Time Series Analysis with Application in Public Health and Biomedical Data

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Abstract: The paper gives a overview of time series modeling and forecasting, using multiplicative SARIMA models, with application in assessing and forecasting of epidemiological data. After presenting of the main models and the methodological issues used in Box-Jenkins approach, the paper presents two case studies having as subject the modeling and forecasting of the cumulative number of individuals infected with severe acute respiratory syndrome, or SARS, in Singapore, from 24 February to 7 May 2003, and the measles infections, in Great Britain, 1971-1994, quarterly recorded. For the last series an example of intervention analysis, using as the exogenous data the measles infections, and as endogenous variable the number of vaccinated persons, in the same time period, is presented, proved to be a useful approach, when the time series is affected by the effect of population vaccination.

Keywords- Time series analysis, modeling, forecasting, intervention analysis, Box-Jenkins approach, epidemiological data, case study.

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1. Introduction

ALTHOUGH the incidence of epidemic diseases has reached historic lows in many parts of the world, these diseases still causes substantial morbidity globally. Even where control programs have succeeded in epidemic diseases locally extinct, unless vaccination coverage is maintained at extremely high levels, susceptible numbers may increase sufficiently to spark large outbreaks. Human mobility will drive potentially infectious contacts and interact with the landscape of susceptibility to determine the pattern of epidemic diseases outbreaks. These interactions have proved difficult to characterize empirically.

So, it is of great interest to explore the degree to which new sources of data, combined with existing public health data, can be used to evaluate the landscape of immunity and the role of vaccination in the eradication of epidemic diseases. The understanding of data dynamics of people affected by epidemic diseases from year to year is important for the management of infectious disease epidemics. In this context, different public health surveillance systems have been developed to facilitate the detection of abnormal behavior of infectious diseases and other adverse health events. To achieve this goal, different approaches have been used for assessing and forecasting of infectious disease incidence. The dynamics and control of infectious diseases in terms of mathematical models are discussed in, [1], among others. Time series analysis enjoys of great interest in this field. It makes use of statistical models able to forecast the epidemiological behavior of the historical surveillance data. Different methods have been reported in the literature. So, exponential smoothing, [2], and generalized regression, [3], methods were used to forecast in-hospital infection and incidence of cryptosporidiosis respectively. Decomposition methods, [4], and multilevel time series models, [5], were used to forecast respiratory syncytial virus.

Seasonal autoregressive integrated moving average ($SARIMA$) models have been extensively used for epidemic time series forecasting including the hemoragic fever renal syndrome, [6], [7], dengue fever, [8], [9], and tuberculosis, [10].

Model based on artificial neural networks were also used to forecast the incidence of hepatitis A, [4], [11], and typhoid fever, [12]. The decomposition methods are the most traditional methods in time series analysis, [13], [14]. Recently, machine learning based time series models such as artificial neural networks have been successfully applied for modeling infectious disease incidence time series, [15], [16]. Support vector machines (SVM), a new type of machine learning methods based on statistical learning theory, [17], are used for epidemic time series forecasting, [18].

Two epidemic diseases will make the object of assessing, modeling and forecasting using time series analysis, in the case studies presented in the paper: severe acute respiratory syndrome and measles infections. Different approaches are used for severe acute respiratory syndrome (SARS) assessing, making the object of many papers, [19], [20], [21], among others. The

problem of modeling and forecasting of measles infection is present in many papers. So, in [22] is provided an early signal of infectious disease epidemics by analyzing the disease dynamics. The model consisted of a seasonal autoregressive integrated moving average $SARIMA(3,1,0)(0,1,1)_{12}$ model, used in measles dynamics analysis in Bangladesh. A mathematical model of the dynamics of measles in New Zealand, to predict an epidemic in 1997, which was used in the decision to carry out an intensive immunization campaign in 1997 is presented in [23]. In [24] is developed a model, the TSIR (Time-series Susceptible Infected Recovered), that can capture both endemic cycles and episodic out- breaks in measles. It is a doubly stochastic model for disease dynamics, and includes seasonality in the transmission rates. All parameters of the model are estimated on the basis of time series data on reported cases and reconstructed susceptible numbers from a set of cities in England and Wales in the pre-vaccination era (1944-1966). A new prediction analysis procedure for measles epidemics, a combination of nonlinear squares method with the maximum entropy spectral analysis method, is presented in [25].

The paper is organized as follows. In Section 2 is given a general view on the time series models, regression and intervention models, to be used in modeling and forecasting of epidemiological surveillance data. Section 3 discusses some methodological aspects of time series modeling and forecasting, based on Box-Jenkins methodology, with the emphasis on practical aspects. Section 4 discusses a case study having as object modeling and forecasting of a time series representing the cumulative number of individuals infected with severe acute respiratory syndrome, or SARS, in Singapore, from 24 February to 7 May 2003. Section 5 presents a case study of modeling and forecasting, using a multiplicative $SARIMA$ model, for a time series representing the number of measles infections, in Great Britain in the period 1971-1994, and an example of intervention analysis, using as the exogenous data the measles infections, and as endogenous variable the number of vaccinated persons, in the same time period.

