Otoacoustic emissions at different click intensities: invariant and subject dependent features.

Giovanna Zimatore¹, Alessandro Giuliani², Stavros Hatzopoulos³, Alessandro Martini³, and Alfredo Colosimo1&

1 Dept. of Human Physiology and Pharmacology, Univ. of Rome "La Sapienza", 00185 Rome, Italy

2 Ist. Superiore di Sanità, 00185 Rome, Italy.

3 Audiology Dept and Center of Bioacoustics, Univ. of Ferrara, 44100 Ferrara, Italy.

Short title: Invariant and individual features in CEOAE responses

Keywords: Hearing physiology, Click evoked otoacoustic emissions, Recurrence quantification analysis, Determinism.

ABBREVIATIONS:

ENT: Entropy ; CEOAE: Click Evoked Otoacoustic Emission; CHL: Conductive Hearing Loss; LDA: Linear Discriminant Analysis; OHC: Outer Hair Cell; PCA: Principal Component Analysis; REPRO: Pearson correlation between waveforms A and B in CEOAEs; RQA: Recurrence Quantification Analysis ; SHL: Sensorineural Hearing Loss; %DET: Percent determinism ; %REC: Percent recurrence

ABSTRACT

A study of Click Evoked Otoacoustic Emissions (CEOAEs) elicited at stimulation intensities from 35 to over 80 dB was carried out by Recurrence Quantification Analysis (RQA) on signals from both normal and hearing impaired subjects. In normal subjects, a clear scaling of determinism with increasing stimulation intensity was observed in the click intensity range from 41 to 59 dB. Outside that range and, in particular, above its upper end, subject-dependent features appeared in the form of different maximal levels of determinism. A comparative analysis of responses from hearing impaired subjects with conductive hearing losses and sensorineural hearing losses suggested that the principal contributor to this behavior is the middle ear and allowed to discriminate the two pathologies solely on the basis of CEOAEs. These observations are consistent with a simple phenomenological model of the auditory periphery in which different functional modules are sequentially recruited at increasing stimulus intensities, with a consequent rise in CEOAEs coherence.

[&]amp; **Mail and correspondence to:** Prof. Alfredo Colosimo

Department of Human Physiology and Pharmacology, University of Rome "La Sapienza" P.le A.Moro 5, 00185 Roma - ITALY

TEL.: +39 06 49910732 ; FAX: +39 06 440062 ; E-MAIL: colosimo@caspur.it

1. INTRODUCTION

Otoacoustic emissions are sounds generated from the activity of the Outer Hair Cells (OHCs) of the inner ear [15]. They can be recorded from all normal subjects when the auditory periphery is solicited by external acoustic stimuli and, from most subjects, even in the absence of stimulation [19]. The responses elicited by a brief rectangular stimulus including a broad range of frequencies (click), are defined as Click Evoked Otoacustic Emission (CEOAEs)**.** CEOAEs have been exploited as research tools in the physiology and biophysics of the hearing system. A number of studies reported the non-linear increase of otoacoustic emissions amplitude with increased stimulus intensity [4, 14, 16, 22], suggesting that useful information on the peripheral processing of complex sounds can be derived from the analysis of CEOAEs under these conditions. The current clinical applications of CEOAEs include the objective, noninvasive assessment of auditory (mis)functions and, more importanly, the hearly detection of hearing impairment in newborns **[**18**].**

In previous papers [27, 28] the authors have demonstrated the efficacy of a nonlinear signal analysis tool, recurrence quantification analysis (RQA) [23], in extracting physiological information from otoacoustic emissions at fixed stimulation intensity. In the present study we address the goal of investigating the effect of varying stimulus intensity on the dynamical features of CEOAE's, and in particular towards the lower bound of the stimulus intensity region. Our specific aim was, for both normal and hearing impaired subjects, to provide clues concerning: i) the discrimination between subject-dependent and population dependent features, and ii) the identification of morpho-anatomical and functional factors contributing to normal and altered responses.

