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A TIME SERIES ANALYSIS OF THE INTER-EPIDEMIC PERIOD FOR MEASLES IN ITALY

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Summary. The number of cases of measles reported are generally characterized by the presence of a seasonal component and a long-term cyclical component, *the inter-epidemic period*, which is said to vary around three years. Researchers tend to resort to causal mathematical models in order to explain the inter-epidemic period, ignoring almost completely stochastic statistical models. This paper illustrates how time series analysis may be used for obtaining useful information on the length of this cycle, for modelling such cyclical behaviour as well as for estimating it's path in time. Attention is given to pre-vaccination data since the true dynamics of the diffusion of the infection are not affected and altered by an external regulator such as vaccination.

Keywords. Infectious diseases, compartmental mathematical models, parametric estimate of spectrum, autoregressive moving average models.

1. Introduction

Many time series reporting the cases of infectious disease on a monthly basis exhibit a decreasing trend, a 12 month cycle and a longer cycle, often called the inter-epidemical period, of length varying from two to three years. Italian data collected for each of the 20 Regions appears to have an inter-epidemical period which is slightly longer than three years. This paper attempts to gain knowledge on the long-term cycle by means of time series analysis carried out mostly in the frequency domain.

We begin by comparing results on the identification of the long-term cycle using a deterministic compartmental mathematical model and a non-harmonic Fourier analysis. Univariate autoregressive moving average models capable of reproducing the long-term cyclical behaviour in each series are identified and estimated. The paper then proceeds with the estimation of the long-term cyclical components and an analysis of their evolution in time.

This study considers only the pre-vaccination data, i.e. January 1949 to December 1976, for the simple reason that the true dynamics of the diffusion of the illness are not affected and altered by an external regulator such as vaccination. The Italian regions are treated as separate epidemiological units an assumption which is backed by the results.

Before being analysed, the series were log transformed, then detrended using a deterministic function of time and finally deseasonalised using monthly dummies; several tests, including those by Dicky and Fuller (1979) and by Philips and Perron (1988) rejected the unit root hypothesis. A value of one was added to each data point before the log transformation to avoid the problem of log(zero) for those months, few in number, when no cases were reported.

2. Identification of the peak frequency of the inter-epidemic period

Research into the transmission dynamics of infectious diseases has tended to favour a mechanistic approach focusing on the causal mechanisms underlying the infection process. Such an approach largely relies on deterministic compartmental models (Anderson and May 1991) often having the SEIR structure by which individuals who experience the infection are assumed to move from the susceptible (S) state to the exposed state (E), in which individuals are infected but not yet infectious, then to the infected (I) state, in which individuals are capable of transmitting the infection, and finally recover from the disease, by entering the removed (R) state, in which they are permanently immune. Statistical modelling, on the other hand, has rarely been taken into account.

A simple form of the SEIR model, for details see Manfredi et al. (2002), provided among other results estimates of the inter-epidemic period, reported in the first column of Table 1, for each of the 20 Italian Regions. These results are in agreement with the belief that the inter-epidemical period varies around three years.

As against this procedure based on causal relationships, we propose a univariate time series approach, based on the estimation of simple univariate autoregressive moving average models.

In Manfredi et al. (2002) and Cleur et al. (2003) results were reported on a preliminary frequency domain analysis carried out on the number of measles cases reported on a regional basis for each month during the pre-vaccination period 1949 – 1976 and the post-vaccination period 1977 – 1996. Briefly, it was observed that the non-parametric estimate of the spectral density for each series was concentrated in three narrow frequency bands: (in order of magnitude) around frequency $\pi/6$ corresponding to the annual cycle, around zero frequency which was identified as being due to a gradually decreasing trend and, finally, around a frequency with periodicity varying between 3 and 5 years. As often happens, the spectral analysis was able to establish only tentatively the peak frequency at which the long-term cycle was present. A more precise knowledge of the peak frequency was obtained via the following procedure:

