HEART-RATE ADAPTIVE MATCH FILTER BASED PROCEDURE FOR AUTOMATIC DETECTION OF T-WAVE ALTERNANS FROM 24-HOUR ECG RECORDINGS

Issues Related to Filter Implementation

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Abstract: Twenty-four hour T-wave alternans (TWA) analysis is a promising approach for risk stratification, which still remains unpractical because TWA identification algorithms are complex and require long computation time (CT). The aim of the present study was to test the applicability to 24-hour ECG recordings of our heart-rate adaptive match filter (AMF) which allows TWA detection by submitting ECG data to a band-pass filter centered at the TWA fundamental frequency f_{TWA}, equal to a half heart rate. Two implementations are possible: 1) the passing-band is adapted to a varying f_{TWA} value (FA_AMF), and 2) the filter band is fixed while conditioning the ECG data (SA_AMF). Simulated ECG tracings, characterized by no TWA or by different kinds of TWA, and 24-hour ECG recordings from healthy subjects and coronary artery disease patients were used to identify the fastest of these two implementations. Our results yielded the conclusions that the CT of our AMF-based procedure is independent of the amount of TWA present in the tracing, but depends on ECG sample length and filter implementation. If filter-design tools are available while performing ECG analysis, the FA_AMF implementation is to be preferred because its CT is about one third of SA_AMF CT.

1 INTRODUCTION

T-wave alternans (TWA) is an ECG phenomenon consisting of every-other-beat changes in the T-wave morphology. After Adam et al. (1984) reported the existence of microvolt TWA, too small in amplitude to be visually detected at standard display scales, increasing evidence has been found of a link between TWA and vulnerability to life-threatening ventricular arrhythmias (Adam et al., 1984; Rosenbaum et al., 1994; Verrier et al., 1994; Bloomfield et al., 2004; Narayan, 2007; Chow et al., 2008; Gold et al., 2008). Original observations of this link arose from applications of fast Fourier transform spectral method (Smith et al., 1988) for TWA detection from ECG tracings of populations at high risk for ventricular arrhythmias. To reach a target heart-rate and meet data stationarity requirements, Fourier analysis was applied to short-term ECG tracings (typically 128 beats) recorded under strictly controlled conditions, such as pacing (Smith et al., 1988; Rosenbaum, 1994) or exercise (Estes et al., 1997; Hohnloser et al., 1998; Gold et al., 2000; Klingenheben et al., 2000; Hennersdorf et al., 2001). Later on, time-domain based techniques, with less restrictive requirements than Fourier analysis, were proposed for more flexible TWA analysis extended to long-term (20-minute to 24-hour) ambulatory recordings (Nearing et al., 1991; Burattini et al., 1999; Nearing et al., 2002; Martínez et al., 2005; Burattini et al., 2006). These techniques highlighted a strongly non-stationary nature of TWA (Nearing et al., 1991; Martínez et al., 2006; Burattini et al., 2008a and b). Especially, 24-hour Holter ECG analysis was suggested as a promising approach for risk stratification relative to cardiac arrest and arrhythmic death in relatively low-risk subjects, such as postmyocardial infarction patients (Verrier et al., 2003, Sakaki et al., 2009). Analysis of long-term ECG recordings for TWA identification is costly in computation time (CT). This may limit real-time analysis of ambulatory ECG recordings, unless an optimized fast-running algorithm is set up.

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To automatically detect stationary, as well as time-varying TWA, we have recently proposed a heart-rate adaptive match filter (AMF) based procedure, which was tested by applications to a) simulated ECG tracings, characterized by no TWA or by different kinds of TWA, and b) ECG recordings (up to 20-min long) from healthy subjects and cardiac disease patients (Burattini et al., 2006, Burattini et al., 2008a and b, Burattini et al., 2009a and b). This procedure allows TWA detection by submitting ECG data to bandpass filtering with narrow passing band centered around the TWA fundamental frequency f_{TWA} (which, by definition, equals a half heart rate), so that the TWA signal is provided as output. Adaptation of the AMF to heart-rate, and thus to f_{TWA}, can be accomplished by two different implementations. The first adapts the AMF passing-band to the current f_{TWA} value (adaptation at the filter level; FA_AMF); the second assumes a fixed filter band for conditioning the ECG data (adaptation at the signal level; SA_AMF).

The aim of the present study was to set-up a low-CT procedure suitable for real-time TWA analysis by testing the applicability of our AMF-based procedure to 24-hour ECG recordings, and to analyze pros and cons of its FA_AMF and SA_AMF implementations.