For the normal hearing subjects, we present data on the deterministic features of CEOAEs which, above a given threshold of stimulation intensity, confirmed significant differences among individuals in terms of the maximal attainable amount of signal autocorrelation measured by determinism. Below that threshold, however, we observed a scaling of determinism with increasing stimulation intensity remarkably similar among individuals. A possible explanation assumes that a subject-independent portion of CEOAEs dynamical features comes from the progressive recruitment of functional modules in the auditory periphery, according to a basically invariant physiological process, while the individual variability is related to the maximal attainable synchronized behaviour of such units, different among subjects. It is worth to stress that we use "recruitment" here to indicate an increase of functionally coordinated units induced by an increased stimulation intensity, not the altered perception of sound loudness and frequency components, as in the common clinical audiological practice.

A relevant conclusion of the present study is that determinism, as measured by RQA, can faithfully quantify the dynamical features of CEOAEs in a somewhat unexpectedly broad range of conditions. As for hearing impaired subjects, in particular, we show that the measure of determinism is actually able to discriminate between Conductive Hearing Losses (CHL) and Sensorineural Hearing Losses (SHL), corresponding to middle and inner ear disorders, respectively. Beside the physio-pathological implications, the possible clinical use of such a finding seems also relevant.

2. METHODS

CEOAE recording protocols

The CEOAE signals were collected in the Audiology Department of the University of Ferrara, (Italy). They were responses to click stimuli with a relatively flat acoustic spectrum for frequencies between 0.5-5 kHz, according to a non-linear stimulation protocol [12, 13]. Each stimulus sequence contains 4 clicks, of which three clicks of positive polarity followed by a fourth click with inverse polarity and intensity equal to the sum of the previous three. The CEOAEs were recorded in a sound-attenuated booth, using an Otodynamics ILO-292 system running software v. 5.6 with standard adult ILO probes. In the study of normal ears CEOAEs were collected from 9 adult female subjects (age range: 26.8 ± 7.1 years) chosen on the basis of the absence of : i) any pathophysiological objective signs of clinical relevance, and ii) any systematic pharmacological treatment within three months from the acquisition of the signals. 16 responses were collected for each subject, corresponding to levels of click stimuli ranging from 35 dB to over 80 dB. The intensity of the stimuli was monotonically decreased down from the maximun level in discrete steps of 3 dB sound pressure level. The time elapsed between exposures to different stimuli was on the average one minute (time necessary for the operator to set the new stimulus settings on the ILO-292 system). In this context there was no hysteresis in the recorded signals. Responses were high-pass filtered at 500 Hz. Every accepted response was the average of at least 260 individual responses for each subject.

The same recording setup was adopted for the collection of the TEOAE signals aiming to compare normal and ears with hearing deficits: for each subject at least 4 TEOAE responses were recorded, elicited by click stimuli with intensity 50, 65, 70 and 80 dB respectively. Forty nine subjects were tested and a total of 224 responses (108 from the left and 116 from the right ear) were recorded. The subjects were subdivided into three classes: normal (10 cases); SHL, sensorineural hearing loss (21 cases); CHL, conductive hearing loss (18 cases).

Recurrence Quantification Analysis (RQA) and Determinism

At difference with classical methods of signal analysis (e.g. Fourier), RQA is not limited by specific requirements on signals, like stationarity or length and, as compared to other semiempirical techniques (e.g. wavelets [24]), it has the virtue of a relatively simple implementation and intuitive meaning. The RQA procedure projects a signal into a multidimensional space by means of an embedding matrix having as columns the lagged copies of the original signal by a fixed delay. On this matrix, RQA identifies time correlations that cannot be observed in one dimension. The first step of the analysis is the computation of the Euclidean distance between every row pair in the embedding matrix, in order to work out a distance matrix and visualize it in the form of a recurrence plot **[**6, 9, 23]. In this plot any pair of rows whose Euclidean distance falls below a user-defined threshold (radius) marks a recurrence, and the corresponding point is darkened. Finally, RQA works out a number of variables describing the non linear dynamical features of the signal which proved very useful in several contexts ranging from physiology to molecular biophysics [5, 10, 11, 17, 25, 26].