2. Time series models

The statistical approaches adopted in time series modeling and forecasting usually rely on multiplicative $SARIMA$ (Seasonal Auto Regressive Integrated Moving Average) model. A such model has the following form for the time series z_t, [26]:

$$\phi(B)\Phi(B^s)\bigtriangledown^d\bigtriangledown_s^D z_t = \theta(B)\Theta(B^s)a_t \qquad (1)$$

where a_t is a white noise and

$$\phi(B) = 1+\phi_1 B+\phi_2 B^2+\cdots+\phi_p B^p;$$

$$\theta(B) = 1+\theta_1 B+\theta_2 B^2+\cdots+\theta_q B^q;$$

$$\Phi(B^s) = 1+\Phi_s B^s+\Phi_{2s} B^{2s}+\ldots+\Phi_{Ps} B^{Ps};$$

$$\Theta(B^s) = 1+\Theta_s B^s+\Theta_{2s} B^{2s}+\ldots+\Theta_{Qs} B^{Qs};$$

with B the time delay operator, $Bz_t = z_{t-1}$, $\bigtriangledown z_t = (1-B) = z_t - z_{t-1}$, nonseasonal differentiating operator, and $\bigtriangledown_s z_t = (1-B^s) = z_t - z_{t-s}$, seasonal differentiating operator: d is the nonseasonal differentiating order, D is the seasonal differentiating order and s is the seasonal period of the series.

The model is defined as $SARIMA(p,d,q)(P,D,Q)_s$ where (p,d,q) denotes nonseasonal orders, and (P,D,Q) seasonal order of the model. The model is presented in Fig. 1.

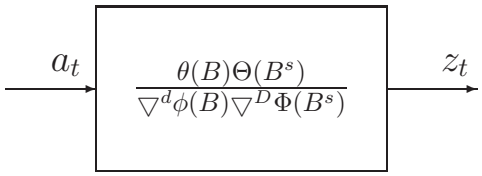

Fig. 1: Multiplicative $SARIMA(p,d,q)(P,D,Q)_s$ model

The multiplicative form of the model simplifies the stationarity and invertibility conditions checking; these conditions can be separately checked, for seasonal and nonseasonal coefficients of the model.

Starting from the general model form of the model $SARIMA$ it can be obtain related models: AR (Auto Regressive), MA (Moving Average), $ARMA$ (Auto Regressive Moving Average) and $ARIMA$ (Auto Regressive Integrated Moving Average), with or without seasonal components. These models are identified by the mean of the autocorrelation (ACF) and the partial autocorrelation functions ($PACF$).

In some situations, it is known that some external events can affect the variables for which the practitioner intends to forecast the future time series values. Dynamic models, used in this case, include several variables, as input variables, which are intended to take into account in the dynamics model, the mentioned exception events. A special kind of $SARIMA$ model with input series is called an intervention model or interrupted time series (ITS) model, [27]. In an intervention model, the input series is an indicator variable that contains discrete values that flag the occurrence of an event affecting the response series. This event is an intervention in or an interruption of the normal evolution of the response time series, which, in the absence of the intervention, is usually assumed to be a pure $SARIMA$ process. As examples of practical interventions can be mentioned: the effect of different promotions activities on the sales, the effect of strikes on the volume of the products and the price of the products, the effect of medication on the health of the patient, the effect of the exchange of the laws in the legislation on the mortalities resulting from car accidents, etc. In this case, some variables as step function, consisting of "zero" values and "unit" values, before and after application respectively change policy, medication, or exchange of laws are included in the model, as an external variable.

A such intervention model can be represented like a

transfer function (TF) model (see Fig. 2), where z_t is the value of the endogenous variable at time t, $\mathbf{u}_t = [u_{1t}, \ldots, u_{rt}]^T$ is the vector of exogenous variables, and a_t is a white noise error.

$$\Omega_i(B) = \omega_{i0} + \omega_{i1}B + \omega_{i2}B^2 + \cdots + \omega_{in_i}B^{n_i};\ i = 1, 2, \ldots, r$$

$$\Delta_i(B) = 1 + \delta_{i1}B + \theta_{i2}B^2 + \cdots + \delta_{in\delta_i}B^{n\delta_i};\ i = 1, 2, \ldots, r$$

$\phi(B)$, $\theta(B)$,$\Phi(B^s)$ and $\Theta(B^s)$ have been described above.