2 METHODS

2.1 Heart-Rate Adaptive Match Filter Implementations

Our AMF is conceptually a bandpass filter (Burattini et al., 2006 and 2008a and b), having a passing band of 0.12 Hz (2·df=0.12 Hz implies df=0.06 Hz) wide centered at the TWA fundamental frequency (f_{TWA}). When applied to a 128-beat ECG tracing, f_{TWA} is defined by the following equation:

$$f_{TWA} = \frac{1}{2 \cdot MRR} \quad (1)$$

where MRR denotes mean RR interval, over 128 beats.

2.1.1 FA_AMF Implementation

After defining $\omega_1=2\pi(f_{TWA}-df)$ and $\omega_2=2\pi(f_{TWA}+df)$, the AMF is implemented as a 6th order Butterworth bandpass filter, whose transfer function $H_{BP}(\omega)$ is expressed as follows (Burattini et al., 2008):

$$|H_{BP}(\omega)|^2 = \frac{1}{1+\left(\frac{\omega}{\omega_2}\right)^6} \cdot \frac{\left(\frac{\omega}{\omega_1}\right)^6}{1+\left(\frac{\omega}{\omega_1}\right)^6} \quad (2)$$

The input of the AMF is a 128-beat ECG signal (ecg(t), t denoting time) potentially affected by TWA. Its output is a constant phase and, possibly, amplitude-modulated sinusoid, which represents TWA and is, then, denominated 'TWA signal' (twa(t)). Consequently, if $h_{BP}(t)$ is the impulse response function associated to $H_{BP}(\omega)$, twa(t) is given by the following equation:

$$twa(t) = ecg(t) * h_{BP}(t) \quad (3)$$

This implementation procedure is graphically displayed in Fig. 1. When TWA is analyzed from long-term ECG recordings by recursively (for example every 10 s) extracting a 128-beat ECG string from the entire recording (Burattini et al., 2008), the passing band has to be relocated at f_{TWA}, which is a function of heart rate (eq. 1). Consistently, this AMF implementation was called filter-adapting AMF (FA_AMF). Specific steps for TWA analysis are as follows:

1. Extraction of a 128-ECG string, ecg(t), from the long-term recording.
2. f_{TWA} computation from mean heart rate (eq. 1).
3. Setting of the 6th order Butterworth passing-band at f_{TWA} (eq. 2).
4. Filtering of ecg(t) with FA_AMF, according to eq. 3, to obtain twa(t).
5. Exit, if the end of long term tracing is reached; otherwise restart from step 1 after 10 seconds time-increase.

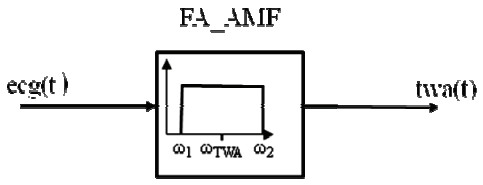

Figure 1: Filter-adapting AMF implementation (FA_AMF).

2.1.2 SA_AMF Implementation

The impulse response function $h_{BP}(t)$, associated to the transfer function of eq. 2, can be synthesized by using an appropriate designed low-pass filter. Specifically, it is possible to show (see Appendix) that $h_{BP}(t)$ can be expressed as:

$$h_{BP}(t) = 2h_{LP}(t)\cos(\omega_{TWA}t) \quad (4)$$

where $\omega_{TWA}=2\pi f_{TWA}$, and $h_{LP}(t)$ is the impulse response of a lowpass filter having $\omega_{df}=2\pi \cdot df$ cut-off frequency. Indeed, the basic idea is to translate the passing band around 0 Hz, so that it becomes independent of f_{TWA}, and move the heart-rate dependency into the cosine (translation in the frequency domain corresponds to modulation in the time domain).