The RQA variables used in this study are defined as follows: REC (% Recurrence) is the density of recurrent points in recurrence plots; DET (% Determinism) is the fraction of recurrent points that occur in lines parallel to the main diagonal; ENT (Entropy) is an entropy computed by the application of the Shannon formalism to the length distribution of deterministic lines. Besides their operational definition, all the RQA variables are endowed with a specific meaning. In particular, REC is a measure of both periodic and autosimilar features in the signal, DET indicates the degree of structuring of the phase space of the system, i.e. of regions in which the system lies for longer times than expected by chance alone; ENT is linked to the richness of deterministic structuring [23].

The % Recurrence (REC), % Determinism (DET), and Entropy (ENT), were calculated with the following choice of working parameters: lag (delay in the embedding procedure) = 1; embedding dimension (number of elements in the rows of the embedding matrix) = 10; radius = 15; line (minimum number of consecutive, recurrent points scored as deterministic) $= 8$. This choice derives from our previous experience in applying RQA to CEOAEs [27, 28] and, in all cases, the results were checked as for their robustness against alternative choices. The radius is expressed as percentage of the mean Euclidean distance between rows, in order to make varianceand amplitude-independent the observed dynamical features of the signal. This is relevant in consideration of the known large differences in amplitude induced by different stimulation intensities [14].

Statistical analyses

Principal Component Analysis (PCA)

Principal Component Analysis (PCA) is a quite common statistical technique [3] whose aim is to project a multivariate data set into a space of orthogonal axes - called principal components – selected, one after the other, on the basis of the maximal variance explained in the space of the original variables. The presence of correlations between the original variables allows for the reduction of dimensionality of the data set in the new space without noticeable loss of information. Since the principal components are by construction orthogonal to each other, a clearcut separation of the different and independent features characterizing the data set is made possible. In other words, going from the original variables to a principal component space, any statistically significant observation made on any axis points to a truly autonomous effect. We applied PCA on the space spanned by the RQA variables to estimate the subject dependent features of CEOAEs.

Linear Discriminant Analysis (LDA):

LDA is a supervised pattern recognition method whose aim is to find the best linear discrimination between two (or more) groups of statistical units defined into a multivariate space. In the case of two *a priori* defined A and B groups, LDA generates a linear function of the "symptoms" variables $X_1 - X_n$ of the form:

$$
Y = \sum_{i} A_i X_i \tag{1}
$$

so that the plane having as equation the {1} separates the elements pertaining to the A and B groups as neatly as possible (e.g. all the A group elements are above the plane and all the B group below).

Inferential Statistics

In order to generate statistical inferences from independent CEOAE observations, only one ear per subject was considered in the analysis. Statistical comparisons of determinism (DET) in CEOAE signals were performed by means on Student's t-test, ANOVA and linear discriminant analysis.

3. RESULTS

Figure 1. Amplitude of CEOAEs at low and high stimulation intensity.

Panels a) and b) contain the two waveforms (A, B) of typical CEOAE responses evoked by intensities of 35 and 80 dB, respectively. On the time axis, 20.48 ms. correspond to 512 digitized data points. The stimulation and the response recording procedures are detailed in the Methods section. The vertical lines at 7 ms mark the exhaustion of the click ringing artifact and the starting point of the analyzed signals. The inset to panel a) contains the same signals amplified by a factor seven, corresponding to the approximate ratio of the total amplitudes at 80 and 35 dB.