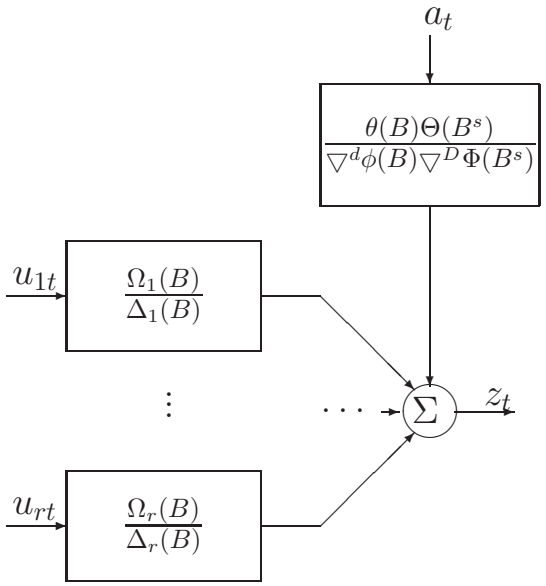

Fig. 2: Transfer function (TF) model

3. Methodological Aspects

The time series model construction usually include the following stages, [26]:

- Identification (specification) of the time series model using some data analysis tools (different graphical representations, autocorrelation functions (ACF) and partial autocorrelation functions ($PACF$)) in order to determine the types of transformations to obtain stationarity and to estimate the degree of differentiation needed to induce stationarity in data, as well as the polynomial degrees of autoregressive and moving average operators in the model.

- Model parameter estimation of the time series implies the use of efficient methods (such as maximum likelihood, among others) for parameter estimation, standard errors and their correlations, dispersion of residuals, etc.

- Model evaluation (validation) aims to establish the model suitability, or to make some simplifications in structure and parameter estimates. Key elements for model validation refers to residuals which can not be justified, these being any residuals of abnormal value that can not be explained by the action of known external factors or other variables; also the correlations and partial correlations of the residuals prove useful tools in model evaluation.

More explanations of the process, [28], often add a preliminary stage of data preparation and a final stage of model application, or forecasting.

Visual analysis of series data allows a first image on the series' non-stationarity and on the presence of a seasonal pattern in the data. The final decision on the inclusion of seasonal elements in the time series model will be taken after the autocorrelation function (ACF) and partial autocorrelation function ($PACF$) analysis, as well as after the estimation results analysis; the visual analysis of the data can provide useful additional information.

Significant changes in the mean value of the series data require non seasonal differentiation of the first order, while the varying of the rate for average value imposes the nonseasonal differentiation of the second order of the series. Strong seasonal variations usually require, not more than the seasonal differentiation of the first order of the series'data. Autocorrelation function of the series offers information on the nonseasonal and seasonal degrees to be used to obtain the stationarity of the data.

An $ARMA$ stationary process is characterized by theoretical autocorrelation and partial autocorrelation functions tending to zero. The autocorrelation function tends to zero after the first $q - p$ values of the delay, following the evolution of a exponential function or of a damped sinusoidal function, and the partial autocorrelation function is canceled after the first $p - q$ values of the delay, [29].

An AR or MA seasonal process is characterized by similar autocorrelation and partial autocorrelation functions, corresponding to nonseasonal processes, but the coefficients of autocorrelation and partial autocorrelation functions, significant for the seasonal process, appear at multiple seasonal delay values.

At the stage of model identification a special attention will be given to nonseasonal autocorrelation coefficients with absolute values of the associated t statistic test exceeding the value 1.6, [29]. Model parameters, associated to these coefficients prove to be significant from the statistical point of view, in the estimation stage.

In the identification and validation-diagnosis stages, the attention will be focused on the coefficients of seasonal autocorrelations with the absolute values of the t statistic test associated which overcome 1.25 value. The seasonal parameters estimates AR or MA , associated to these coefficients, will appear more significant in the estimation stage. If the residual autocorrelation function has zeros values, from statistical point of view, to seasonal delays: $s, 2s, \ldots$, and to the delays of the form $0.5s, 1.5s$, and in the vicinity of seasonal delays: $s+1, s-1, 2s+1, 2s-1, \ldots$, the same warning level will be used: 1.25. More information on the methodology used in this case can be find in [29] and [30].

In the estimation stage, the use of the initial estimates of the model parameters of the value of 0.1 leads to good results in most cases; better initial estimates

for model parameters can be obtained based on the autocorrelation and partial autocorrelation functions, used to determine the structure of the model. In this stage as model parameters will be retain those for which $|t| \geq 2$, [29]. The criteria Akaike Information Criterion (AIC), Bayesian information criterion (BIC) or Schwarz information criterion (also SIC, SBC, SBIC), [31], Adjusted Root Mean Square Error (ARMSE) and Absolute Mean Percent Error (AMPE), [29], offer information on the parameter estimation quality.

