Med Biol Eng Comput (2009) 47:323–331
DOI 10.1007/s11517-008-0415-y

ORIGINAL ARTICLE

Enhanced modified moving average analysis of T-wave alternans using a curve matching method: a simulation study

D. Cuesta-Frau · Pau Micó-Tormos · M. Aboy · Marcelo O. Biagetti · D. Austin · Ricardo A. Quinteiro

Received: 30 January 2008 / Accepted: 2 October 2008 / Published online: 21 October 2008

Abstract T-wave alternans (TWA) are beat-to-beat amplitude oscillations in the T-waves of electrocardiograms (ECGs). Numerous clinical studies have demonstrated the link between these oscillations and ventricular arrhythmias. Several methods have been developed in recent years to detect and quantify this important feature. Most methods estimate the amplitude differences between pairs of consecutive T-waves. One such method is known as modified moving average (MMA) analysis. The TWA magnitude is obtained by means of the maximum absolute difference of even and odd heartbeat series averages computed at T-waves or ST–T complexes. This method performs well for different levels of TWA, noise, and phase shifts, but it is sensitive to the alignment of the T-waves. In this paper we propose a preprocessing stage for the MMA method to ensure an optimal alignment of such averages. The alignment is performed by means of a continuous time warping technique. Our assessment study demonstrates the improved performance of the proposed algorithm.

D. Cuesta-Frau (✉) · P. Micó-Tormos
Technological Institute of Informatics,
Polytechnic University of Valencia, Campus Alcoi Plaza
Ferrándiz y Carbonell, 2, 03801 Alcoi, Spain
e-mail: dcuesta@disca.upv.es

M. O. Biagetti · R. A. Quinteiro
Cardiac Electrophysiology Laboratory,
Department of Physiology, Favaloro University,
Buenos Aires, Argentina

M. Aboy · D. Austin
Department of Electronics Engineering Technology,
Oregon Institute of Technology, Klamath Falls, OR, USA

Keywords T-wave alternans · Modified moving average · Continuous dynamic time warping

1 Introduction

The introduction of digital electrocardiography and digital computing has enabled the clinical use of advanced signal processing techniques and the detection of subtle electrocardiogram (ECG) features of clinical significance. Some of these features are not detectable by expert visual inspection but have proven to be important markers for serious heart illnesses [15]. An example of such a feature is T-wave alternans (TWA).

TWA are beat-to-beat amplitude oscillations in the T-waves of ECGs (Fig. 1). Numerous clinical studies have demonstrated the link between these oscillations and ventricular arrhythmias.

Several methods have been developed in recent years to detect and quantify TWA, and use it as a non-invasive test to identify patients who are at increased cardiac risk. Over 100 patents have been issued by the United States Patent and Trademark Office (USPTO) on methods, processes, and systems related to TWA. Assignees include major medical device firms such as Medtronic, Inc. and GE Medical Systems, Inc.

Time-domain analysis methods of TWA involve subtracting T-waves of even versus odd beats as in the commercially available modified-moving average (MMA) method [10]. This paper describes an improvement for such methods. MMA performs very well under different conditions, but its accuracy can be improved if waves are better aligned prior to distance calculation. To this end, we added a preprocessing stage based on continuous dynamic time warping (CDTW).

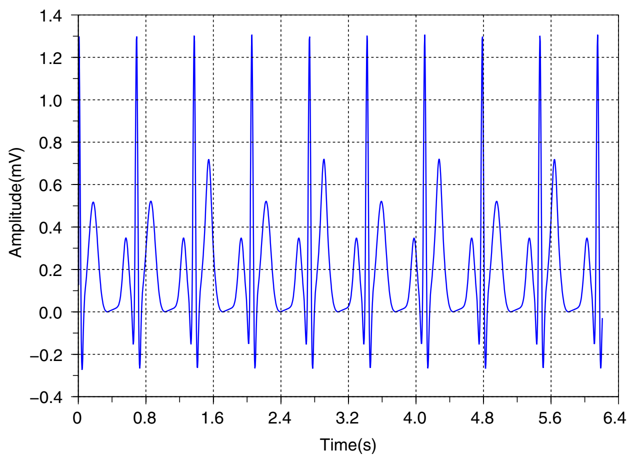

Fig. 1 Example of an ECG with TWA. Heartbeats 3, 5, and 7 exhibit T-waves 200 μV higher than those in heartbeats 1, 2, 4, 8, and 10. Additionally, there is a TWA phase shift at heartbeat 2

In the following subsections we describe the relationship between TWA and ventricular repolarization, its clinical significance, and the state of the art of TWA analysis methods. In Sect. 2 we present the alignment stage to improve the accuracy and robustness of the standard MMA method. Next, the assessment study is presented in Sect. 3. The results of the assessment study are discussed in Sect. 4 and concluding remarks are provided in Sect. 5.

1.1 Ventricular repolarization

Repolarization is the electrophysiological phenomenon associated with the recovery of cardiac cells after their excitation. T-waves in an ECG are the electrical manifestation of this repolarization process and may reflect electrical disturbances in normal electrophysiology associated with some cardiac diseases. Thus, T-waves provide physicians with indicators of cardiac abnormalities and a means to assess therapy.

