Chapter 3

Threshold Based Acceleration Change Index

3.1 Background

Threshold Based Acceleration Change Index (TACI) is the modified form of acceleration change index (ACI). Garcia-Gonzalez *et al* (2003) proposed ACI for characterizing the dynamics of cardiac inter-beat interval time series. Ashkenazy and coworkers used the sign of difference of the time series (sign series) as an intermediate time series in their scaling analysis of RR time series (Ashkenazy *et al.* 2000). They decomposed the original time series into two sub series: magnitude series $m_i=|\Delta RR_i|$ and sign series $s_i=\mathrm{sign}(\Delta RR_i)$. They used detrended fluctuation analysis (DFA) (Peng *et al.* 1995a) on sign series to obtain scaling exponent. They investigated that sign series is robust in handling complex signals, which include spikes. Instead of this approach, Gonzalez *et al* (2003) proposed acceleration change index (ACI) obtained from the sign of differences of the RR time series. A theoretical study shows an expression that relates ACI to the autocorrelation function (ACF) of the time series (Garcia-Gonzalez *et al.* 2003). The mathematical background of relation between ACI and ACF of the time series has been described in detail by Garcia-Gonzalez *et al* (2003).

ACI index was obtained from sign of differences of RR time series, which characterizes the dynamics of zero crossings, i.e., the sign of differentiated time series (*DX*) is taken as '+1' (if $DX>=0$) and its sign is taken as '0' (if $DX<0$). ACI increases only when a local maximum is followed by local minimum or vice versa. It detects the presence of very high frequency content on the HRV time series when the tachogram is analyzed. ACI is fast, robust in the presence of artifacts because of its insensitivity to fast changes due to sign operation and easy for the physicians to understand.

In order to understand the information provided by the ACI, Gonzalez et al tested the ACI for uncorrelated random data, sinusoidal time series and self-similar and chaotic time series. By considering time series with ACF equal to zero except for the lag '0', they theoretically demonstrated that the value of ACI_∞ is 0.625 for uncorrelated random variables. They also investigated that this result is independent of variance and histogram of the time series, with the constraint that probability distribution function should be the result of monotonic transformation. In order to verify this result, they generated 1000 realization of uncorrelated random data with uniform and normal probability distributions functions having 256, 1024, 16384 and 131072 samples. They observed that mean value of ACI is in good agreement with the theoretical value of 0.625 and standard deviation of the ACI decreases with the increase in number of samples.

The following relation gives the autocorrelation function for a sinusoidal wave having frequency f

$$\rho(n) = \cos(2\pi f n) \tag{3.1}$$

Gonzalez *et al* (2003) tested the above equation for sinusoidal signals with random initial phase at ten different linearly spaced frequencies from 0.05 to 0.5 Hz. 1000 realizations were generated for each frequency with data samples 256, 1024 and 16384. They investigated that for frequencies lower than 0.25 Hz, the ACI is zero and increases gradually with the increase in the frequency and become exactly 1 at 0.5 Hz. A decrease in standard deviation with the increase of number samples was observed. Gonzalez *et al* (2003), also calculated ACI_∞ of fractal Brownian noise (Togo and Yamamoto 2000) for 100 different β linearly spaced from 1.01 to 2 using the relation

$$\begin{aligned} \rho_d(n)\big|_{FBN} &= \rho(n)\big|_{FGN} \\ &= \frac{|n+1|^{\beta-1} - 2|n|^{\beta-1} + |n-1|^{\beta-1}}{2} \end{aligned} \tag{3.2}$$

Moreover, they generated 100 realizations of fractal Brownian noise (FBN) with known β having values heal using simulator proposed by (Paxson 1997) for 256, 1024, 16384 data samples. Mean and standard deviation of ACI were computed and results were compared with ACI_∞. They investigated that standard deviation decreases with increase in number of data samples. Gonzalez *et al* (2003) also applied ACI on the time series of logistic map, which is a chaotic process (Ott 1993). The logistic map can be expressed by using the recursive relation:

$$x_{n+1} = rx_n(1 - x_n) \qquad r \in [0,4] \tag{3.3}$$

where r varies from 0 to 4 and initial value of x was restricted between 0 and 1. Gonzalez et al tested ACI four thousand different values of r ranging from 0.01 to 4 and for

50 different initial values of x ranging from 0.01 to 0.99. In order to remove transitory effects last five hundred samples were employed to calculate ACI. They observed that for $r < 3$, ACI=0, for $3 < r < 3.68$ ACI varies with value of r, for $r = 3.84$, ACI =0.5.

When applied to heart rate signals Gonzalez et al studied that variation of ACI due to the change of the respiratory sinus arrhythmia (RSA), variation of ACI due to the exercise, variation of ACI from diurnal to the nocturnal period and for classifying healthy subjects and post-infarct patients. In order to study the dependence of respiratory sinus arrhythmia (RSA), they investigated that how ACI is affected by the way the subjects breathe. Twenty subjects (12 males and 8 females) aged 30.9 ± 5.1 years participated in the study. Each ECG recording was of five minute duration and was sampled at 500 Hz. Mean and standard deviation of ACI was computed while the subjects were breathing at will, breathing periodically and breathing synchronously with frequency modulated signal. The results demonstrated that when breathing periodically or quasi-periodically, the ACI was lower than when breathing at will.

To study the dependence of ACI on physical effort, Gonzalez *et al* (2003) recruited twenty male healthy subjects in the test and measured RR interval time series for 3 minutes before starting the exercise, 3 minutes during the maximal effort and 3 minutes after the recovery. Garcia-Gonzalez *et al* (2003) investigated that ACI increases during exercise and remains almost same before exercise and after recovery. To study the variation of ACI for night and day periods, Garcia-Gonzalez *et al* (2003) obtained RR interval time series data of 18 subjects (13 males and 5 females) aged 34.4 ± 8.5 years. ACI of RR interval time series obtained during day and night periods was computed. The results revealed that ACI was lower during night period as compared with the day period. In order to assess whether ACI can discriminate between healthy and post-infarct patients subjects, a groups of post-infarct patients (seven males and two females) aged 63.4 ± 7.3 years who had suffered from MI one month previously and a group of healthy subjects (seven males and two females) aged 64.7± 9.3 years without any cardiac complication in their clinical history were taken. For each subject ECG recording of 5 minutes duration were acquired and sampled at 2 kHz. RR intervals were extracted and characterized by using, the mean RR, SDNN, RMSDD, LF/HF ratio and ACI. Garcia-

Gonzalez *et al* (2003) investigated that ACI was lower in control groups than in PI groups and no other index except ACI provide significant difference between the groups.

3.2 Threshold Based Acceleration Change Index (TACI)

The classification ability of acceleration change index (ACI) for certain heart diseases such AF and neurodegenerative diseases (ALS, Huntington and Parkinson) was poor. To improve the classification ability of ACI, threshold hold based acceleration change index (TACI) (Arif and Aziz 2005; Aziz *et al.* 2004; Aziz *et al.* 2005) was proposed. Following is the procedure to calculate threshold based acceleration change index.

Step1. Given a time series *X*, the differentiated time series (*DX*) is obtained as:

$$DX(n) = X(n+1) - X(n), \qquad n = 1, \dots, N-1 \tag{3.4}$$

Where N is the total number of data points in the time series.

Step2. The differentiated time series (*DX*) is quantized into '-1' and '+1' and Sign of differentiated series (*SDX*) is generated. *SDX* is '-1' if $DX < T$ and '+1' if $DX \geq T$. *SDX* series in TACI becomes similar to ACI series if the value of the threshold T is equals to zero.

Step3. Starting from n=2 to n=N, the sign change (SC) series is generated as follows

$$SC(j) = n \quad if\; SDX(n) \neq SDX(n+1) \quad j \in [1, M+1] \tag{3.5}$$

where j runs from 1 to M and M is the number of sign changes in *SDX*. SC (j) will always be a non-decreasing function of j. ACI proposed by Garcia-Gonzalez *et al* (2003) is a special case of TACI when $T = 0$. Sign change is counted in ACI when *DX* crosses zero. ACI gives the probability of a local maximum just after a local minimum or vice versa out of total occurrences of local maxima and minima. Where as in TACI, sign series is generated relative to a threshold value, not necessarily on a local maximum or minimum of the time series. It means that for a positive threshold, sign change may occur when the difference may still be positive but less than a threshold value.