By substituting eq. 4 into eq. 3 (and recalling that cos(x-y)=cos x cos y + sin x sin y):

$$\begin{aligned}
&twa(t) = \\
&= ecg(t) * (2h_{LP}(t)\cos(\omega_{TWA}t)) = \\
&= 2\int_{-\infty}^{+\infty} ecg(\tau)\ h_{LP}(t-\tau)\cos(\omega_{TWA}(t-\tau))d\tau = \\
&= 2\int_{-\infty}^{+\infty} ecg(\tau)\ h_{LP}(t-\tau)\cos(\omega_{TWA}t)\cos(\omega_{TWA}\tau)d\tau + \\
&+ 2\int_{-\infty}^{+\infty} ecg(\tau)\ h_{LP}(t-\tau)\sin(\omega_{TWA}t)\sin(\omega_{TWA}\tau)d\tau = \\
&= 2\cos(\omega_{TWA}t)\int_{-\infty}^{+\infty} ecg(\tau)\cos(\omega_{TWA}\tau)\ h_{LP}(t-\tau)d\tau + \\
&+ 2\sin(\omega_{TWA}t)\int_{-\infty}^{+\infty} ecg(\tau)\sin(\omega_{TWA}\tau)\ h_{LP}(t-\tau)d\tau
\end{aligned}$$

Consequently,

$$\begin{aligned}
&twa(t) = \\
&= 2\cos(\omega_{TWA}t)[(ecg(t)\cos(\omega_{TWA}t)) * h_{LP}(t)] + \\
&+ 2\sin(\omega_{TWA}t)[(ecg(t)\sin(\omega_{TWA}t)) * h_{LP}(t)]
\end{aligned} \quad (5)$$

Based on this implementation, graphically shown in Fig. 2, when TWA is recursively analyzed from long-term ECG recordings, the passing band of the two lowpass filters (which are identical) keeps constant, while their input and output signals are modulated to adapt to heart rate variations. This AMF implementation is referred to as signal-adapting AMF (SA_AMF), and each one of the lowpass filters incorporated is set-up as a 3rd order Butterworth filter. Specific steps for TWA analysis are as follows:

1. 'A priory' design of a 3rd order Butterworth lowpass filter with a cutoff frequency set at a fixed df value.
2. Extraction of a 128-ECG string, ecg(t), from the long-term recording.
3. Computation of $\omega_{TWA}=2\pi f_{TWA}$, being f_{TWA} defined by eq. 1.
4. Filtering of ecg(t) with SA_AMF, according to eq. 5, to obtain twa(t).
5. Exit, if the end of long term tracing is reached; otherwise restart from step 2 after 10 seconds time-increase.

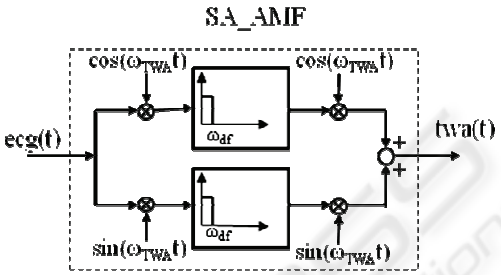

Figure 2: Signal-adapting AMF implementation (SA_AMF).

2.2 FA_AMF vs. SA_AMF

Simulated and clinical ECG tracings (described in 2.3) were analysed by extracting 128 beats every 10 seconds (Burattini et al., 2008). Comparison between FA_AMF and SA_AMF based TWA detection procedures was performed in terms of computation time (CT).

2.3 ECG Data

2.3.1 Simulated 128-Beat ECG Tracings

Basic simulated ECG tracing consisted of an 128-fold repeated real and clean ECG complex sampled at 200 samples/s. The RR interval was 0.750 s. Thus, TWA fundamental frequency (f_{TWA}) was 0.67 Hz , that is 1/(0.750×2 s) or 0.5 cycles per beat. T wave was identified in a 160 ms window centred around the T-wave apex. The endpoints samples of the T-wave window (T_{onset} and T_{offset}) were localized 120 ms and 280 ms after the R peak.

All simulated 128-ECG tracings are displayed in Fig. 3. The first simulated ECG (NO_TWA) represents the ideal case of a tracing not affected by any kind of variability (basic cardiac complex repeated with no changes). The second simulated ECG (STATIONARY_TWA) was affected by a stationary 10 μV TWA. Eventually, the third and the forth simulated ECG tracings were affected by time-varying (non-stationary) TWA, respectively characterized by a smoothed step profile (STEP_TWA; with 24 beats or 18 s transition time-duration), and by a sinusoidal profile

(SINUSOID_TWA; with the sinusoid period of 60 beats or 45 s, and amplitude of 5 μV, yielding to a maximum TWA amplitude of 10 μV).

Simulated long-term (20-minute and 24-hour) tracings were obtained by repetition of the basic 128-beat ECG simulated strings.