T-waves correspond to the ECG manifestation of the differences in action potential durations in the myocardium. The beginning of the T-wave is linked to the first cells that repolarize, and the end of the T-wave is defined by the last cells in repolarizing. The contour of the complete wave is directly related to the path of repolarization, and alterations have a counterpart in the shape of the T-wave. This phenomenon can occur on a beat to beat basis, as in TWA.

Ventricular repolarization heterogeneity has been demonstrated to constitute a risk indicator of possible malignant arrhythmias and sudden cardiac death [10]. The assessment of repolarization instability can be improved by analyzing the repolarization shape changes represented by TWA. In the ACC/AHA/HRS 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, TWA was defined as a class 2a indication. It was stated that is reasonable to use TWA for improving the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias. Although numerous modalities exist at present for assessing this risk, only two are approved by the US Food and Drug Administration: signal-averaged ECG and TWA.

1.2 Clinical significance

Many clinical studies have demonstrated the correlation between TWA and the vulnerability to ventricular arrhythmias by means of ECG record analysis in patients who experienced sudden cardiac arrest and other cardiac events [17]. For instance, TWA magnitude has been found to be linked to malignant arrhythmias under diverse clinical conditions: myocardial infarction and ischemia, heart failure, electrolyte disorders, cardiomyopathy, long QT syndrome, and drug intoxications [5]. Additionally, higher levels of TWA are correlated with a higher ventricular fibrillation (VF) risk.

1.3 State of the art

Over 100 patents have been issued by the USPTO on methods related to TWA developed by medical device corporations.

In recent years, the research community has also developed methods to detect and quantify TWA. Some of the most widely employed methods in clinical practice are [7]:

- Spectral methods. A time series is created by taking samples from consecutive T-waves, and then the Fourier spectrum is computed. Peaks at frequency 0.5 cycles/beat indicate the presence of TWA [13].
- Complex demodulation method. The same time series as in the previous case is demodulated and low pass filtered. Amplitude and phase of the alternans are derived from this filtered signal [12].
- Correlation method. A single cross-correlation coefficient is computed for every ST–T complex against a representative for a heartbeat series. If the correlation index alternates for some consecutive beats, a TWA episode is detected [1].
- Poincare mapping. Poincare maps are formed by plotting T-wave magnitude of alternate beats [15]. Semiperiodic signals such as TWA, appear as tight clusters. TWA magnitude is the intercluster distance.
- MMA. TWA magnitude is obtained by means of the maximum absolute difference of even and odd

heartbeat series averages computed at T-waves or ST–T complexes [11].

Although the diversity of approaches and the lack of a reference database makes method comparison difficult, there are some known issues that led us to choose MMA as the basic TWA analysis method. Spectral methods are very sensitive to changes in data stationarity and artifacts, whereas repolarization heterogeneities can be transient events [15], the complex demodulation method requires a significant analytical complexity, and in the correlation and Poincare mapping methods, it is not possible to determine the temporal position of TWA.

2 Materials and methods

2.1 Standard MMA

The MMA is one of the most successful TWA analysis methods and it is used by commercially available devices. This method has proven to be very robust against noise [14] and provides a high sensitivity and specificity for predicting impending VF. Additionally, MMA analysis achieves a good signal-to-noise ratio, it is relatively tolerant of nonstationary data such as changing heart rates or motion artifacts, and it is independent of phase shifts [18].

MMA considers the ECG as a series of heartbeats (for TWA measurement purposes, only T-waves or ST–T complexes are processed). Odd and even heartbeats are labeled as A_n and B_n, respectively, where n as the order index. The ECG signal can then be defined as a combination sequence of consecutive A_n and B_n heartbeats:

$$\mathrm{ECG} = \{A_1, B_1, A_2, B_2, \ldots, A_{\frac{N}{2}}, B_{\frac{N}{2}}\}.$$

where N is the total number of heartbeats in the ECG, A_n is the $2n-1$ heartbeat, and B_n is the $2n$ beat, for $1 \leq n \leq \frac{N}{2}$. The length of each heartbeat is k. In general, k is different for each one, that is:

$$A_n = \{A_n(1), A_n(2), \ldots, A_n(k_{A_n})\},$$

and

$$B_n = \{B_n(1), B_n(2), \ldots, B_n(k_{B_n})\}.$$

Using these definitions, computation of TWA is described in the following steps:

1. Initialization. This is carried out by taking the first heartbeat as the initial average:

   $$\overline{A}_1 = A_1$$

2. Proceed with all the heartbeats in the series to update the weighted average accordingly $\overline{A}_n(i) = \overline{A}_{n-1}(i) + \Delta_i$, for $1 < n \leq \frac{N}{2}$, and $1 \leq \ i \leq \ k$. Updating factor Δ_i is calculated using the following rules:

   $$\begin{aligned}
   \Delta_i &= -32 && \text{if } \eta_i \leq -32\\
   \Delta_i &= \eta_i && \text{if } -1 \geq \eta_i > -32\\
   \Delta_i &= -1 && \text{if } 0 > \eta_i > -1\\
   \Delta_i &= 0 && \text{if } \eta_i = 0\\
   \Delta_i &= 1 && \text{if } 1 \geq \eta_i > 0\\
   \Delta_i &= \eta_i && \text{if } 32 \geq \eta_i > 1\\
   \Delta_i &= 32 && \text{if } \eta_i \geq 32
   \end{aligned}$$

   where $\eta_i = \frac{1}{8}[A_n(i) - \overline{A}_{n-1}(i)]$. Threshold values (32 and 1) may vary depending on the heartbeat amplitude scale, and a temporal normalization is necessary in order to make $k_{A_n} = k_{\overline{A}_{n-1}}$ (uniform resampling to make the two lengths equal).

