Long-range correlations of serial FEV₁ measurements in emphysematous patients and normal subjects

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Dirksen, Asger, Niels-Henrik Holstein-Rathlou, Flemming Madsen, Lene T. Skovgaard, Charlotte S. Ulrik, Thomas Heckscher, and Axel Kok-Jensen. Long-range correlations of serial FEV₁ measurements in emphysematous patients and normal subjects. J. Appl. Physiol. 85(1): 259-265, 1998.—In obstructive lung disease the annual change in lung function is usually estimated from serial measurements of forced expiratory volume in 1 s (FEV₁). Frequent measurements in each patient may not improve this estimate because data are not statistically independent; i.e., the measurements are autocorrelated. The purpose of this study was to describe the correlation structure in time series of FEV₁ measurements. Nineteen patients with severe α₁-antitrypsin deficiency (phenotype PiZ) and moderate to severe emphysema and two subjects with normal lungs were followed for several years with daily self-administered spirometry. FEV₁ measurements fulfilling standard criteria were detrended, and the autocorrelation profile and the power spectrum were calculated. On average the subjects were followed for >3 yr and performed >1,000 acceptable spirometries. The autocorrelation of FEV₁ measurements in the emphysematous patients was −0.35 for short intervals and decreased almost exponentially with a half time of 38 days. Between 3 and 4 mo, the autocorrelation function became negative. It reached a minimum of −0.1 at −8 mo and then increased toward zero over the following 12 mo. The autocorrelation function in the two normal subjects showed a similar pattern, but with a faster decay toward zero. In the patients, the power spectrum had a peak at 1 cycle/wk and showed a 1/f pattern, where f is frequency, with a slope of −0.88 at lower frequencies. We conclude that serial spirometric measurements show long-range correlations. The practical implication is that FEV₁ need not be measured more often than once every 3 mo in studies of the long-term trends in lung function.

spirometry; periodicity; Fourier analysis; power spectrum; autocorrelation; time series

THE INTRODUCTION IN RECENT YEARS of small handheld spirometers with timer and data-storage capability has made it possible to monitor pulmonary function daily by patient-administered serial spirometry (15). The accumulation of such information has made it relevant to describe in more detail the temporal structure of repeat spirometric tests. Previous studies from other organ systems, especially the cardiovascular system, have revealed the presence of significant fluctuations in many physiological variables. Both the heart rate and the arterial blood pressure show considerable variability even under conditions in which the animal or the individual is at rest (10, 16). The fluctuations appear to be due to the intrinsic, complex dynamics of the regulatory systems that govern a given physiological variable and thus cannot be explained simply as the result of measurement errors.

It is well known that when observations are made far apart in time they will, in general, not be correlated; i.e., they are independent. However, as the sampling frequency increases, correlations will be present between the consecutive measurements, and they can no longer be treated as independent. Such correlations between repeated measurements made on the same subject are technically known as autocorrelations. The surprising result that has emerged from many studies in the cardiovascular system is that the time until measurements can be regarded as independent can be very long (on the order of many hours) (10, 16). The consequence of such long-range correlations is a considerable persistence in the pattern of the fluctuations. Thus, if a given measurement is found to be above its mean value at a given time, there will be a high probability that the same will be the case for measurements made during the following hours. The mechanisms underlying the long-range correlations seen in many physiological variables are presently not well understood (10).

Besides being of fundamental physiological interest, the autocorrelation structure of longitudinal data also has implications for statistical data analysis. Although the autocorrelation structure may be less critical when parameters such as the slope of decline in pulmonary function are estimated, it has substantial impact on parameters like the SE of the slope, which will be underestimated if the autocorrelation is ignored and the observations are treated as independent (18, 20).

In this study we have analyzed time series consisting of patient-administered serial spirometry data from a controlled clinical trial in which emphysematous patients were followed with daily spirometric measurements for several years. Furthermore, two coauthors of this study (A. Dirksen and A. Kok-Jensen) performed daily self-administered spirometry for 14–24 mo.

MATERIALS AND METHODS

Twenty-two patients with severe α₁-antitrypsin deficiency (phenotype PiZ, verified by isoelectric focusing) (9) and moderate to severe emphysema [30% predicted < forced expiratory volume in 1 s (FEV₁) < 80% predicted] participated in a randomized trial of augmentation therapy with α₁-antitrypsin (250 mg/kg) every 4 wk vs. a placebo. All refrained from...
smoking at least 6 mo before entering the study, and urinary cotinine was checked every 4 wk during the trial. All patients gave their informed consent to participate in the study, which was approved by the local medical ethics committee of the city of Copenhagen. Of the 22 patients, 3 were excluded because of poor cooperation and too few measurements (<500). Furthermore, the two coauthors of this study mentioned above performed daily home spirometry for a period of 14–24 mo.