Forecasting is what the whole procedure is designed to accomplish. Once the model has been selected, estimated and checked, it is usually a straight forward task to compute forecasts. The forecasting problem can be solved, in the most direct way, using the multiplicative $ARIMA$ model of the form (1). The description of the model by an infinitely weighted sum of current values and the earlier noise is proving useful, in particular, to estimate the variance of forecasting values, as well as to determine their confidence intervals. Standards and practices for time series forecasting are given in, [32].

4. Modeling and forecasting of cumulative number of individuals infected with severe acute respiratory syndrome (SARS)

The time series making the object of the case study represents the cumulative number of individuals infected with severe acute respiratory syndrome (SARS) in Singapore 24.02.2003-8.05.2003, [19], and is given in Fig. 3.

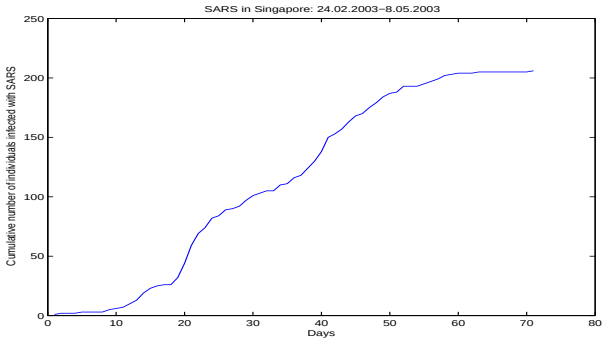

Fig. 3: SARS series 24.02.2003-8.05.2003.

We present in Fig. 4 the autocorrelation (ACF) and partial autocorrelation ($PACF$) functions of the original data, and the Ljung-Box-Q (LBQ) test.

It can be noted, from the data analysis, the non-stationary character of the series, due to presence of a trend component in the data. The series of differences of the original series is given in Fig. 5 and the ACF and $PACF$ functions are presented in Fig. 6.

The results mentioned above suggested the following model of the original SARS series:

$$(1+\phi_1 B)z_t = (1+\theta_1 B+\theta_2 B^2+\theta_3 B^3)a_t, \quad v[a_t]=\sigma^2 \tag{2}$$

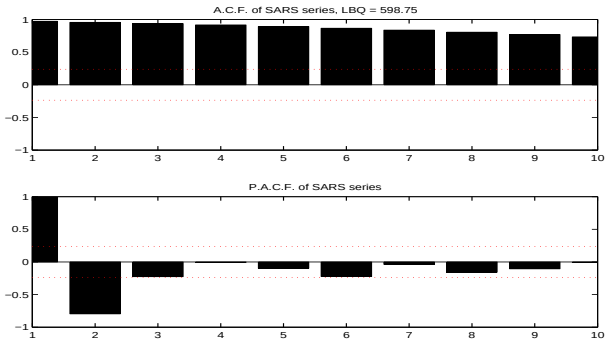

Fig. 4: ACF and $PACF$ functions of SARS series.

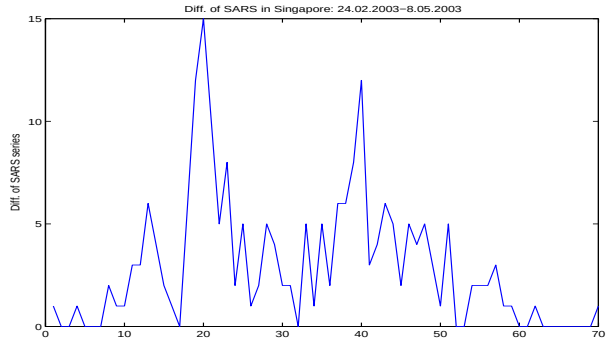

Fig. 5: Differences of SARS series.

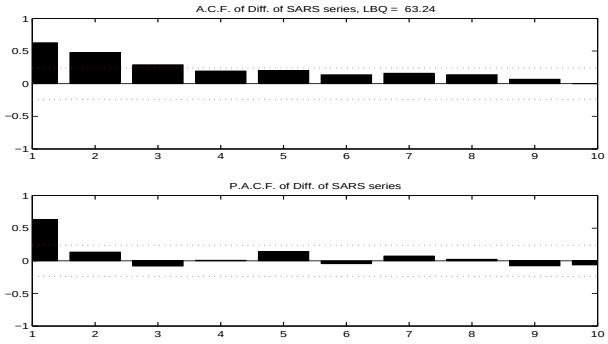

Fig. 6: ACF and $PACF$ functions of SARS series differences.

The model parameters: $\phi_1, \theta_1, \theta_2, \theta_3$ and σ^2 have been initialized with 0.1 value. The model parameter estimation has been performed using the Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm, [33]. The results are presented in Table 1 and Table 2, with the objective function = 168.3458, nr. of iterations = 120 and information criteria: AIC = 4.883 and SBC = 5.0423.