Suppose that the true frequency of a cycle in the series analysed is λ; since λ need not be a function of the length of the series analysed, the cycle often corresponds to a non harmonic function. Then one might estimate λ by minimizing the quantity (as in Damsleth and Spjotvoll (1982)).

$$Q = \sum \left[x_t - \alpha_0 - \alpha_j \cos(\lambda t) - \beta_j \sin(\lambda t) \right]^2 \qquad (1)$$

The spectral density may be used to provide a starting value for λ. This procedure encounters problems if many cycles are present at nearby frequencies. For this reason, the procedure followed in this paper was to apply ordinary least squares in minimizing (1) over a grid of frequencies centred around the starting value suggested by the spectral density estimate. This grid search method finally provides estimates of λ as well as of the corresponding α and β. As can be seen from *Table 1* the starting value and the final result in column three are not too far apart. The peak frequencies correspond to periods varying from approximately 28 months in Piemonte to 70 months in Molise. On the other hand, in most cases there is little agreement between the periodicity identified this way and that predicted by the SEIR model which consequently obliges us to conclude that the mathematical modelling, although useful for causal analysis, needs to be refined if we are to have a clearer understanding of the phenomena.

3. *Isolating the long-term cycle*

Cyclical behaviour in phenomena like the diffusion of measles is never regular, but varies in periodicity as well as in amplitude; for instance, the annual cycle identified and estimated by time series methods is a sort of average of oscillations with periodicity varying around 12 months, i. e. in a frequency band around frequency $\pi/6$. Hence when attempting to estimate the annual cycle, we are never interested in the component at frequency $\pi/6$, but rather in components varying in a band of frequencies around frequency $\pi/6$. The same is true of the long-term cycle. This objective may be realised by applying demodulation-remodulation techniques (see Granger and Hatanaka (1964) for a clear and simple description). Briefly the method consists in the following:

Suppose we are interested in isolating the component around frequency λ_0 in the series X_t. First demodulate by forming the series

$$Y_t^c = X_t \cos(\lambda_0 t) \qquad \text{and} \qquad Y_t^s = X_t \sin(\lambda_0 t)$$

Next, filter the series Y_t^c and Y_t^s using a low pass filter, $F[.]$, with a narrow bandwidth to form the series

$$\tilde{Y}_t^c = F[Y_t^c] \qquad \text{and} \qquad \tilde{Y}_t^s = F[Y_t^s]$$

The quantity

$$f_t(\lambda_0) = 2[(\tilde{Y}_t^c)^2 + (\tilde{Y}_t^s)^2]$$

is the instantaneous power of the spectrum of X_t and is useful for discovering changes in the spectrum over time.

An estimate of the desired component may be obtained by remodulating, i. e. by forming

$$X_t(\lambda_0) = 2\tilde{Y}_t^c \cos(\lambda_0 t) + 2\tilde{Y}_t^s \sin(\lambda_0 t)$$

Often moving averages are used in defining the low pass filter. This has the big disadvantage of resulting in losses of averages at the beginning and end of the series. This problem is overcome here by applying kernel smoothing as a low pass filter. In particular, if X_t is to be smoothed, the following kernel smoothing is carried out:

$$y_t = \sum_{t=1}^{T} W_t(i) X_t$$

where $$W_t(i) = K\left(\frac{t-i}{b}\right) \Big/ \sum_{j=1}^{T} K\left(\frac{t-j}{b}\right)$$

which is the Naradaya-Watson density estimator. $K(\cdot)$ is the standard normal kernel function with $b = 40$ which was set after experimenting a number of values.

The instantaneous power of the inter-epidemical period for the 20 Italian Regions are shown in *Figure 1*. It is important that an interpretation of these figures be made of the general patterns only and not of single or brief changes. With this in mind and together with an examination of the estimated long term component in each series shown in *Figure 2*, we note resemblances between the Regions Campagna, Lazio, Marche, Sardegna and Umbria, between the Regions Friuli, Trentino and Veneto, and finally between Calabria and Sicilia. In other words there appears to be some similarities in near by Regions. Figure 2 also shows that the component corresponding to the inter-epidemical period in some Regions, like Toscana and Molise, underwent drastic changes in time not present in the other Regions.