3. Obtain final average as the last computed weighted average, for $n = \frac{N}{2} : \overline{A} = \overline{A}_{\frac{N}{2}}$.
4. Repeat steps 1 to 3 for B series.
5. Measure TWA as the maximum absolute value of the difference between $\overline{A}$ and $\overline{B}$, $d_{\mathrm{TWA}} = \max|\overline{B} - \overline{A}|$.

2.2 Wave alignment

The curve matching problem has been widely studied since it can be found accross different domains. Many experiments yield data where the same phenomena exhibits variations at different positions or may have different durations. Analogously, the measurements for the single samples can have different time scales or axes, or the sample vectors may have different lengths. This applies to ECG heartbeats, and therefore, to TWA measurement.

Dynamic time warping (DTW) is one of the numerous methods that have been proposed to correct time shifts. DTW is described as a method that can eliminate shift-related artifacts from measurements by correcting a sample vector of length J towards a reference of length I. Identifying the global optimum for the warping path is transformed into an efficient iterative procedure divided into a forward step and a backward step:

- Starting from point (1, 1), and according to a minimization equation, construct the mapping grid $G(I, J)$, in which element $G(i, j)$ is the optimal accumulated distance up to point (i, j) (forward step).
- Find the optimal warping path by backtracing from $i(L)$, $j(L) = (I, J)$ down to point (1, 1) (backward step), where L is the alignment path length.
- Synchronization. Usually L is larger than either I or J due to warping corrections. The extent of elongation is unpredictable until the warping process is finished and may vary from sample to sample. An additional

synchronization step yielding vectors of length I is required [16].

In order to apply this technique to the alignment of a pair of heartbeats, ST–T complexes, or T-waves A_n and A_m, we consider them as two curves in a 2D space: $A_n = \{P_n(t), t = 1,\ldots,k_{A_n}\}$, and $A_m = \{P_m(t), t = 1,\ldots,k_{A_m}\}$. We assume there is a correspondence map between these two curves, $\varphi = [\varphi_{A_n}(t), \varphi_{A_m}(t)]$ such that a point $P_n(\varphi_{A_n}(t)) \in A_n$ corresponds to a point $P_m(\varphi_{A_m}(t)) \in A_m, t \in \{1,\ldots,L\}$.

The dissimilarity S_d between these two curves is computed as [9]:

$$\begin{aligned} & S_d(A_n, A_m) \\ & = \sum_{t=2}^{T} d\left(\left(A_{n(\varphi_{A_n}(t-1))}, A_{m(\varphi_{A_m}(t-1))}\right), \left(A_{n(\varphi_{A_n}(t))}, A_{m(\varphi_{A_m}(t))}\right)\right) \\ & = \sum_{t=2}^{T} \left\| \overrightarrow{A_{n(\varphi_{A_n}(t))}A_{m(\varphi_{A_m}(t))}} - \overrightarrow{A_{n(\varphi_{A_n}(t-1))}A_{m(\varphi_{A_m}(t-1))}} \right\|^2 \end{aligned} \tag{1}$$

where $\|\cdot\|^2$ is the Euclidean norm.

The objective of this method is to find the alignment path between A_n and A_m that minimizes the dissimilarity. Analytically, this objetive is defined as:

$$\varphi = \left[\varphi_{A_n}, \varphi_{A_m}\right]^T = \arg\min_{\varphi}\{S_d(A_n, A_m)\} \tag{2}$$

The solution to this minimization problem can be achieved by means of dynamic programming [2]:

$$\begin{aligned} S_d(\varphi(t)) = \min_{\varphi(t-1)} \Big\{ & S_d(\varphi(t-1)) + \\ & d\left(\left(A_{n(\varphi_{A_n}(t-1))}, A_{m(\varphi_{A_m}(t-1))}\right), \left(A_{n(\varphi_{A_n}(t))}, A_{m(\varphi_{A_m}(t))}\right)\right) \Big\} \end{aligned} \tag{3}$$

where $d\left(\left(A_{n(\varphi_{A_n}(t-1))}, A_{m(\varphi_{A_m}(t-1))}\right), \left(A_{n(\varphi_{A_n}(t))}, A_{m(\varphi_{A_m}(t))}\right)\right)$ accounts for the distance between a pair of aligned samples of A_n and A_m.

Graphically, this procedure corresponds to finding the optimal warping path on the mapping grid $G(I, J)$. In principle, the path can reach any node in the grid. However, constrained DTW is superior to unconstrained DTW since the last is too flexible, resulting in an overfitting of the observed shifts in some cases.

