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Eugene M. Cleur, Piero Manfredi[1] and John R. Williams[2]

Abstract. This paper provides a preliminary investigation of the regional time series of case notifications data for measles in Italy. Standard tools (autocorrelation functions and spectral densities) are used to characterise the periodicity structures of data at the Regional level for both the pre- and post vaccination era. Such results are then systematically compared with the corresponding predictions provided by mathematical models for the transmission dynamics of measles. Subsequently, a preliminary analysis of the mechanisms governing the synchronisation of the local dynamics, by using cross-spectra analysis. Comparisons with other work on available time series of measles data are also made.

1. Introduction

The control, of childhood infectious diseases (such as measles) by vaccination is a first public health concerns in both developed and developing countries. As showed in the literature in the past fifteen years (Anderson and May 1991 and references therein, Edmunds et al. 2000) mathematical models of the transmission dynamics of infectious diseases can be of great help in both i) gaining understanding of the observed transmission patterns, ii) predicting the likely effects of the continuation of existing policies, iii) assisting the design of optimal vaccination programmes.

Modelling work, however, must be based upon sound data if full confidence is to be placed in results. Sero-epidemiological surveys provide reliable information about patterns of experience of infection, but, in absence of continuing large scale representative serological surveillance, reliance must be placed upon case notification data for information about patterns of infection over time. Much important analysis in epidemiology (Anderson and May 1991, Earn et al. 2000 and references therein) has been based on a small number of long case notification data series. Such series provide a valuable information on the true scale and pattern of infection but their value relies heavily upon the consistency and the reliability of the relevant systems of case reporting. One noteworthy example is case notification data from England & Wales which has provided the raw material for much work in the field (Earn et al. 2000, Anderson and May 1991), and is widely considered to be of good quality.

Elsewhere in Europe, the availability and quality of case notification data varies widely between countries and, in some instances, within countries. Compared to other countries Italy has, since 1949, a long and potentially valuable time series of measles case notifications data at the regional level. Despite this, however, there have no been up to now studies aimed to characterise the Italian time series of measles data. This lack of interest lies in the general belief by public health workers that there is a considerable degree of under-reporting for childhood diseases (Santoro et al. 1984), and that, moreover, the degree on under-reporting varies considerably between regions, so that Italian case notifications data should be of little reliability, in that the ensuing estimates of national epidemiological parameters would necessarily be biased. In recent times, however, we have provided a robust characterisation of patterns of under-reporting of measles cases in the Italian regions (Williams and Manfredi 2000, Manfredi and

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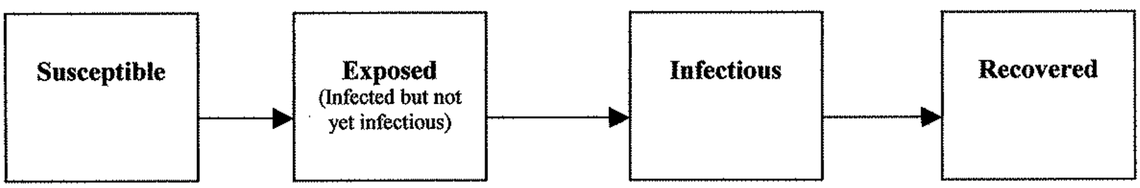
Williams 2000), therefore recovering interest for the aforementioned case notifications data from a public health perspective.

In this paper standard time series techniques, spectra and cross spectra, are used for characterising time patterns of measles case notifications data for the twenty Italian regions in both the pre- and post vaccination period. As a preliminary investigation the role of space has been ignored and the Italian regions are treated as separate epidemiological units.

The paper is organised as follows. In the second section the basic facts and predictions of mathematical models for the transmission dynamics of measles are summarised. Section three reports some basic facts on measles transmission dynamics in Italy. In section four the results of spectral analysis are reported and these are systematically compared with predictions from mathematical models for measles in section five. The conclusions are summarised in section six.

2. Models for the transmission dynamics of infectious diseases

Among modern approaches to mathematical modelling of the population dynamics of infectious diseases a very popular one (Anderson and May 1991) tend to favour mechanistic approaches focusing on the causal mechanisms underlying the infection process. Such approaches have largely relied upon deterministic compartmental models (Anderson and May 1983). Compartmental models postulate that the population within which the disease evolves can be splitten into compartments, i.e. states describing the sequences of epidemiologically relevant transitions undergone by individuals who experience the infection process. In the case of measles, and of most childhood infectious diseases, the chosen compartmental formulation is the so called 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 state (in which individuals are capable of transmitting the infection) and finally recover from the disease, by entering the removed state, in which they are permanently immune. A flow-diagram of the compartmental structure of the SEIR model for measles is represented below.



The simplest form of the SEIR model used to represent measles dynamics during the pre-vaccination period is the following:

$$
\begin{aligned}
\dot{X}(t) &= \mu N - \mu X - \beta X(t)Y(t) \\
\dot{H}(t) &= \beta X(t)Y(t) - (\mu + \sigma)H(t) \\
\dot{Y}(t) &= \sigma H(t) - (\mu + v)Y(t) \\
\dot{Z}(t) &= vY(t) - \mu Z(t)
\end{aligned}
\qquad (1)
$$

where X,H,Y,Z are functions of the time respectively denoting the number of susceptible, latent, infectious and permanently immune individuals in the population at time t, μ is the mortality rate which is assumed to be identical to the birth rate (so that the overall population is stationary), β the transmission rate, σ and v the transition rates from the E to the I, and from the I to the R class. N=X+H+Y+Z is the total population, which is assumed to be stationary thanks to the exact balancement of births (μN) and deaths. Model (1) represents the simplest formulation of the dynamics of a SEIR-type disease (such as measles) in a large stationary population whose individuals are homogeneously mixing according to a bilinear mass action incidence term of the type βXY, which is the commonest representation of incidence for childhood diseases in constant populations. More general and complex formulations have been also considered in the literature in order to take into account further realistic factors such as inhomogeneous mixing by age, seasonality in transmission rates to take into account of schooling and vacation periods during the year, spatial dynamics and so on. Nonetheless even very simple models as (1) have proved to be quite robust in that their predictions are often only quantitatively, but not qualitatively, modified under more general formulations. In the simplest case (β constant) model (1) predicts that, provided some condition on the survivability of the disease is met[3], the disease will, in absence of vaccination, fluctuate endemically in the long term around some equilibrium level, a fact well observed in all developing countries. Such oscillations are damped but the damping term is weak, so that the corresponding damping time is long. In particular, when $K=1/\sigma+1/v$, the sum of the expected lengths of sojour in the latent and infectious states, is short compared to the expectation of life of the host ($1/\mu$) (this is always the case for childhood diseases) then the inter-epidemic period, i.e. the period of the oscillation, is given, with an excellent approximation, by the formula (Anderson and May 1991)

$$T = 2\pi\sqrt{AK} \qquad (2)$$

where A is the average age at which infection is acquired, and $K=1/\sigma+1/v$ is the sum of the expected lenghts of the sojours in the latent and infectious states. Prediction (2) is straightforwardly comparable with observed patterns of time series. Once vaccination is introduced, model (1) predicts that (unless the vaccination programme is strong enough so that the disease can be eradicated) the diseases will in the long term achieve a new equilibrium level characterised by i) a reduced incidence, ii) an increased average age at infection A, iii) an increased the inter-epidemic period (as clear from ii) and formula (2)). A further noteworthy prediction concerns the long term effects of changes in the birth rate μ (observed in Italy during the switch from the pre to the post-vaccination era): coeteris paribus a reduction in μ causes a long term increase of the average age at infection, and therefore of T.[4] The basic model (1) with constant transmission rates is not capable of capturing a main characteristic of measles pre-vaccination dynamics, i.e the existence of patterns of sustained rather than damped oscillations, with a sharp annual oscillation, usually explained with the yearly patterns of schooling recruitment. This failure is resolved by allowing seasonality in transmission rates.

[3] Such condition is usually expressed by saying tha the so called Basic Reproduction Rate is greater than one.

[4] When the vaccination is administered at an age close to birth to a randomly chosen fraction p of all newborn individuals, then model (1) predicts that the equilibrium average age at infection A_V in the post-vaccination era is related to its value A in pre-vaccination era by: $A_V=A/(1-p)$. Moreover the relation $A=1/\mu R_0$ holds between the average age at infection and the population "turnover" rate μ.

3. Data and patterns of measles transmission dynamics in Italy during the pre- and post-vaccination periods

Monthly measles case notification data were provided by the Istituto Nazionale di Statistica (ISTAT) for the period from the first available year, 1949, to 1996. For a certain range of years the data referred to the month of observation rather than notification, but available data suggested no evidence of significant difference between the two. In Italy vaccination for measles is not compulsory but only recommended as it is the case for mumps and rubella as well. The national vaccination policy against measles began towards the end of 1976, although initial vaccine uptake is believed to have been quite low and, for the first 10 years at least, to have remained at disappointingly low levels. Data on the age at infection of notified cases were also provided by ISTAT for the time window 1971-1996. Age structured data on the pre-vaccination window 1971-1976 were used to compute the estimates of the average age at infection A in order to apply formula (2).

Figure 1 at the end of the text jointly reports the twenty time series of measles case notifications data in the Italian regions during the pre-vaccination period. The main observed features are therefore: i) the substantial stationarity of measles dynamics during the pre-vaccination era which well justifies the standard assumption by epidemiologists, namely that measles during the pre-vaccination era was a system in a regime of dynamical equilibrium (despite the interference with important external phenomena such as the baby-boom in births during the sixties, observable in some regions through a hump in the trend); ii) the tendency of the measles system to evolve with sustained oscillations, in which regular annual oscillations are superimposed to longer term oscillations, with large epidemics occurring only every three years or so. Though data in Figure 1 are disturbed by substantial levels of under-reporting, with strong heterogeneity in the regional reporting rates, nonetheless, as showed in Williams and Manfredi (2000), and Manfredi and Williams (2000), the under-reporting rates seemed to have remained fairly constant over time, so that the series represented in Figure 1 nonetheless represent a sufficiently reliable view of the regional dynamics of measles.

Seemingly Figure 2, also at the end of the text, reports the corresponding regional time series during the post-vaccination era. Figure 2 shows how uneffective has apparently been the adopted immunization policy. For many regions no clear trends of decreasing incidences appear unless quite late in time, especially in the South of the country (a fact confirmed by age structured data) despite an apparently favourable situation from the demographic side, in that the decline in fertility has quite sharply reduced both the yearly number of births and the average family size, which represents an important factor in determining the speed of transmission of the infection. These considerations have to be taken with some caution in that in absence of data on vaccination coverages it is much harder to assess the under-reporting rates during the post-vaccination era according to the approach followed by Williams and Manfredi (2000). Some evidence in fact exists that reporting rates are, for some regions, increasing, especially in the very last years, so that the interpretation of the data could be more "favourable". In any case the existence of trends in reporting rates hardly limits the time series analysis developed in the forthcoming section.

4. Time series analysis

Within the aforementioned mechanistic approach traditional time series techniques can be of great help. In particular, the detailed characterisation of periodicites is a very preliminary step in the analysis of patterns of childhood infectious diseases both in the pre and post vaccination era.