It is interesting to note that when the cycle in it's ascending phase remains at a low level, suggesting the absence of a normal epidemic, it takes some time before it regains it's usual pattern and levels. This might mean that the dynamics of the infection in one Region are not affected by those in other Regions.

4. ARMA models for the inter-epidemic period.

Having identified the lengths of the inter-epidemical periods we turn our interests to time series modelling and in particular to identifying univariate autoregressive moving average models which are able to generate the long-term cyclical behaviour present in each regional series. The procedure used here is the opposite to that used in applying the SEIR model.

It is a well known result that an autoregressive moving average model, ARMA(p,q),

$$x_t - \varphi_1 x_{t-1} - \varphi_2 x_{t-2} - \ldots - \varphi_p x_{t-p} = c + \varepsilon_t - \vartheta_1 \varepsilon_{t-1} - \ldots - \vartheta_q \varepsilon_{t-q} \qquad (2)$$

has a population spectrum given by (see Hamilton (1994), Priestley (1981))

$$\mathrm{f}(\lambda) = \frac{\sigma^2}{2\pi} \frac{(1-\vartheta_1 \exp(-i\lambda) - \vartheta_2 \exp(-i2\lambda) - \ldots - \vartheta_q \exp(-iq\lambda)}{(1-\varphi_1 \exp(-i\lambda) - \varphi_2 \exp(-i2\lambda) - \ldots - \varphi_q \exp(-ip\lambda)}$$
$$\mathrm{x} \quad \frac{(1-\vartheta_1 \exp(i\lambda) - \vartheta_2 \exp(i2\lambda) - \ldots - \vartheta_q \exp(iq\lambda)}{(1-\varphi_1 \exp(i\lambda) - \varphi_2 \exp(i2\lambda) - \ldots - \varphi_q \exp(ip\lambda)} \qquad (3)$$

When the estimates of the parameters are inserted in (3) we obtain the so-called parametric estimate of the spectrum. This expression may be calculated for any value of λ and hence may be used for identifying the values of p and q which, along with the parameter estimates, reproduce the same form of the non-parametric spectral density estimate. In other words, for each series we search for that ARMA model which reproduces the same long-term cyclical variations identified above. This is the opposite to the SEIR model analysis where it was the model itself which suggested the inter-epidemical period.

As can be seen from *Table 2*, the long-term cycles reproduced by the estimated ARMA models are in close agreement with those identified in each series above using a direct estimate of the peak frequency. This suggests that stochastic statistical models could provide a good alternative to the more popular mathematical models used in this field of research. The ARMA model, although lacking in the explanation of causal relationships present in the SEIR model considered, have the proven advantage of being superior for forecasting.

The estimates of the 20 Arma models are reported in Table 2. Backcasting was used and as the reader familiar with these models is well aware of, the estimates depend to some extent on the length of the backcasting. Consequently, this length was adjusted so as to obtain a spectrum from equation (3) with the desired characteristic.

5. Conclusion.

In this paper we have given a description of the inter-epidemical period for measles infection and have shown how time series analysis may be usefully applied for understanding and explaining the transmission dynamics of measles infection. This approach, as against causal compartmental mathematical models, does not pretend to give theoretical explanations, but has the advantage of giving a closer description of the various cyclical movements (annual and long-term) contained in each series.