Table 1: Results for $ARIMA$ model parameter estimation

Parameter	Estimate	Appr.Std.Dev.	t-test
ϕ_1	-1.0014	0.0050	-202.1841
θ_1	0.6421	0.1137	5.6490
θ_2	0.5229	0.1060	4.9349
θ_3	0.2453	0.1145	2.1422
$v[a_t]$	6.8256	1.1011	6.1986

Table 2: Correlation matrix of $ARIMA$ model parameter estimates

	ϕ_1	θ_1	θ_2	θ_3	$v[a_t]$
ϕ_1	1.00				
θ_1	0.04	1.00			
θ_2	0.04	0.52	1.00		
θ_3	0.03	0.09	0.05	1.00	
$v[a_t]$	0.03	-0.05	-0.04	-0.02	1.00

The model residuals are presented in Fig. 7, and the residual ACF, $PACF$, with Ljung-Box-Q test, are given in Fig. 8.

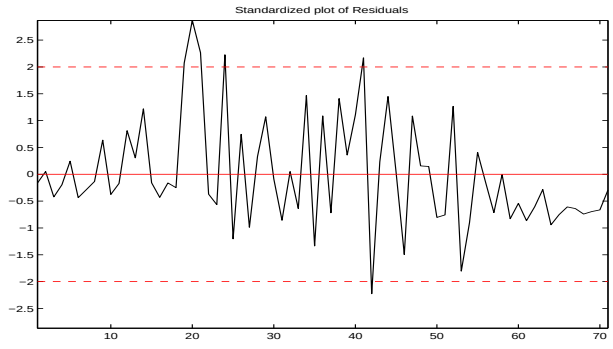

Fig. 7: Model residuals.

The forecasting, for the resulted model, has been performed, started from the 64 day, for a horizon time of 7 days, and 95% confidence limits, to compare the original data with the forecasting results. It can be noted that the forecasting results follow the evolution trend of the original time series, and are in the confidence limits 95%. The forecasting results and confidence limits are given in Fig. 9.

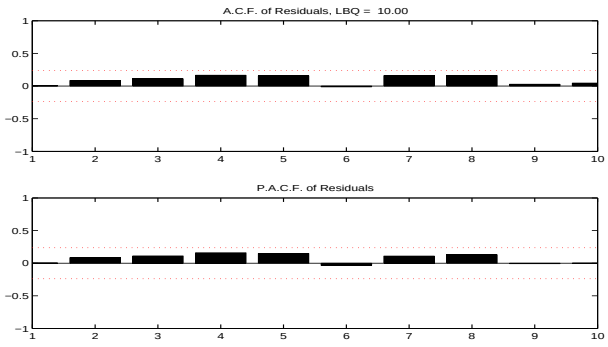

Fig. 8: ACF and $PACF$ of model residuals.

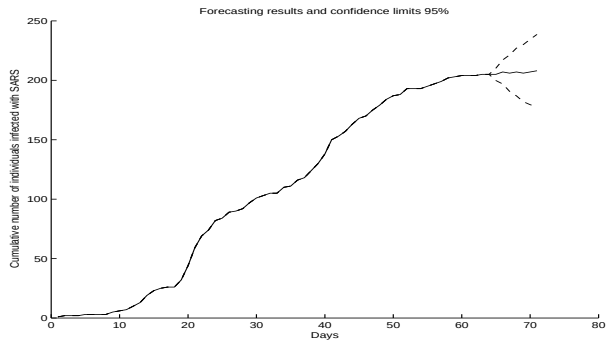

Fig. 9: Forecasting results and confidence limits 95% for 7 days using the resulted model.

5. Modeling and forecasting of measles Infections

The case study making the object of this section has as subject the modeling and forecasting of a time series representing the measles infections, in Great Britain in the period 1971-1994, quarterly recorded, and an example of intervention analysis, using as the exogenous data the number of measles infections, and as endogenous variable the number of vaccinated persons, in the same time period, using a transfer function (TF) model.

5.1. Modeling and forecasting of measles infections with a regression model

The time series representing the measles infections, in Great Britain in the period 1971-1994, quarterly recorded, is presented in Fig. 10.

We present in Fig. 11 the autocorrelation (ACF) and partial autocorrelation ($PACF$) functions of the original data, and the Ljung-Box-Q (LBQ) test.

It can be noted, from the data analysis, the non-stationary and seasonal character of the series. Because the data are quarterly recorded, it can be supposed the presence in the data series of a seasonal component of period $s = 4$ (yearly); it is also confirmed by the autocorrelation function ACF. So, the original time series has been seasonal differentiated with period $s = 4$, and it is presented in Fig. 12.

The ACF and $PACF$ of differentiated series, and Ljung-Box-Q test, are given in Fig. 13.