Spectral Analysis Results

Vaccination against measles started in Italy in 1976. Separate spectral analyses were performed for both the pre- and post vaccination era for each Italian regions. The data were log transformed before detrending in order to stabilize the variance. Many of the series exhibit a slight trend in both the pre-vaccination (perhaps as a consequence of the baby boom in births during the sixties) and the post-vaccination periods (perhaps due to vaccination, but also to the interference with other large demographic changes massively occurred in the post-vaccination era) which was removed by linear or quadratic time functions; first differencing was discarded as this greatly changed the pattern of the resulting spectral estimates as well as for the fact that it removed frequency components which included the long-term cycle in which we were particularly interested (see Figures 3, 4 and 5 for an axample with the data for Molise). The results for all the regions may be found at the end of the text.

Periodic components were identified by use of the Fisher's test on the periodogram and spectral analysis. A non-parametric estimate of the spectral density function with the Parzen window was calculated. Various truncation points were used in order to identify and evidence more clearly the periodic components.

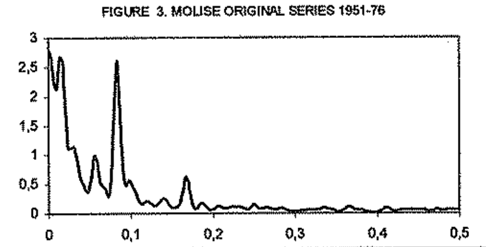


FIGURE 3. MOLISE ORIGINAL SERIES 1951-76

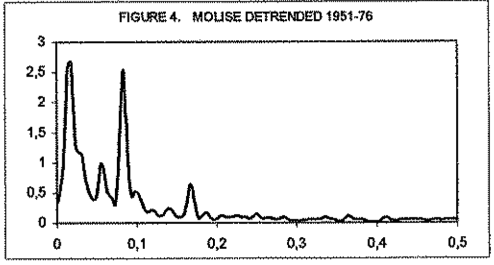


FIGURE 4. MOLISE DETRENDED 1951-76

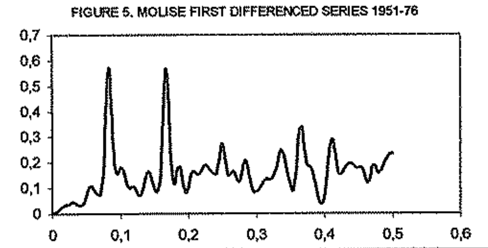


FIGURE 5. MOLISE FIRST DIFFERENCED SERIES 1951-76

Most series exhibit only a slight trend, but in those with appreciable power at zero frequency the subtraction of an estimated quadratic function in time proved excelent whereas first differences caused havoc as can be seen in Figure 5. Several tests, including those by Dicky and Fuller (1979) and by Philips and Perron (1988) rejected the unit root hypothesis.

Pre-vaccination Dynamics

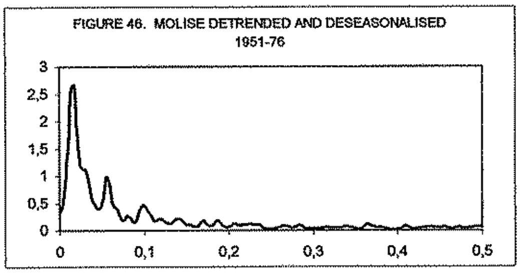
Inspection of the regional spectra for the period 1951-76 revealed the following common features:

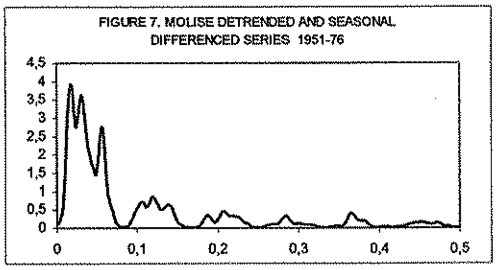
i) a sharp peak at the annual frequency, a fact well evident from the data;

ii) a second, usually smaller, peak at a lower frequency, denoting a long-term cycle. This longer cycle is characterised by a period varying from 2 years (Basilicata) to 5 years (Molise); details are reported in Table 1. Only the regions of Lazio and Puglia did not exhibit regular long-term cyclical movements. It is worth noting that the annual component dominates the long-term cycle in almost all the Italian regions with the ecceptions of Sardegna, Abruzzo, Molise and Valle d'Aosta;

iii) in most cases a small peak is present at a frequency usually around six months. These inter-year fluctuations are also well evident from the data (the winter and spring peaks in the monthly data).

Following the above observations, the yearly component was removed from the spectra in order to obtain a better pattern of the long-term cyclical movements. This was done through regression on sine-cosine terms at the annual frequency and its harmonics (i.e. a deterministic seasonal component) and through 12-month differences (i.e. a stocastic seasonal component). The results were completely different. The deseasonalized data using a deterministic seasonal model exhibits a deflated spectrum similar, apart from the seasonal frequencies, to the spectrum of the original data. In particular the longer term oscillation emerged quite sharply. On the other hand, 12-month differences significantly changed the whole pattern of the spectrum (see Figures 6 and 7 below for an example with the data for Molise).





This suggests that the deterministic approach should be preferred and that the long term and yearly components are most probably governed by independent, possibly additive, mechanisms, a fact which strongly agrees with the seasonally forced version of the SEIR model (1).

From a cross-spectral analysis we observed that, whereas the annual components in all the series are very highly correlated (coherencies around 0.9 or higher), there appears to be very little correlation between the long term cycles. In this latter case, coherencies greater than 0.7 were observed, as expected, for a few neighbouring regions such as Emilia-Romagna and Marche, Marche and Umbria, Friuli and Trentino, Lombardia and Piemonte, Liguria and Piemonte.

Post-vaccination dynamics

The frequency domain analysis revealed the presence of an annual cycle and a long-term cycle; the long-term cycle for the whole of southern Italy has a 4 year period. This cyclical behaviour is also present in the eastern regions of Liguria, Piemonte and Valle d'Aosta. The remaining regions in central and northern Italy have a 3.5 year periodic component. Compared to the pre-vaccination period, the role of the longer term oscillation, dominated by the annual one in the pre-vaccination period, appears to be more important. As with the pre-vaccination data, the annual component was best removed, without altering the remaining frequency components, through a deterministic model based on sine-cosine regressors. This again suggests that the annual and long-term periodic components are probably independent and additive.

Cross-spectral analysis provided results very similar to those obtained for the pre-vaccination period. There was a slight increase in the number of neighbouring regions with long term oscillations which were highly correlated (coherency greater than 0.7), especially in Southern Italy.

5. Comparisons with predictions from mathematical models

Predictions via formula (2) required the estimation of the average age at infection (A) from the age distributions of measles cases during the pre-vaccination period. Age structured data at the regional level are available, during the pre-vaccination period, for the years 1971-1974 and 1976, with a "whole" in 1975. Age data for 1975 were reconstructed via interpolation, but we expect that this should'nt be a serious cause of error as the age distribution of cases were quite stable in the period considered. The reconstructed 1971-76 age structured data were used to estimate A. This 6-years long pre-vaccination window was considered adequate in that about two full long term three years long epidemic cycles were so considered. Table 1 reports the values of A and the corresponding values of the inter-epidemic period (T) computed from the SEIR model (1) for the pre-vaccination period, and the length of the long-term cycles (TS) as identified by spectral analysis for both the pre- and post-vaccination periods. With respect to the pre-vaccination period, table 1 shows a substantial agreement between predictions from the SEIR model, and the lengths of the cycles identified by spectral analysis, with a few exceptions, which were Liguria, Basilicata, and Molise. For Lazio and Puglia the absence of an identifiable long term oscillation prevented any comparison. As mentioned above, the SEIR model predicts an increase in the long term oscillation as a consequence of vaccination. This is largely confirmed by spectral analysis.

6. Discussion

In this paper we compared predictions on the lengths of the epidemic cyclical oscillations of measles in Italy based on the SEIR model, with the lengths of the cycles identified by spectral analysis. With a few exceptions the two analyses provide results which are in good agreement. The spectra of the Italian regions are dramatically different from the classical spectra observed for England and Wales (EW), see Fine and Clarkson (1982), Anderson et al. (1985), Earn et al. (2000). In the EW (and in most of the EW large cities) time series of notifications of measles cases, the longer term periodicity sharply dominates the seasonal one, and the period very often is, a nowadays classical fact, around two years. This fact is sharply reversed in most of the Italian time series, where the seasonal yearly component is the dominant one, and the longer period oscillation, though existing, is much less important.[5] This agrees with a further result from the forced SEIR model (Earn et al. 2000), by which in areas with higher birth rates the annual component tend to become more important compared to the longer term one.
Of course the results presented here are intended to be preliminary in that we used the simplest mathematical model, and, as a consequence, a lot of potentially important factors, such as demographic changes, heterogeneity in both births and vaccination rates, geographic distribution of the population within different regions, spatial structure of the interactions between regions, have been ignored. The present time series analysis reveals could be of great help in finding more appropriate models.

An interesting point is the fact that in the post-vaccination period there is a substantial similarity between those regions (Northern Italy) with higher vaccination coverages,

[5] Edmunds et al. (2000) were in fact observing that, from the national time series for measles, "no clear epidemic long term patterns could be discerned for Italy".

and those (especially in the South) with lower vaccination coverage. There are many possible reasons for this, for instance the compensating effect played by the fact that Southern regions mantained a higher fertility rate for a longer period compared to Northern ones.

We are undertaking further research in the following directions. First we intend to deep out time series analysis by using more systematically spatial autocorrelations. We also intend to consider those factors, such as demographic and spacial factors, which have been ignored in the present analysis.

TABLE 1

REGION	SEIR Model		Spectral Analysis	
	A	T	1951-76 (pre-vacc)	1977-96 (post-vacc)
PIEMONTE	6.3	3.1	2.5	4
VALLE D'AOSTA	6.4	3.1	3.5	3.5 – 4
LOMBARDIA	5.7	2.9	2.5	3.5
TRENTINO A.A.	5.4	2.9	3	3 – 5
VENETO	5.9	3.0	3 – 3.5	3.5
FRIULI V.G.	5.8	3.0	3	3.5
LIGURIA	7.0	3.3	4 – 5	4
EMILIA R.	6.3	3.1	3.5	3.5
TOSCANA	7.2	3.3	3	3.5
UMBRIA	6.8	3.20	3.5	3.5
MARCHE	6.9	3.2	3.5	3.5
LAZIO	6.4	3.1	none	3.5
ABRUZZO	6.4	3.1	4	4
MOLISE	5.8	3.0	5	4
CAMPANIA	5.4	2.9	3	4
PUGLIA	5.0	2.8	none	4
BASILICATA	5.1	2.8	2	4
CALABRIA	5.6	2.9	3 – 3.5	4
SICILIA	5.2	2.80	3	4
SARDEGNA	5.6	2.9	4	4