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APPENDIX

TABLE 1. *Periodicity (in months) of long term cycle identified by non-parametric spectral analysis, by direct estimation of the peak frequency, and by the parametric estimate of the spectrum*

	Periodicity of long-term cycle				ARMA(p,q)	
	SEIR model 1971-76	Nonparamet. spectrum	Direct method	Parametric spectrum	p	q
Abruzzo	37.2	48	40.80	40.20	3	2
Basilicata	33.6	48	44.88	43.33	4	1
Calabria	34.8	36-42	41.34	39.52	4	5
Campania	34.8	36	36.32	35.90	5	3
Emilia-Rom.	37.2	42	40.02	40.20	4	5
Friuli	36.0	36	33.24	34.91	3	1
Lazio	37.2	42	38.79	38.55	3	5
Liguria	39.6	60	64.11	63.45	5	3
Lombardia	34.8	30	28.43	34.91	2	2
Marche	38.2	42	39.27	39.26	2	3
Molise	36.0	60	70.60	66.84	3	5
Piemonte	37.2	30	28.69	34.91	2	2
Puglia	33.6	48	45.53	45.20	4	1
Sardegna	34.8	48	45.53	45.86	3	2
Sicilia	33.6	36	37.62	37.62	2	3
Toscana	39.6	36	34.15	34.91	2	5
Trentino	34.8	36	34.15	34.91	3	1
Umbria	38.2	42	40.80	41.61	3	5
Val d'Aosta	37.2	42	38.55	39.27	3	1
Veneto	36.0	36-42	38.55	38.55	4	3

TABLE 2. *Estimates of the ARMA models for the 20 Regions*

ABRUZZO ARMA (3 , 2)
AR COEFFS = 1.13445 0.436431 -0.610200
MA COEFFS = 0.330430 0.624670

BASILICATA ARMA (4 , 1)
AR COEFFS = 2.06209 -1.30524 0.180804 0.549728E-01
MA COEFFS = 0.998767

CALABRIA ARMA (4 , 5)
AR COEFFS = 1.32793 0.145461 -0.534017 0.248255E-01
MA COEFFS = 0.723331 0.671220 -0.272541 -0.781656E-01 -0.779946E-02

CAMPANIA ARMA (5 , 3)
AR COEFFS = 2.41012 -1.98152 0.760786 -0.327534 0.127505
MA COEFFS = 1.67370 -0.653254 -0.383392E-01

EMILIA-ROMAGNIA ARMA (4 , 5)
AR COEFFS = 1.70360 0.239465 -1.68064 0.727169
MA COEFFS = 0.733529 1.00074 -0.740156 0.461337E-01 -0.889934E-01

FRIULI ARMA (3 , 1)
AR COEFFS = 1.60846 -0.509055 -0.146491
MA COEFFS = 0.818979

LAZIO ARMA (3 , 5)
AR COEFFS = 2.80972 -2.65062 0.837879
MA COEFFS = 1.95794 -0.788486 -0.421343 0.320932 -0.833825E-01

LIGURIA ARMA (3 , 2)
AR COEFFS = 1.40148 0.338047E-01 -0.449426
MA COEFFS = 0.738530 0.248303

LOMBARDIA ARMA (2 , 2)
AR COEFFS = 1.86802 -0.900548
MA COEFFS = 1.01665 -0.765565E-01

MARCHE ARMA (2 , 3)
AR COEFFS = 1.84174 -0.866318
MA COEFFS = 1.02849 -0.152600 0.860963E-01

MOLISE ARMA (3 , 5)
AR COEFFS = 2.32793 -1.70857 0.375632
MA COEFFS = 1.74027 -0.758107 0.506677E-01 -0.850416E-02 -0.204915E-01