Starting from these functions, the following

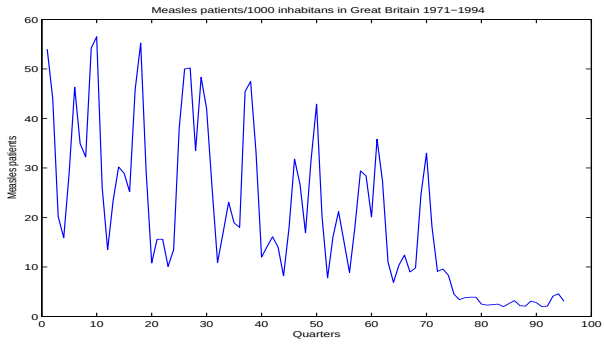

Fig. 10: Number of measles infections/1000 inhabitants, Great Britain, 1971-1994.

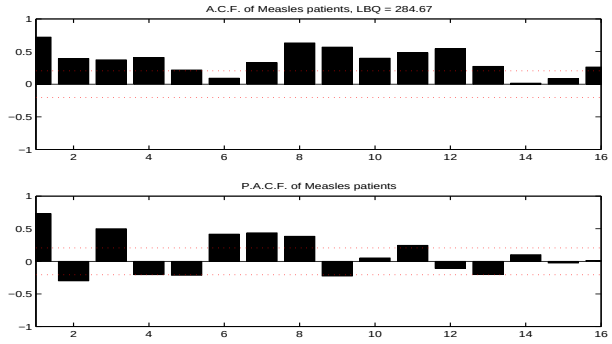

Fig. 11: ACF and PACF functions of measles infections/1000 inhabitants, Great Britain, 1971-1994.

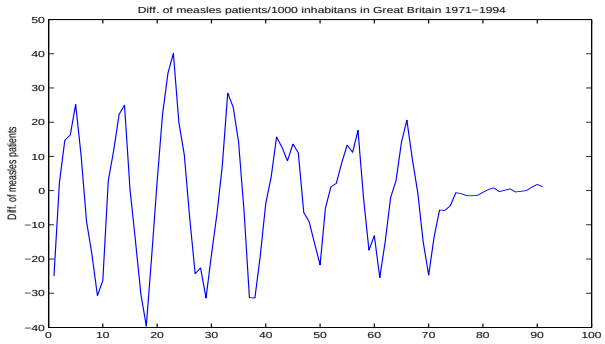

Fig. 12: Differentiated series with s = 4.

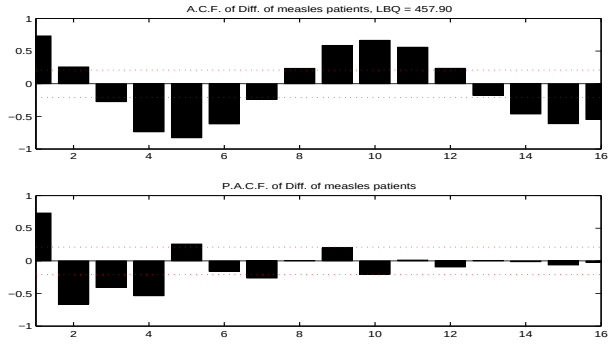

Fig. 13: ACF and $PACF$ of differentiated series with s = 4.

$SARIMA$ model structure resulted:

$$(1+\Phi_4 B^4+\Phi_8 B^8)(1-B^4)z_t = (1+\theta_1 B+\theta_2 B^2)(1+\Theta_4 B^4)a_t \quad (3)$$

and $v[a_t] = \sigma^2$.

The model parameter estimation has been performed using the Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm, [33]. The results are presented in Table 3 and Table 4, with the objective function = 315.7083, nr. of iterations = 24 and information criteria: AIC = 6.7728 and SBC = 6.9341.

Table 3: Results for $SARIMA$ model parameter estimation

Parameter	Estimate	Appr.Std.Dev.	t-test
Φ_4	-0.4614	0.1040	-4.4357
Φ_8	-0.5098	0.1003	-5.0846
θ_1	1.0436	0.1062	9.8243
θ_2	0.5074	0.0882	5.7555
Θ_4	-0.4927	0.0964	-5.1107
$v[a_t]$	40.6531	5.9866	6.7907

Table 4: Correlation matrix of $SARIMA$ model parameter estimates

	Φ_4	Φ_8	θ_1	θ_2	Θ_4	$v[a_t]$
Φ_4	1.00					
Φ_8	-0.88	1.00				
θ_1	-0.01	0.04	1.00			
θ_2	0.13	-0.11	0.78	1.00		
Θ_4	0.53	-0.48	-0.18	-0.21	1.00	
$v[a_t]$	-0.03	0.04	0.01	-0.04	-0.00	1.00

The model residuals are presented in Fig. 14, and residual ACF, $PACF$, Ljung-Box-Q test, are given in Fig. 15.