Figure 1 shows CEOAE responses elicited by low (35 dB, panel a) and high (80 dB, panel b) stimulation intensities, the latter being in the region of signal saturation. In clinical studies [12, 13], CEOAE responses are evoked by high intensity stimuli (>65 dB), and the hearing function is evaluated in terms of the waveforms reproducibility. This is indicated by the so called REPRO variable, corresponding to an estimate, on a 0-100 scale, of the Pearson correlation between two CEOAE digitized waveforms (A, B) recorded in alternating sampling times. For the 35 dB stimulus the resulting signals are barely distinguishable from the baseline noise and the two waveforms are quite poorly correlated (REPRO = 4.4 at 35 dB, to be compared with REPRO = 99.1 at 80 dB). A pictorial view of the chaotic nature of the signals elicited by low stimulation intensities is provided in the inset to panel A. As shown in Figure 1, going from a very low stimulus intensity (a) to the CEOAE saturating phase (b) the signal increases both in amplitude and in organization: an irregular and noisy pattern (see also the inset to panel a) changes into a markedly oscillatory behavior. It should be noted that, by virtue of RQA, attention may exclusively focus on the variation in the signal ordering upon increasing the stimulation intensity, and any change in variance and amplitude is ruled out.

Figure 2 reports the changes of the deterministic character (DET) of CEOAEs from normal subjects , at click intensities from 35 to 80 dB.

Figure 2. Dependance of CEOAEs dynamics on stimulation intensity.

Each point indicates the average (and St Dev) values of determinism measured on the recurrence plots of signals recorded and analyzed under identical conditions from nine normacoustic subjects (see the Methods section). The stimulation intensity range of increasing determinism, marked by (B), is flanked by a subthreshold (A) and a saturation (C) region, limited by the vertical lines at 41 and 59 dB, respectively.

For all subjects three different phases can be distinguished in the DET changes: a first phase (A) corresponds to a sub-threshold stimulation; a second phase (B), corresponding to a steady increase in determinism, and a third phase (C), where DET does not change with the increasing stimulus intensity. During phase A the signals appear quite noisy, while phase C corresponds to quasi-harmonic, extremely ordered signals (see also Fig. 1a, b). The boundaries of the B phase were estimated according to the following procedure: first, for each subject and for each possible couple of click intensities, we fitted the DET values (shown as averages in Figure 2) to straight lines; then, we chose the click intensity couple maximizing the average slope of the straight lines, namely 41 and 59 dB. The corresponding linear fitting of DET for each subject is reported in Table 1.

Table 1 Scaling of determinism with stimulation intensity.

The DET values (shown as averages in figure 2) were fitted to straight lines for each subject in the (B) region in figure 2, according to the expression: DET = Slope*dB + Intercept. The regression parameters and R square values are listed in columns 2, 3 and 4, respectively. Notice the absence of any correlation between slope values and subjects' age (Pearson $r = 0.33$), and the similar quality of the linear fitting indicated by the R square values.

The clear linear relations (scaling) between %DET and stimulus intensity, observed for all subjects in the intermediate phase (B), do not allow, under our conditions, to distinguish among individuals in that stimulus intensity range, at odds with the other two phases (see below). This points to a relative invariance of the (B) phase even in the presence of relatively large deviations in slopes (0.91 to 2.50), and suggests the presence of similar self-organization mechanisms in all individuals possibly based upon the sequential involvement of different portions of the auditory periphery. A previous study [28] indicated that in the saturation phase the CEOAEs show a marked individual character and act as a sort of "auditory fingerprint" of each individual. In order to contrast the common trend observed in the scaling phase (B) with the individual character of the saturation phase (C), first we generated, for each phase, the space of the RQA variables, REC, DET and ENT. Then, the matrix having as rows the signals and as columns the corresponding RQA variables, was subjected to a principal component analysis (PCA). The percentage of total variability explained by the first two principal components, was 85.42% for PC1 and 9.23% for PC2, corresponding to an almost complete RQA description of the signals.

To highlight differences (if any) in the discrimination ability of the B and the C phases, independent analyses were carried out for the two phases. Then, the signals were projected onto a principal component space derived from a previous set of 78 responses of normal, adult subjects, recorded (under identical conditions) at high stimulus intensity [28], acting as a reference set. Figure 3 reveals that the intemediate phase (panel a) does not allow to recognize signals pertaining to the same individual, while clusters of signals of the same individual clearly appear in the saturation phase (panel b).