2.3.2 Clinical ECG Tracings

Clinical tests were performed on 24-hour Holter ECG recordings from 3 healthy (H) subjects and 3 coronary artery disease (CAD) patients. All subjects pertain to the Intercity Digital Electrocardiology Alliance (IDEAL) Study conducted following the required rules for human subjects' research principles, according to the Declaration of Helsinki, as well as to Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. The IDEAL protocol was approved by Research Subject Review Board of the University of Rochester. ECG tracings were acquired using the SpaceLab-Burdick digital Holter recorder (SpaceLab-Burdick, Inc., Deerfield, WI; sampling frequency 200 samples/s).

2.4 Statistics

Each ECG tracing (either 128-beat, 20-minute or 24-hour long) was analyzed five times, and mean and standard deviation values of the CT were reported (0.1 s resolution) and compared using Student's t-test. Associations between quantities was evaluated using the correlation coefficient (r). Statistical significance was assumed at $P<0.05$. Analysis were performed on PC (Intel® Core™ Quad CPU Q9300 @ 2.50GHz, 3GB of RAM) using the MATLAB 7.0 development environment.

3 RESULTS

Fig. 4 shows the TWA signals obtained from both FA_AMF-based (dotted line) and SA_AMF-based (solid line) procedures when the input is represented by the simulated data. For all simulated conditions (namely NO_TWA, STATIONARY_TWA, STEP_TWA, SINUSOID_TWA), the TWA-signal outputs of FA_AMF implementation are not distinguishable from the corresponding SA_AMF ones. Thus, solid lines superimpose to dotted line in the four panels of Fig.4.

Table 1 shows CT values of the two competing filter implementations, in relation to different simulated tracings lengths and to the four simulated conditions specified above. FA_AMF column of this table clearly shows that, for any given ECG tracing-length (either 128 beats, or 20 minutes or 24 hours), the CT is irrespective of TWA presence and kind. This is true also for the SA_AMF implementation, as judged from CT values in the related column of Table 1. Comparison between corresponding CT values of columns FA_AMF and SA_AMF, at 0.1 s time resolution, shows no significant differences for 128-beat ECG analysis, while the FA_AMF procedure is significantly faster than the SA_AMF when applied to long-term (20-minute and 24-hour) tracings. In absolute terms, for 20-minute ECGs, the mean CT of FA_AMF differs by less than 2 seconds compared to the FA_AMF implementation (1.2±0.0 s vs. 3.0±0.0; $P<0.001$). For 24-hour ECGs, the SA_AMF mean CT (203.3±2.9 s) and the FA_AMF mean CT (73.5±1.5 s) differ in such a way that the ratio between the two is 2.77±0.03.

Mean (±SD) values for the FA_AMF and SA_AMF implementations in individual H and CAD cases are compared in Table 2. In the three H-subjects, the MRR (0.74±0.08 s) is similar to that (0.75 s) used in simulated cases. Also the mean CT values of 24-hour simulations for FA_AMF (73.4±0.8) and SA_AMF (203±2) are comparable with the corresponding mean CTs from the three H subjects (75.5±6.1 and 201±15, respectively).

On average, the ratio between SA_AMF CT and FA_AMF CT is 2.67±0.13, a value comparable ($P<0.05$) with that found in 24-hour simulated cases. MRR variation between 0.660 and 1.130 s, over all H and CAD cases, compared with corresponding CT variations of SA_AMF and FA_AMF, suggests a MRR-CT correlation, which is characterized by $r=0.99$ and $P<0.05$ for both implementations.

4 DISCUSSION

Our AMF–based TWA identification algorithm is substantially a bandpass filter which identifies TWA by filtering out every ECG frequency component but the TWA typical one (f_{TWA}). This method has been applied to 128-beat ECG recordings (Burattini et al., 2006, 2008a and 2008b, 2009a) and to 20-minute recordings (Burattini et al., 2008a and 2008b, 2009b). The latter study involved a recursive application of the AMF procedure to 128-beat ECG strings extracted every 10 seconds. On this basis, from a theoretical point of view, our method appears suitable for application to longer term tracings such as 24-hour ECGs. Nevertheless, practical, routine

applications of this technique to long recordings is potentially limited by the CT required to identify TWA. This possibility was tested in the present study by analyzing the CT of two different implementations of the AMF.

The first AMF implementation, referred to as FA_AMF (Fig. 1), consists of a single 6th order Butterworth bandpass filter. Since heart-rate is time variant, the $f_{TWA,}$ defined as a half of mean heart rate, is also time variant. Consequently, the FA_AMF passing-band has to be recursively adapted to properly detect TWA. This requires a real-time (i.e. while analyzing TWA from the ECG) filter setting. Thus, in the environment where TWA is analyzed (for example in an ECG analysis machine), availability of filter-design tools is required, such as those provided by MATLAB.

