimate, $s = \sqrt{\frac{\sum_{t=1}^n [Y_t - (\hat{\alpha} + \hat{\beta} Time_t)]^2}{n-2}}$, and t-distributions are used for confidence intervals and significance tests if errors follow a normal distribution. See Chapter 2 of Abraham and Ledolter [2].

Methods

The linear trend model revisited

Caprioli, *et al* [3], in their analysis of visual field data, comment that there is no consensus about which statistical model is most appropriate for clinical or investigative use and that efforts to measure and define change remain hampered by several inconvenient realities of visual field progression. Deterioration is neither linear nor constant over time, and psychophysical measurements are notoriously noisy generating unusual values (outliers). These inherent properties can limit the detection of progression.

Independence of the errors is a strong assumption of the model in equation (1). Independence assumes that trend-adjusted observations on the same subject taken at different time periods are not correlated. Serial (auto) correlation can arise for several reasons. Measurement errors ε_t at successive time periods may be related. This may be true when there is carry-over in the measurement process and observations are taken in rapid succession, but may be less of a problem when observations are spaced further apart such as the six months between typical clinic visits. A second reason for serial correlation of errors in the model in equation (1) is that the assumed linear trend, $T_t = \alpha + \beta Time_t$, is not appropriate. The true trend may be nonlinear and/or even stochastic, and then the autocorrelation in the deviations from an assumed linear trend model reflects the inaccurate specification of the time trend.

The presence of serial correlation can have an impact on the statistical inference, as the correlation affects both parameter estimates and standard errors of the estimates. The least squares estimates discussed above are no longer the best estimates. Generalized least squares estimates that incorporate the autocorrelation of the errors are more efficient than the usual least squares estimates that are derived under independence (this follows from the Gauss-Markov theorem; see Section 4.6 in Abraham and Ledolter [2]). Furthermore, and this is more critical, the standard errors shown in equation (3) – that is, the standard errors of the (inefficient) least squares estimates derived under independence – are no longer correct when errors are autocorrelated. Depending on the autocorrelation, they can be too small leading to spurious significance of the trend coefficient, or too large leading the investigator to miss the presence of a trend. See Box and Newbold [4] and Granger and Newbold [5] for early papers on the presence of spurious regressions when ignoring the autocorrelation of the errors.

Because of these consequences it is important to check whether serial correlation is present. This can be done as follows. The autocorrelations among the deviations from the linear trend, $\tilde{Y}_t = Y_t - (\alpha + \beta Time_t)$, can be estimated with the residuals from the fitted trend model, $e_t = Y_t - (\hat{\alpha} + \hat{\beta} Time_t)$. For the following discussion we assume that the time-spacings between successive observations are the same (such as the six months in the typical clinic situation), which allows us to write $Time_t = t$. The autocorrelation between errors m periods apart, $\rho_m = Corr(\tilde{Y}_t, \tilde{Y}_{t-m})$, is estimated with the sample autocorrelation at lag m ,

$$r_m = \frac{\sum_{t=m+1}^n (e_t - \bar{e})(e_{t-m} - \bar{e})}{\sum_{t=1}^n (e_t - \bar{e})^2} = \frac{\sum_{t=m+1}^n e_t e_{t-m}}{\sum_{t=1}^n e_t^2}; \text{ the last term follows because}$$

regression residuals always add to zero. The standard error of the lag m sample autocorrelation, $\sigma(r_m) = 1/\sqrt{n}$, see Box, Jenkins, Reinsel and Ljung [6], can be used to assess whether models for serial correlation need to be considered. Sample autocorrelations r_m outside the 2-sigma limits $\pm 2/\sqrt{n}$ indicate that $\rho_m \neq 0$.