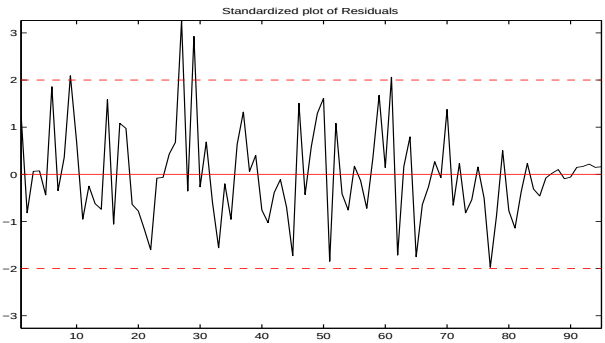

Fig. 14: Model residuals

The estimation results confirm the model quality, according with the Box-Jenkins methodology used in time series analysis, [29].

The forecasting, for the resulted model, has been performed, started from the 92 quarter, for a horizon time

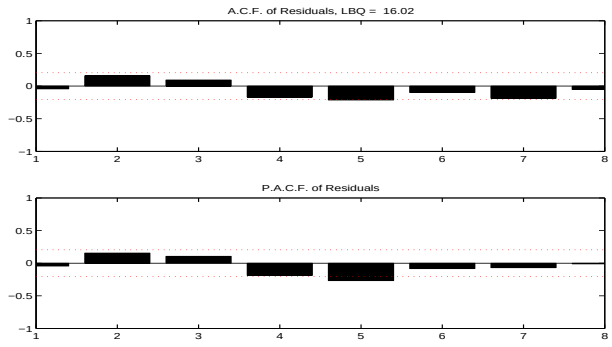

Fig. 15: ACF and $PACF$ of model residuals.

of 4 quarters, and 95% confidence limits, to compare the original data with the forecasting results. It can be noted that the forecasting results follow the evolution trend of the original time series, and are in the confidence limits 95%. The forecasting results and confidence limits are given in Fig. 16.

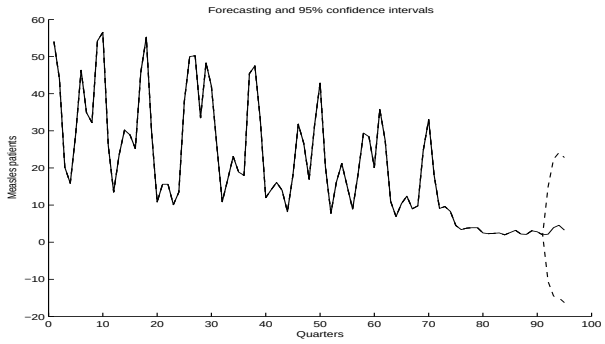

Fig. 16: Forecasting results and confidence limits 95% for 4 quarters.

5.2. Modeling and forecasting of measles infections with an intervention model

In this case an intervention model, a transfer function (TF) model, has been used, with the exogenous variable the number of measles infections, z_t,and with endogenous variable the percent of vaccinated persons, u_t, in the time period making the object of the analysis. The percent of measles vaccinations, Great Britain, 1971-1994 is presented in Fig. 17.

After preliminary analysis of the data, and different model structures, resulted the following structure of the transfer function model, representing the intervention model:

$$(1-B^4)z_t = \frac{\omega_1}{1+\delta_1 B}u_t + \frac{(1+\theta_1 B+\theta_2 B^2)(1+\Theta_4^4)}{1+\Phi_4 B^4+\Phi_8 B^8}a_t; \quad (4)$$

with $v[a_t]=\sigma^2$ and $s=4$, due to the nostationarity of the data. For the model parameters and variance, σ^2, have been used as initial values 0.1. Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm, [33], was used for parameter estimation, resulting the follow-

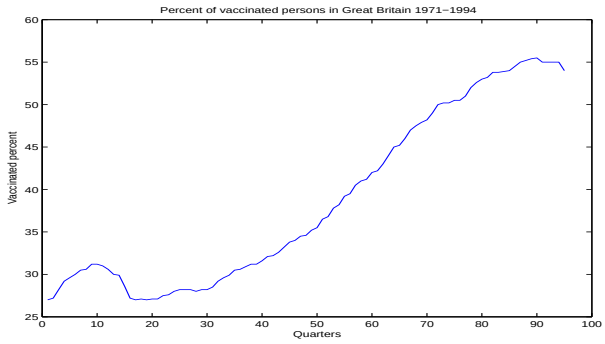

Fig. 17: Percent of measles vaccinations, Great Britain 1971-1994.

ing values for model parameters and correlation matrix (see Table 5 and Table 6, respectively):

Table 5: Results for TF model parameter estimation

Parameter	Estimate	Appr.Std.Dev.	t-test
Φ_4	-0.5800	0.0907	-6.3979
Φ_8	-0.3495	0.0860	-4.0657
θ_1	1.0556	0.0888	11.8939
θ_2	0.5293	0.0792	6.6838
Θ_4	-1.0000	0.0379	-26.3829
ω_1	-0.2891	0.1183	-2.4435
δ_1	0.8736	0.0637	13.7216
$v[a_t]$	25.6828	4.1370	6.2081

for an objective function = 290.7013, nr. of iterations = 50 and information criteria: AIC = 6.2884, and SBC = 6.5035.