Step4. Sign change series is differentiated to obtain DSC, which is the distance (in beats for heart rate signals and in strides for stride interval signals) between successive changes of sign of the *DX* time series:

$$DSC(j) = SC(j+1) - SC(j) \tag{3.6}$$

The threshold based acceleration change index (TACI) is defined as:

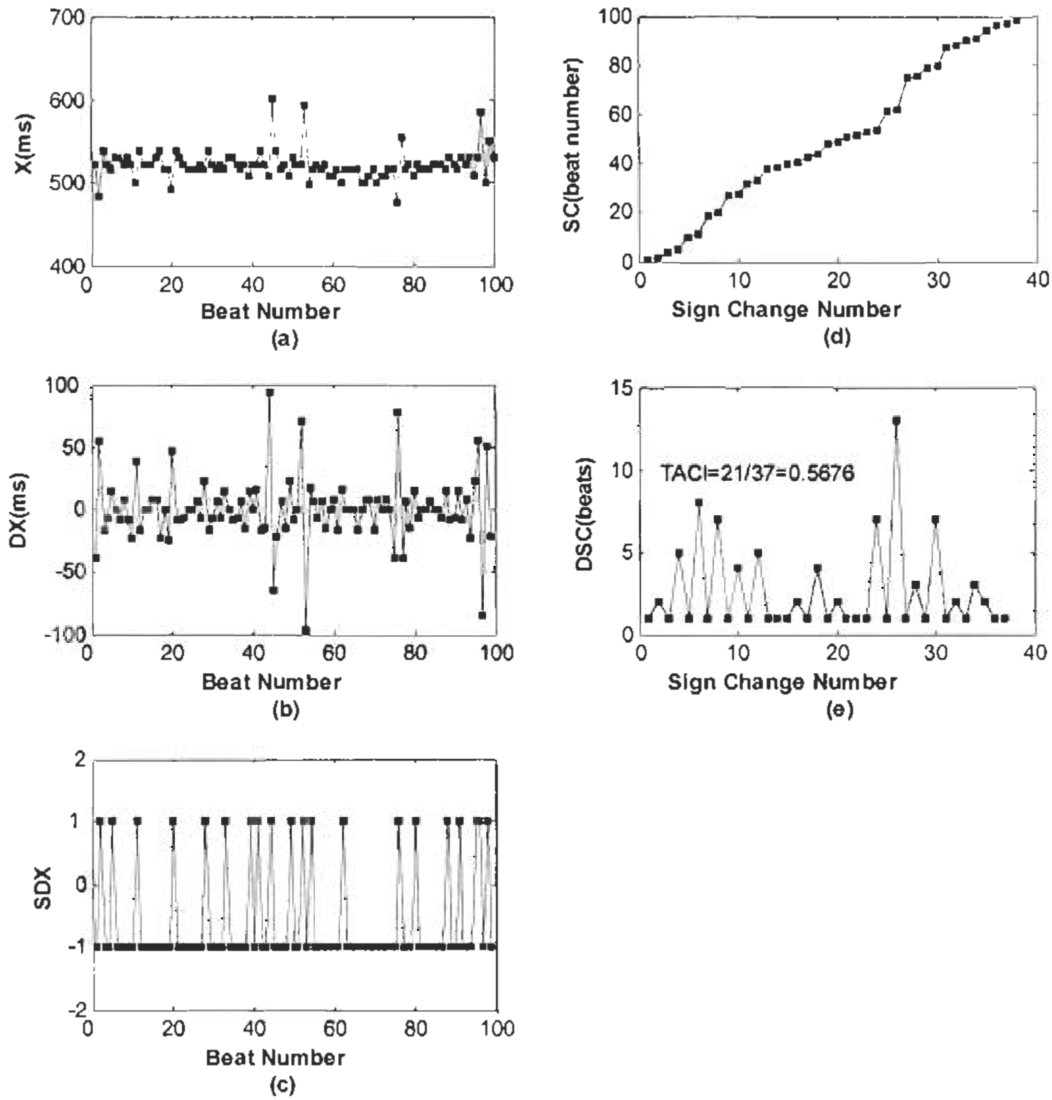


Figure 3.1: TACI computation (a) Original time series (X), (b) Differentiated time series (DX) (c) Sign of DX (SDX), (d) Sign change series (SC) and (f) Distance between successive sign changes.

$$ACI = \frac{K}{M} \tag{3.7}$$

Where K is the number of times DSC series equal to 1 and M is the total number of samples of DSC series. Figure 3.1 shows a graphical example how ACI was computed from a time series. If we analyse the local behaviour of three consecutive samples of SDX (a series of '1' or '-1'), K increases only when sequence {-1,1,-1} or {1,-,1,1} is present and M increases when the sequence {-1,1} or {1,-1} is present.

3.3 Data Sets

3.3.1 Cardiac Interbeat Interval Time Series

The cardiac inter beat interval (RR interval) time series data was taken from Physionet database (http://www.physionet.org). The data for normal sinus rhythm (NSR) subjects was taken from 24 hour holter monitor recordings of 92 subjects (54 from RR-interval normal sinus rhythm database and 18 from MIT BIH normal sinus rhythm database) (Goldberger *et al.* 2000). The measured group consists of 35 men and 37 women, aged 54.6±16.2 years (mean ± SD) and range of 20-78 years. ECG data was sampled at 128 Hz.

The data for congestive heart failure (CHF) group was obtained from 24 hour holter monitor recordings of 44 subjects (29 from RR interval congestive heart failure database and 15 from MIT-BIH Bidmic congestive heart failure database) (Goldberger *et al.* 2000). CHF group consists of 29 men and 15 women aged 55.5±11.4 (mean ± SD), range 22-78 years. Fifteen recording were sampled at 250 Hz and 29 recordings were sampled at 128 Hz. Atrial Fibrillation (AF) data was taken from "MIT-BIH Atrial Fibrillation database (afdb)" (Goldberger *et al.* 2000). The individual recordings are of 10 hours duration. The original analog recordings were made using ambulatory ECG recorders with a typical recording bandwidth of approximately 0.1 Hz to 40 Hz. The ECG data was sampled at 250 Hz.

Representative RR interval time series of healthy, congestive heart failure and atrial fibrillation subjects are shown in the Figure 3.2.

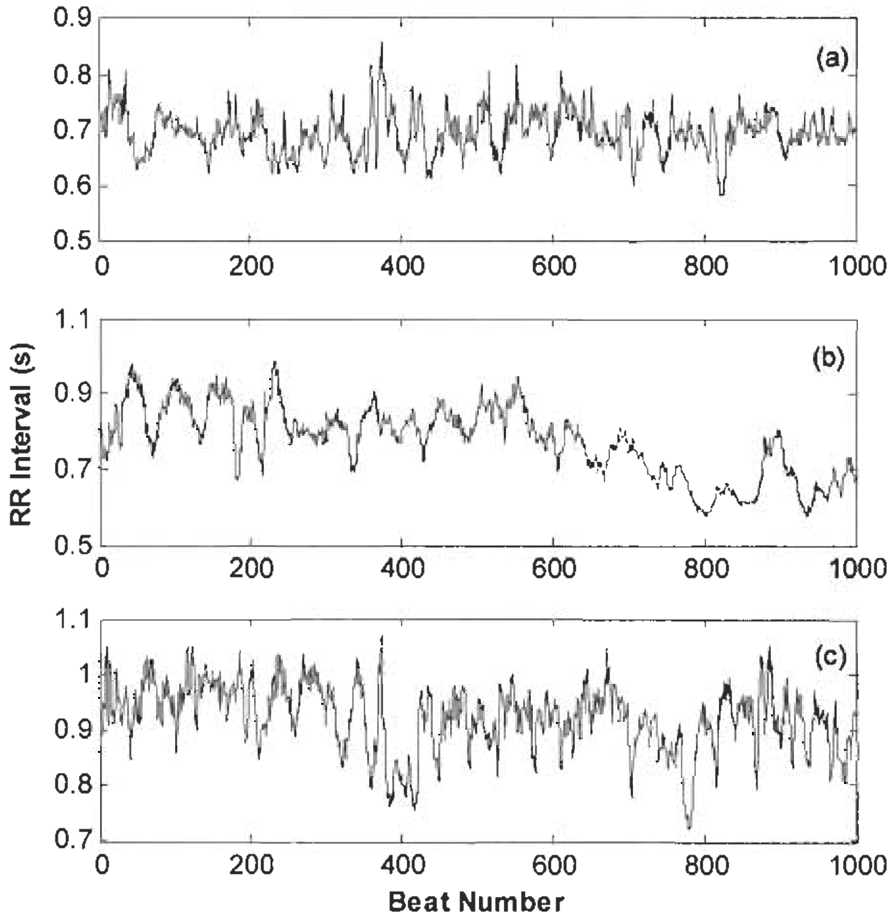


Figure 3.2: Representative RR interval time series of (a) NSR (b) CHF (c) AF Subjects.

3.3.2 Stride Interval Time Series

Data sets for analysis were taken from gait dynamics in neurodegenerative database (Goldberger *et al.* 2000). The database contains 64 recordings of gait from 16 healthy controls, 20 Huntington's disease subjects, 13 subjects with Amyotrophic lateral sclerosis and 15 subjects with Parkinson's diseases. Control group consists of (14 females and 2 males with age range 20-74), Huntington's disease subjects (14 females, 6 males and age range 29-71), ALS subjects (3 females, 10 males and age range 36-70) and Parkinson's diseases subjects (5 females, 10 males with age range 44-80). Subjects of all the four groups were recruited from the Neurology outpatient clinic at Massachusetts General Hospital (Hausdorff *et al.* 2000; Hausdorff *et al.* 1997). Subjects were instructed to walk at their normal pace along a 77 m long hallway for 5 minutes. Force sensitive switches (Hausdorff *et al.* 1995a) were placed in the subjects shoes, output of these switches provides a force applied on the floor. A 12-bit on-board analog-to-digital converter sampled the output of foot switches at 300 Hz. The digitized data was automatically analyzed to determine the initial contact time of each stride. Finally stride time interval (time from initial contact of one foot to subsequent contact of same foot) was determined for each gait cycle of walk from these signals.