For small numbers of observations (as is the case in our clinical setting where n is usually not much larger than 10) this diagnostic check can spot at most gross violations of independence. For small n, sample autocorrelations can be calculated reliably only for small lags m such as lag 1 (measuring the association between adjacent observations) and lag 2 (measuring the association two time periods apart), and sample autocorrelations would have to be quite large to exceed the 2-sigma limits. In the case of multiple subjects, the lag 1 autocorrelations can be visualized on a dot plot, and a one-sample t-test can be used to assess whether the mean lag 1 autocorrelation is different from zero.

Books on time series analysis (such as Box, Jenkins, Reinsel and Ljung [6], Abraham and Ledolter [7]) propose several useful parsimonious models to characterize the autocorrelation in the errors. The (first-order) autoregressive model extends independence in a very simple way. The ARMA(1,1) model (a first-order autoregression combined with a first-order moving average component) is another useful model. This model is discussed in Ledolter and Kardon [8] and can be motivated as follows. The measurement errors ϵ_t in model (1) are assumed independent as there is little reason for an instrument carry-over from one measurement error to the next. But the deterministic linear trend (regression) component $T_t = \alpha + \beta Time_t$ may not be appropriate as the progression of the biological signal may also be affected by stochastic perturbations r_t that lead to persistent deviations from the deterministic linear trend. Persistence implies that a signal at time t above the trend line increases the likelihood that signals at subsequent time points are also above the trend line. In other words, signals tend to stay above (or below) the trend line for several periods in a row. Persistence can be modeled with a first-order autoregressive model $r_t = \frac{1}{(1-\phi B)} \xi_t = \xi_t + \phi \xi_{t-1} + \phi^2 \xi_{t-2} + \dots$. Here B is the backshift operator (that is, $B^m \xi_t = \xi_{t-m}$), ϕ is the autoregressive parameter (which, for statistical stationarity, has to be between -1 and 1), and ξ_t are independent mean zero random variables with variance σ_ξ^2 . The first-order autoregressive model for r_t implies autocorrelations $Corr(r_t, r_{t-m}) = \phi^m$ and variance $\sigma_r^2 = \frac{\sigma_\xi^2}{1-\phi^2}$, and persistence is achieved when

the autoregressive parameter is positive and close to 1. For $\phi = 1$ the autoregressive model becomes the (non-stationary) random walk which generates long persistent excursions from the deterministic model.

Adding biological persistence to the linear deterministic trend model in equation (1) leads to a more realistic model of change,

$$Y_t = \alpha + \beta t + r_t + \epsilon_t \quad \dots\dots(4)$$

Subtracting the deterministic linear trend from the measurements, leads to

$$\tilde{Y}_t = Y_t - (\alpha + \beta t) = r_t + \epsilon_t = \frac{1}{(1-\phi B)} \xi_t + \epsilon_t.$$

This model can be written as $(1-\phi B)\tilde{Y}_t = \xi_t + (1-\phi B)\epsilon_t$, or $\tilde{Y}_t = \phi \tilde{Y}_{t-1} + \xi_t + \epsilon_t - \phi \epsilon_{t-1}$. It is known as the autoregressive-moving average ARMA(1,1) model: there is just one lagged autoregressive term and the autocorrelations of the moving average component on the right-hand side of the model are zero after lag 1. It is straightforward to show that the standard deviation and the autocorrelations of the deviations from the linear trend model $\tilde{Y}_t = Y_t - (\alpha + \beta t)$ are given by

$$\sigma_{\tilde{Y}} = \sqrt{\sigma_r^2 + \sigma_\epsilon^2}, \rho_1 = \phi \frac{1}{1+(1-\phi^2)(\sigma_\epsilon^2/\sigma_\xi^2)} = \phi \frac{1}{1+(\sigma_\epsilon^2/\sigma_r^2)} \quad \dots\dots(5)$$

$$\rho_m = (\rho_1)\phi^{m-1} = \frac{1}{1+(\sigma_\epsilon^2/\sigma_r^2)} \phi^m \text{ for } m \geq 1.$$

For $\sigma_\epsilon^2 = 0$ (implying that there is no measurement error) the ARIMA(1,1) model simplifies to the first-order autoregressive model with standard deviation σ_r and autocorrelations $\rho_m = \phi^m$.