PIEMONTE ARMA (2 , 2)
AR COEFFS = 1.75075 -0.795866
MA COEFFS = 0.800890 0.173077E-01

PUGLIA ARMA (4 , 1)
AR COEFFS = 1.56327 -0.480747 -0.680475E-01 -0.379859E-01
MA COEFFS = 0.960769

SARDEGNA ARMA (3 , 2)
AR COEFFS = 1.90812 -0.956821 0.310317E-01
MA COEFFS = 1.28118 -0.315546

SICILIA ARMA (2 , 3)
AR COEFFS = 1.84786 -0.873730
MA COEFFS = 1.06157 0.500253E-01 -0.114037

TOSCANA ARMA (2 , 5)
AR COEFFS = 1.91489 -0.948313
MA COEFFS = 1.15523 -0.155694 0.410468E-01 0.206977E-01 -0.137533

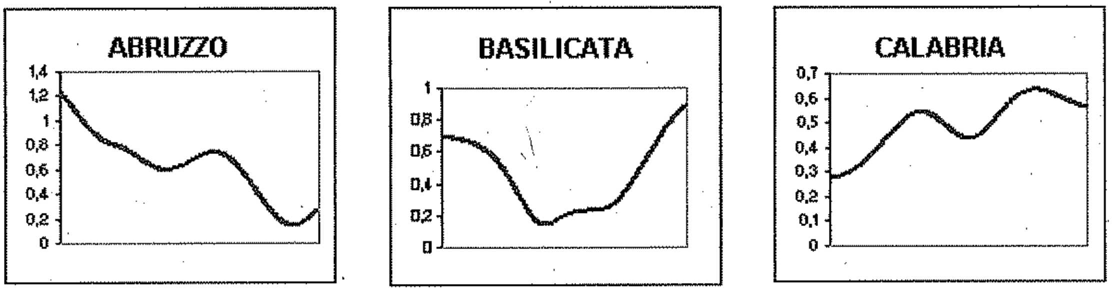
TRENTINO ARMA (3 , 1)
AR COEFFS = 1.60456 -0.509735 -0.132745
MA COEFFS = 0.919860

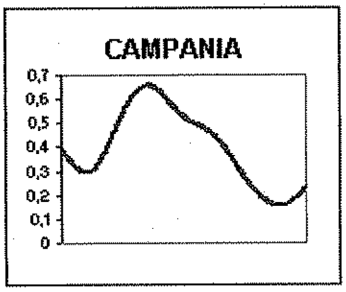
UMBRIA ARMA (3 , 5)
AR COEFFS = 0.652995 0.955970 -0.670622
MA COEFFS = -0.156245 0.830356 0.280361E-01 0.910534E-01 0.187816E-01

VALLE D'AOSTA ARMA (3 , 1)
AR COEFFS = 1.65960 -0.611471 -0.726228E-01
MA COEFFS = 0.998147

VENETO ARMA (4 , 3)
AR COEFFS = 1.36734 -0.421841 0.324911 -0.314391
MA COEFFS = 0.636073 0.441998E-01 0.345366

FIGURE 1. INSTANTANEOUS POWER OF SPECTRUM AT LONG TERM PEAK FREQUENCY.