However, standard discrete DTW suffers from some drawbacks, most importantly the fact that it is defined between sequences of points rather than curves. The way in which a curve is sampled to yield such sequence can dramatically affect the quality of the alignment [9]. In contrast, a continuous version of DTW that is usually termed CDTW does not suffer from this drawback, since a point in A_n is allowed to match a point between two samples in A_m

In CDTW the recursion equation is the same as Eq. 3, with the additional condition that if $\varphi_{A_n}(t)$ takes values on $\{1,\ldots,k_{A_n}\}$, then $\varphi_{A_m}(t)$ is allowed to take non-integer values, and viceversa [9]. This is possible by means of a linear interpolation model assumed for the curves, that is, new intermediate matching points are computed by a curve parameterization method:

$$x = x(i-1) + r\frac{\Delta_x}{\Delta}$$

$$y = y(i-1) + r\frac{\Delta_y}{\Delta}$$

where $x(i-1)$ and $y(i-1)$ represent the coordinates of a point of the wave, and x and y represent a calculated new point. r is the independent variable. Parameters are defined as:

$$\Delta_x = x(i) - x(i-1)$$

$$\Delta_y = y(i) - y(i-1)$$

$$\Delta = \sqrt{{\Delta_x}^2 + {\Delta_y}^2}$$

For a unidimensional curve, Δ_x becomes 1, and $\Delta_y = A_n(i) - A_n(i-1)$. The same applies to A_m.

DTW equations are updated accordingly to fit in CDTW. A thorough description of DTW and CDTW methods can be found in [2, 9]. The output of the method is an optimal alignment between input waves A_n and A_m. Thus, the enhanced MMA (EMMA) method proposed in this work adds a CDTW-based alignment to the standard MMA method. The process stages are the same as in MMA, but in the last one, the dissimilarity between the two averages is computed using CDTW instead: $d_{\mathrm{TWA}} = \max|\overline{B} - \overline{A}|_{\mathrm{CDTW}}$, that is, $\overline{B}$ and $\overline{A}$ are aligned as described prior to finding the maximum difference between them. A block diagram is shown in Fig. 2 and examples of the alignment in MMA and EMMA methods are shown in Figs. 3 and 4, respectively.

2.3 Assessment study data

Unfortunately, there is no gold standard public TWA database annotated by experts [7] as in other similar fields [3]. In order to provide an objective assessment of TWA analysis methods, it is important to know parameters in advance (waveform location, amplitude, beginning, end, noise and artifacts, etc.) which currently can only be achieved by designing a simulation study with synthetic ECGs. Some researchers have created ECG registers by replication of a real or synthetic single noiseless heartbeat to which different kinds of noise and alternans episodes were added [6, 4], but the resulting signals do not include the physiological variability that may influence TWA analysis. Others have included real recorded physiological noise and time scaled basic heartbeat to better simulate a real ECG [7]. In a few studies, researchers have used real

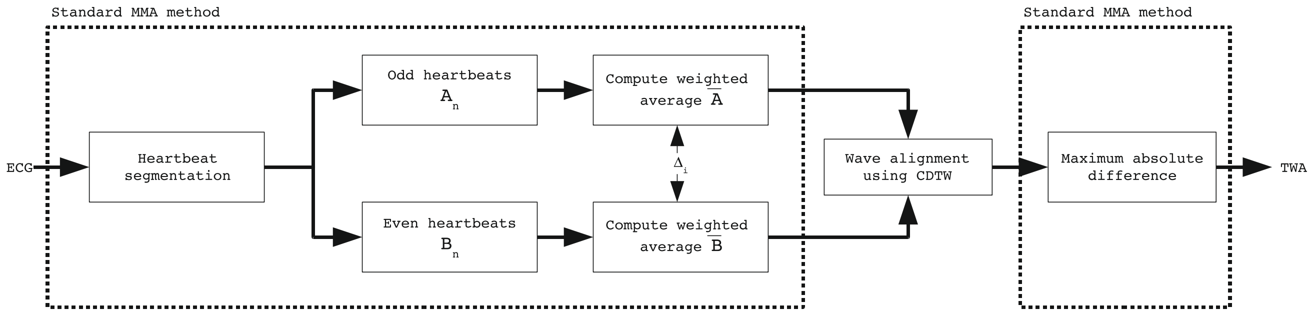

Fig. 2 Block diagram of the EMMA method proposed. Most of the stages coincide with standard MMA method except averages alignment using CDTW

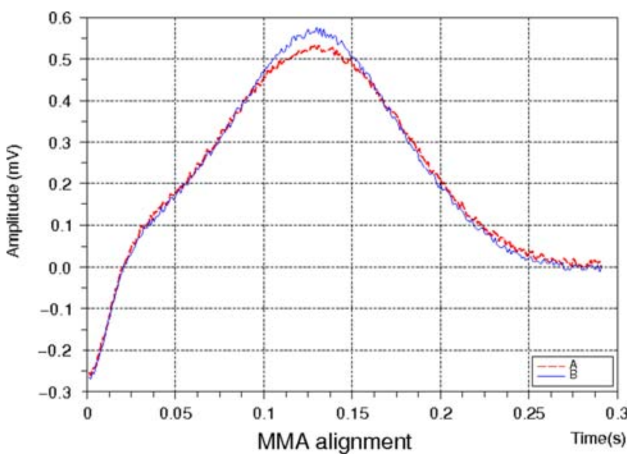

Fig. 3 No feature alignment, just linear length normalization. Maximum distance calculation may be corrupted by local peaks shifts, specially when noise is present