Representative stride interval time series of control, ALS, Huntington and Parkinson disease subjects are shown in the Figure 3.3.

3.4 Applications of Threshold Based Acceleration Change Index

3.4.1 Simulation Studies

The behaviour of threshold based acceleration change index (TACI) for simulated time series (Uncorrelated random data and logistic map) was studied.

Forty realizations of 40000 data samples of uncorrelated random data having variance 0.04 were generated and TACI was computed using equation for various threshold values. The mean and standard deviations of TACI at different threshold values (-50 to 50 ms) were computed. At threshold zero, TACI has maximum value and a decrease in TACI was observed when the increase in threshold value in positive direction. Similar behaviour was observed for negative threshold value as shown in Figure 3.4. Although

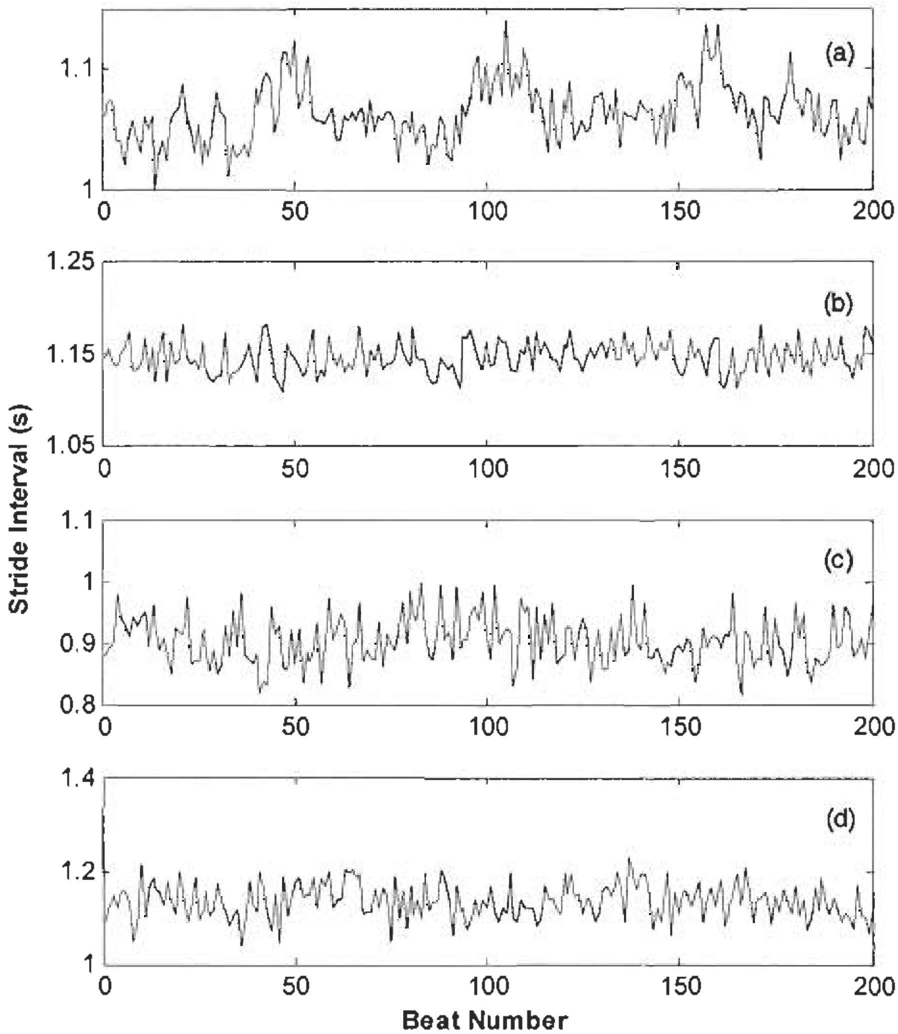


Figure 3.3: Representative stride interval time series of (a) Control (b) ALS (c) Huntington (d) Parkinson disease subjects.

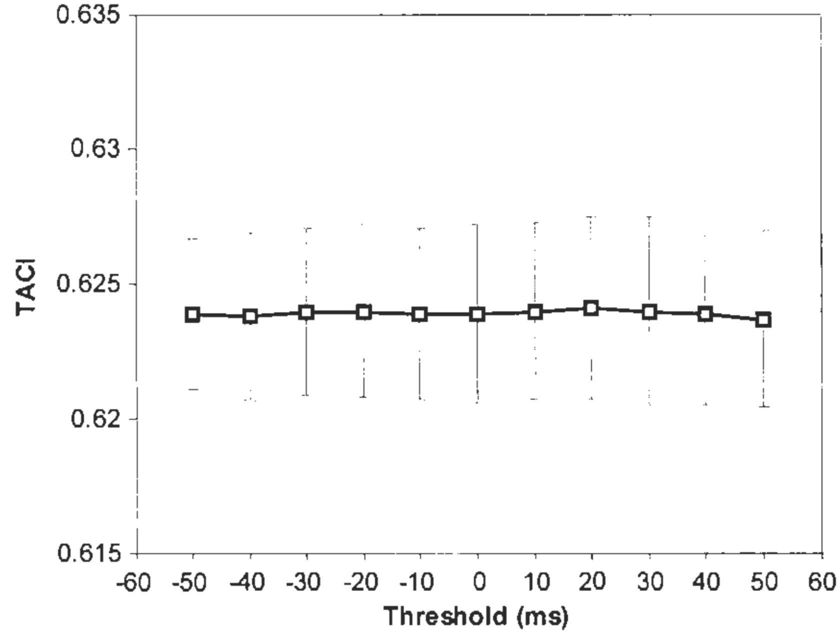


Figure 3.4: The value of TACI at different thresholds for uncorrelated random data.

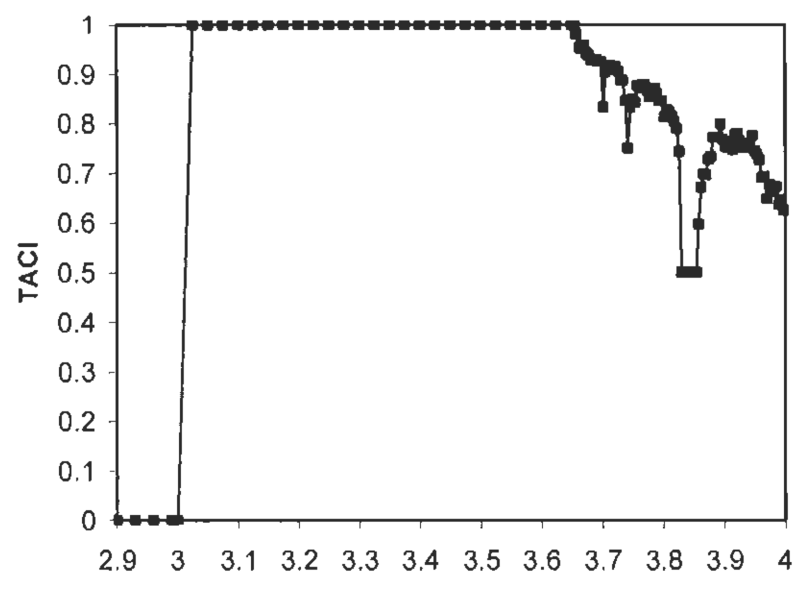


Figure 3.5: The value of TACI at threshold =50 ms for logistic map.

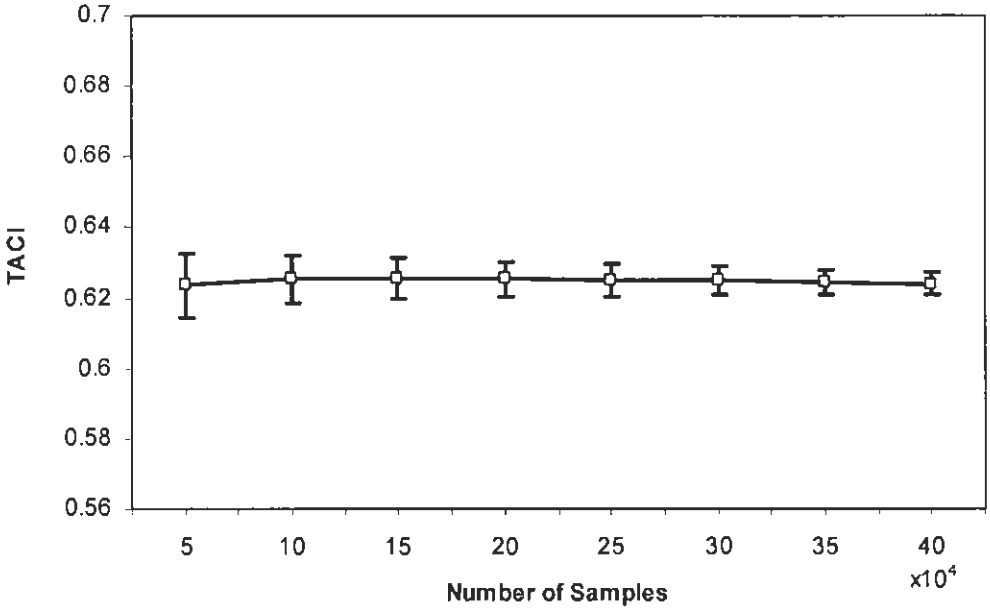


Figure 3.6: Mean ± SD of TACI at threshold of 20 ms for uncorrelated random data with number of data points.