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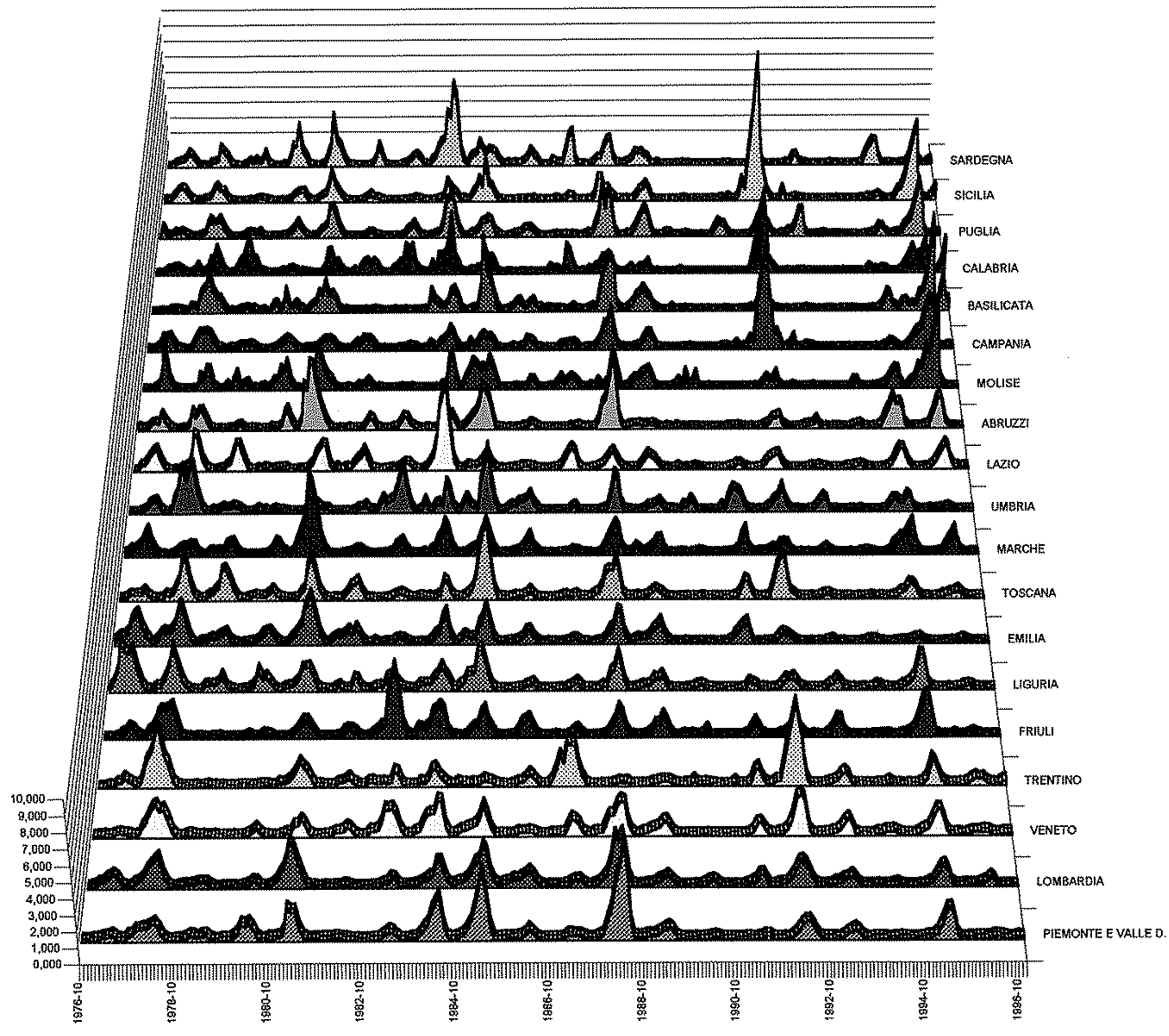
FIGURE 1


SARDEGNA
SICILIA
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TOSCANA
EMILIA
LIGURIA
FRIULI
TRENTINO
VENETO
LOMBARDIA
PIEMONTE E VALLE D.
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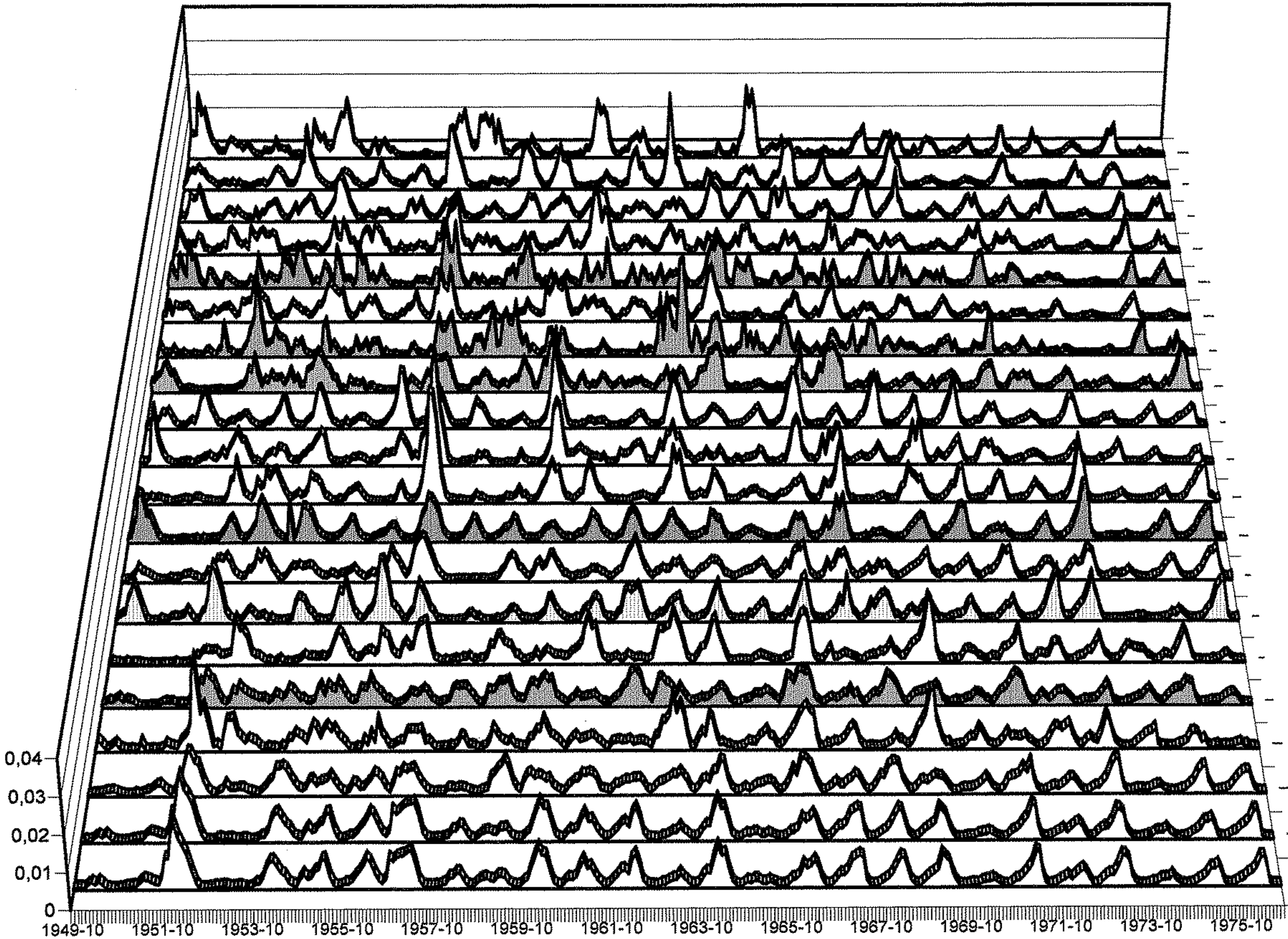
FIGURE 2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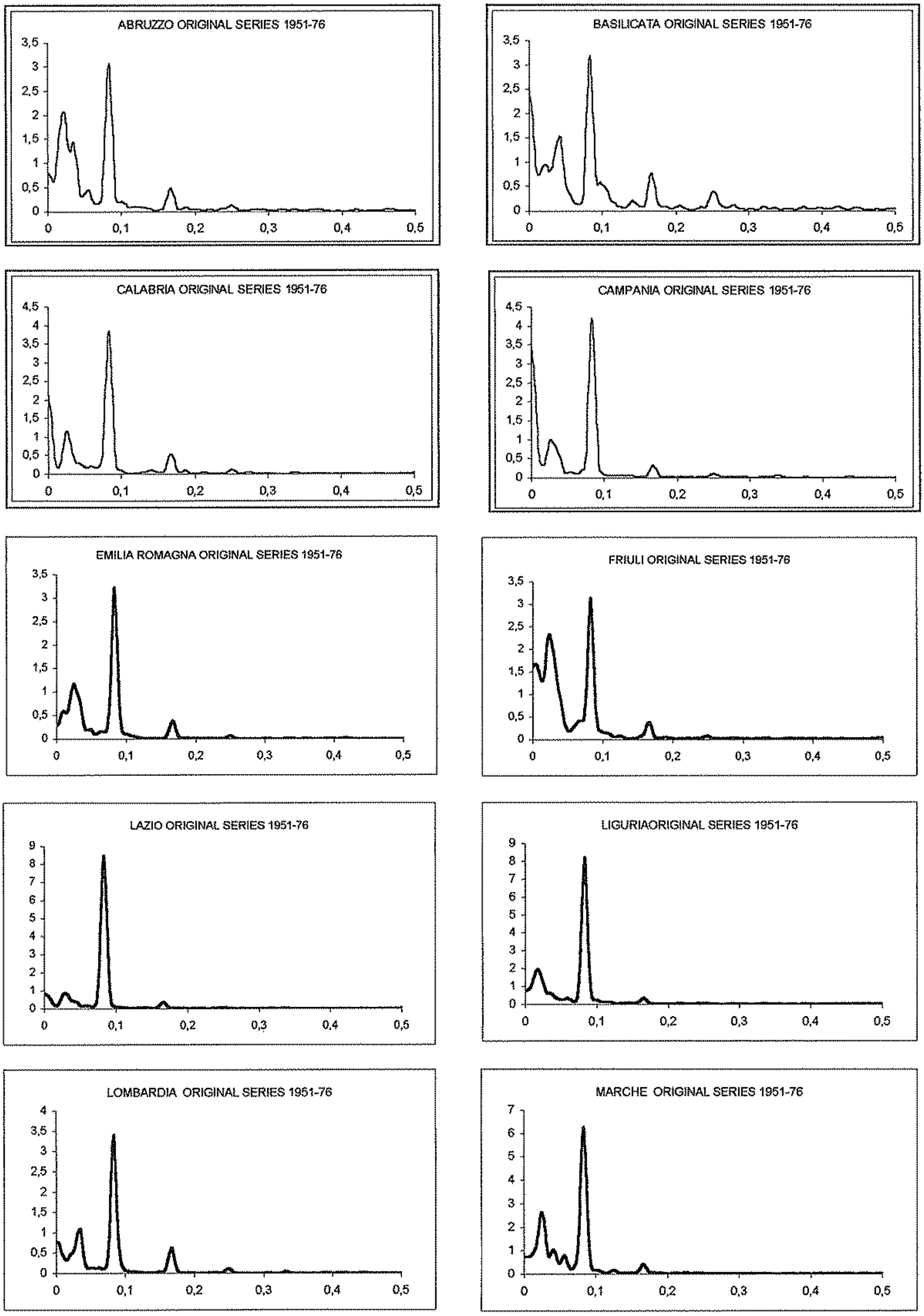
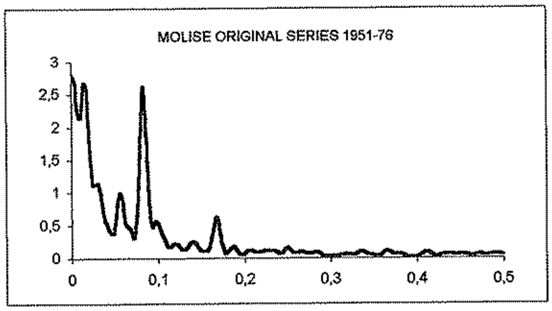
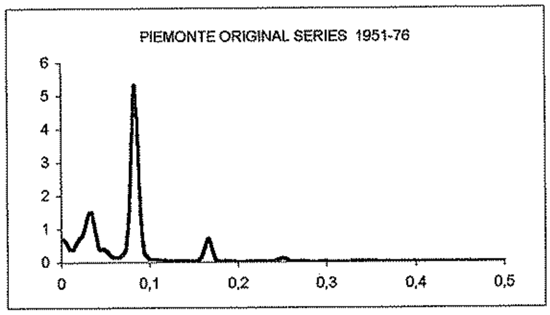
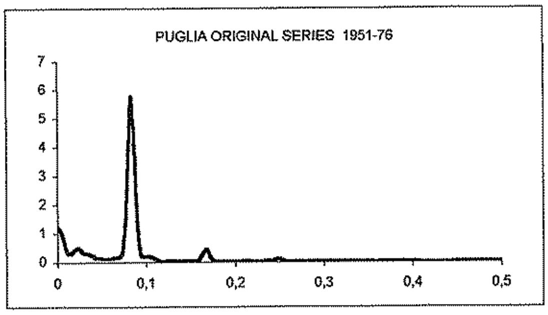
SPECTRAL DENSITY OF ORIGINAL TIME SERIES FOR PERIOD 1951-76