The second AMF implementation, referred to as SA_AMF (Fig. 2), is more complex for it involves two identical lowpass filters and repeated signal modulation. The 3rd order lowpass Butterworth implementation of each one of these filters is independent of heart rate and, thus, of f_{TWA}. Consequently, it can be designed 'a priory' and imported in the TWA analysis environment, thus releasing the need of recursive filter setting.

In this study we performed a quantitative comparison of the two implementations, in terms of CT, when analyzing 128-beat, 20-minute and 24-hour simulated ECG recordings, and 24-hour clinical ECG recordings. Both simulated and clinical tracings were characterized by the same sampling

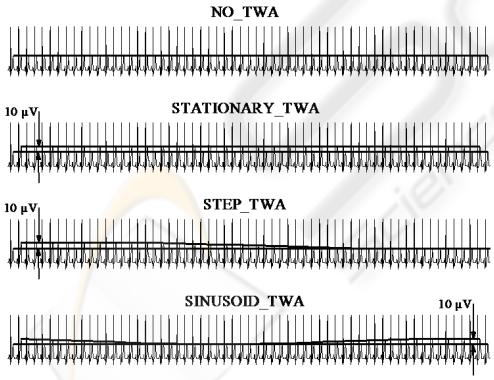

Figure 3: Central strings (about 45 s) of simulated 128-beat ECG tracings. NO_TWA represents the ideal case of a tracing not affected by any kind of modulation. STATIONARY_TWA represents an ECG affected by a stationary TWA of 10 μV. STEP_TWA represents an ECG affected by TWA that varies from 10 μV to 0 μV following a smoothed step profile. SINUSOIDAL_TWA represents an ECG affected by TWA that varies from 10 μV to 0 μV following a sinusoidal profile.

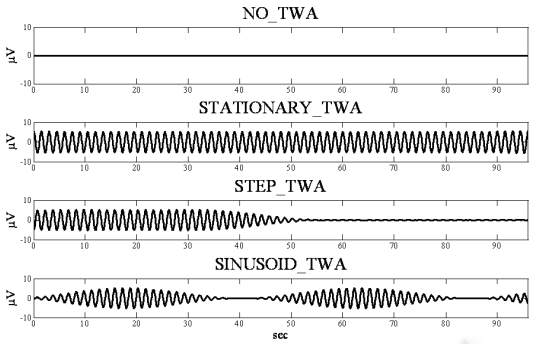

Figure 4: Output TWA signals provided by the FA_AMF (dotted line) and SA_AMF (solid line) based procedures, when the inputs are the 128-beat simulated ECG tracings with: no TWA (NO_TWA), stationary TWA (STATIONARY_TWA), smoothed step TWA (STEP_TWA) and sinusoidal TWA (SINUSOID_TWA). For all the simulated conditions, the two estimated TWA signals superimpose, so that dotted lines are not visible.

frequency (200 samples/sec), so that the number of samples in a 24-hour recording is the same.

Results of the simulation study show that, for any given ECG tracing length, the CT of related filter implementation is irrespective of TWA presence and kind. Comparison between corresponding CT values of FA_AMF and SA_AMF implementations indicates that, for short-time ECG recordings, the two are equivalent, while the FA_AMF procedure is significantly faster when applied to long-term tracings (Table 1). In the specific, when analyzing 24-hour recordings, the ratio between CT of SA_AMF and CT of FA_AMF was, on average, almost three times larger.

These observations are confirmed by the results on the 24-hour clinical data. Indeed, the ratio of 2.67 between the CT of SA_AMF and FA_AMF is not significantly different from that of 2.77 found for the simulated 24-hour tracings.

In our clinical data, a strong correlation ($r=0.99$; $P<0.05$) was observed between MRR over 24 hours and corresponding CT of either one of the two implementations. This result finds an explanation in that 128-beat ECG are recursively submitted to the AMF. These ECG segments, although matching in terms of number of beats, are characterized by a different length in terms of number of samples. The longer the RR interval, the higher the number of samples, and thus, the longer the required CT. This observation is supported by the facts that simulated and clinical data are characterized by similar MRR and similar mean 24-hour CTs for both FA_AMF and SA_AMF implementations (see Results). The

Table 1: Computation time (CT, seconds) of FA_AMF- and SA_AMF-based TWA detection procedures applied to 128-beat, 20-minute and 24-hour simulated ECG recordings, in the absence of TWA, or in the presence of different kinds of TWA. Mean CT±SD values are computed over five algorithm runs.