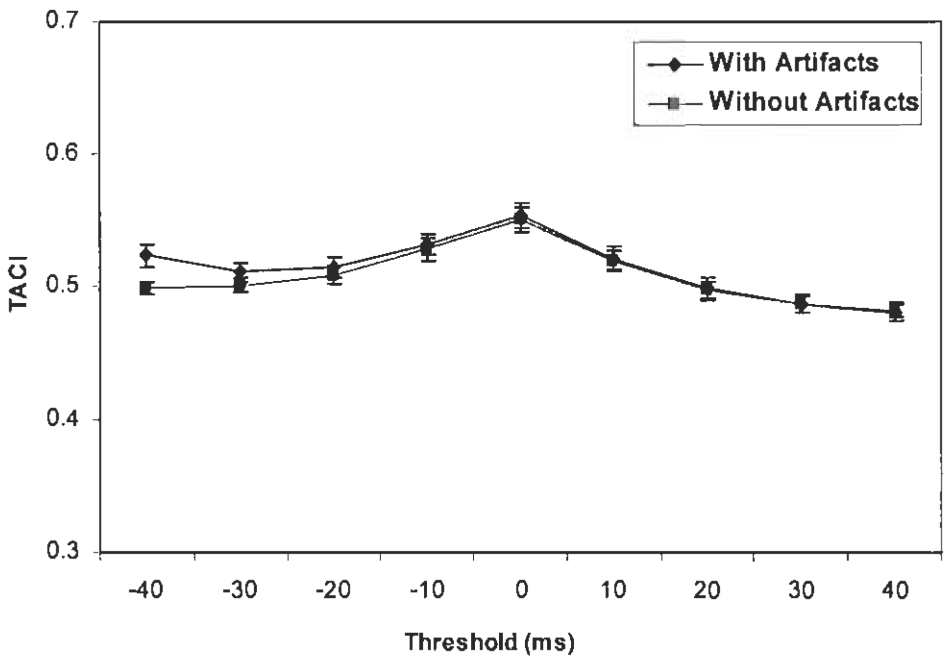


Figure 3.7: TACI for NSR subjects with and without artifacts at different threshold values.

TACI decreased for both positive and negative thresholds but this variation is not as much significant. However, by choosing higher threshold values, significant variation can be achieved.

TACI was also applied on time series of logistic map, which is a chaotic process (Ott 1993). The initial value of x is restricted between 0 and 1. TACI for different values of r ranging from 0.01 to 4, at different initial values of x was tested. The value of TACI was maximum at threshold 'T = '0' (ACI) and decreases for both positive and negative values of threshold. At threshold value of 50 ms, TACI=0 for $r < 3.006$, TACI=1 for $3.006 < r < 3.668$ and for $r > 3.668$, TACI depends on the value of r. Figure 3.5 shows the plot of TACI versus r at threshold value of 50 ms.

Figure 3.6 shows the effect of the data sample size on the values of TACI at threshold level of 20 ms for uncorrelated random data. Forty data sets have been used. The mean value of TACI does not change much with the increase in the data size; however the standard deviation reduces as we increase the size of data samples.

3.4.2 Analysis of Cardiac Interbeat Interval Time Series

Threshold based acceleration change index (TACI) was next applied to the cardiac interbeat (RR) interval time series derived from 24 hour continuous electrocardiographic (ECG) recordings of healthy subjects, subjects with congestive heart failure, a life-threatening condition, and subjects with cardiac arrhythmia, atrial fibrillation (Goldberger et al 2000).

In Figure 3.7, TACI for NSR subjects with and without artifacts are given at various threshold values. Artifacts are disturbances abnormal intervals, which do not belong to sinus rhythm and can differ in length from normal RR intervals. These can arise from rhythm disturbances (ectopic beats) or error in detection of QRS complexes of technical or physiological origin. Adaptive filtering algorithm described in Wessel et al (1994) was used for preprocessing of data. It clear from Figure 3.7, negligible difference between the values of TACI with and without artifacts was observed, thus showing robustness of TACI in the presence of artifacts.

For RR-interval time series of NSR, CHF and AF subjects, threshold based acceleration change index (TACI) was calculated at different threshold values. An unpaired student's t-test was used to check statistically significant differences between these groups. The degree of separation between groups for different TACI thresholds was quantified by obtaining the area under the receiver operator curve (McNeil and Hanley 1984). ROC curve is a graphical presentation of "sensitivity" versus "1-specificity", where sensitivity shows that how good is test at picking the patients and specificity is the ability of the test to pick the normal subjects. The area under the ROC (AUC) serves as well established index of diagnostic accuracy. Maximum value of AUC is 1 corresponding to perfect separation of two classes and a value of 0.5 means picking a class by a pure chance.

Table 3.1, shows the mean ± standard error of ACI (T = 0) and TACI for NSR and CHF groups. In the case of ACI when threshold T is zero, NSR group has the value of 0.5731±0.0106 and CHF group has the value 0.6152±0.0121. Difference in both groups is statistically significant (p-value is 0.0124) but the area under the ROC is 0.64 which is a moderate value. Maximum separation between NSR and CHF groups was obtained at the threshold value of 40ms (0.4872±0.0062, 0.5450±0.0083, $P=1.21 \times 10^{-07}$ and AUC=0.81). Higher value of AUC shows excellent separation between NSR and CHF groups. The values of TACI with error bars at threshold level of 40 ms and ACI with error bars are shown in Figure 3.8 for NSR and CHF groups

Mean ± standard error of ACI (T = 0) and TACI for NSR and AF groups are given for different threshold values. In the case of ACI (T=0), NSR group has the value of 0.5731±0.0106 and AF group has the value of 0.5706±0.0103. Difference in both groups is not statistically significant and the area under the ROC is 0.5794. But as we change the threshold value, we get better separation between these two groups. Maximum separation between these NSR and AF groups was obtained at the threshold value of 40 ms (0.4872±0.0062, 0.5869±0.0105, $P=4.06 \times 10^{-11}$ and AUC=0.95). The ideal value of AUC is 1.0. The value of AUC obtained in this case is very near to the ideal value. Hence we can obtain excellent separation between NSR and AF groups at the threshold value of 40 ms. The values of TACI at threshold level of 40 ms and ACI along with error bars for NSR and AF groups are shown in Figure 3.9.

Mean ± standard error of ACI (T = 0) and TACI for CHF and AF groups are given in. In the case of ACI, when threshold T is zero, CHF group has the value of 0.6152 ±0.0121 and AF group has the value of 0.5706 ± 0.0103. The difference between the

Table 3.1: TACI for NSR and CHF subjects at different threshold values.

T(ms)	NSR	CHF	p-value
40	0.4872±0.0062	0.5450±0.0083	1.21×10^{-07}
30	0.4968±0.0074	0.5440±0.0084	7.64×10^{-05}
20	0.5102±0.0083	0.5500±0.0083	1.76×10^{-03}
10	0.5358±0.0097	0.5707±0.0091	1.61×10^{-02}
0	0.5731±0.0106	0.6152±0.0121	1.24×10^{-02}
-10	0.5522±0.0089	0.5924±0.0112	5.78×10^{-03}
-20	0.5350±0.0079	0.5950±0.0128	4.85×10^{-05}
-30	0.5301±0.0077	0.6118±0.0139	1.70×10^{-07}
-40	0.5400±0.0086	0.6266±0.0144	2.41×10^{-07}

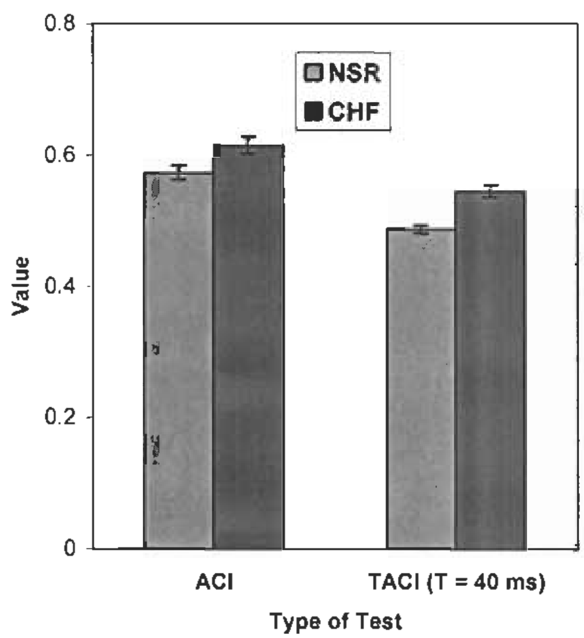


Figure 3.8: Comparison of ACI and TACI (T=40 ms) for NSR and CHF subjects

Table 3.2: TACI for NSR and AF subjects different threshold values and their corresponding p-values.