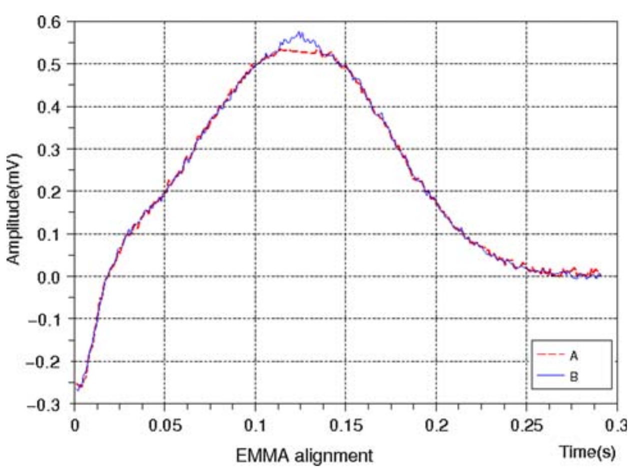

Fig. 4 Alignment using CDTW. Local peaks are aligned and therefore artifact influence is reduced

noiseless annotated ECG signals, added real physiological noise, and only TWA were synthetic. These signals achieved very realistic registers although not all the parameters were known. We also used this approach to confirm that the results on real ECGs followed the same pattern as with completely synthetic signals. Three registers from European ST–T database [3] were employed: e0123, e0103, and e0105, preprocessed, and not-preprocessed

A few clinical studies have used real ECGs with real TWA. However, these datasets are not publicly available, do not have a gold-standard for algorithm assessment, and often are very specific to a certain cardiac disorder or experimental set or were obtained invasively.

Our assessment study uses a few real ECGs with artificial TWA but mainly synthetic ECG registers with known parameters. In order to achieve a high degree of realism, we used the synthetic ECG generator recently developed and described in McSharry et al. [8]. This method enabled us to determine the positions and limits of the different waves, change the heart rate, use variable levels of TWA and noise, and add baseline wander. It is very important to note that this work is not aimed at developing a new TWA analysis method but to improve an already existing and assessed method. Therefore, it is more convenient to use controlled signals for an objective and sound comparative analysis.

In the synthetic ECG generator, users can specify ECG parameters of the ECG such the mean and standard deviation of the heart rate, morphology of the PQRST cycle, amplitude, sampling frequency, and the power spectrum of the RR tachogram. The model generates a trajectory in a 3D state space with coordinates (x, y, z) where semiperiodicity of the ECG corresponds to the rotation of the trajectory in an attracting limit cycle of unit radius in the (x, y) plane. Each revolution on this circle corresponds to one heartbeat. Interbeat variation in the ECG is simulated using the motion of the trajectory in the z direction. Different points on the ECG, such as P, Q, R, S and T-waves, are described by events corresponding to negative and positive attractors/repellors in the z direction. These events are placed at fixed angles along the unit circle given by θ_P, θ_Q, θ_R, θ_S, θ_T. All these values were experimentally set by real ECG analysis [8]. Synthetic TWA was created by adding a Hamming function to the T-wave every two beats.

Table 1 TWA amplitude measurements using standard MMA and EMMA methods (EM), for real amplitudes ranging from 0 to 20 μV

Noise σ	TWA = 0 μV		TWA = 2 μV		TWA = 5 μV		TWA = 10 μV		TWA = 20 μV	
	MMA	EM	MMA	EM	MMA	EM	MMA	EM	MMA	EM
0 μV	4.6	6.4	5.5	7.0	7.4	8.0	11.0	10.9	20.4	20.3
5 μV	15.2	12.1	15.4	12.2	16.5	12.3	19.1	13.5	27.1	20.2
10 μV	27.6	19.7	27.8	19.6	28.6	19.8	30.6	20.4	36.7	24.0
25 μV	66.4	44.7	66.4	44.8	66.8	44.7	68.1	44.8	72.3	45.7
50 μV	127.3	91.0	127.4	90.6	127.6	89.9	128.2	89.6	130.7	90.2
100 μV	255.4	197.2	255.5	197.1	255.7	197.6	256.1	197.3	257.4	198.1
200 μV	505.0	427.6	505.2	427.6	505.5	427.6	506.0	426.6	507.3	426.7
300 μV	805.7	696.4	805.9	696.5	808.6	697.5	809.1	698.3	811.9	696.1
e0123	0.231	0.163	2.10	2.14	4.79	5.00	9.27	9.53	18.28	18.56
	0.238	0.167	2.07	2.06	4.57	4.69	8.81	9.01	17.62	17.85
e0103	0.262	0.124	1.84	1.88	4.51	5.38	8.80	9.89	17.42	18.54
	0.299	0.157	1.89	1.93	4.48	5.38	8.71	9.80	17.13	18.29
e0105	0.471	0.371	2.02	2.32	4.84	6.34	9.47	10.95	18.66	20.15
	0.608	0.489	2.01	1.62	4.48	6.13	8.56	10.43	16.51	18.35

Results for real signals are shown at the bottom, first row with preprocessing

Figure 1 shows a portion of a synthetic TWA ECG created in this way.

3 Assessment study and results

Experiments were conducted for several cases in order to assess TWA measurement accuracy using MMA and EMMA methods. The parameters used to generate the test data were taken from similar works [14]:

- Levels of TWA: 10, 20, 50, 100, 200, 500, and 1,000 μV. Synthetic ECG of 2,000 beats sampled at 1,000 Hz. $V_{\max} = 1.2$ V. $V_{\min} = -0.4$ V.
- Sixteen heartbeats epochs. Choice of an appropriate time window for TWA analysis is not straightforward. Selection of a long window might hinder detection of short transients, whereas selection of a short window would increase the influence of spurious artifacts on the results. Final TWA measurement corresponds to the average of measurements obtained for each epoch in the ECG register.
- Heart rate increasing from 30 to 200 bpm, in 10 bpm increments where the length of cardiac complexes was scaled according to the change in heart rate. Results were averaged in order to reduce the amount of data.
- Phase reversals (5 phase shifts/min).
- Different levels σ of random noise to assess the accuracy and robustness of each method: 5, 10, 25, 50, 100, 200, and 300 μV.
- Simulated baseline wandering (changing amplitude and frequency). Sinusoidal signal of 0.3 or 0.08 Hz. Amplitudes from 1 to 25 μV.