Table 6: Correlation matrix of TF model parameter estimates

	Φ_4	Φ_8	θ_1	θ_2	Θ_4	ω_1	δ_1	$v[a_t]$
Φ_4	1.00							
Φ_8	-0.89	1.00						
θ_1	-0.14	0.14	1.00					
θ_2	0.13	-0.12	0.72	1.00				
Θ_4	0.34	-0.33	0.11	0.07	1.00			
ω_1	0.22	-0.13	-0.05	0.04	0.21	1.00		
δ_1	0.13	-0.07	-0.15	-0.07	0.27	0.59	1.00	
$v[a_t]$	0.43	-0.40	0.14	0.15	0.40	0.31	0.38	1.00

The model residuals are presented in Fig. 18, and the residual ACF and $PACF$, with Ljung-Box-Q test, are given in Fig. 19.

The results confirm the model quality, according with the Box-Jenkins methodology used, [29]. The forecasting results, for the transfer model resulted, started from the 92 quarter for a horizon time of 4 quarters and the 95% confidence limits are given in Fig. 20; the values used, as percent of vaccinations for the forecasting measles infections, in forecasting, represent the values recorded for the last 4 quarters of the original series. It can be noted

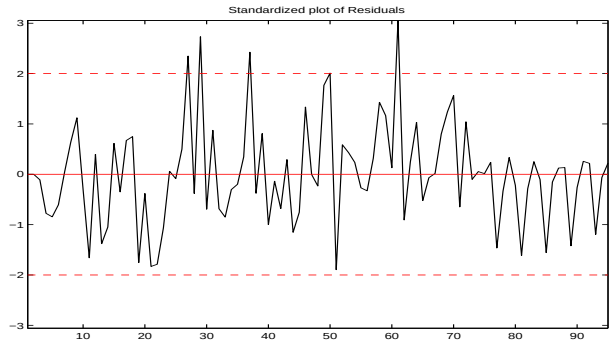

Fig. 18: Transfer function model residuals.

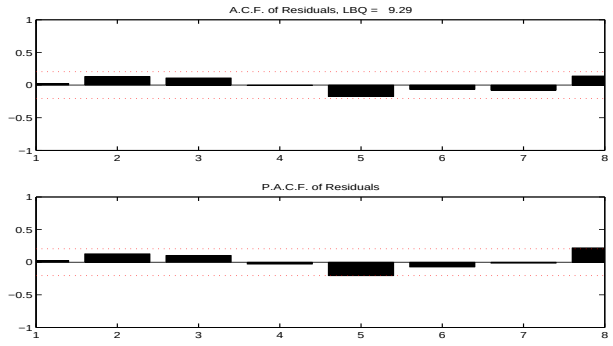

Fig. 19: ACF and $PACF$ transfer function residuals.

that the forecasting results follow the evolution trend of the time series of measles infections, and are in the confidence limits 95%.

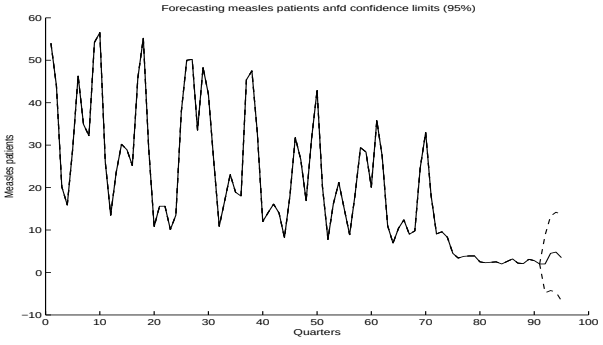

Fig. 20: Forecasting results and confidence limits 95% for 4 quarters using transfer function model.

6. Conclusions

The time series modeling and forecasting of epidemiological surveillance data using seasonal multiplicative $SARIMA$ models and the attractive features of the Box-Jenkins approach provide an adequate description to the data in this field. The $SARIMA$ processes are a very rich class of possible models and it is usually possible to find a process which provides an adequate description to the data. Also, the intervention analysis proved to be a useful approach to model interrupted time series, in this case, when such time series are affected by the effect of medication on the health of the patient, population vaccination policies, some economical constraints, etc. The case studies presented in the paper proved the efficiency of the approach. The underlying strategy of Box and Jenkins is applicable to a wide variety of statistical modeling situations in assessing and forecasting of epidemiological data series. It provides a convenient framework which allows an analyst to think about the data, and to find an appropriate statistical model which can be used to help answer relevant questions about the data.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.