For illustration, assume that the increase over a three-year period amounts to 1 unit, and that we have available seven equally-spaced observations (six months apart) over this interval. Hence $t = 1, 2, \dots, 7$ and $\beta = 1/6$. Assume that persistence is modeled with autoregressive parameter $\phi = 0.8$, and assume variance ratio $\sigma_\epsilon^2/\sigma_r^2 = 3$. Measurements on ophthalmic characteristics are notoriously noisy which implies that the measurement error should be larger than the difference between the actual trend and the deterministic linear trend. With these choices of parameters the autocorrelations of $\tilde{Y}_t = Y_t - (\alpha + \beta t)$ are $\rho_1 = 0.8/(1+3) = 0.2$ and $\rho_m = (0.2)(0.8)^{m-1}$ for $m \geq 1$. The lag 1 autocorrelation (the correlation between observations six months apart) is moderate in size (0.2),

but there is a persistent slow decay in the autocorrelations from lag 1 onwards; for larger measurement error, the persistent decay in the autocorrelations starts at an even smaller initial autocorrelation. For illustration, we have simulated time series of length 7 with these parameters (and total variance $\sigma_r^2 + \sigma_\varepsilon^2 = 1$). Figure 1 shows 10 replications of the trend $\alpha + \beta t + r_t$ on the left and of the time series $Y_t = \alpha + \beta t + r_t + \varepsilon_t$ on the right. Trends increase, but now the change over time is no longer constant across the whole time period.

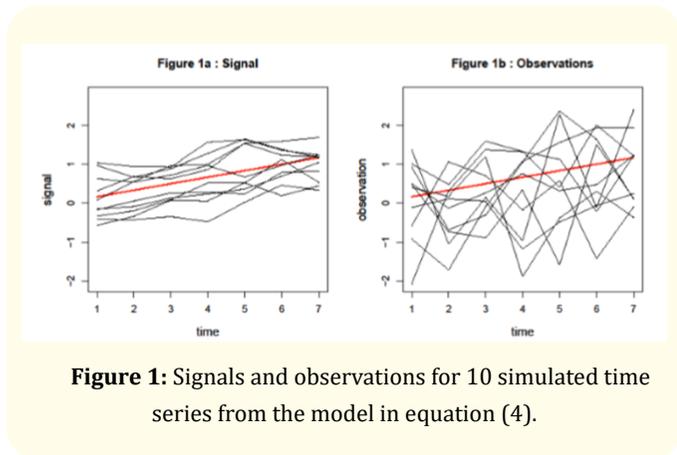


Figure 1: Signals and observations for 10 simulated time series from the model in equation (4).

There is empirical evidence [9,10] that errors in regressions of time series measurements taken on humans (anthropometric data) on deterministic functions of age follow ARMA(1,1) models. For example, Carrico, *et al* [10] show that – in a regression of blood pressure of young adults on linear and quadratic functions of age, BMI and height – ARMA(1,1) errors are preferable to AR(1) and compound symmetry errors. Here we have given an explanation why an ARMA(1,1) represents a reasonable model.

The adequacy of the linear trend model in equation (1) should always be checked. If there is evidence of autocorrelation, the commonly-used independence assumption for the error terms must be generalized. The error can be represented more generally with time series models such as the ARMA(1,1) model discussed here. The estimate of the trend parameter and its correct standard error depend on autocorrelation matrix of the errors, and can be obtained through generalized least squares; see Abraham and Ledolter [2] and the equations in the Appendix.