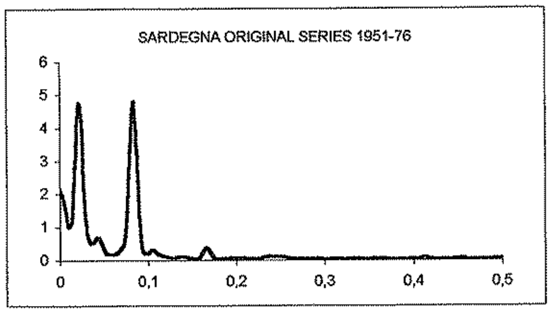


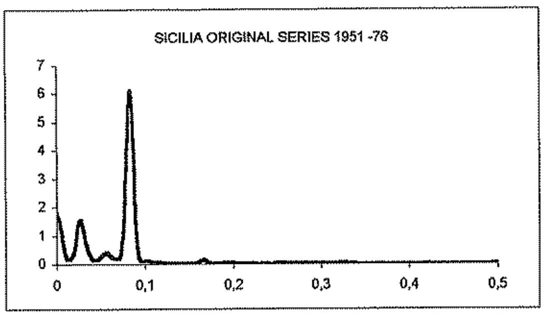
SPECTRAL DENSITY OF ORIGINAL TIME SERIES FOR PERIOD 1951-76

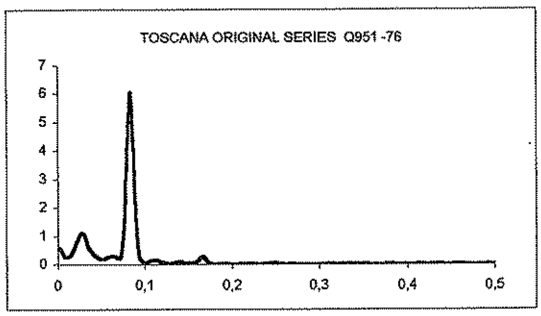


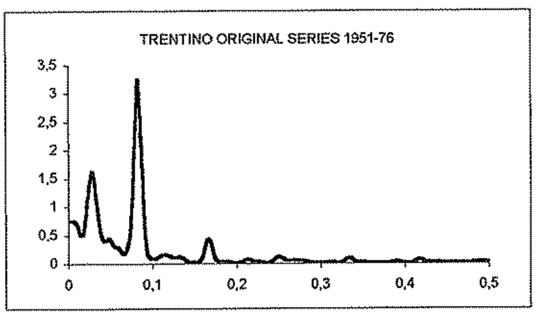


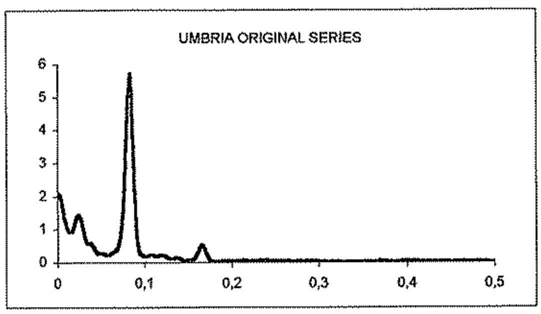


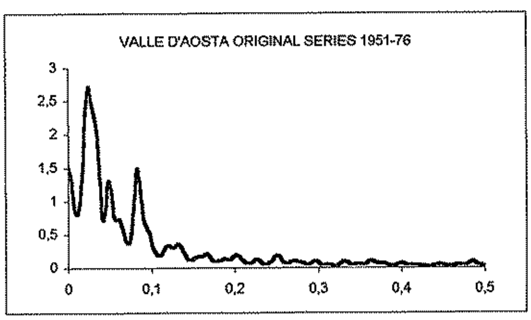


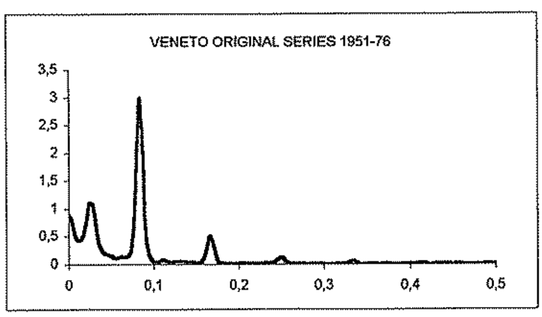




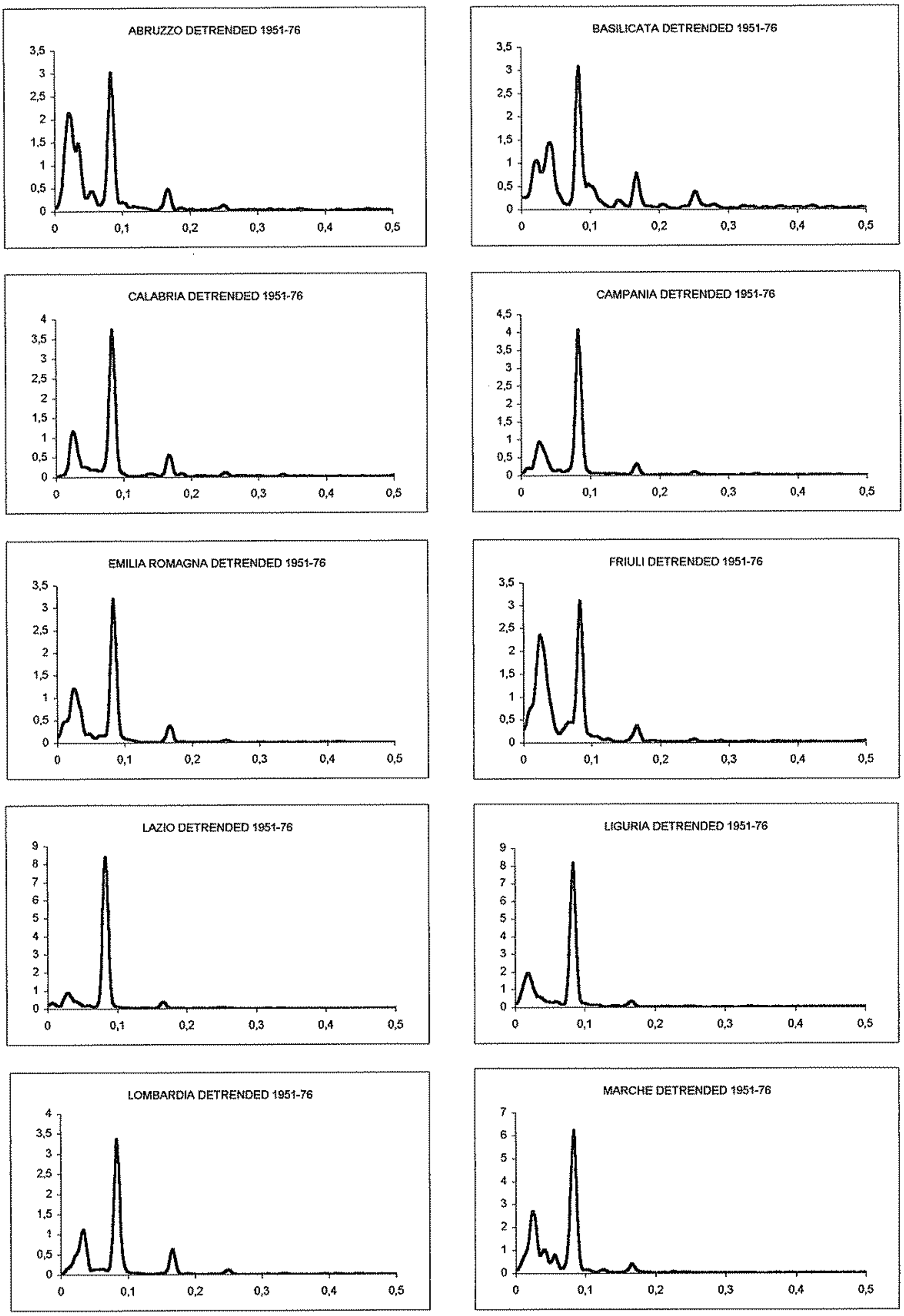




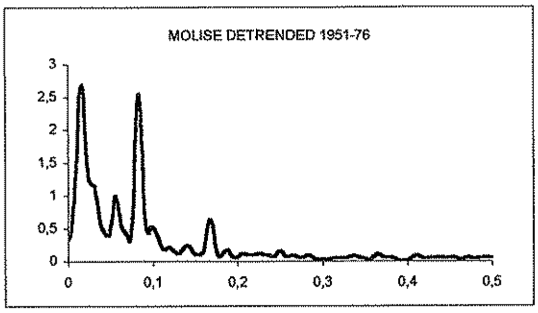


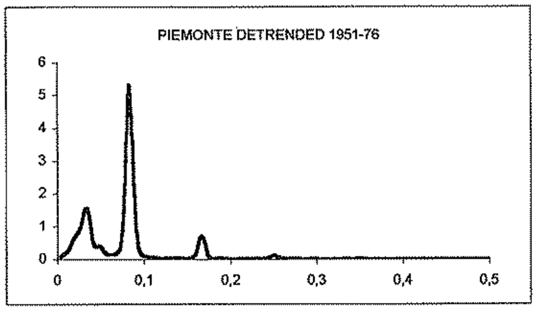


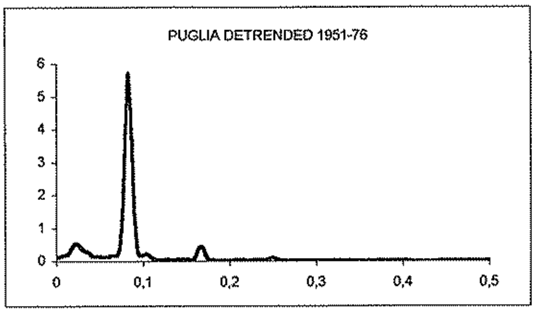
SPECTRAL DENSITY OF DETRENDED SERIES FOR PERIOD 1951-76

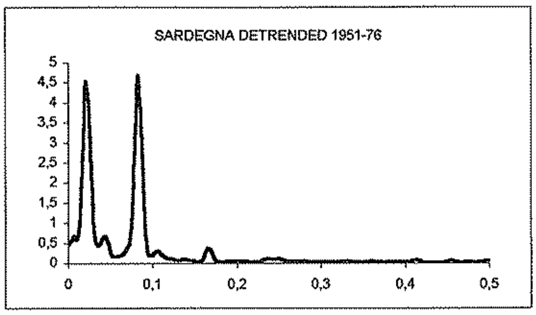


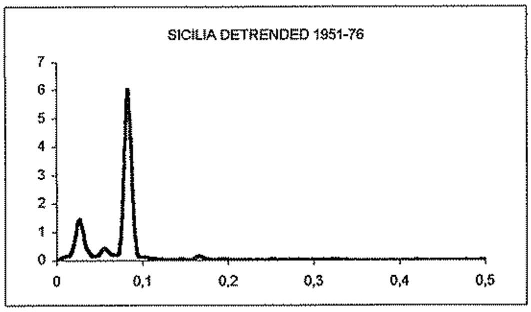
SPECTRAL DENSITY OF DETRENDED SERIES FOR PERIOD 1951-76

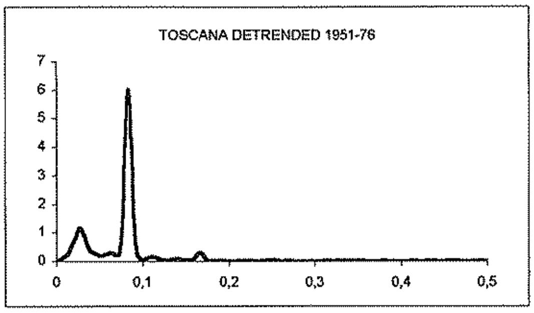


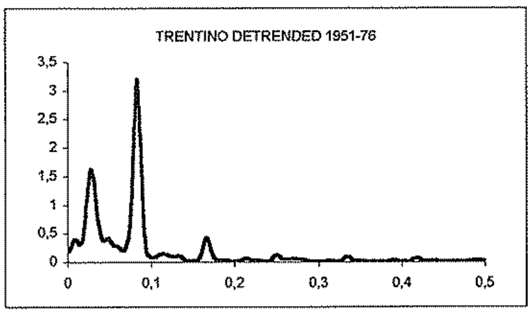


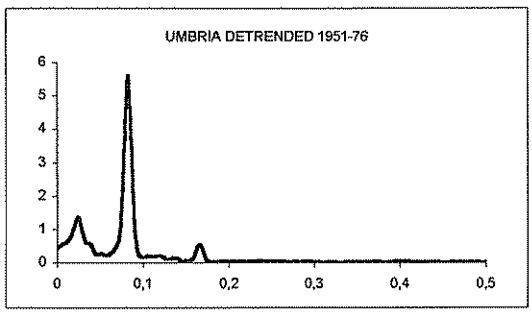


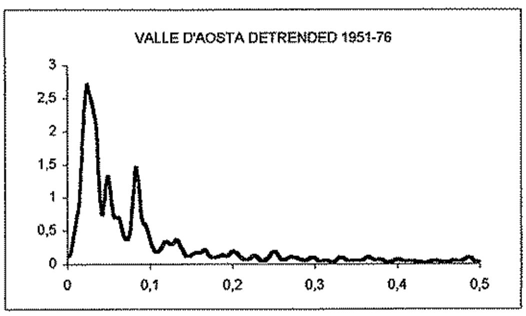