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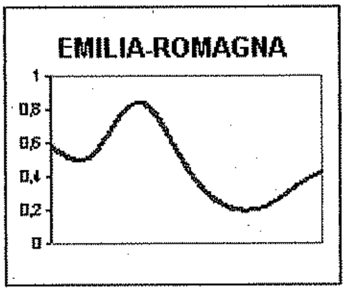
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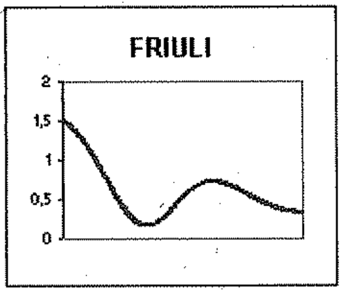
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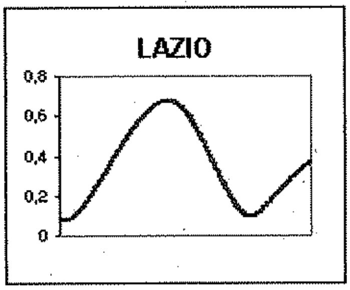
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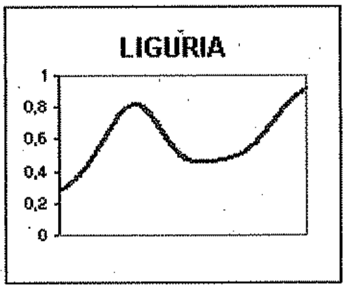
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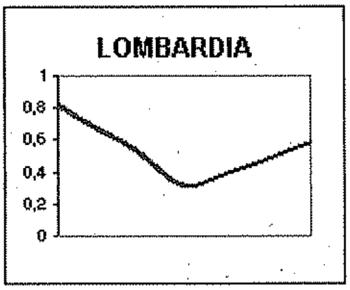
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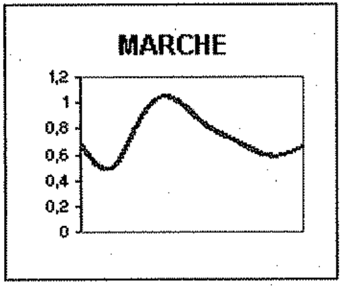
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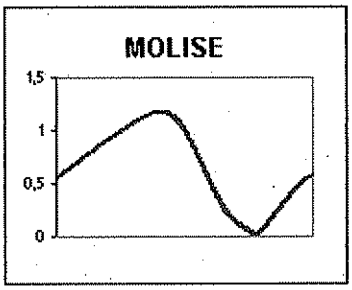
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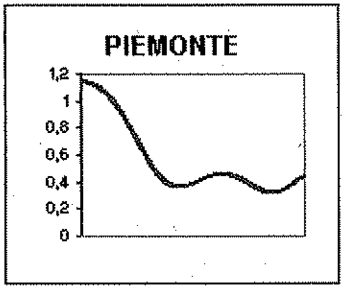