For the ARMA(1,1) model and n equally-spaced observations, we have shown that the $n \times n$ correlation matrix has entries $\rho_{ij} = 1$ in the diagonal and $\rho_{ij} = \frac{1}{1 + (\sigma_\varepsilon^2 / \sigma_r^2)} \phi^{|i-j|}$ for $i \neq j$. The calculations of the autocorrelations are easily adapted to the situation when observations are not equally-spaced. The entries of the correlation matrix for n unequally-spaced observations, with pair-wise time differences $d_{ij} = \text{Time}_i - \text{Time}_j \neq 0$, are given by $\rho_{ij} = \frac{1}{1 + (\sigma_\varepsilon^2 / \sigma_r^2)} \phi^{|d_{ij}|}$. This correlation matrix, together with the standard deviation $\sigma = \sqrt{\sigma_r^2 + \sigma_\varepsilon^2}$, are used in the calculation of the generalized least squares estimates of the parameters α and β in the trend model (4) and their correct standard errors that reflect the autocorrelation in the errors. Note, however, that the calculations assume that both the autoregressive parameter ϕ and the variance ratio $\sigma_\varepsilon^2 / \sigma_r^2$ are known.

Results

Consequences of ignored autocorrelation

We assume that observations are generated from the linear trend model in equation (4), with first-order autoregressive persistence and independent measurement errors. The standard regression analysis in the Introduction ignores persistence. Ignoring the autocorrelation has consequences on (1) the efficiency of the estimate of the trend parameter and (2) the significance test of the trend parameter estimate. In this section we illustrate the consequences of ignored autocorrelation by comparing:

- The standard error of the generalized least squares estimate with the standard error of the least squares estimate, assuming in both cases that observations come from the trend model in equation (4) with correlated errors. The ratio of the two standard errors reflects the relative efficiency of the two estimates.
- The probability of falsely finding a significant trend regression when using the incorrect least squares analysis with the probability of falsely finding a significant trend regression when using then correct generalized least squares approach. The probability should be five percent if tests are carried out at the 5-percent significance level.

We make these comparisons for trend regressions on $\text{Time}_t = t$ for $t = 1, 2, \dots, n$, for three different sample sizes ($n = 7$ as in a typical clinical setting, $n = 25$, and $n = 50$ when considerably more observations are available). We consider variance ratios $\sigma_\varepsilon^2 / \sigma_r^2$ from 0

to 9 (with 0 representing persistence without measurement error), and autoregressive persistence Φ from 0 to 0.99.

For comparison (1) we use the well-known algebraic expressions for the variances of the least squares and the generalized least squares estimates when errors follow model (4); the standard errors are given by the square roots of the second diagonal elements of the matrices in equation (A2) of the appendix. The ratio of the two standard errors, $\sigma(\hat{\beta}_{GLS}) / \sigma(\hat{\beta}_{LS})$, in Figure 2 expresses the efficiency of the least squares estimate relative to the generalized least squares estimate. A ratio smaller than one indicates a loss in efficiency of the least squares estimate. The efficiency loss of the least squares estimate changes with variance ratio $\sigma_\epsilon^2 / \sigma_r^2$, persistence autocorrelation Φ , and sample size. While there is always inefficiency when using the least squares estimate when errors are correlated, the efficiency loss – especially for small sample sizes – is rather small. Even in the worst case (large sample size $n = 50$, without measurement error) the efficiency loss of the standard least squares estimate is at most 12 percent [this occurs at $\Phi = 0.82$ when the standard deviation of the optimal GLS estimator is 0.88 times of the standard deviation of the inefficient least squares estimator]. For small sample size $n = 7$ and for the case when measurement errors exceed the trend persistence (ratio $\sigma_\epsilon^2 / \sigma_r^2 = 3$ or more), the efficiency loss is negligible.

Remark: This first comparison compares the standard errors of the two competing estimates assuming that the observations are generated under the correlated error structure that makes the GLM estimate optimal. It is not comparing the standard error of the GLS estimate under the correct correlation structure with the standard error of the incorrect LS estimate under independence.