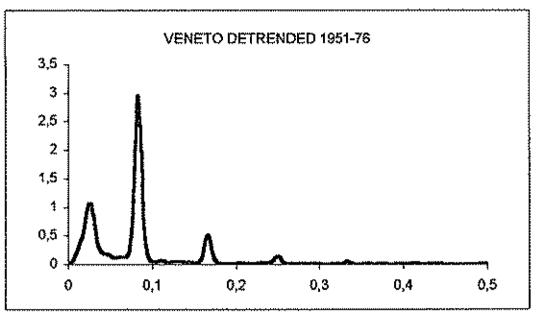




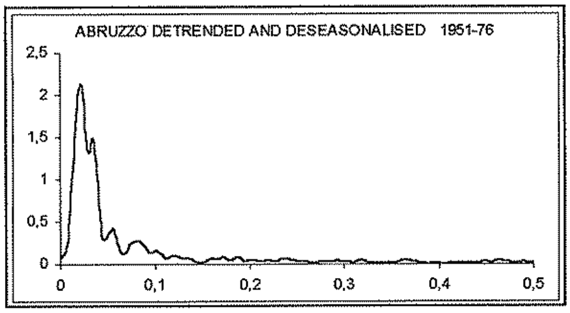


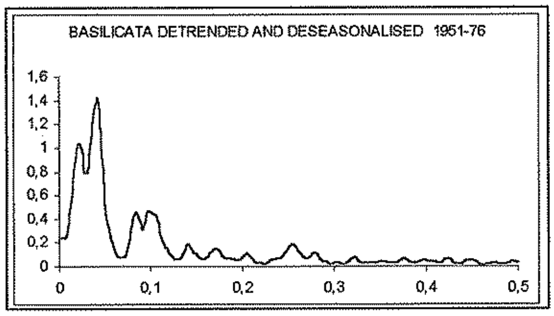


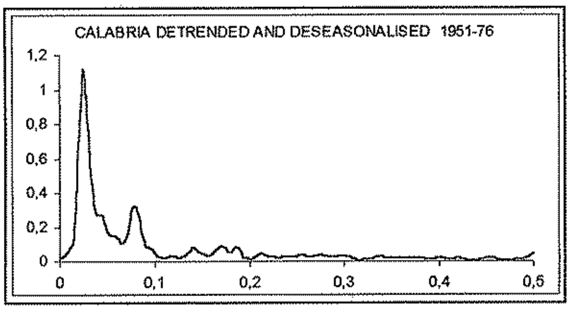


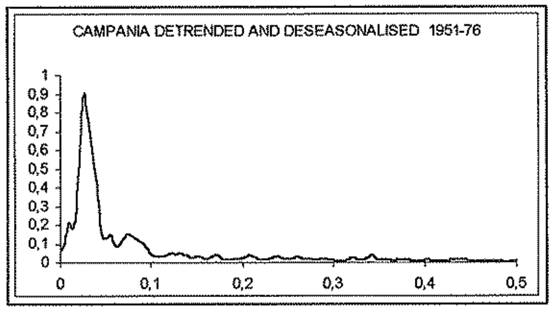


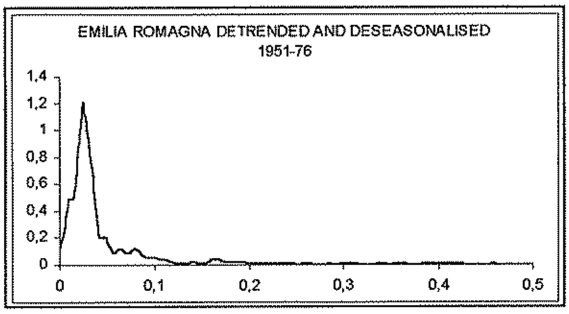
SPECTRAL DENSITIES OF DETRENDED AND DESEASONALISED SERIES FOR PERIOD 1951-76

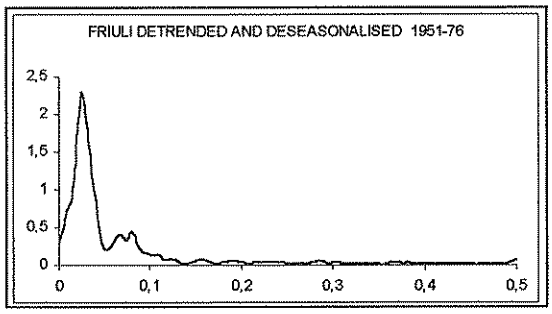


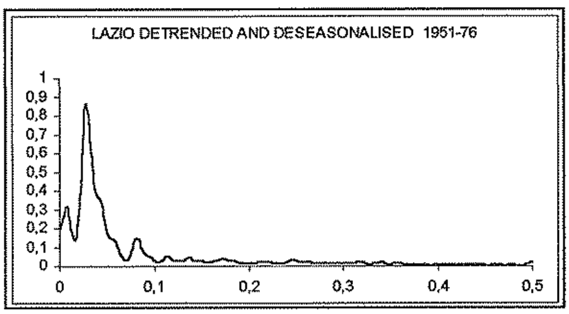


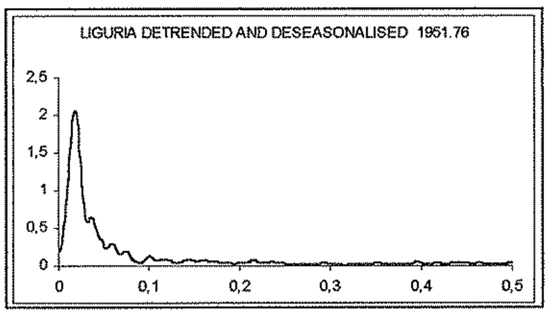


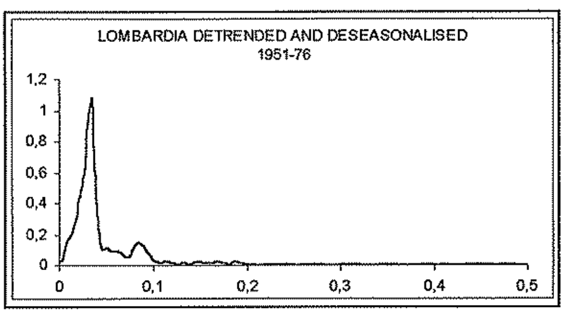


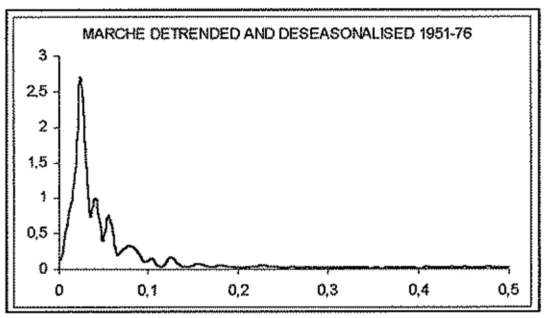




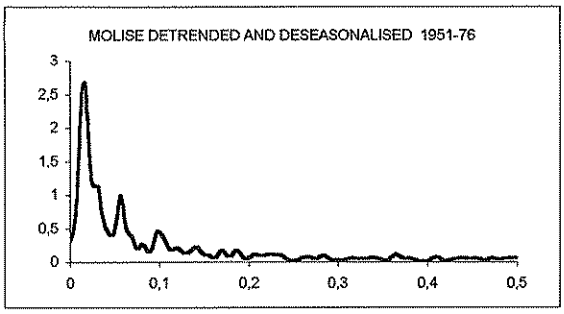


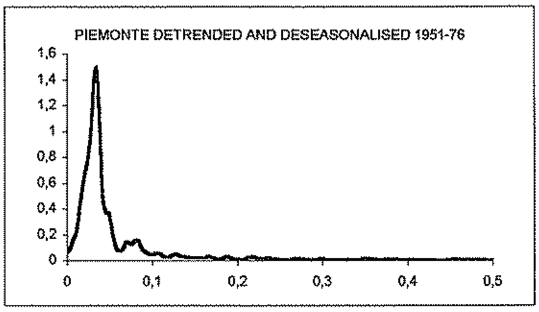


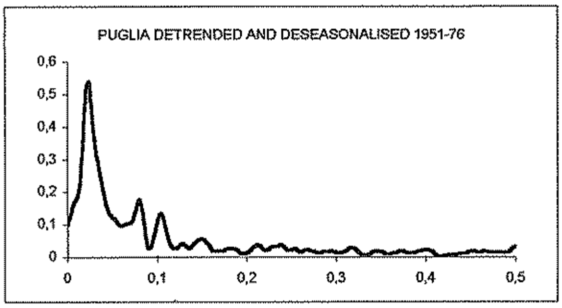


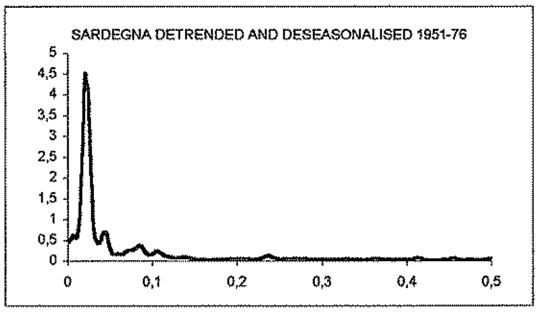


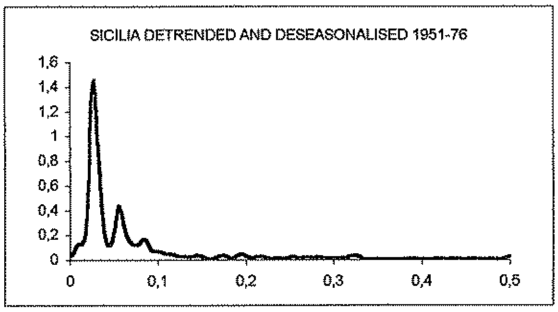
SPECTRAL DENSITIES OF DETRENDED AND DESEASONALISED SERIES FOR PERIOD 1951-76

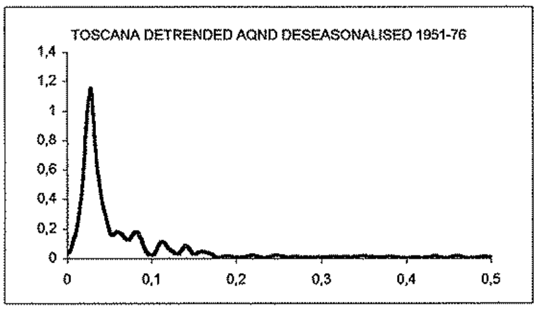