T(ms)	NSR	AF	p-value
40	0.4872±0.0062	0.5869±0.0105	4.06×10^{-11}
30	0.4968±0.0074	0.5834±0.0103	1.20×10^{-07}
20	0.5102±0.0083	0.5766±0.0104	1.80×10^{-04}
10	0.5358±0.0097	0.5712±0.0122	ns
0	0.5731±0.0106	0.5706±0.0163	ns
-10	0.5522±0.0089	0.5871±0.0124	ns
-20	0.5350±0.0079	0.6022±0.0120	1.02×10^{-04}
-30	0.5301±0.0077	0.6174±0.0119	6.36×10^{-07}
-40	0.5400±0.0086	0.6236±0.0121	1.15×10^{-05}

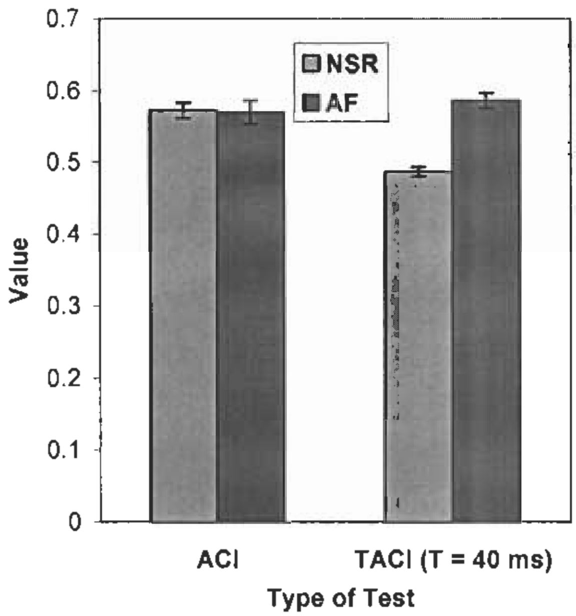


Figure 3.9: Comparison of ACI and TACI (T=40 ms) for NSR and AF subjects

Table 3.3: TACI for CHF and AF subjects different threshold values and their corresponding p-values.

T(ms)	CHF	AF	p-value
40	0.5450±0.0083	0.5869±0.0105	4.99×10^{-03}
30	0.5440±0.0084	0.5834±0.0103	8.29×10^{-03}
20	0.5500±0.0083	0.5766±0.0104	ns
10	0.5707±0.0091	0.5712±0.0122	ns
0	0.6152±0.0121	0.5706±0.0163	ns
-10	0.5924±0.0112	0.5871±0.0124	ns
-20	0.5950±0.0128	0.6022±0.0120	ns
-30	0.6118±0.0139	0.6174±0.0119	ns
-40	0.6266±0.0144	0.6236±0.0121	ns

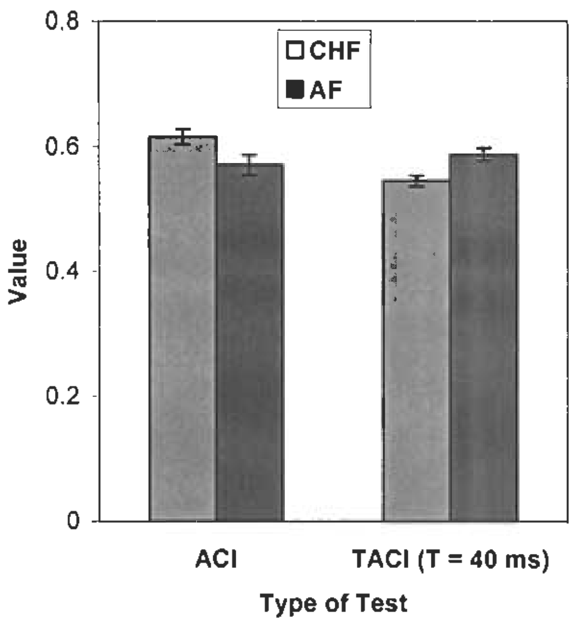


Figure 3.10: Comparison of ACI and TACI (T=40 ms) for CHF and AF subjects.

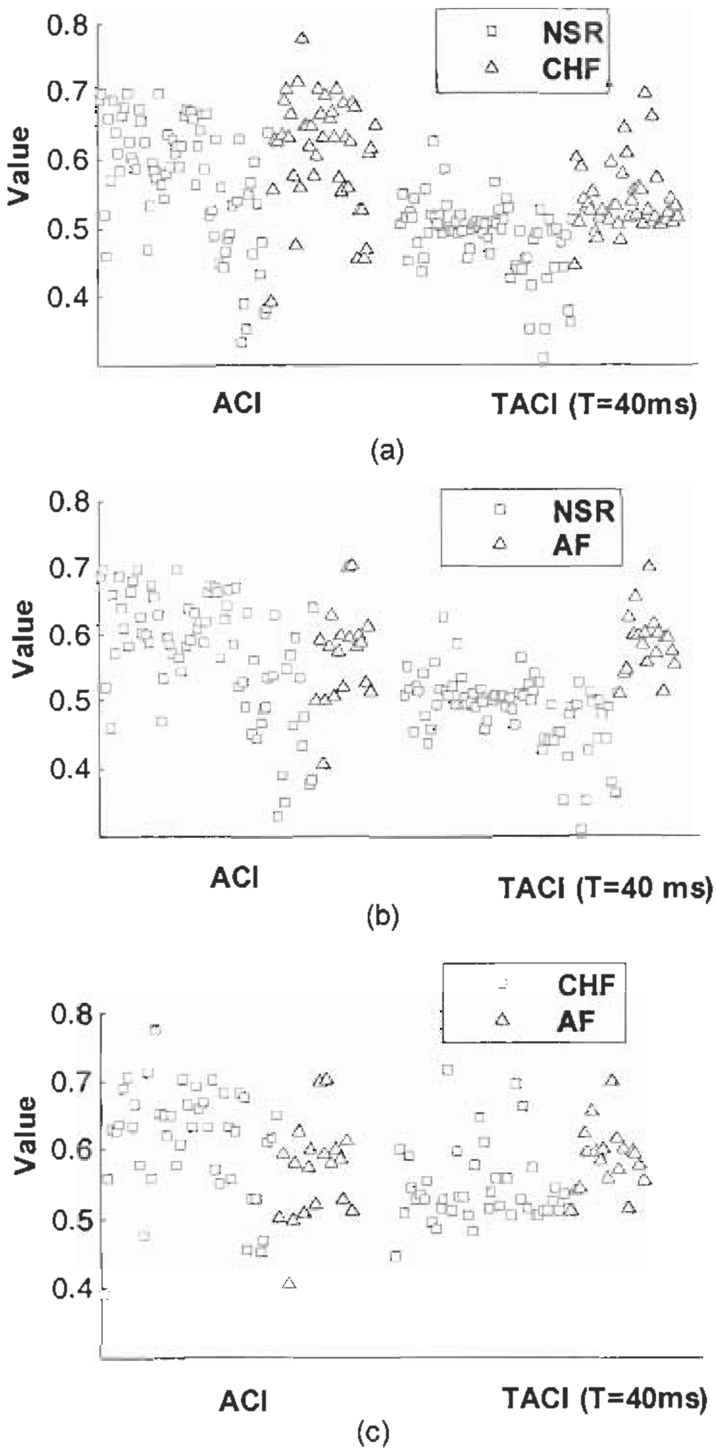


Figure 3.11:Comparison of scattergrams of TACI (a) NSR and CHF (b) NSR and AF (c) CHF and AF.

