

COMMENTARY

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“...when multiple repeated observations are available, it would make a lot of sense to measure the outcome in the form of a time series; accounting trends, seasonal effects and change points during the trial.”

Autoregressive integrated moving average in clinical trials

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Clinical trials are, usually, performed to assess the effects of predictors such as treatment modalities, environmental factors, or health risk factors on health outcomes. Health outcomes can be measured as a single end point at the completion of the trial; however, when multiple repeated observations are available, it would make a lot of sense to measure the outcome in the form of a time series; accounting trends, seasonal effects and change points during the trial. Autoregressive integrated moving average (ARIMA) analysis is, particularly, suitable for that purpose, since it can assess all of these effects simultaneously. It is based on autoregression (AR), a technique invented in the early 1960s by Udney Yule [1], a University of Cambridge (Cambridge, UK) professor of statistics. Time curves are cut into pieces and then compared with one another using linear regression. In this way it can demonstrate significantly repetitive patterns, meaning patterns that are more strongly repetitive than could happen by chance. However, in order to demonstrate change points from a repetitive pattern and to demonstrate upward or downward trends, the comparison of the averages of a number of observations is more sensitive. An extended method for the purpose was proposed by Box and Jenkins in 1994 [2]; it is called autoregressive moving average (ARMA), and assesses autocorrelations, change points and up/downward trends simultaneously.

It would be nice if – as in multiple regression – independent predictors of the outcome, such as treatments, could be included. This is accomplished by the ARIMA method, a multivariate and computationally intensive method available in major software programs (e.g., in SPSS module forecasting [101]). ARIMA is currently widely applied in social sciences for making predictions [3], but is little used in clinical research, despite the recognized need for better predictive models in this field [4,102]. When searching Medline, ARIMA studies were found sporadically: in two organizational healthcare studies [5,103], two single-subject studies [6,104] and only one therapeutic study [105].

Autoregressive modeling

Autocorrelation is a technique that cuts time curves into pieces. These pieces are subsequently compared with the original data curve using linear regression analysis. For example, in an outpatient clinic, CRP values may be higher in winter than in summer. The original data curve is cut into pieces four times, and the cut pieces are called lag curves and are moved to the left end of the original curve. The first lag curve is very close to the original data curve. When performing a linear regression analysis with the original data on the y-axis and the lag data on the x-axis, a strong positive correlation will be found. The second lag curve is not close anymore and linear regression of the two curves produces a correlation coefficient of approximately zero. The third lag curve then gives a mirror image of the original data curve and, thus, has a strong negative correlation.

Keywords: autoregressive integrated moving average • autoregressive model
• autoregressive moving average • moving average • time series

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Finally, the fourth lag curve is in phase with the original data curve and, thus, has a strong positive correlation.

If, instead of a few lag curves, monthly lag curves are produced, then we will observe that the magnitude of the autocorrelation coefficients changes sinusoidally in the event of seasonality.

Autocorrelation coefficients significantly larger or smaller than zero must be observed in order to conclude the presence of a statistically significant autocorrelation. The equation below shows the mathematical equation of autocorrelation of two subsequent observations in a time series. The equation is derived from the correlation coefficient of linear regression.

$$ACC = r = \frac{\sum (x_t - \bar{x})(x_{t+1} - \bar{x})}{\sum (x_t - \bar{x})^2}$$

x_t is observation 't' in a time series and \bar{x} is the mean of all observations. With one observation per time unit (day, week or month) an autocorrelation coefficient versus the first observation is calculated and all of them are drawn along the time axis. In this way an overview of the autocorrelation function is given. We wish to find an appropriate equation for the curve of the autocorrelation coefficients. For that purpose, we simply use changing linear functions (a = intercept; b = direction coefficient).

$$\begin{aligned} y &= a + bx \\ ACC_1 &= ACC_0 + b_1 t_1 \\ ACC_2 &= ACC_0 + b_1 t_1 + b_2 (t_2 - t_1) \end{aligned}$$

The above equation can also be described as:

$$ACC_2 = ACC_0 + (b_1 - b_2)t_1 + b_2(t_2)$$

With multiple ACCs and replacement of the 'b - b' terms by 'φ' terms, the equation will look like:

$$ACC_1 = ACC_0 + \varphi_1 t_1 + \varphi_2 t_2 + \varphi_3 t_3 + \varphi_4 t_4 + \varphi_5 t_5 + \dots \varphi_t t_t$$

The above equation is called an autoregressive model of the t-th order. We wish to test whether the equation is significantly different from zero. For that purpose, standard errors are required. Instead of t-tests, Ljung-Box tests are used, which assess overall randomness on numbers of lags instead of randomness at each lag and are calculated according to:

$$\text{Chi-square} = n(n+2) \sum \left[\frac{r_k^2}{(n-k)} \right]$$

n = sample size; k = lag number; Σ = sum of terms from $k = 1$ to h , with h = total number of lags tested. It produces better p-values than does the t-statistic; however, the p-values are given lack of meaning without

adjustment for multiple testing. SPSS uses Hochberg's false discovery rate method. Using this approach, we can assess whether the data are stationary or change periodically. As long as the 95% CIs are not crossed, we conclude that the AR model is stationary. The best fit φ values (otherwise called parameters) are calculated as with multiple linear regression using ordinary least squares.