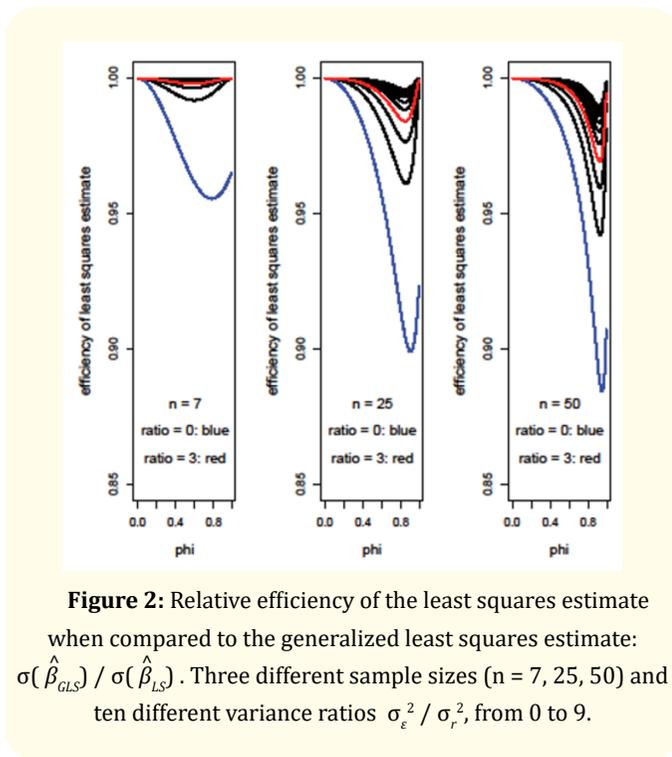


Figure 2: Relative efficiency of the least squares estimate when compared to the generalized least squares estimate: $\sigma(\hat{\beta}_{GLS}) / \sigma(\hat{\beta}_{LS})$. Three different sample sizes ($n = 7, 25, 50$) and ten different variance ratios $\sigma_\epsilon^2 / \sigma_r^2$, from 0 to 9.

For comparison (2) we use simulations of 100,000 independent time series, for each selected variance ratio, autoregressive parameter, and sample size. We use the rmvnorm function of the R library mvtnorm [11] to generate time series with slope 0. Assuming independence, we obtain the least squares estimate of the slope (equations (1) and (A1) in the appendix), the estimate $\hat{\sigma}_{LS} = \sqrt{(y - X\hat{\gamma}_{LS})'(y - X\hat{\gamma}_{LS}) / (n - 2)}$, of the error standard deviation σ (in Introduction), and the estimated standard error of the slope which we get by replacing σ in $\sigma(\hat{\beta}_{LS})$ of equations (3) and (A3) with its estimate $\hat{\sigma}_{LS}$. The left panels of Figure 3 show the probabilities of falsely finding a significant trend regression when using a five percent significance test with cutoffs provided by the t-distribution with $n-2$ degrees of freedom. The right panels of Figure 3 show the probabilities of falsely finding a significant trend regression when basing the five percent significance test on the generalized least squares analysis that incorporates the autocorrelation. This test statistic uses the generalized least squares estimate $\hat{\beta}_{GLS}$ from equation (A1) and its estimated standard error that we obtain by replacing the error standard deviation σ in $\sigma(\hat{\beta}_{GLS})$ of equation (A2) with its estimate $\hat{\sigma}_{GLS} = \sqrt{(y - X\hat{\gamma}_{GLS})'\Omega^{-1}(y - X\hat{\gamma}_{GLS}) / (n - 2)}$.