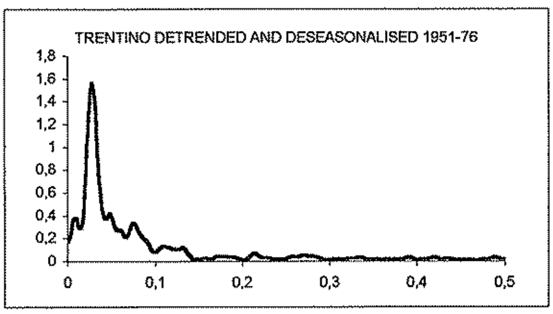


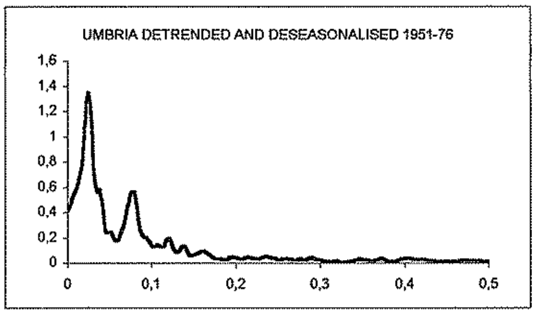


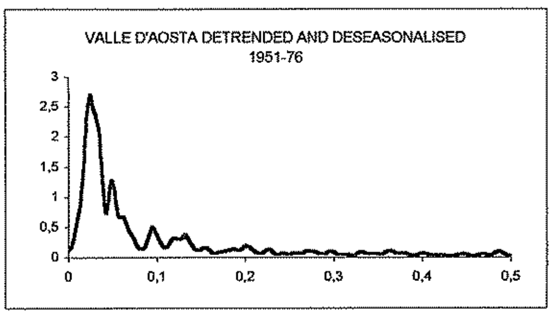


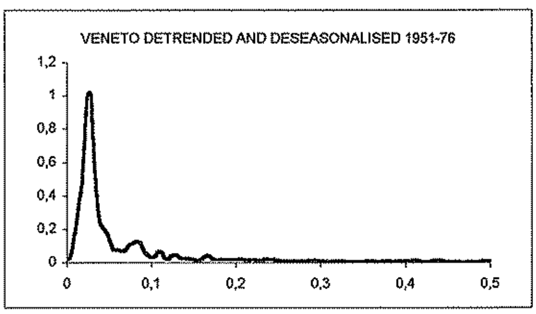




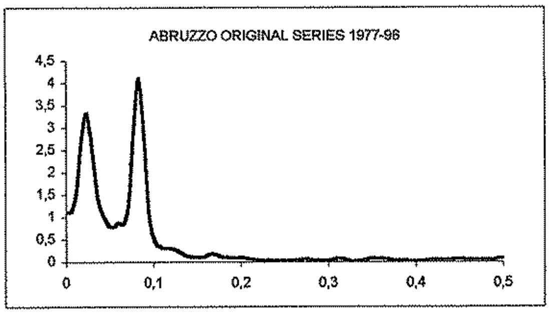


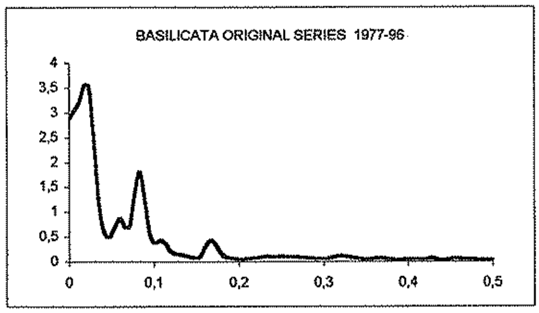


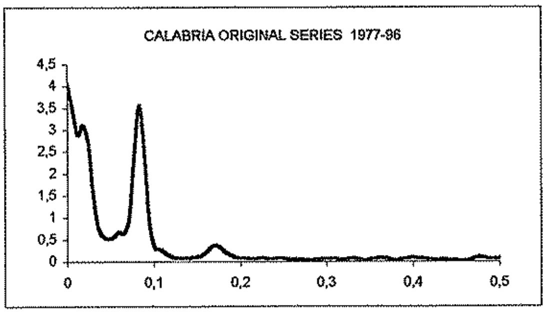


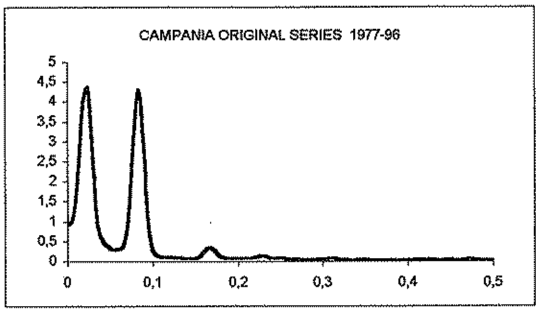


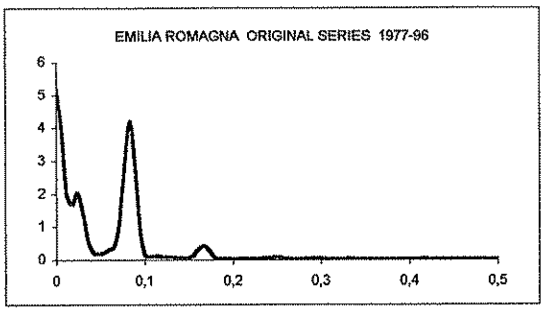
SPECTRAL DENSITY OF ORIGINAL TIME SERIES FOR PERIOD 1977-96

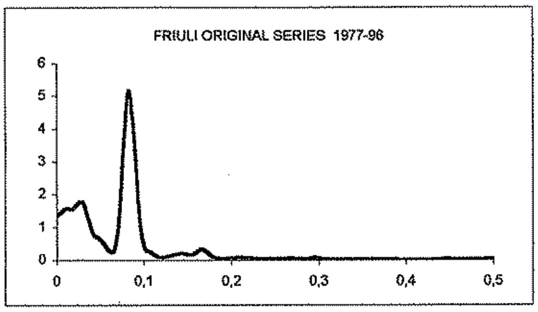


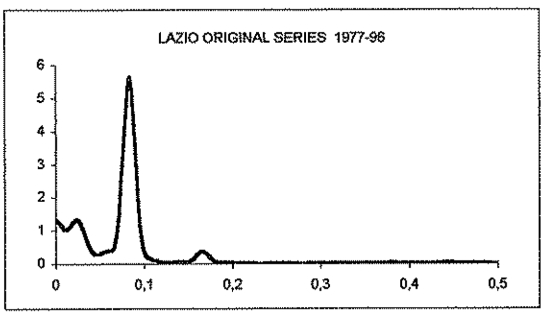


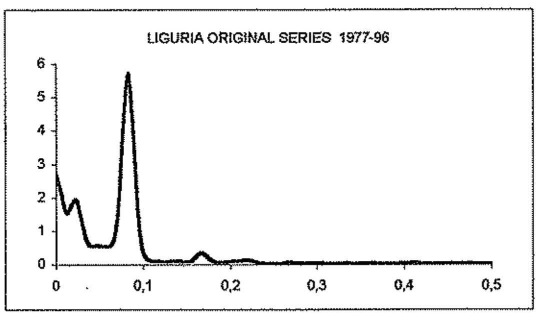


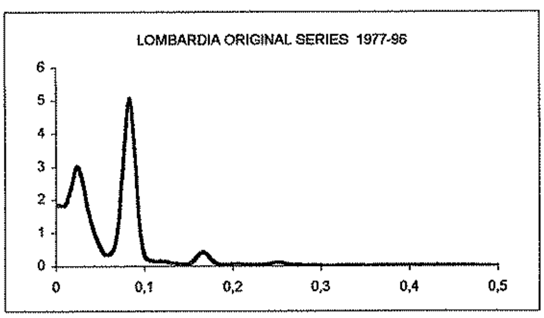


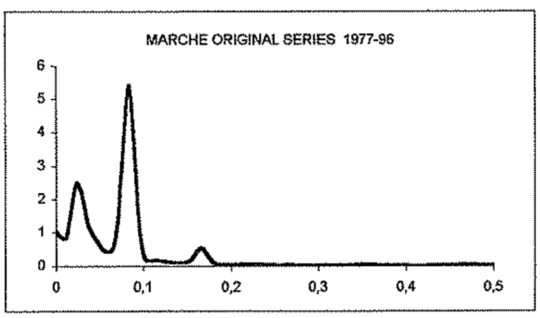




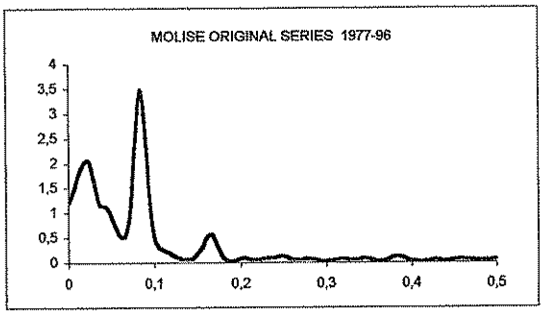


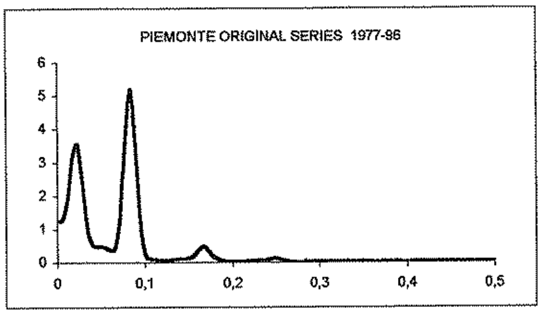


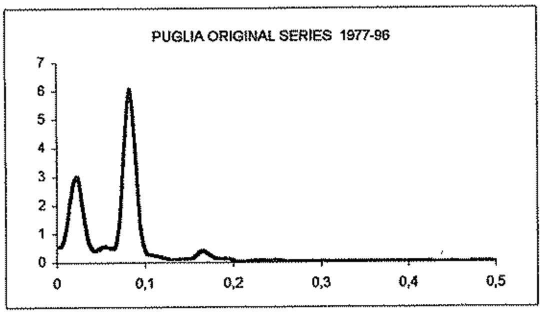


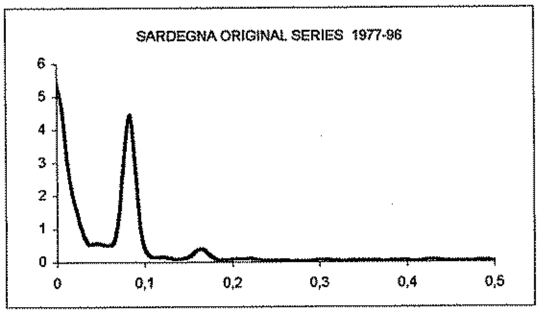


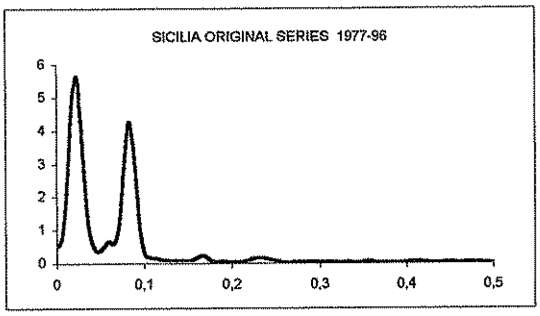
SPECTRAL DENSITY OF ORIGINAL TIME SERIES FOR PERIOD 1977-96