Figure 3. CEOAE responses of normal subjects in a PC1/PC2 plane.

Panels a) and b) refer to responses evoked by stimulations in the scaling and in the saturation phase (see Figure 2), respectively. The same symbol is used for responses of the same ear of the same subject in different experimental sessions. Each response was separately analyzed and plotted in the plane of the first two principal components (PC1, PC2) extracted from the RQA variables (REC, DET, ENT) in a previous set of 78 signals (learning set) recorded, under identical conditions, in the saturation phase of the stimulus intensity [28].

The lack of subject-related features in the B phase of Figure 2 suggests the same type of scaling of DET in all subjects, even with some differences in the slope due to factors related to biological and measurement variability. This general resemblance points to a similar mechanism of progressive involvement of the corresponding structures in the auditory system by stimuli of increasing intensity. This phenomenon could be analogous, in a way, to the progressive magnetization of paramagnetic materials subject to a static, magnetic field.

Given the presence in the plateau phase of markedly individual-specific features [28] , it is important to validate whether these features can be evidenced even in the sub-threshold phase, since that may reflect some morphoanatomical, stimulus independent, peculiarity of individual systems. A statistical confirmation of the latter conjecture lies in the significant correspondence in the relative positions of single signals in the A and C phases. This link was demonstrated by: i) computing all the differences in determinism between any of the $(9*8/2 = 36$ possible couples of the nine signals both at the initial (41 dB) and at the final (59 dB) point of the scaling phase in figure 2, and ii) checking for the mutual correlation between the ordered series of corresponding differences. The two series scored a Pearson correlation of 0.77, to be compared with the value $=$ 0.05 scored upon arbitrarily shuffling the order of their elements. Thus, passing from the A to the C phase, the significant invariance of the mutual location of the different individuals indicates that, in principle, individual features in the structural organization of the auditory system are distinguishable at both the sub-threshold and saturation phases.

In order to give an anatomical (and possibly functional) interpretation of this behavior we investigated whether it is possible to discriminate, by means of the same analytical procedure, the CEOAE responses of two different classes of pathologies, Conductive Hearing Losses (CHL) and Sensorineural Hearing Losses (SHL), referring to malfunction of the middle and of the inner ear, respectively [2, 20]. The results reported in Table 2 indicate that this is true at all the studied stimulation intensities, namely 50, 65, 70 and 80 dB. Table 2, also indicates that: i) signals from the CHL class, when compared with the normal group for the amount of determinism (DET), showed significantly different; ii) a repeated measures ANOVA computed over all the four intensities indicates a marked effect of decreased determinism, passing from normal to CHL; iii) no statistically significant difference between the normal and the SHL groups was scored by both t-test and ANOVA run under identical conditions.

Table 2 Difference in DET between pathological and normal CEOAEs.

The table reports the difference in DET between the two groups of pathological (Sensorineural Hearing Loss, SHL, and Conductive Hearing Loss, CHL) signals studied in this work (row 1), as well as between each ot two pathologies and the control group (rows 2,3). In all cases differences were estimated at each of the four studied click intensities (50, 65, 70 and 80 dB) by t-test (columns 2-5) and by repeated measures ANOVA (column 6). In parenthesis the significance (p) is reported.

Thus, the possible hypothesis that only SHL, being directly related to the function of the hair cells, could significantly change the CEOAEs dynamical properties and make them distinguishable from normal responses was contradicted, and the role played by the middle ear in determining the overall shape of CEOAEs emphasized. The combined influence of outer hair cells and middle ear on the CEOAEs dynamical features is confirmed by representing in a principal component space the information in the whole set of RQA variables for the two groups of pathological signals under different stimulation regimes.

Figure 4. Clustering of CEOAE responses in normal and pathological subjects.