For home spirometry the Vitalograph R model, 24 direct-written, 7-liter, dry-wedge spirometer (Vitalograph, Buckingham, UK) was used during the first half of the study (1991–1993) (15), and during the last half (1993–1995) we used a handheld turbine spirometer with timer and datastorage capability (DiaryCard, MicroMedical, Rochester, UK) (6). The above-mentioned coauthors used the handheld turbine spirometer only. As previously described (6, 15), the spirometers were calibrated every 4 wk when the patients came for infusions.

At inclusion, patients were carefully instructed in spirometry for ~1 h, and they received written information on how to perform spirometry at home. Spirometry was to be performed every morning and evening throughout the study. A measuring sequence included at least three maximal forced vital capacity maneuvers. The individual spirometry results were presented in a blind fashion to ensure that the participants’ expiratory efforts and number of trials would not be affected by previous results. To obtain blinding, Vitalograph charts without preprinted grids were produced, and the software of the turbine spirometer was modified to suppress the continuous display of results. Every 4 wk when the patients came for infusions, results of the last 4-wk spirometries were displayed graphically and presented to the participant to promote motivation. Instructions in spirometry were repeated as needed, and the importance of a maximal inspiration at the start of the test was emphasized regularly. Quality control was performed by visual inspection of time-volume curves (for the Vitalograph) or flow-volume curves (for the DiaryCard), and only measurements fulfilling strict criteria were accepted for further analysis; this meant that the highest FEV1 of three technically satisfactory attempts and the chosen FEV1 did not exceed the next highest measurement by >5% or 100 ml, whichever was greater (17). For the majority of the subjects, the number of discarded measurements was <5% of the total.

At inclusion and every 3 mo throughout the study, patients visited the respiratory laboratory in the morning. Pulmonary function testing was performed according to American Thoracic Society recommendations (1). A constant-volume body plethysmograph and a dry rolling seal spirometer (SensorMedics 2800 and 2450, Anaheim, CA) were applied. Fifteen minutes after bronchodilatation (5 mg nebulized terbutaline), with the patient seated and wearing a noseclip, a slow vital capacity maneuver was obtained first, followed by a forced vital capacity maneuver, from which the maximal flow-volume loop and FEV1 were derived. Static lung volumes (i.e., total lung capacity, functional residual capacity, and residual volume) were measured by both the closed-circuit helium-dilution technique and plethysmography, in which lung volumes and airway resistance were determined during panting, with a frequency of <1/s. The carbon monoxide diffusion constant (KCO) was measured by the single-breath technique, and because the hemoglobin was always within normal limits, the values were not corrected for hemoglobin. The diffusion capacity (DLCO) was calculated as the product of KCO and the alveolar volume. The latter was obtained from the dilution of helium during the single-breath maneuver. All measurements were performed in triplicate except for helium dilution. Gas volumes are reported with STPS corrections, and results are expressed in absolute values and as percentages of predicted values that were calculated according to European reference equations (4, 17).

Data analysis. For estimation of autocorrelations, the FEV1 measurements were detrended by ordinary linear regression for each subject separately. The standardized residuals were used for calculation of the correlations (Pearson) between measurements made at a given interval, ranging from 1 day to 30 mo. To minimize the effect of the circadian variation in FEV1, autocorrelations were calculated separately for the morning and evening measurements. This resulted in two autocorrelation functions for each subject, which were then averaged so as to yield one autocorrelation function. Calculation of the autocorrelations in a given individual was terminated when the number of paired observations fell below 50 for either the morning or evening measurements. The above-mentioned procedure was chosen because it allowed for the presence of missing data while making use of all available data. The normalized power spectrum of the fluctuations in the FEV1 was obtained as the Fourier transform of the mean of the empirical autocorrelation functions by use of the fast Fourier algorithm.

For use in the theoretical calculations, the mean of the empirical autocorrelation functions for the emphysematous patients were approximated by a theoretical structure of the form

\[ r_i = \begin{cases} \frac{k^i}{\alpha^i} & \text{if } i \neq 0 \\ 1 & \text{if } i = 0 \end{cases} \]

where k and a are constants and i is the interval between measurements in days (see APPENDIX for details). The parameters were estimated by the method of least squares, using a quasi-Newtonian algorithm.