Input signals underwent no preprocessing or treatment aimed at improving signal quality; TWA was measured directly. Results shown correspond to those obtained by averaging partial results for all the heartbeat rates.

First, robustness against noise for several TWA levels was analyzed. Results shown in Table 1 correspond to TWA ranging from 0 to 20 μV for all the noise levels mentioned above. Table 2 shows results for TWA level from 50 to 1,000 μV.

In TWA analysis, there are other artifacts that may influence measurement, such as baseline wandering. Some experiments were conducted to assess the comparative performance of MMA and EMMA methods under five baseline wandering conditions. They were created using two sinusoids of frequencies 0.3 and 0.08 Hz, and amplitudes 1, 4, 10 and 25 mV. Four different noise levels were also added. The results for this case are shown in Table 3.

Phase shifts may also occur in registers with TWA. Sometimes a phase reversal is triggered so that alternans pattern changes, that is, heartbeat series become ...ABA**BB**ABABA... or ...ABABA**AA**BAB... An uncorrected phase reversal can mistakenly modify the TWA estimate [11]. MMA method is intrinsically robust to these phase shifts, and these experimental set was aimed at assessing the vulnerability of EMMA to it in comparison to MMA method. Table 4 shows some results obtained in this case. Several noise levels were also added.

Another important source of errors in TWA measurement is ECG fiducial point detection accuracy (QRS or T detection, mainly). Incorrect detection of T-wave apex may introduce a bias in the computation of the TWA. In order to

Table 2 TWA amplitude measurements using standard MMA and EMMA methods (EM), for real amplitudes ranging from 50 to 1,000 μV

Noise σ	TWA = 50 μV		TWA = 100 μV		TWA = 200 μV		TWA = 500 μV		TWA = 1,000 μV	
	MMA	EM	MMA	EM	MMA	EM	MMA	EM	MMA	EM
0 μV	50.3	50.3	100.3	100.2	200.3	200.2	500.2	500.1	1000.0	1000.1
5 μV	56.2	50.0	105.4	99.8	204.4	199.4	502.8	498.5	1001.1	997.1
10 μV	63.1	49.6	111.6	99.3	209.9	198.8	506.7	497.4	1003.8	995.1
25 μV	91.5	57.5	133.8	99.1	229.7	197.7	522.5	495.0	1015.0	991.1
50 μV	145.1	89.9	180.8	114.6	268.1	198.4	555.4	493.6	1041.9	986.7
100 μV	265.9	197.7	291.1	203.8	357.9	238.4	621.4	485.4	1098.4	974.9
200 μV	512.6	426.3	528.7	426.9	579.4	441.5	794.8	562.1	1243.5	992.0
300 μV	815.9	711.0	827.0	695.3	859.5	717.1	1045.6	784.9	1365.8	999.5
e0123	45.19	45.48	90.22	90.52	180.21	180.52	451.33	451.63	910.79	911.10
	43.85	44.08	87.25	87.50	174.77	175.04	445.71	445.99	908.24	908.51
e0103	43.67	44.82	87.09	88.27	173.70	174.94	434.17	435.41	872.95	874.21
	42.80	43.97	85.18	86.37	169.83	171.04	423.74	424.96	848.50	849.71
e0105	46.00	47.46	91.44	92.92	182.4	183.85	455.55	457.00	911.16	912.60
	40.95	42.76	81.83	83.66	163.46	165.28	408.14	409.97	814.33	816.15

Results for real signals are shown at the bottom, first row with preprocessing

Table 3 TWA amplitude measurements using standard MMA and EMMA (EM) methods, for different baseline wandering and noise scenarios