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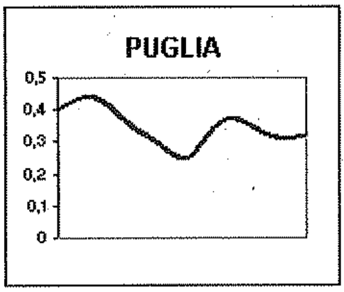
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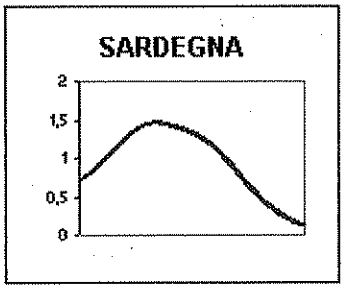
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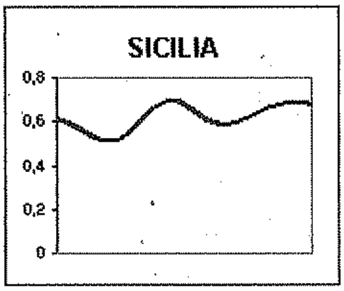
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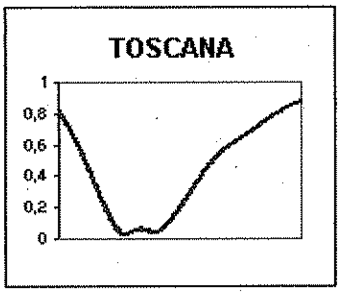
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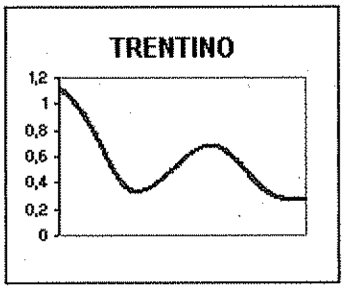
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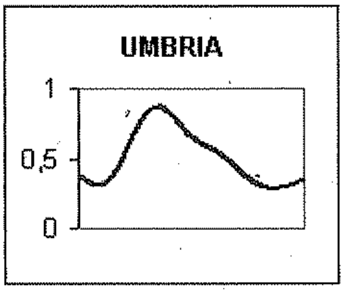
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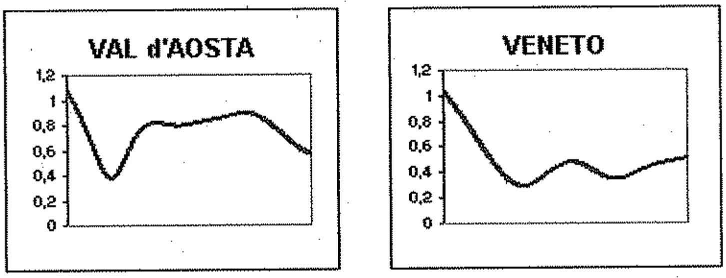
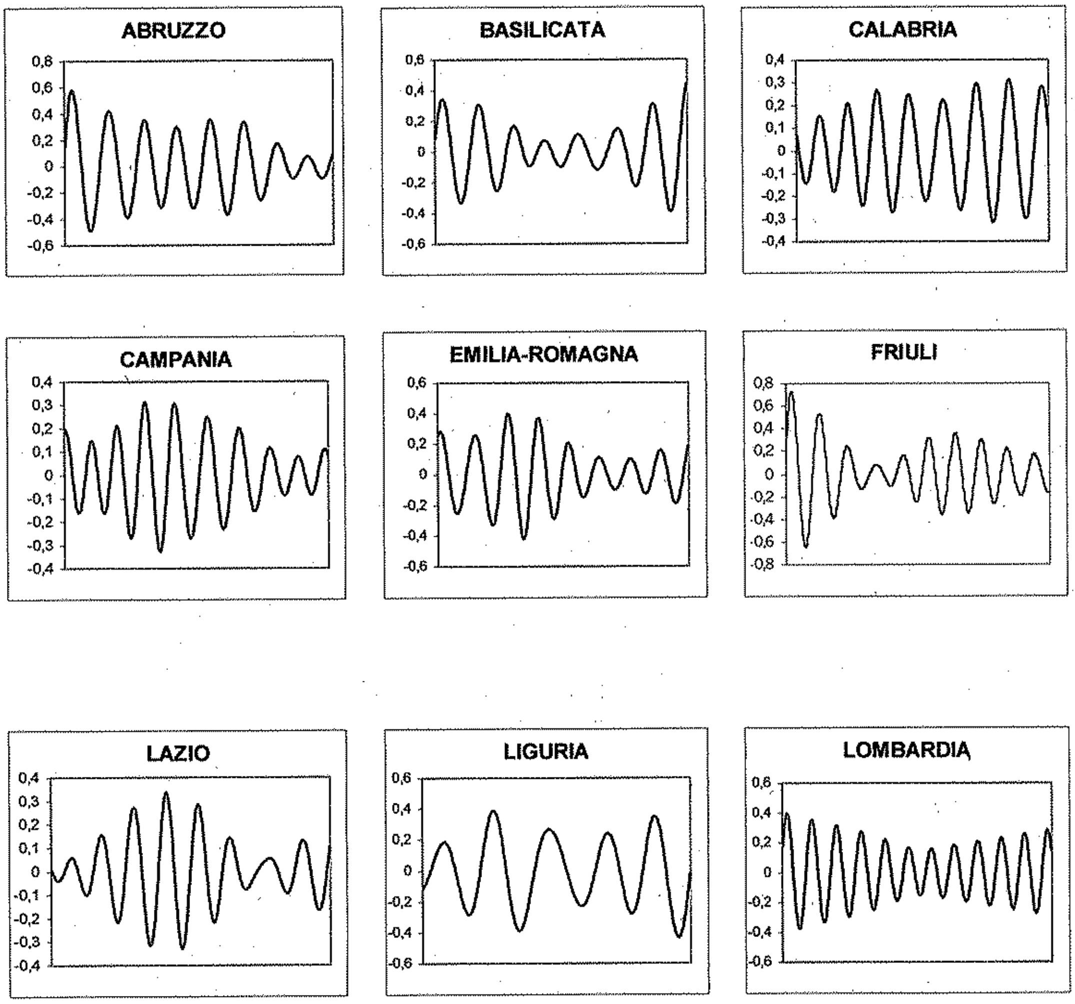