RESULTS

Table 1 shows that the 19 patients with α1-antitrypsin deficiency had moderate to severe emphysema. On average they were followed for >3 yr and performed >1,000 acceptable spirometries.

Raw data (FEV1) from two of the emphysematous patients and one normal subject are delineated in Fig. 1. In absolute terms the diurnal variations are of approximately the same magnitude in all three individuals, but seasonal fluctuations were larger in the subject with normal lung function. Gaps in the recordings indicate missing data, e.g., measurements not taken during holidays. The subject with normal lungs was appendec-tomized in September 1994.

The mean autocorrelation structure for the emphyse-matous patients is shown in Fig. 2A. The best fit for the model given in Eq. 1 was achieved with the values k = 0.3556 and a = 0.9910874 for the two constants. With these values for the constants, the model explained 74% of the variance in the data (R2 = 0.74). The correlation between measurements taken on consecutive days was found to be −0.35, with a slow, approximately exponential decline (the half time was ~38 days). Between 3 and 4 mo, the autocorrelation function
became negative. It reached a minimum of $-0.1$ at $\approx 8$ mo and then increased toward zero over the following 12 mo. The mean autocorrelation profile shows moderate peaks at 12 and 24 mo, which were not accounted for by the model given in Eq. 1.

The autocorrelation profiles of the two subjects with normal lungs (Fig. 2B) showed a more rapid decline during the first months. Seasonal variations were large in one of these subjects (raw data for this subject are delineated in Fig. 1), and weekly fluctuations were pronounced in both of them. Although weekly variations were less obvious in the time series from the emphysematous patients, power spectral analysis reveals a distinct peak at 1 cycle/wk even in this group (Fig. 3).

### DISCUSSION

The results of the present study show that there are substantial fluctuations in the FEV$_1$ when measured over several years. Initially, the autocorrelation profile of the fluctuations (Fig. 2) declines almost exponentially, with a half time of $\approx 1$ mo. After $\approx 100$ days, the autocorrelation function becomes negative, reaching a minimum at $\approx 8$ mo. Thereafter, it approaches zero over the following year. The implications of this finding are

### Table 1. Characteristics and lung function at enrollment of 19 patients with severe $\alpha_1$-antitrypsin deficiency (phenotype PiZ)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (Range)</th>
<th>% Predicted ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>51 ± 8.7 (39–64)</td>
<td>113 ± 16.2 (76–142)</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>4.54 ± 1.42 (2.01–7.14)</td>
<td>48 ± 11.8 (30–77)</td>
</tr>
<tr>
<td>FEV$_1$, liters</td>
<td>1.56 ± 0.48 (0.91–2.72)</td>
<td>127 ± 14.0 (98–151)</td>
</tr>
<tr>
<td>VC, liters</td>
<td>5.18 ± 1.47 (2.79–7.49)</td>
<td>131 ± 12.8 (103–151)</td>
</tr>
<tr>
<td>TLC, liters</td>
<td>8.22 ± 1.56 (5.51–10.7)</td>
<td>164 ± 38.1 (114–246)</td>
</tr>
<tr>
<td>RV, liters</td>
<td>3.30 ± 0.70 (2.40–4.96)</td>
<td>160 ± 26.1 (114–213)</td>
</tr>
<tr>
<td>FRC, liters</td>
<td>5.11 ± 1.18 (3.11–7.31)</td>
<td>113 ± 24.6 (72–160)</td>
</tr>
<tr>
<td>FRC-He, liters</td>
<td>3.66 ± 1.12 (1.95–5.84)</td>
<td>59 ± 16.7 (17–87)</td>
</tr>
<tr>
<td>$D_L$CO, ml·min$^{-1}$·mmHg$^{-1}$</td>
<td>16.8 ± 5.11 (5.80–25.5)</td>
<td>56 ± 16.8 (15–86)</td>
</tr>
<tr>
<td>$K_CO$, ml·min$^{-1}$·mmHg$^{-1}$·l$^{-1}$</td>
<td>2.55 ± 0.80 (0.60–3.94)</td>
<td>24.6 (17–87)</td>
</tr>
<tr>
<td>PASS</td>
<td></td>
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</tr>
<tr>
<td>Period of observation, yr</td>
<td>3.1 ± 1.0 (1.5–4.5)</td>
<td></td>
</tr>
<tr>
<td>No. of accepted measurements</td>
<td>1,095 ± 471 (400–2,300)</td>
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</tr>
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</table>