The CEOAEs responses elicited at 50 (upper panel) and 80 dB click intensity are represented in the same PC1/PC2 plane as in Figure 3. In both panels, the conductive hearing loss, CHL (triangles), signals lie quite apart from those concerning both normal subjects (circles) and sensorineural hearing losses, SHL (squares). CHL and SHL responses were distinguished from each other with 84% and 90% correctness at low (50 dB) and high (80 dB) click intensity, respectively, by a linear discriminant analysis.

In Figure 4 the clustering in a reference PC1,PC2 plane (identical to the Figure 3 one) of CEOAEs from normal and pathological subjects, according to the same procedure applied to the data in Figure 3, is reported for the two extreme stimulation conditions, 50 (upper panel) and 80 dB (bottom panel). Under both conditions the data show that signals of the CHL class, in contrast to SHL, fall clearly outside the region of physiological variability of healthy subjects, and linear discriminant analysis scored 84% and 90% correctness in separating CHL from SHL signals at 50 and 80 dB, respectively. As a consequence, discrimination between CHL and SHL is possible in both cases, although easier at the higher stimulation regime.

4. DISCUSSION

In clinical applications CEOAEs are usually studied at stimulation intensities of 80 dB, a "response saturation" region (see Figure 2) where any decrease of the REPRO variable, namely the Pearson correlation between the A, B waveforms, can be directly associated to a decreased response intensity, and hence to a sort of hearing deficit. At lower stimulation intensities, the less favourable signal/noise ratio induces an overall decrease of REPRO values and makes difficult the study of response signals. In addition, at these stimulus levels it is difficult to evaluate any physiological and mechanical factors on the global performance of the auditory system [1, 21].

We have tackled this problem by taking advantage of the remarkable independence of the Recurrence Quantification Analysis (RQA) from changes in signal amplitudes, illustrated in Figure 5. The figure shows, in contrast to REPRO, the much lower sensitivity to click intensity of REC, the basic RQA variable. Thus, the relatively stable trend of REC allows the estimation of any significant change in the DET (see the Methods section and Figure 2) at stimulation levels usually out of the range of clinical and basic investigations.

Figure 5. Changing features of CEOAE responses at different stimulation intensities.

For each click intensity, averages reckoned over signals from 9 normoacoustic subjects are reported (see also Figure 2). The vertical axis is adimensional: CEOAE is the integral of the rectified response signals normalized to the maximum value in the explored click intensity range; REPRO is the Pearson correlation coefficient between the A,B waveforms (see Fig. 1; % REC is the basic quantifier of recurrence density worked out by ROA (see the Methods section).

In previous papers [27, 28], we could demonstrate that, at high stimulation intensity, appears a marked degree of individuality in both adult and newborn normacoustic subjects, producing distinguishable CEOAEs in terms of RQA variables. In the present work we explored a click intensity region well below the response saturation for normacoustic and hearing impaired subjects. In the former case, our observations can be summarized as follows:

1. A progressive increase in DET of CEOAE signals scaling with the increasing click intensity, in a subject invariant fashion. However, in different subjects, different plateaus are reached starting at about 60 dB stimulation intensity, and such differences correlate with those estimated at very low intensity.

2. A clear separation between a common and a subject dependent portions in the dynamical features of CEOAEs, as outlined by statistical analysis.

A plausible interpretation is that the common portion reflects the recruitment of an increasing number of outer hair cells: in other words, we postulate that the increasing determinism corresponds to an increased synchronization of the active elements processing the acoustical stimuli, while the subject-dependent portion may be related to specific features of the passive, conductive section of the auditory system.