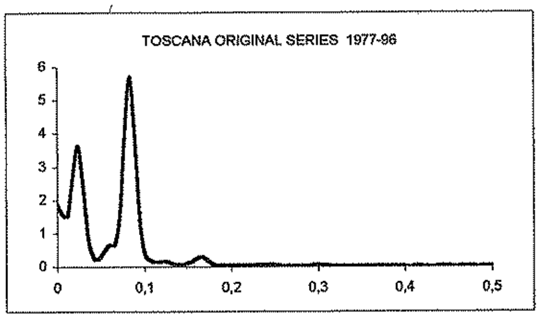


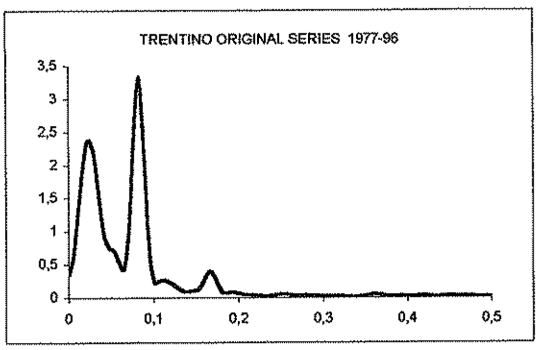


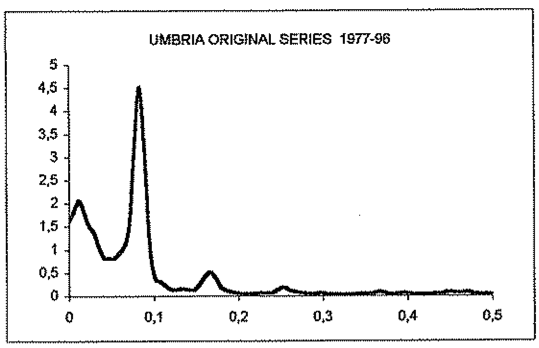


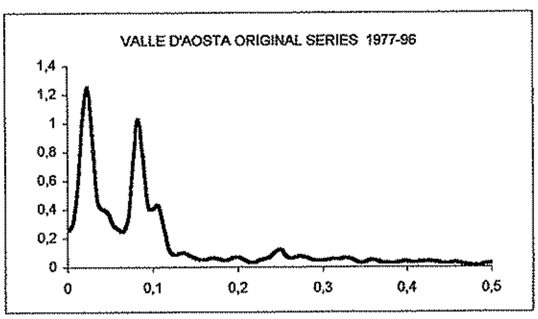


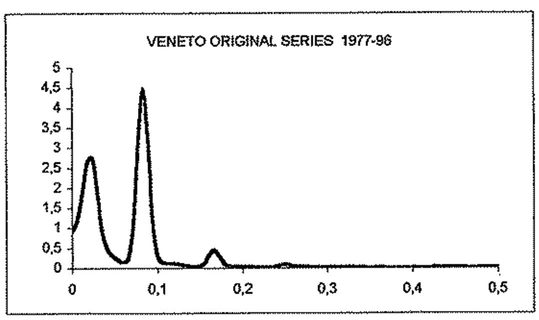




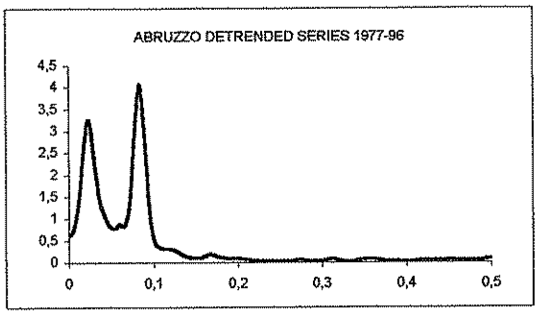


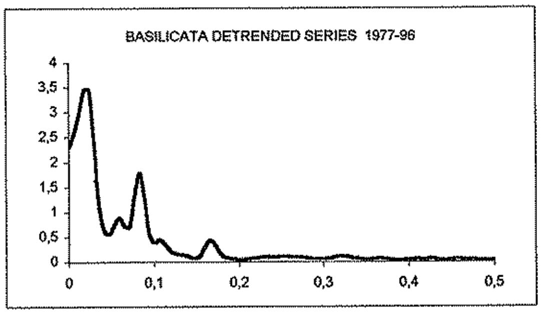


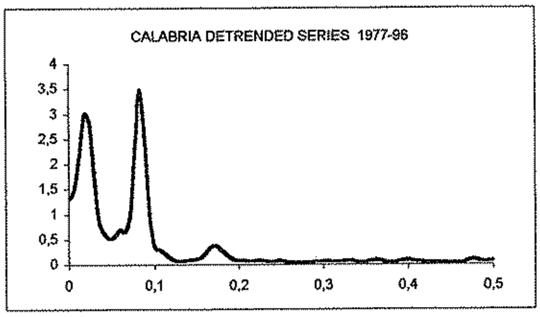


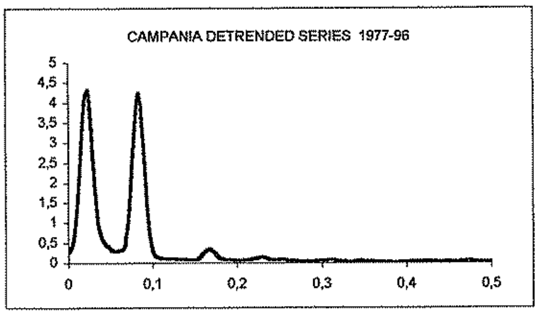


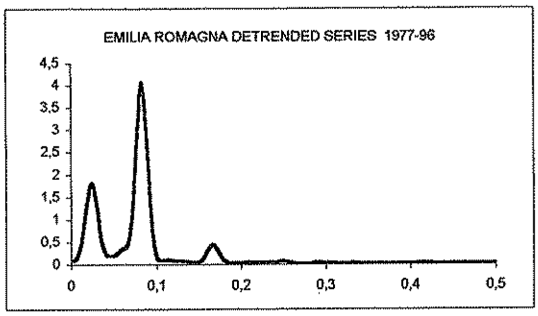
SPECTRAL DENSITY OF DETRENDED SERIES FOR PERIOD 1977-96

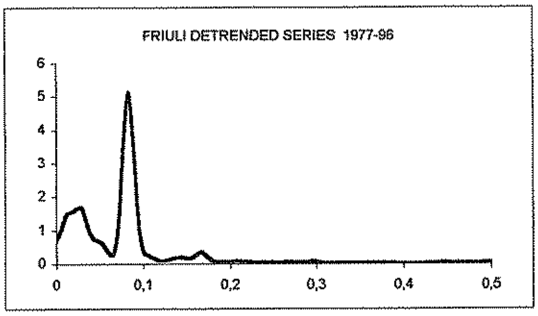


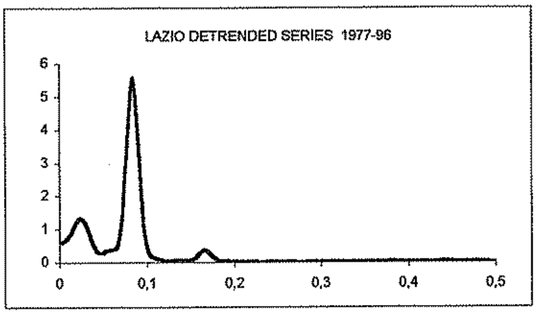


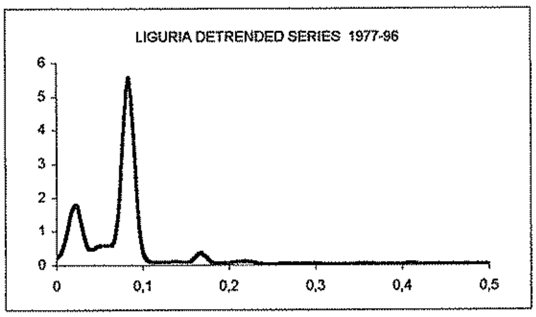


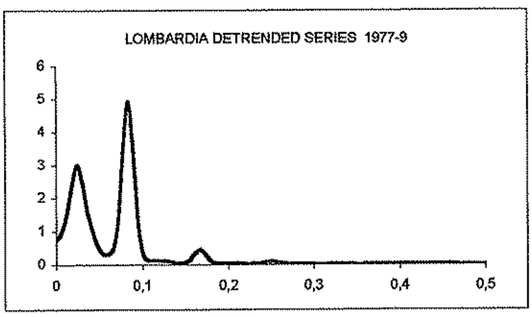


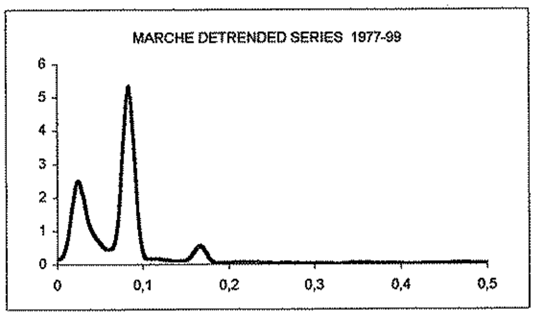




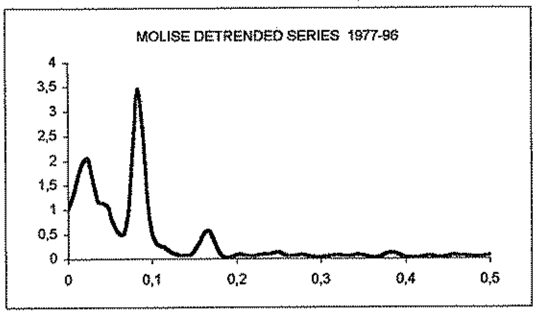


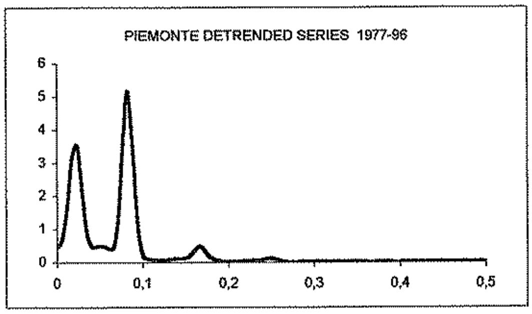


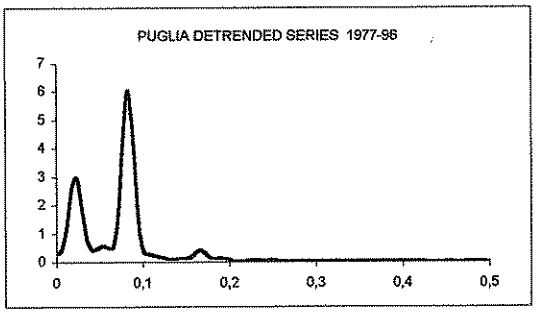


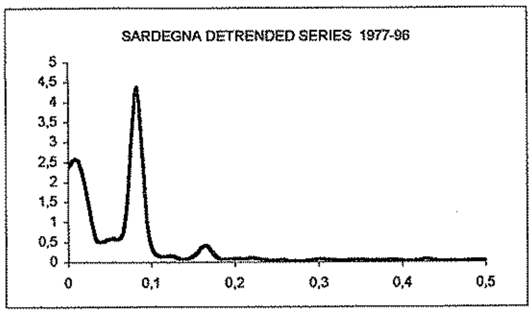