Baseline	TWA = 0		TWA = 5		TWA = 10		TWA = 20		TWA = 50	
	MMA	EM	MMA	EM	MMA	EM	MMA	EM	MMA	EM
(1, 0.3 Hz, 0)	8.9	10.8	10.1	10.8	13.0	12.7	21.1	21.0	50.4	50.4
(1, 0.3 Hz, 5)	17.7	14.6	18.6	14.8	20.7	15.7	28.1	21.5	56.4	50.1
(1, 0.3 Hz, 10)	29.5	20.7	30.1	20.6	31.7	21.2	37.7	24.6	63.2	49.9
(1, 0.3 Hz, 25)	65.6	44.2	66.1	44.6	67.1	44.6	71.1	45.6	91.2	57.4
(4, 0.3 Hz, 0)	24.8	25.5	25.5	25.5	27.1	26.8	32.5	32.3	56.4	56.4
(4, 0.3 Hz, 5)	31.9	28.1	32.4	28.2	34.0	29.1	39.1	33.3	62.2	56.0
(4, 0.3 Hz, 10)	41.6	31.9	42.1	32.0	43.3	32.4	47.5	35.1	68.8	55.6
(4, 0.3 Hz, 25)	74.9	51.7	75.2	52.1	76.1	52.1	79.0	53.1	96.3	63.5
(10, 0.3 Hz, 0)	54.2	53.0	54.5	53.1	55.6	54.1	59.0	58.0	76.8	76.3
(10, 0.3 Hz, 5)	60.7	55.3	61.1	55.4	62.0	56.1	65.5	59.4	82.9	76.9
(10, 0.3 Hz, 10)	69.0	58.8	69.2	58.9	69.8	59.2	72.9	61.3	88.8	76.7
(10, 0.3 Hz, 25)	100.3	77.4	100.5	77.0	101.1	77.1	103.4	77.9	116.6	86.2
(25, 0.3 Hz, 0)	105.7	103.9	105.9	103.9	106.4	104.7	108.9	107.6	121.8	120.8
(25, 0.3 Hz, 5)	110.7	105.2	111.0	105.4	111.6	105.8	114.0	108.4	126.7	121.1
(25, 0.3 Hz, 10)	118.8	109.7	119.0	109.8	119.5	110.1	121.8	111.7	134.3	123.4
(25, 0.3 Hz, 25)	145.6	125.0	145.7	125.2	146.0	125.3	147.2	125.6	158.3	132.1
(25, 0.08 Hz, 0)	17.6	17.9	18.5	18.2	20.8	20.3	28.0	27.6	54.7	54.2
(25, 0.08 Hz, 5)	26.5	21.8	27.1	22.0	28.9	23.0	35.2	28.3	72.3	66.0
(25, 0.08 Hz, 10)	37.2	27.6	39.2	28.5	42.2	30.8	49.8	36.4	74.6	59.9
(25, 0.08 Hz, 25)	71.8	52.3	72.1	52.4	73.4	53.3	78.1	56.4	118.6	89.7

Baseline column reads as (Sinusoidal amplitude, Sinusoidal frequency, Noise level). All values in μV unless otherwise stated

assess the performance of EMMA versus MMA method in this case, additional experiments were conducted with random shifts of T-waves peak position (±15 ms). Results are shown in Table 5.

4 Discussion

Experiments assessed the performance of MMA and EMMA methods under different conditions of noise level,

Table 4 TWA amplitude measurements using standard MMA and EMMA(EM) methods, for phase shifts

	TWA = 10, $\sigma = 0$		10, 5		TWA = 20, $\sigma = 0$		20, 5		20, 10	
	MMA	EM	MMA	EM	MMA	EM	MMA	EM	MMA	EM
Phase shift	10.4	9.9	18.8	13.2	19.8	19.6	27.3	22.5	37.1	27.1

All values in μV

Table 5 TWA amplitude measurements using standard MMA and EMMA (EM) methods, with T-wave position errors

Noise σ (μV)	TWA = 0 μV		TWA = 5 μV		TWA = 20 μV		TWA = 100 μV		TWA = 500 μV	
	MMA	EM	MMA	EM	MMA	EM	MMA	EM	MMA	EM
0	80.5	69.3	84.3	72.6	80.1	68.6	119.9	112.7	504.3	499.9
5	86.3	71.3	84.9	70.0	86.0	70.6	124.5	112.1	508.5	499.2
50	168.7	124.4	173.2	127.2	167.2	123.8	196.7	136.0	562.3	494.9

heart rate, and TWA amplitude. Results were obtained in an unfavourable scenario of no signal preprocessing to reduce noise or any other artifacts such as baseline wandering. The objective was to conduct a comparative analysis between EMMA and MMA under the same conditions.

4.1 Noise

MMA error is greater than EMMA error in most cases. For TWA = 0 μV, that is, registers without TWA, both methods yielded measures greater than 0, even for $\sigma = 0$ μV. This is because synthetic registers have a small, but not negligible, wave amplitude variation. For TWA < 10 μV or noise levels greater or equal than TWA levels, measures were not accurate. It does not mean MMA and EMMA methods can not detect low TWA levels, since registers were not preprocessed. Actually, in a real case, it is very unlikely to have noise levels greater than TWA levels, but experiments were aimed at assessing comparative accuracy between EMMA and MMA methods, not at obtaining absolute measures.

As the noise level increases, TWA measurement error based on MMA increases too. Regarding EMMA, a higher level of noise does not necessarily imply a higher error. This is because EMMA algorithm is able to align noise peaks and therefore reduce its influence. Thus, EMMA method is able to provide accurate TWA measures up to noise levels half the level of the TWA itself in these experiments.

When applied to the three real signals with synthetic TWA, EMMA also outperformed MMA. However, differences were not so great since signals noise was low (preprocessing had a little influence on the results) and specially because there were other factors such as ST–T changes or other heartbeat types that influenced the results (that is why we preferred complete synthetic signals). A proper database of real ECG signals with TWA annotated by experts is still lacking.

4.2 Baseline wandering

The experiments under different baseline wandering conditions also demonstrated that EMMA is more robust than MMA in these circumstances (Table 3). The effect of baseline wandering is an increase in the low detection threshold for TWA amplitude because of the additional wave amplitude offset. These methods are more sensitive to baseline wandering than to noise, that is, for sinusoidal amplitudes greater or equal than 10 μV, it is not possible to get accurate TWA measures in these experiments for a frequency of 0.3 Hz (an otherwise high baseline wandering frequency). For a more usual frequency, 0.08 Hz, baseline influence on TWA measurement reduces drastically.