The generalized least squares approach reproduces the expected five percent false rejection probabilities for a five percent significance test. On the other hand, the incorrect least squares analysis in the left panel rejects too often, depending on variance ratio $\sigma_\epsilon^2 / \sigma_r^2$, persistence autoregression parameter Φ , and sample size n . The standard least squares regression performs poorly if there is no measurement error and all deviations from the constant trend are due to the autoregressive persistence ($\sigma_\epsilon^2 / \sigma_r^2 = 0$). The false rejection probabilities increase steadily with the autoregressive parameter Φ . When Φ approaches 1 (random walk persistence), the proportions of false rejection are 0.43 ($n = 7$), 0.74 ($n = 25$) and 0.83 ($n = 50$). While the presence of measurement error ($\sigma_\epsilon^2 / \sigma_r^2 > 0$) improves the situation, the false rejection rates for large sample size ($n = 50$) remain considerably larger than the expected 5 percent. When $\sigma_\epsilon^2 / \sigma_r^2 = 3$, the false rejection rate can be as large as 30 percent. On the other hand, for small sample size $n = 7$, the false rejection rates increase by at most 2.5 percentage points (from the expected five percent to about 7.5 percent) when the variance of the measurement errors exceeds the variance of the persistence by a factor of 3 ($\sigma_\epsilon^2 / \sigma_r^2 \geq 3$).

In our simulations we assume that the correlation structure is known (a simplifying assumption as in practice the variance ratio and the autoregressive parameter have to be estimated), but estimate the error standard deviation σ . The (least squares)-based estimate of the error standard deviation, $\hat{\sigma}_{LS} = \sqrt{(y - X\hat{\gamma}_{LS})'(y - X\hat{\gamma}_{LS}) / (n - 2)}$, tends to be too small if errors are positively correlated – and this is the reason for the spurious regression. With correlated errors, the sum of squares

$(y - X\hat{\gamma}_{LS})(y - X\hat{\gamma}_{LS})' / \sigma^2$ has no longer a chi-square distribution with $n-2$ degrees of freedom. For extreme positive correlation, $(y - X\hat{\gamma}_{LS})(y - X\hat{\gamma}_{LS})' / \sigma^2$ approaches a multiple (a multiple of the

sample size) of a chi-square distribution with 1 degree of freedom. This implies that with correlated errors many of the estimates $\hat{\sigma}_{LS} = \sqrt{(y - X\hat{\gamma}_{LS})(y - X\hat{\gamma}_{LS})' / (n-2)}$ tend to be too small.