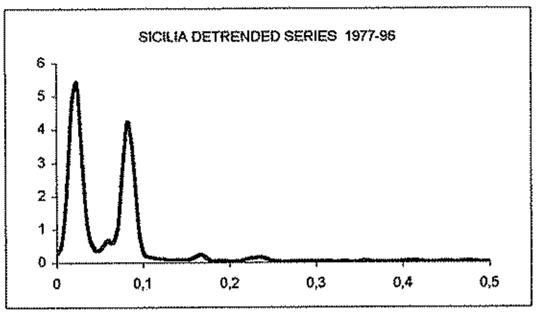
SPECTRAL DENSITY OF DETRENDED SERIES FOR PERIOD 1977-96

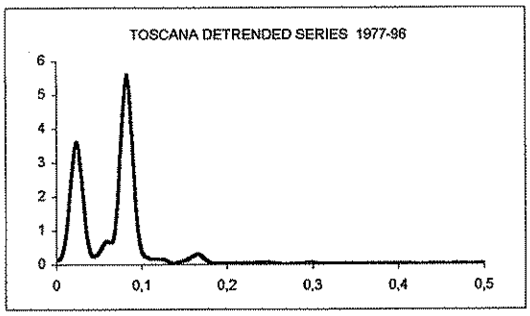


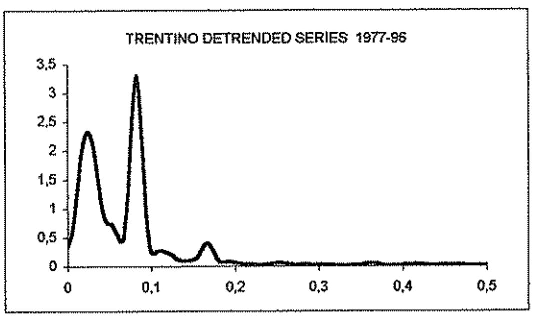


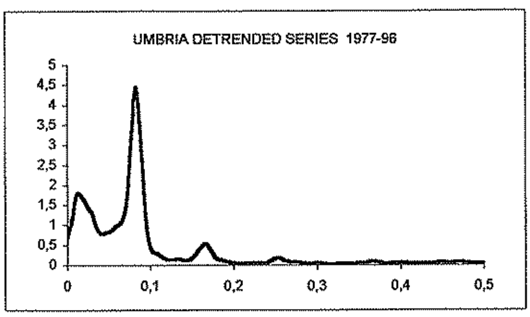


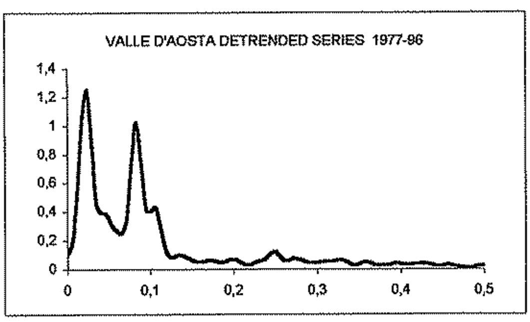


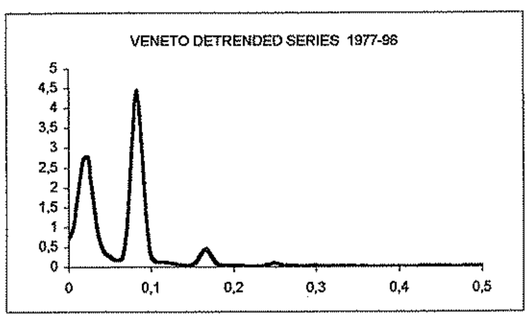




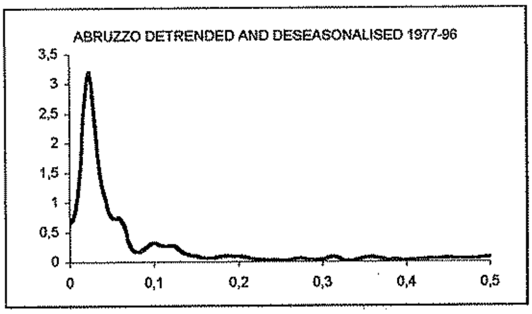


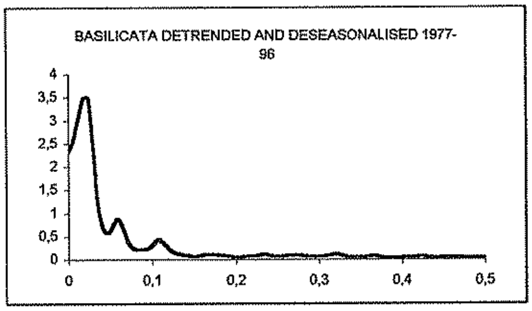


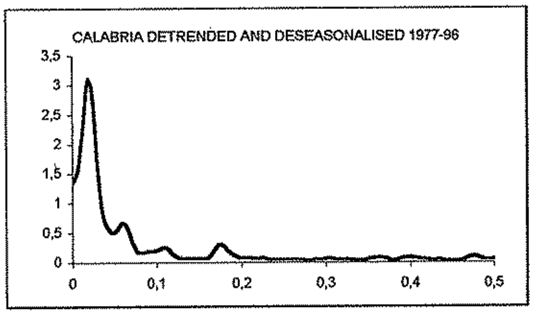


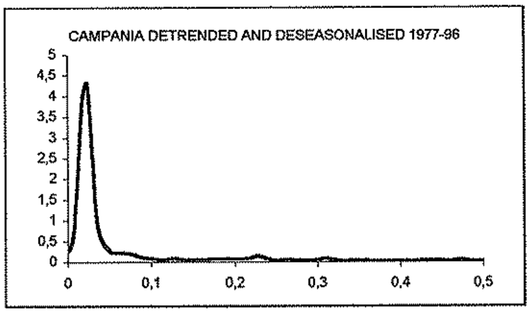


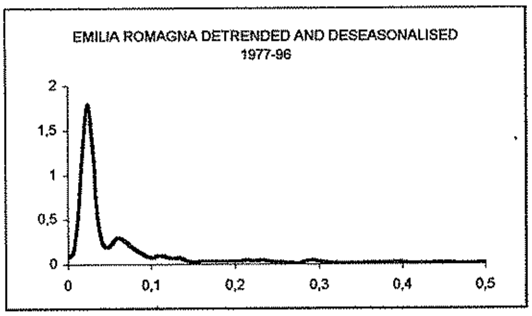
SPECTRAL DENSITIES OF DETRENDED AND DESEASONALISED SERIES FOR PERIOD 1977-96

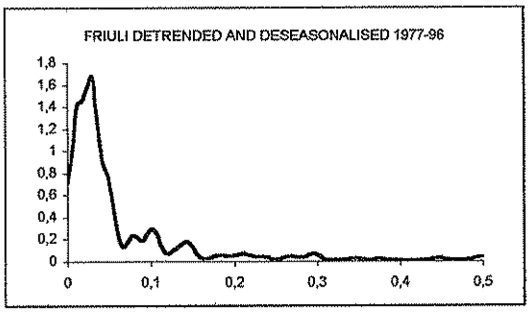


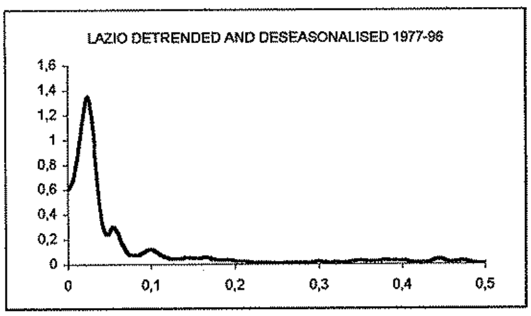


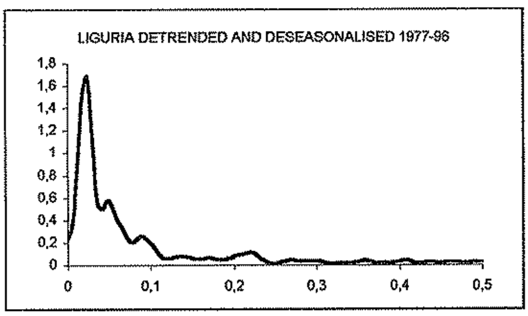


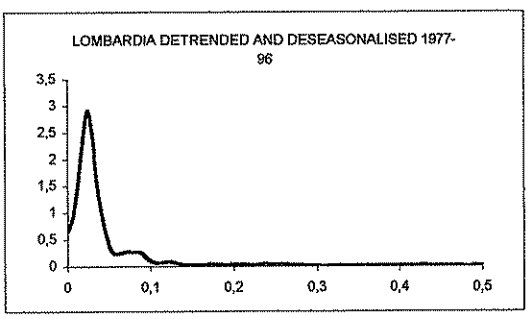


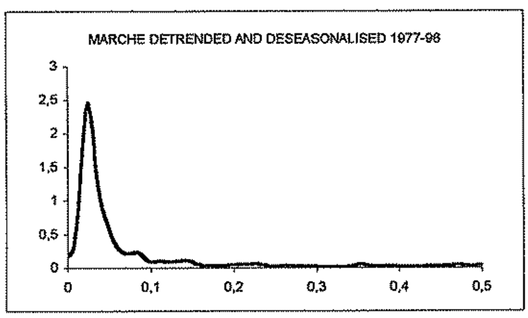












SPECTRAL DENSITIES OF DETRENDED AND DESEASONALISED SERIES FOR PERIOD 1977-96