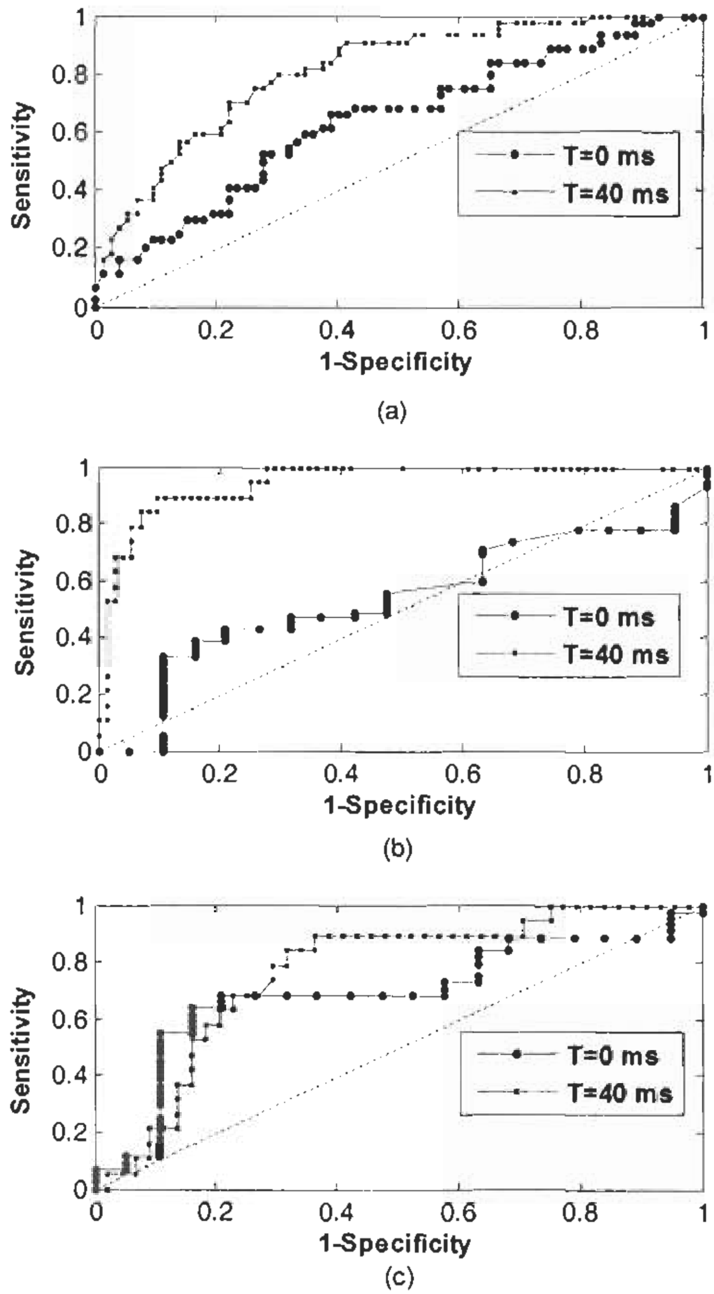


Figure 3.12: Operator receiver curve (a) NSR Vs CHF (b) NSR Vs AF (c) CHF Vs AF

groups is not statistically significant. It shows that ACI cannot perform good classification between these two groups. But as we change the threshold value, we get better separation between these two groups. Maximum separation between these groups (CHF and AF subjects) was obtained at the threshold value of 40 ms (0.5450±0.0083, 0.5869 ± 0.0105, $P=4.99\times10^{-03}$ and AUC= 0.78). The value of TACI at threshold level of 40 ms and ACI is shown in Figure 3.10 with error bars for CHF and AF groups.

Scattergram of TACI with subjects along x-axis and value of TACI along y-axis for NSR Vs CHF, NSR Vs AF and CHF Vs AF are shown in the Figure 3.11. In case of ACI (T=0), the degree of overlap is high and classification is poor between the groups. It is clear from that the degree of overlap between the groups has decreased and classification ability has improved by choosing an appropriate threshold value. Figure 3.12 shows an operator receiver curve for (a) NSR VS CHF and (b) NSR Vs AF (c) CHF and AF subjects. Greater the area under the curve better is the separation between the groups.

TACI was further tested to compare cardiac interbeat interval time series of young and elderly NSR and CHF subjects. The data for young and elderly CHF and NSR subjects was taken from physionet databases (Goldberger *et al.* 2000). Healthy elderly group consists of 22 subject aged 69.14±3.24 years (mean ± SD) and healthy young group consists of 21 subjects aged 69.14±3.24 years (mean ± SD). The elderly CHF group contain 18 subjects aged 64.94±4.78 years (mean ± SD) and young CHF group contain 19 subjects 45.90.±5.92 years (mean ± SD) As shown in the Figure 3.13, for all the threshold values, the TACI for young subjects was smaller than both elderly and CHF subjects. Figure 3.13 shows the values of TACI healthy young and healthy elderly subjects and CHF subjects. It was investigated that TACI is considerably small for healthy young subjects as compared to both healthy elderly and CHF subjects. For small threshold values (both positive and negative) the healthy elderly and CHF subjects have almost same TACI values but for larger threshold values (both positive and negative), the values of TACI are considerably high for CHF subjects. In Figure 3.14, the values TACI for young and elderly subjects are presented. The results demonstrated that the difference young and elderly CHF subjects is not significant.

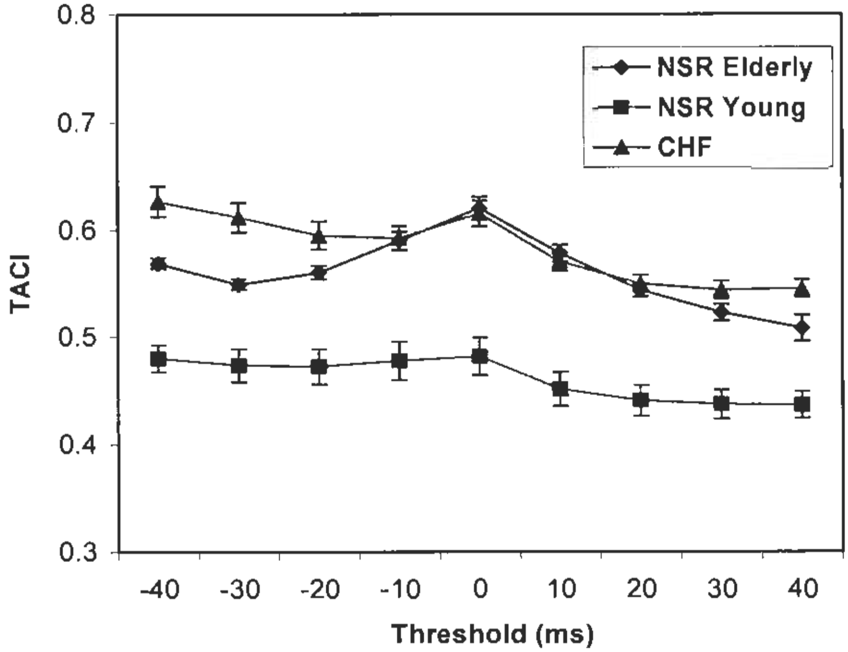


Figure 3.13: TACI for NSR elderly, NSR young and CHF subjects at different threshold values.

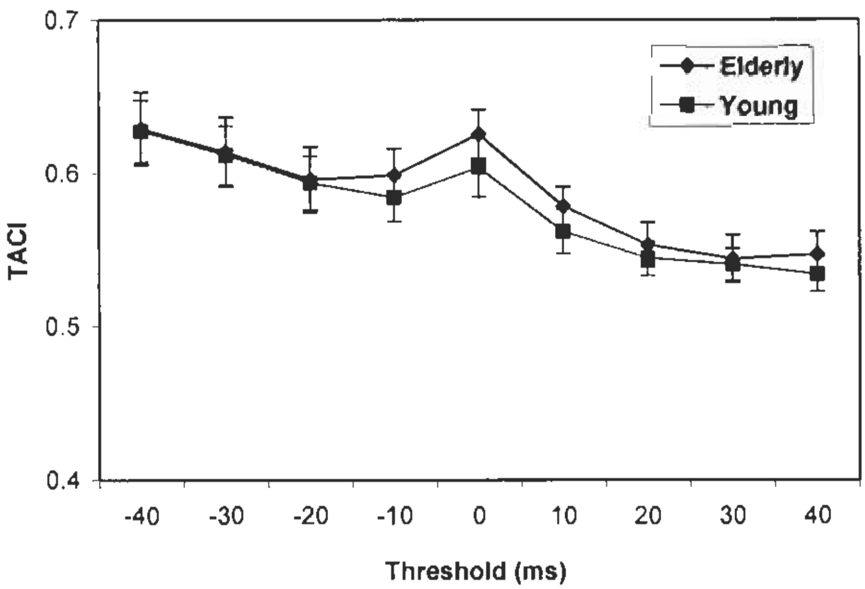


Figure 3.14: TACI for young and elderly CHF subjects at different threshold values.

3.4.3 Analysis of Stride Interval Time Series

Threshold based acceleration change index (TACI) of 16 control subjects, 11 ALS subjects, 19 Huntington's disease subjects and 14 Parkinson disease subjects was calculated. All the calculations were carried out using the right foot data. Student's t-test was used to find the significant difference between the groups and degree of separation between the groups was quantified using area under the receiver operator curve (McNeil and Hanley 1984).