FIGURE 1. INSTANTANEOUS POWER OF SPECTRUM AT LONG TERM PEAK FREQUENCY.

FIGURE 2. LONG TERM COMPONENTS ESTIMATED BY DEMODULATION - REMODULATION



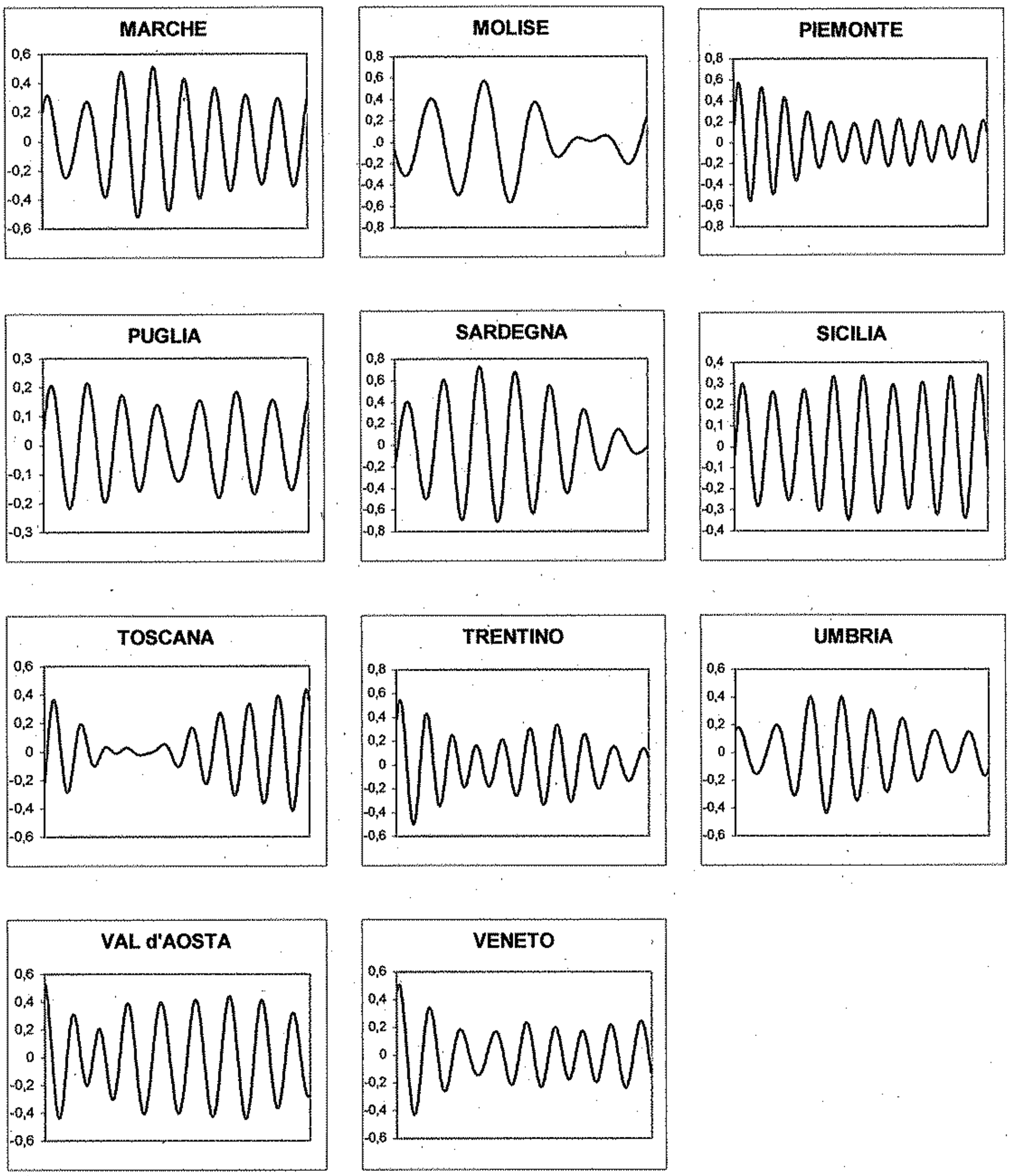


FIGURE 2. LONG TERM COMPONENTS ESTIMATED BY DEMODULATION - REMODULATION

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