4.3 Phase shifts

When there are phase shifts in the register, EMMA is again more accurate and robust. When no noise is present, results are equal (slightly better for EMMA if TWA = 10 μV, and better for MMA in the rest). With some noise, EMMA outperforms MMA in all cases by 25%. Since EMMA is based on MMA, the effect on the results of the phase shifts is negligible if noise is present, namely, there are no differences between EMMA and MMA as for phase shifts provided there is no noise in the signals. However, this is an unrealistic case because even after signal filtering, it is almost impossible to remove all the noise in a real signal.

4.4 Wave detection errors

Wave detection errors also add measurement bias since peaks are not correctly aligned. In all cases tested, EMMA results were more accurate, although measurements started to be acceptable for TWA greater than 100 μV. However, it has to be noted that heart rate is important in this case since 15 ms fiducial point shift is more significant for 120 bpm than for 60 bpm.

5 Conclusion

We presented a method to improve the accuracy of the MMA TWA analysis, based on DTW curve alignment. The results of our assessment study demonstrate EMMA to be more accurate than MMA. Specifically, our proposed method is more robust against noise, baseline wandering, phase shifts, and wave detection errors.

EMMA is simple to implement and computationally inexpensive. It only requires an additional stage before distance calculation in a standard MMA method. Accuracy can be further improved since curve alignment was only applied at the last stage of the distance calculation between averages $\overline{A}$ and $\overline{B}$, namely, intermediate averaging was computed without wave alignment, just wave length normalization. Thus, some alignment errors are already present before final curve matching takes place. However, the application of this method at every MMA algorithm step would be computationally very expensive, and therefore that possibility was discarded.

Experimental parameters were set for an unfavourable scenario. No filtering or preprocessing was applied as in a real case since the objective was to compare EMMA and MMA methods in a relative way to determine which one is more accurate and robust. There are other studies were MMA performance and accuracy was assessed and demonstrated (including minimum TWA amplitude detection threshold) in an absolute way [11, 14].

References

1. Burattini L, Zareba W, Couderc J, Titlebaum E, Moss A (1997) Computer detection of non-stationary t wave alternans using a new correlation method. In: Proceedings of computers in cardiology, vol 24. pp 657–660
2. Cuesta-Frau D, Biagetti MO, Quinteiro RA, Micó-Tormos P, Aboy M (2007) Unsupervised classification of ventricular extrasystoles using bounded clustering algorithms and morphology matching. Med Biol Eng Comput 44(3):229–239
3. Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK, Stanley HE (2000) Physiobank, physiotoolkit, and physionet: components of a new research resource for complex physiologic signals. Circulation 101(23):e215–e220. http://circ.ahajournals.org/cgi/content/full/101/23/e215
4. Janusek D, Kania M, Maniewski R (2006) Effect of electrocardiogram signal quality on t-wave alternans measurements: a simulation study. In: Proceedings of computers in cardiology, vol 33. pp 505–508
5. Kaufman ES, Mackall JA, julka B, Drabek C, Rosenbaum DS (2000) Influence of heart rate and sympathetic stimulation on arrhythmogenic t wave alternans. Am J Physiol Heart Circ Physiol 279(3):1248–1255
6. Martínez J, Olmos S, Laguna P (2000) T wave alternans detection: A simulation study and analysis of european st-t database. In: Proceedings of computers in cardiology, vol 27. pp 155–158
7. Martínez JP, Olmos S (2005) Methodological principles of t wave alternans analysis: a unified framework. IEEE Trans Biomed Eng 52(4):599–613
8. McSharry PE, Clifford GD, Tarassenko L, Smith LA (2003) A dynamical model for generating synthetic electrocardiogram signals. IEEE Trans Biomed Eng 50(3):289–294
9. Munich ME, Perona P (1999) Continuous dynamic time warping for translation-invariant curve alignment with applications to signature verification. In: Proceedings of 7th international conference on computer vision
10. Narayan S (2006) T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 47(2):269–281
11. Nearing BD, Verrier RL (2002) Modified moving average analysis of t-wave alternans to predict ventricular fibrillation with high accuracy. J Appl Physiol 92:541–549
12. Nearing BD, Huang A, RL V (1991) Dynamic tracking of cardiac vulnerability by complex demodulation of the t wave. Science 252(5004):437–440
13. Serinagaoglu Y, Sabuncuoglu D, Ider Y (1996) Spectral analysis of t wave alternans signal. In: Proceedings of 18th annual international conference of the IEEE engineering in medicine and biology society, pp 1353–1354
14. Shusterman V, Goldberg A (2004) Tracking repolarization dynamics in real-life data. J Electrocardiol 37:180–186
15. Strumillo P, Ruta J (2002) Poincaré mapping for detecting abnormal dynamics of cardiac repolarization. IEEE Eng Med Biol 21(1):62–65
16. Tomasi G, van den Berg F, Anderson C (2004) Correlation optimized warping and dynamic time warping as preprocessing methods for chromatographic data. J Chemomet 18(5):231–241
17. Verrier RL, Kwaku KF, Nearing BD, Josephson ME (2005a) T-wave alternans: does size matter? J Cardiovasc Electrophysiol 16(6):625–628
18. Verrier RL, Nearing BD, Kwaku KF (2005b) Noninvasive sudden death risk stratification by ambulatory ecg-based t-wave alternans analysis: evidence and methodological guidelines. ANE 10(1):110–120