In an audiological clinical context, the term "recruitment" indicates the copresence of *hyperacusis* (super-sensitivity to normal sounds) and fuzzy (poor frequency discrimination) hearing, namely the most common symptom of neurosensorial hearing loss. In fact, assuming that: i) each hair cell belongs to a functional unit sensitive to specific frequency band and contributing to the intensity perception by a "unit" loudness, and ii) in case of malfunction of some cell the adjacent ones are "recruited" for an extra work-load added to their own one, numerous phenomena of this sort produce an exceedingly loud and noisy sound (and speech)

perception. To account for the higher determinism in CEOAE responses at higher stimulation intensities, we actually used recruitment in a broader sense, namely to indicate an increasing number of physiologically coordinated modules. Although this assumption seems fully justified by the analogy with similar situations occurring in many other systems, particularly in the context of motor units activation [8], it leaves unclarified, however, the basic question concerning the identification/location of the involved modules in the organ of Corti.

In the case of CEOAEs responses from hearing impaired subjects, the pathological events involving different regions of the auditory system were helpful to confirm in the middle ear the origin of the individual features previously reported for normal hearing responses [28]. Only the Conductive Hearing Losses (related to the middle ear structures) were clearly distinguishable from the control group in a global analysis of CEOAEs determinism at all the considered stimulation intensities The Sensorineural Hearing Losses (related to the inner ear structures) were responsible for relatively minor changes in the signals, mainly in the scaling region (B region in Figure 2). This point is more evident by examining the data from Figure 4, where the differences between the SHL, CHL and Controls are represented in a principal component space and appear to be more significant at a stimulation level of 80 than at 50 dB.

An immediate use of these results and, in particular, the unequivocal distinction between SHL and CHL, could be envisaged in clinical applications. In fact, if SHL and CHL can, in principle, be discriminated also by the REPRO variable, the information on the signal dynamics extracted through the RQA variables appears more reliable since: i) it is less affected by noise and/or possible instrumental flaws over a wide range of stimulation intensities, and ii) it is solidly rooted on the global morphoanatomical features of the auditory system.

A future development of our work includes the use of frequency- instead of intensitymodulated click stimuli, to characterize the deterministic behavior of different sub-populations of hair cells corresponding to specific critical frequency bands, as suggested by current modelsimulation approaches to cochlear function [1, 7, 21].

ACKNOWLEDGMENTS

This work was partially supported by grants of the Italian M.U.R.S.T. (60%) to A.C.

Note

The programs for RQA are available from http://homepages.luc.edu/~cwebber/ in self-extracting file format (RQA62.EXE).