ARMA modeling

In case of a more lasting crossing of the 95% CI, the moving average model is more sensitive. It does not apply autocorrelation coefficients, but rather the actual observations and their means. Otherwise, it also makes use of the same method of changing linear functions. It uses the following mathematical equation:

$$\begin{aligned} y &= a + bx \\ \text{observation}_1 &= \text{observation}_0 + b_1 t_1 \\ \text{observation}_2 &= \text{observation}_0 + b_1 t_1 + b_2 (t_2 - t_1) \end{aligned}$$

The above equation can also be described as:

$$\text{observation}_2 = \text{observation}_0 + (b_1 - b_2)t_1 + b_2(t_2)$$

With multiple observations and replacement of the 'b - b terms' by 'λ terms' the equation looks like:

$$\text{observation}_t = \text{observation}_0 + \lambda_1 t_1 + \lambda_2 t_2 + \lambda_3 t_3 + \dots \lambda_t t_t$$

The best fit λ values are calculated as with multiple linear regression using ordinary least squares.

ARIMA modeling

A more sophisticated approach is the ARIMA methodology. It is a multivariate method that finds the best fit parameters for the AR part of the data and the best fit parameters for the moving average part of the data and, at the same time, adjusts the two parts for one another. The mathematics are more computationally intensive, requiring sum of squares and cross products (SSCP) matrices and iteration methods; however, excellent software is available, such as the module forecasting in SPSS. Data analysis using SPSS statistical software requires the following commands:

Command: Analyze → Forecast → Sequence Charts → Variables: enter the main outcome variable → Time Axis Labels: enter date → OK.

Covariates can be addressed using the Expert Modeler:

Command: Analyze → Forecast → Time Series Modeler → Dependent Variables: main outcome

variable → *Independent Variables: enter the potential covariates* → *Click Methods: expert modeler* → *Click Criteria* → *Click Outlier Table* → *Select automatically* → *Click Statistics Table* → *Select Parameter Estimated* → *Click Plots Table* → *Click Series, Observed values, Fit values* → *Click OK*.

The accuracy of fit of the observed data is given in addition to trends, seasonality, outliers, change points and significant predictors as identified.

Discussion

Of course, there are other ways for assessing each of the above effects. For example, trends can be assessed by trend tests such as chi-square and linear regression tests, seasonality can be assessed by curvilinear regression including Fourier analysis and polynomial regression. However, ARIMA can assess all of these effects simultaneously.

In addition, the traditional methods are unable to assess the effects of independent predictors of the outcome patterns. ARIMA can be used to adjust for multiple predictors, and is thus helpful to explain why certain patterns and outliers were observed. It should be added that such a comprehensive method would normally lead to large Type I errors due to multiple testing. However, due to ARIMA's multivariate methodology, this is prevented and the very sensitivity of testing is even improved [3].

ARIMA modeling can include the effects of multiple predictors on the outcome patterns. However, it is different from multiple linear regression, because instead of a single continuous outcome variable, multiple outcome variables along a timeline are used, including trends, seasonal effects and change points. It is also different from Cox regression, because Cox regression assesses time to a single event, rather than specific patterns in a timeline.

ARIMA can also be applied to analyze time series in individual patients. We should emphasize that $n = 1$ studies are not scientific trials, since they are not meant to improve the level of scientific knowledge of the community, but rather to find the best possible treatment for individual patients.

ARIMA is a sensitive method of assessing upward/downward trends and change points along the time line, and this is the case not only for groups, but also for individual patients. It has been successfully applied as a methodology for the latter purpose.

Conclusion

ARIMA modeling is very sensitive for a simultaneous assessment of trends, seasonality, change points and the effects of multiple predictors.

- ARIMA modeling is appropriate for assessing trends, seasonality and change points in a time series;
- It can assess all of these effects simultaneously;
- It can also be used to adjust for multiple predictors, and is thus helpful to explain why certain patterns and outliers were observed;
- It is multivariate methodology, thereby preventing the Type I error risk of multiple testing;
- It is different from multiple linear regression because instead of a single continuous outcome variable, multiple outcome variables along a time-line are used;
- It is also different from Cox regression, because Cox regression assesses time to a single event, rather than pattern characteristics along a time line.

In clinical trials with multiple repeated observations it makes a lot of sense to measure the outcome in the form of a time series accounting trends, seasonal effects and change points during the trial. ARIMA analysis is particularly suitable for that purpose, because it can assess all of these effects simultaneously and it can also adjust concomitant variables.

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