Values are means ± SD with range in parentheses; n = 10 men and 9 women. FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; VC, slow vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; FRC-He, FRC measured by He dilution; $K_CO$, CO diffusion constant; $D_L$CO, diffusion capacity calculated from the product of $K_CO$ and alveolar volume; PASS, patient-administered serial spirometry. TLC, RV, and FRC were measured by body plethysmography.
that fluctuations in lung function have a considerable temporal persistence and that they are dominated by fluctuations with a very low frequency. When plotted as the power spectrum against frequency ($f$), the relationship between the frequency and the contribution of each frequency ($V$) to the total variance could be expressed approximately as $V = 1/f^x$, or "one over $f$ spectrum," where $x$ is the slope of the line in the log-log plot, and $x$ is $\sim 0.88$ (Fig. 3). Thus in the patients the fluctuations were dominated by the slow frequencies ($f > 1$ cycles/wk).

Presently, we have no explanation for the irregular fluctuations in FEV$_1$ observed in this study. Longitudinal variations in pulmonary function may be due to either biological variation or measurement error (21). Because it was the chief purpose of the present study to explore the long-range fluctuations in pulmonary function tests, we only determined the FEV$_1$ twice daily. It is well known that pulmonary function undergoes circadian variability of FEV$_1$ may have been grossly underestimated in the present study (5). To minimize any possible effects from diurnal variation, all measurements were made at the same time of day. This is in accordance with the recommendations of both the American Thoracic Society and the European Respiratory Society (1, 17). In addition, the autocorrelation profiles for morning and evening values were calculated independently. Thus it appears unlikely that the observed variability can be explained by the diurnal variation in lung function.

Diurnal variation is usually explained by a complex interaction of several coincident circadian rhythms (2). Possible biological mechanisms behind the variability we observed are numerous. Environmental exposures may influence pulmonary function. The weather is a universal, chaotic phenomenon, and thus it is obvious, as is often stated by patients, to suspect the weather as a possible source of variations in pulmonary function.

Denmark is a small, flat country without mountains, and usually the weather is quite similar all over the country. However, in the present study, fluctuations in the patients were totally out of phase. The between-patient correlations were insignificant. Thus the weather was probably not a major source of variation. Another environmental exposure that may be considered is air pollution (7, 8). However, in Denmark the predominant western wind keeps outdoor air pollution low, making it an unlikely source of significant variability in pulmonary function.

A potential source of measurement error was the spirometers, but this was reduced to a minimum by careful quality assurance. The instruments were calibrated every 4 wk throughout the study. The variability in performance (coefficient of variation) was within 1%, and the calibration data showed no autocorrelation (6, 15). Another important source of measurement error is lack of comprehension by or cooperation of the participants. The spirometric maneuver requires a maximum physical effort and coordinated movement by a subject trained to perform it (14). To ensure that the participants continued to follow measurement procedures, the instructions in spirometry were repeated regularly, and the importance of a maximal inspiration at the start of the test was especially emphasized (3).

As already mentioned above, one of the most striking features of the power spectrum was its 1/f pattern. The 1/f spectral pattern occurs widely in nature and is found in both animate and inanimate systems (13, 16, 19). For example, previous studies have shown 1/f spectral patterns in arterial blood pressure and heart rate (13, 16). To the extent that it has been possible to draw generalizations about the meaning of 1/f spectra, it appears that the spectra occur in systems that are spatially distributed and loosely coupled. The value of the FEV$_1$ at any time is the result of all the processes that occur throughout the bronchial system. Examples of such processes could be environmental influences, infectious and/or inflammatory processes, or nervous stimulation of bronchial smooth muscle. Each particular process will have a characteristic time scale, and the finding of a 1/f pattern suggests that all the processes contribute to the variability, and that no single mechanism dominates. If the system was dominated by the action of a single mechanism, a single spectral peak would emerge because the system would be operating in a single mode.

Although we only followed the FEV$_1$ in two normal subjects, it is striking that the autocorrelation function appears to decline toward zero faster in the normal subjects than in patients. The implication of this observation is that the fluctuations in FEV$_1$ are more random in the normal subjects. The mechanism behind this difference is unknown, but a related phenomenon has been observed in patients with heart disease. Patients with heart disease tend to have a reduced heart rate variability, and it has been well documented that a reduced variability is an independent risk factor for sudden cardiac death (12, 22). Further studies are needed to determine whether the apparent change in
the dynamics of FEV₁ by itself has any clinical implications.