5. REFERENCES

- 1. Allen JB. Nonlinear cochlear signal processing. In: Physiology of the Ear. Second Edition. edited by Jahn AF, and Santos-Sacchi J, 2001, p. 393-442.
- 2. Bamiou DE, Savy L, O'Mahoney C, Phelps P, Sirimanna T. Unilateral sensorineural hearing loss and its aetiology in childhood: the contribution of computerised tomography in aetiological diagnosis and management. Int J of Pediatric Otorhinolaryngology. 51(2): 91–99, 1999.
- 3. Bartholomew DJ. The foundation of factor analysis. Biometrika. 71: 221-232, 1984.
- 4. Carvalho S, Büki B, Bonfils P, Avan P. Effect of click intensity on click-evoked otoacoustic emissions waveforms: implications for the origin of emissions. Hearing Research 175: 215- 225, 2003.
- 5. Colosimo A, Giuliani A, Mancini AM, Piccirillo G and Marigliano V. Estimating a cardiac age by means of heart rate variability. Am J Physiol. 273: H1841-H1847, 1997.
- 6. Eckmann JP, Kamphorst SO, and Ruelle D. Recurrence plots of dynamical systems. Europhys Lett. 4: 973–977, 1997.
- 7. Eguiluz VM, Ospeck M, Choe Y, Hudspeth AJ and Magnasco MO. Essential Nonlinearities in Hearing. Phys. Rev. Lett. 84: 5232-5235, 2000.
- 8. Farina D, Fosci M, and Merletti R. Motor unit recruitment strategies investigated by EMG variables.J Appl Physiol 92: 235–247, 2002.
- 9. Gao J and Cai H. On the structures and quantification recurrence plots. Phys Lett A. 270: 75–87, 2000.
- 10. Giuliani A, Piccirillo G, Marigliano V, Colosimo A. A non-linear explanation of aginginduced changes in heartbeat dynamics. Am J Physiol. 275: H1455-H1461, 1998.
- 11. Giuliani A, Sirabella P, Benigni R, and Colosimo A. Mapping protein sequence spaces by recurrence quantification analysis: a case study on chimeric structures. Protein Eng. 13(10):671-678, 2000.
- 12. Hatzopoulos S, Petruccelli J, Pelosi G, Martini A. A CEOAE screening protocol based on linear click stimuli: performance and scoring criteria. Acta Otolaryngol. 119(2): 135, 1999.
- 13. Hatzopoulos S, Tsakanikos M, Grzanka A, Ratynska J, and Martini A. A comparison of neonatal CEOAE responses recorded with linear and QuickScreen protocols. Audiology. 39(2): 70-9, 2000.
- 14. Hood LJ, Berlin CI, Hurley A, Cecola P, Bell B. Controlateral suppression of transientevoked otoacoustic emissions in humans: intensity effects. Hear Res. 101:113-118, 1996.
- 15. Kemp DT. Stimulated otoacoustic emissions from within the human auditory system. J. Acoust. Soc. Am. 64: 1386-1391, 1978.
- 16. Leeuw AR, and Dreschler WA. The relation between otoacustic emissions and the broadening of the auditory filter for higher levels. Hear Res. 126: 1-10, 1998.
- 17. Manetti C, Ceruso MA, Giuliani A, Webber CL and Zbilut JP. Recurrence quantification analysis as a tool for characterization of molecular dynamics simulation. Phys. Rev. E. 59: 992-998, 1999.
- 18. Norton SJ, Gorga MP, Widen JE, Folsom RC, Sininger Y, Cone-Wesson B, Vohr BR, Mascher K, and Fletcher K. Identification of neonatal hearing impairment: transient evoked otoacoustic emission, distortion otoacoustic emission, and auditory brain stem performance. Ear Hear. 2: 508–528, 2000.
- 19. Probst R, Lonsbury-Martin BL, and Martin GK. A review of otoacoustic emissions. J Acoust Soc. 89: 2027–2067, 1991.
- 20. Qiu WW, Yin S, Stucker FJ. Critical evaluation of deafness. Auris Nasus Larynx. 26 (3): 69– 276, 1999.
- 21. Robles L, Ruggero MA. Mechanics of the Mammalian Coclea. Physiol Rev. 81: 1305-1350, 2001.
- 22. Strecker Hesse PA, Gerken GM. Amplitude-intensity functions for auditory middle latency responses in hearing-impaired subjects. Hearing Research 166:143-149, 2002.
- 23. Webber CL and Zbilut JP. Dynamical assessment of physiological systems and states using recurrence plot strategy. J Appl Physiol. 76: 965, 1994.
- 24. Wit HP, van Dijk P, Avan P. Wavelet Analysis of real ear and synthesized click-evoked otoacoustic emissions. Hear Res. 73: 141-147, 1994.
- 25. Zbilut JP, Giuliani A, Webber CL. Recurrence quantification analysis and principal components in detection of short complex signals. Phys Lett A. 237: 131-135, 1998.
- 26. Zbilut JP, Webber CL Jr, Colosimo A, Giuliani A. The role of hydrophobicity patterns in prion folding as revealed by recurrence quantification analysis of primary structures. Protein Eng. 13(2): 99-104, 2000.
- 27. Zimatore G, Giuliani A, Parlapiano C, Grisanti G, and Colosimo A. Revealing deterministic structures in click-evoked otoacoustic emissions. J Appl Physiol. 88: 1431-1437, 2000.
- 28. Zimatore G, Hatzopoulos S, Giuliani A, Martini A, Colosimo A. Comparison of transient otoacoustic emission (CEOAE) responses from neonatal and adult ear. J Appl Physiol. 92: 2521-2528, 2002.