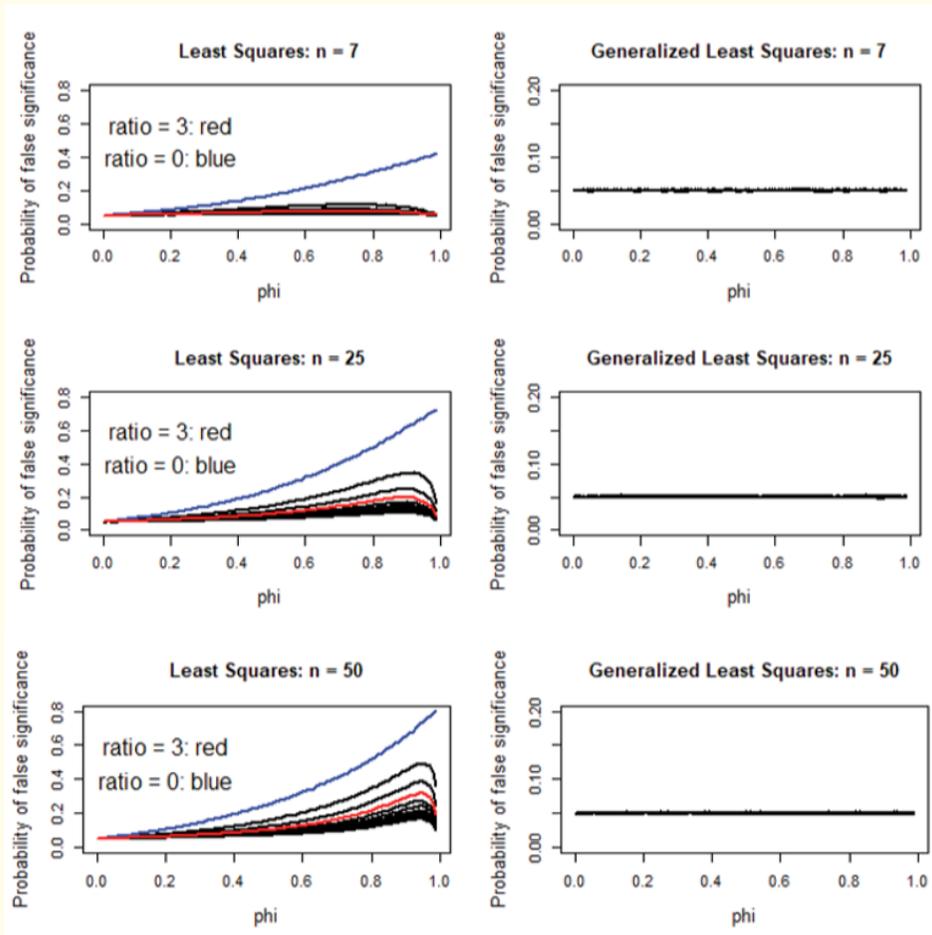


Figure 3: Probabilities of falsely finding a significant trend regression when using the incorrect standard least squares regression analysis (left panels) and the correct generalized least squares analysis (right panel). The ten graphs on the right panel are all very close and cannot be distinguished.

Discussion and Concluding Remarks

Clinicians have limited data to estimate patient progression which leads them to adopt simple models that specify linear trend progression and independent errors. We caution in this paper that autoregressive trend persistence may be present and that deviations from the linear trend may not be independent, and we study

the consequences of ignoring the resulting autocorrelation. We find that one should be concerned about finding spurious regression when ignoring the autocorrelations in series of length 25 and 50. However, for the typical clinic situation with $n = 7$ observations and measurement error, the effects of ignoring the autocorrelation are negligible.

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Conflict of Interest

There are no conflicts of interest to declare.

Appendix

We consider the regression model $Y_t = \alpha + \beta Time_t + \tilde{\varepsilon}_t$ ($t = 1, 2, \dots, n$), with autocorrelated errors $\tilde{\varepsilon}_t = r_t + \varepsilon_t$ that combine independent measurement errors ε_t and autoregressive persistence $r_t = \phi r_{t-1} + \xi$. The errors $\tilde{\varepsilon}_t$ have mean zero and standard deviation $\sigma = \sqrt{\sigma_r^2 + \sigma_\varepsilon^2}$, and correlation matrix Ω with elements $\rho_{ij} = \frac{1}{1 + (\sigma_\varepsilon^2 / \sigma_r^2)} \phi^{|i-j|}$, for $i \neq j$. All parameters of the time series model are assumed known. Linear model matrix results (see, for example, Chapter 4 of Abraham and Ledolter [2]) are used to obtain the least squares and generalized least squares estimates and their variances. The t^{th} row of the $n \times 2$ regression design matrix X is given by $(1, Time_t)$. The estimates of the 2×1 vector of regression coefficients $\gamma = (\alpha, \beta)'$ are

$$\hat{\gamma}_{LS} = (X'X)^{-1}X'y \text{ and } \hat{\gamma}_{GLS} = (X'\Omega^{-1}X)^{-1}X'\Omega^{-1}y, \dots\dots(A1)$$

with variance matrices under the generating regression model

$$Var(\hat{\gamma}_{LS}) = \sigma^2(X'X)^{-1}(X'\Omega X)(X'X)^{-1} \text{ and } Var(\hat{\gamma}_{GLS}) = \sigma^2(X'\Omega^{-1}X)^{-1} \dots\dots(A2)$$

Elements in the second row and second column of these matrices (the element corresponding to the slope β) are used in the efficiency comparisons of the slope estimates.

The variance of the least squares estimate that neglects the autocorrelation in its derivation (the one listed in the standard regression output and used to calculate an incorrect test statistic) is given by

$$Var^*(\hat{\gamma}_{LS})^{ND} = \sigma^2(X'X)^{-1} \dots\dots(A3)$$

The element in the second row and second column of this matrix is used in comparison (2) of the Results section.

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