FEV₁ is the most commonly used pulmonary function measurement in longitudinal studies of obstructive lung disease, and our findings have important implications for the efficient use of serial measurements for estimating the decline in lung function in individual subjects with either normal lungs or relatively stable lung function. When a phenomenon with high autocorrelation is being investigated, frequent sampling will not be worthwhile because measurements at short intervals will add little extra information.

The decline in lung function is often expressed as the slope of the regression line between FEV₁ and the time of measurement. Standard formulas and most statistical software packages assume that the data points are randomly and independently distributed around the regression line. Basically, this assumption implies that if a measurement at one time is above the estimated regression line, there is a 50% chance that the next measurement will also fall above the regression line. This will not be the case for daily measurements of the FEV₁, as demonstrated by the present results. Because of the high degree of autocorrelation between measurements, the probability that the next measurements will also fall above the regression line will be much greater than 50%. Indeed, the measurements need to be spaced more than 3 mo apart before this probability reaches 50%.

This finding has significant implications for the precision of the estimated slopes. To quantify this issue, we investigated the precision of the estimated slope of decline in lung function as a function of sampling frequency.

The slope can essentially be estimated in two ways (see APPENDIX). Either the slope can be calculated as an ordinary least squares estimate (E_{OLS}) or, more correctly, the slope can be obtained by using an appropriately estimated autocorrelation structure, derived as a maximum likelihood estimate (E_{ML}) in this model. As imaginary sampling schemes, we considered an observation period of 365 days, with sampling intervals of 1, 2, 3, 4, 5, 6, 7, 14, 30, 60, 90, 120, 183, and 365 days, respectively. For each of these designs, we calculated the following three SEs: 1) the standard error of E_{ML} under the assumption of autocorrelation, i.e., by using Eq. A1 (see APPENDIX); 2) the standard error of E_{OLS} under the assumption of autocorrelation, i.e., by using Eq. A2 (see APPENDIX); and 3) the standard error of E_{OLS} under the assumption of independence, i.e., by using Eq. A3 (see APPENDIX).

In Fig. 4, the resulting SEs of E_{ML} (assuming the above-mentioned autocorrelation structure) are seen as the middle curve (solid line). It is obvious from Fig. 4 that the real gain in precision by frequent sampling is modest (reducing the SE by 1/3 from worst to best situation, which corresponds to 183 times more measurements). Even with an infinite number of measurements, it will not be possible within an observation period of 1 yr to bring the SE below ±80 ml/year, a value which is quite large compared with a predicted annual decline in FEV₁ in normal subjects of ~30 ml/yr. However, provided we falsely assume the measurements to be independent (which is implicit in most statistical software packages), the resulting SEs of E_{OLS} are shown as the bottom curve (dashed line) in Fig. 4. The estimated SEs are smaller than those of E_{ML}, and erroneously, it seems as if the gain from frequent sampling was large (a decrease of ~10 times). The top curve (dotted line) in Fig. 4 shows the SEs of E_{OLS}, calculated in the appropriate correlation structure, and it can be seen that this curve is close to the curve for E_{ML}, indicating that the extra efficiency obtained by using the correct correlation structure for calculating the slope estimate is small. Thus, for estimation of the decline in lung function, E_{OLS} may be used, as long as its true precision is calculated with due regard to the autocorrelation structure.

The practical implications for estimates of long-term trends in lung function are as follows: 1) it is not cost effective to measure FEV₁ more often than once every 3 mo; and 2) provided measurements are performed more frequently than once every 3 mo, the autocorrelation structure should be taken into account when the SE of the decline in lung function in individual subjects is estimated.

To avoid any misconception, it should be emphasized that this recommendation of less frequent measurements applies to long-term trends in lung function only. The recommendation does not apply to monitoring of short-term changes in lung function, such as exacerbations of chronic obstructive pulmonary disease or asthmatic variations.

APPENDIX

In the investigation of the effect of sampling frequency on SE of the estimated lung function decline, we assumed that the FEV₁ measurements, Yᵢ, could be described by the linear
model
\[ Y_i = \mu + \beta t_i + \epsilon_i \]
or in matrix notation
\[ Y = X \beta + \epsilon \]

Here, \( Y \) denotes the \( N \times 1 \) matrix that contains the \( N \) measurements of FEV1, \( \beta \) denotes the parameter vector \( (\mu, \beta) \), where \( \mu \) is the intercept (level at the start of the investigation period) and \( \beta \) is the slope of the regression line (usually negative), and \( X \) is the design matrix, reflecting the sampling frequency. Thus \( X \) is an \( N \times 2 \) matrix, the first column being only ones (corresponding to the initial level) and the second column indicating times of measurements, \( t_i \). In the designs chosen, \( N \) varies between 2 and 365.