Mean ± standard error of TACI of control and ALS subjects and their corresponding p-values are given. In case of ACI (T=0) and small threshold values, the difference between ALS and control groups is not statistically significant. Better separation between the groups was observed as we changed the threshold values. Maximum separation between control Vs ALS subjects was obtained at a threshold of 40ms (0.5254±0.0143, 0.5798±0.0134, p-value 2.47×10^{-02} and AUC 0.76). The value of TACI at threshold of 40ms and ACI along with error bars are shown in the Figure 3.15 for control and ALS subjects.

The value TACI (mean ± standard error) for control and Huntington's disease subjects and their corresponding p-values are given in the Table 3.5. The difference between the control and Huntington's diseases subjects is not statistically significant at short threshold values. The classification between the groups improved as threshold values were changed. Maximum separation between control Vs Huntington's disease subjects was obtained at a threshold of 30 ms (0.5358±0.0090, 0.5914±0.0097, p-value 4.80×10^{-04} and AUC 0.85). The value of TACI for control and Huntington's disease subjects at threshold of 30 ms and ACI along with error bars are shown in the Figure 3.16.

Table 3.6 shows mean ± standard error and their corresponding p-values for control and Parkinson disease subjects. The classification between the groups was poor at threshold zero, however, better separation between the groups was observed as the threshold values were changed. Maximum separation between the groups was obtained at threshold value of -40ms (0.4973±0.0142, 0.5750±0.02205, p-value 2.24×10^{-03} and AUC=0.76). The value of TACI at threshold of 40 ms and ACI along with error bar for control and Parkinson disease subjects are shown in Figure 3.17.

Table 3.4: TACI for Control and ALS subjects at and their corresponding p-values at different threshold values.

T(ms)	Control	ALS	p-value
40	0.5254±0.0143	0.5798±0.0134	2.47×10^{-02}
30	0.5358±0.0090	0.5756±0.0168	2.80×10^{-02}
20	0.5623±0.0087	0.5890±0.0171	ns
10	0.5858±0.0134	0.5886±0.0165	ns
0	0.6168±0.0098	0.5869±0.0149	ns
-10	0.5937±0.0121	0.5776±0.0161	ns
-20	0.5535±0.0108	0.5720±0.0152	ns
-30	0.5288±0.0125	0.5488±0.0149	ns
40	0.4973±0.0142	0.5344±0.0159	ns

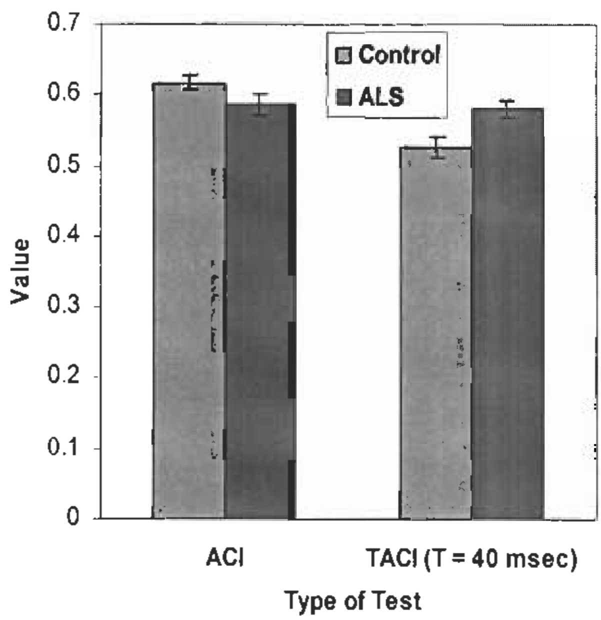


Figure 3.15: Comparison of ACI and TACI (T=40 ms) for control and ALS subjects.

Table 3.6: TACI for Control and Parkinson disease subjects and their corresponding p-values at different threshold values.

T(ms)	Control	Parkinson	p-value
40	0.5254±0.0143	0.5802±0.0146	1.50×10^{-02}
30	0.5358±0.0090	0.5898±0.0169	1.88×10^{-02}
20	0.5623±0.0087	0.5966±.01505	ns
10	0.5858±0.0134	0.5931±0.0186	ns
0	0.6168±0.0098	0.5923±0.0185	ns
-10	0.5937±0.0121	0.5990±0.0177	ns
-20	0.5535±0.0108	0.5910±0.0163	ns
-30	0.5288±0.0125	0.5811±0.0202	1.68×10^{-02}
-40	0.4973±0.0142	0.5750±0.0205	2.24×10^{-03}

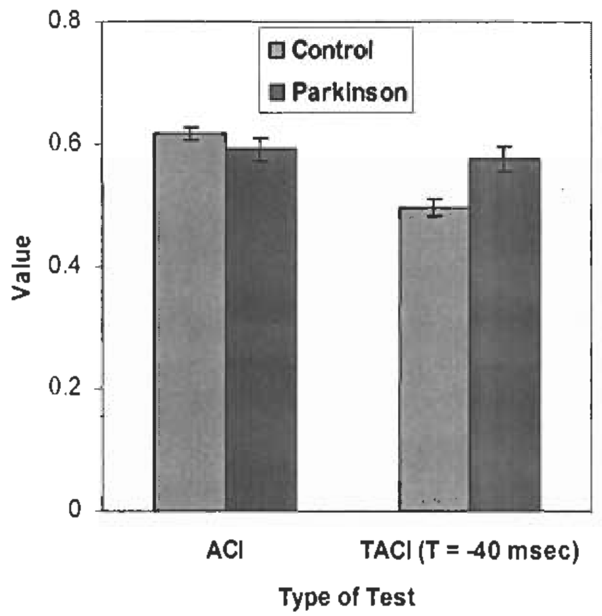


Figure 3.17: Comparison of ACI and TACI (T=-40 ms) for control and Parkinson disease subjects.

Table 3.5: TACI for Control and Huntington disease subjects and their corresponding p-values at different threshold values.

T(ms)	Control	Huntington	p-value
40	0.5254±0.0143	0.5812±0.0099	1.96×10^{-03}
30	0.5358±0.0090	0.5914±0.0097	4.80×10^{-04}
20	0.5623±0.0087	0.5960±0.0101	3.70×10^{-02}
10	0.5858±0.0134	0.6057±0.0097	ns
0	0.6168±0.0098	0.6009±0.0122	ns
-10	0.5937±0.0121	0.5986±0.0122	ns
-20	0.5535±0.0108	0.6051±0.0101	3.38×10^{-03}
-30	0.5288±0.0125	0.5931±0.0124	1.75×10^{-03}
-40	0.4973±0.0142	0.5822±0.0166	6.87×10^{-04}

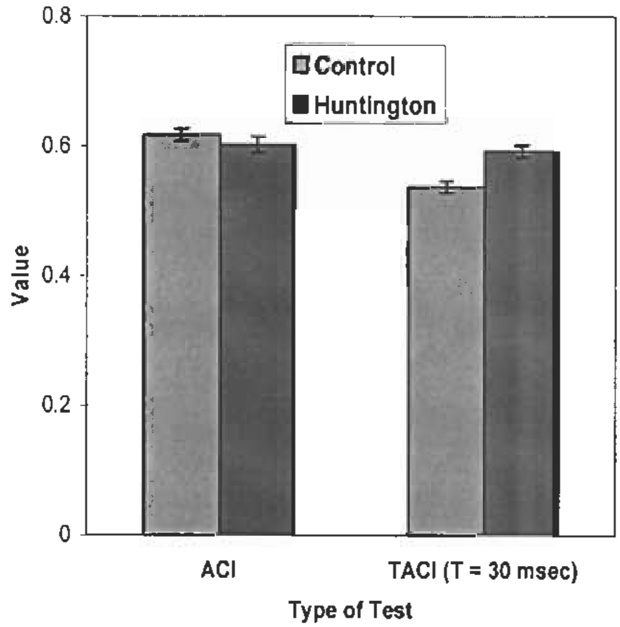
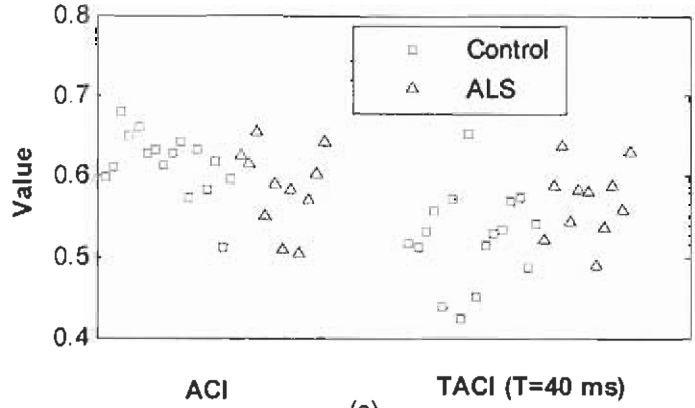
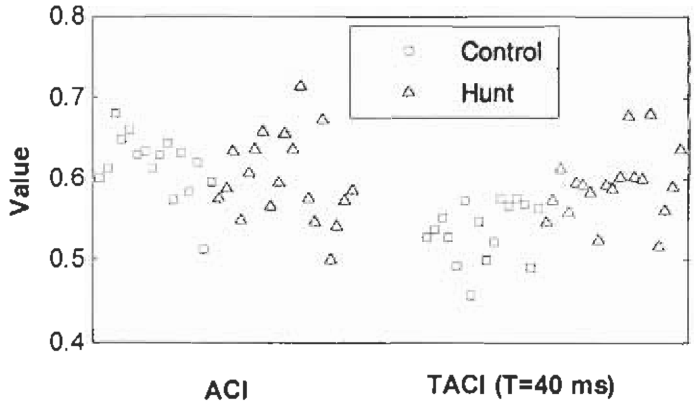


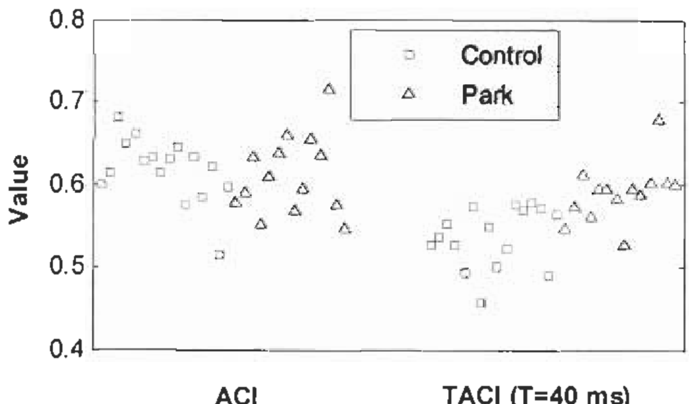
Figure 3.16: Comparison of ACI and TACI (T=30 ms) for control and Huntington's disease subjects.



(a)



(b)



(c)

Figure 3.18: Comparison of scattergrams of TACI (a) Control and ALS (b) Control and Huntington (c) Control and Parkinson.

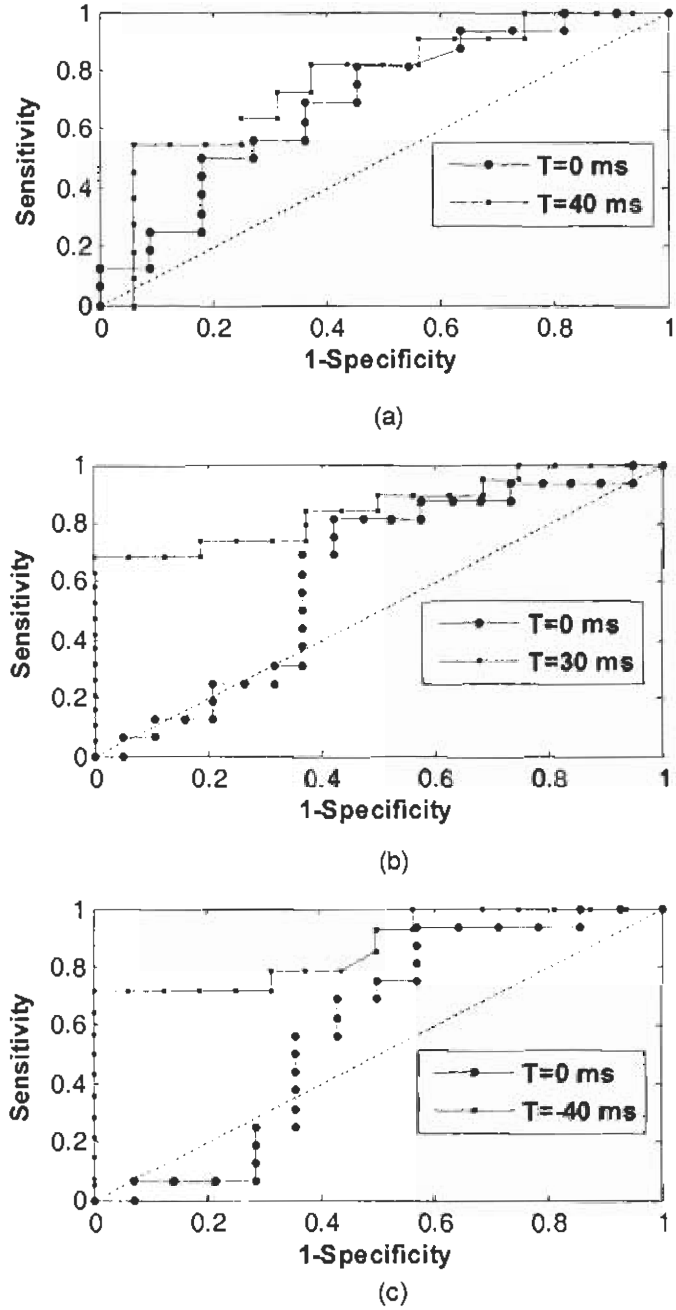


Figure 3.19: Operator receiver curve (a) Control Vs ALS (b) Control Vs Huntington (c) Control Vs Parkinson.

Scattergram of TACI for control Vs ALS, Control Vs Huntington and Control Vs Parkinson diseased with subjects along x-axis and value of TACI along y-axis are shown in the Figure 3.18. In case of ACI, the degree of overlap is high and classification between the groups is poor. It is clear from Figure 3.18 that by choosing an appropriate threshold value, the degree of overlap between the groups has decreased and classification ability has improved.

Figure 3.19 shows an operator receiver curve for (a) Control Vs ALS (b) Control Vs Huntington (c) Control Vs Parkinson disease subjects. Greater the area under the curve better is the separation between the groups.

3.5 Discussion

TACI characterizes the dynamics of threshold crossing. ACI is a special case of TACI when the threshold is zero. In case of ACI, the sign change from '+1' to '−1' or from '−1' to '+1' occurs when there is a local maximum or minimum in RR time series. ACI gives the probability of a local minimum just after a local maximum or vice versa out of the total occurrence of local maxima and minima. In TACI, the sign series is generated relative to the threshold value, not necessarily on a local minimum or maximum of the RR time series.

In the case of positive threshold values, the sign change from '−1' to '+1' occurs when the difference may still be positive but less than the threshold value. Whereas in the negative threshold case, the sign change from '+1' to '−1' will occur when the difference is more negative than the threshold value. Hence, by incorporating a threshold value the dynamics of time series can be more successfully exposed as compared to ACI where the threshold value is zero and we are only searching for local minima and maxima. We have compared TACI using different threshold levels with ACI for uncorrelated random data and logistic map. It was found that the effect of threshold (−50 ms to 50 ms) is not significant in these simulated time series but for RR-interval time series and for stride interval time series data, the threshold value has great importance in separating different groups. For physiological time series data, the differentiated series has a range almost in between −100 ms and +100 ms, whereas for simulated time series data, the range of the differentiated series is very high. Thus smaller threshold values produce a significant variation in physiological time series as compared to simulated time series.

TACI is robust in the presence of artifacts in the sense that the amplitude of the artifacts does not affect the index directly. The presence of ectopic beat can modify the TACI or not depending upon the location of the ectopic beat in the time series.

When applied to the cardiac interbeat interval time series of healthy and pathologic subjects, the results demonstrated that TACI was small in healthy subjects. We have observed that for negative threshold values the TACI is higher than that in the case of positive threshold values. All NSR subjects, more than 93% CHF subjects and more than 90% AF subjects, have high values of TACI for negative threshold values as compared with positive threshold values. The reason for this may be that, for shortening RR intervals, the negative threshold increases the number of sign changes between successive beats, which consequently leads to high TACI. For CHF subjects, the difference between the positive and negative threshold values is considerably high as compared to NSR and AF subjects. Respiratory rates which are high in CHF subjects may be the reason for this asymmetry. We have also observed that TACI has decreased for both positive and negative threshold values for NSR subjects, whereas TACI increased with the negative threshold value in the case of diseased subject (CHF, AF).

On comparing RR interval time series of young and elderly healthy subjects, TACI was found to be smaller in young healthy subjects for all threshold values. At short threshold values, TACI demonstrated that the dynamics of CHF and elderly healthy subjects are almost similar; however, for large magnitudes of threshold values (both positive and negative) elderly healthy subjects have smaller TACI value.

When applied to the stride interval time series, it was found that the values of TACI for control subjects is smaller than diseased subjects for all positive threshold values. For ALS subjects the variation TACI with threshold is smaller for positive threshold values as compared with negative threshold values, however, for Huntington and Parkinson diseased subjects the variation of TACI is small for both positive and negative threshold values.

TACI yield consistent findings at large positive threshold values when applied to physiological control systems (a) cardiac interbeat intervals (b) stride intervals. The heart rate dynamics of pathologic subjects are associated either with decreased variability (CHF subjects) or increased variability (AF subjects), however, the pathologic gait dynamics are always associated with increased variability. Also the dynamics of healthy elderly subjects are associated with decreased variability. The results demonstrated that TACI increased for pathological groups (either associated with decreased or increased variability) and for elderly subjects at positive threshold values. It is clear from results that one can chose a common threshold value of 40 ms for quantifying the dynamics physiological control systems.