The \( \epsilon_i \) notations in the model formula above denote the random fluctuations of lung function around the linear decline. We let \( \Sigma \) denote the covariance matrix for these “errors,” i.e., a matrix of dimension varying from 2 \( \times \) 2 to 365 \( \times \) 365. In traditional linear regression, this matrix is assumed to be diagonal, i.e., \( \Sigma = \sigma^2 I \), where \( I \) is the identity matrix (a matrix with 1's in the diagonal and 0's elsewhere). This corresponds to independence between observations taken at different times. The results of the present study show that this is not the case for daily FEV1 measurements, because an appreciable amount of autocorrelation is present.

As an example of a reasonable covariance structure (reflecting the slowly decaying autocorrelation of moderate size), we chose for descriptive purposes a Laguerre function of the form

\[ \sigma_{ij} = k \sum_{l=1}^{n} a(l + |t_i - t_j|) \]

where \( \sigma_{ij} \) denotes the elements of \( \Sigma \), \( t_i \) and \( t_j \) denote observation times, and \( k \) and \( a \) are constants chosen to make the correlation pattern agree approximately with the one observed. The Laguerre function was chosen because of its built-in exponential term. The correlation \( \rho \) between the measurements taken 1 day apart can be calculated as

\[ \rho = k \sqrt{a(2a - 1)} \]

With the constants \( a = 0.99910874 \) and \( k = 0.3556 \), we have \( \rho = 0.354 \), and we find the correlation structure as shown in Fig. 1. The empirical correlations are also shown in Fig. 1.

The parameter \( \beta \) in the regression model can be estimated by either the maximum likelihood method (ML), which takes the correlation structure, \( \Sigma \), into account

\[ \hat{\beta}_{ML} = (X^T \Sigma^{-1} X)^{-1} X^T \Sigma^{-1} Y \]
or by ordinary least squares (OLS), assuming independence

\[ \hat{\beta}_{OLS} = (X^T X)^{-1} X^T Y \]

The variances (Var) of these two estimates are

\[ \text{Var}_n(\hat{\beta}_{ML}) = (X^T \Sigma^{-1} X)^{-1} \]

and

\[ \text{Var}_n(\hat{\beta}_{OLS}) = (X^T X)^{-1} \Sigma X^T (X^T X)^{-1} \]

respectively. Note, that while \( \hat{\beta}_{OLS} \) is determined under the assumption of independence between measurements, the expression for its variance, Eq. A2, does not assume independence.

However, by ignoring the autocorrelation structure and using the ordinary least square estimate \( \hat{\beta}_{OLS} \), the traditionally quoted variance estimate similarly assumes independence \( (\Sigma = \sigma^2 I) \), and therefore simplifies to

\[ \text{Var}_n(\hat{\beta}_{OLS}) = \sigma^2 (X^T X)^{-1} \]

where \( \sigma^2 \) is estimated \( (s^2) \) from the actual observations, \( Y \), by

\[ s^2 = \frac{1}{n-2} Y^T (I - X(X^T X)^{-1} X^T) Y \]

When dealing with theoretical calculations, we use instead its mean value, which in the general setting is given by

\[ \mathbb{E}_n(s^2) = \frac{1}{n-2} \text{tr}[I - X(X^T X)^{-1} X^T] \Sigma \]

where \( \mathbb{E}_n \) is the expected value, and \( \text{tr} \) denotes the trace of a matrix. Note that \( \Sigma \) in the equation above represents the “true” covariance structure of the underlying stochastic process. The total expression for the traditionally quoted variance of the conventional least square estimator therefore becomes

\[ \text{Var}_n(\hat{\beta}_{OLS}) = \frac{1}{n-2} \text{tr}[I - X(X^T X)^{-1} X^T] \Sigma (X^T X)^{-1} \]

The three variance estimates given by Eqs. A1, A2, and A3 are all \( 2 \times 2 \) matrices, and our interest focuses on the lower right-hand corner because this is the variance of the slope estimate. The square root of this is the SE of the slope, which is depicted in Fig. 4 as a function of the time span between successive measurements.

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