	CT of FA_AMF (s)	CT of SA_AMF (s)	P (Student's t test)
128-beat ECGs			
NO_TWA	0.1±0.0	0.1±0.0	NS
STATIONARY_TWA	0.1±0.0	0.1±0.0	NS
STEP_TWA	0.1±0.0	0.1±0.0	NS
SINUSOID_TWA	0.1±0.0	0.1±0.0	NS
20-minute ECGs			
NO_TWA	1.2±0.0	3.0±0.0	<0.001
STATIONARY_TWA	1.2±0.0	3.0±0.0	<0.001
STEP_TWA	1.2±0.0	3.0±0.0	<0.001
SINUSOID_TWA	1.2±0.0	3.0±0.0	<0.001
24-hour ECGs			
NO_TWA	73.1±1.9	201.1±3.4	<0.001
STATIONARY_TWA	74.5±0.6	204.8±2.5	<0.001
STEP_TWA	72.7±1.6	204.6±1.0	<0.001
SINUSOID_TWA	73.5±1.2	202.5±3.2	<0.001

Table 2: Computation time (CT, seconds) of FA_AMF- and SA_AMF-based TWA detection procedures applied to 24-hour ECG recordings of three H-subjects (H1, H2, and H3) and three CAD patients (CAD1, CAD2, and CAD3). Mean CT±SD values are computed over five algorithm runs.

	MRR (s)	CT of FA_AMF (s)	CT of SA_AMF (s)	P (Student's t test)
24-hour ECGs				
H1	0.660	68.9±1.0	186.1±3.2	<0.001
H2	0.757	76.8±0.8	202.0±3.3	<0.001
H3	0.814	80.9±1.4	215.7±1.1	<0.001
CAD1	0.960	98.5±0.1	241.0±1.4	<0.001
CAD2	1.091	103.9±2.0	281.7±9.7	<0.001
CAD3	1.130	105.9±0.6	303.0±2.6	<0.001

above mentioned high correlation between mean RR and CT was obtained considering together H-subjects, who are not supposed to show significant TWA levels, and CAD-patients, who instead are known to show increased levels of TWA (Burattini et al., 2008a and 2009a). This result agrees with the result, obtained with simulated data, that the CT is irrespective of TWA presence and kind. Altogether, our results suggest that the FA_AMF implementation is preferable as it is faster. This advantage, however, conflicts with the limitation relying on the need of filter-design tools that are not commonly available in clinical environments. On the other hand, when using the SA_AMF, the CT assumes, over 24-hour ECGs, values of few minutes (up to five in our results; Table 1 and Table 2). These CT values can be considered acceptable for real time computation in light of the fact that the operator is made free from the need of filtering design tools.

5 CONCLUSIONS

In conclusion, our AMF-based procedure for TWA identification proved to be appropriate for applications to 24-hour recordings. If filter design tools are available while performing the analysis, the FA_AMF implementation is to be preferred because it allows faster analysis of 24-hour recordings, with CT ratio between SA_AMF and FA_AMF being about 2.7. Otherwise, SA_AMF implementation can be performed, which provides TWA identification with a CT of a few minutes.

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APPENDIX

Consider a filter having the following unit impulse response:

$$h(t) = 2h_{LP}(t)\cos(\omega_{TWA}t) \quad \text{(A1)}$$

where $h_{LP}(t)$ is the unit impulse response of a lowpass filter with cutoff frequency df. By taking the Fourier transform of h(t) we get:

$$\begin{aligned} &H(\omega) = \\ &= \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} 2h_{LP}(t)\cos(\omega_{TWA}t)e^{-j\omega t}dt = \\ &= \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} h_{LP}(t)e^{-j(\omega-\omega_{TWA})t} + h_{LP}(t)e^{-j(\omega+\omega_{TWA})t}dt \end{aligned} \quad \text{(A2)}$$

Upon examination of eq. A2, it is seen that the first summation term is equal to a right-shifted by ω_{TWA} version of the LP frequency response, while the second term corresponds to a left-shifted by ω_{TWA} version of the LP frequency response. Thus, the frequency response associate to h(n) is:

$$H(\omega) = H_{LP}(\omega - \omega_{TWA}) + H_{LP}(\omega + \omega_{TWA}) \quad \text{(A3)}$$

The magnitude of the first component in eq. A3 is seen to equal the magnitude of LP shifted by ω_{TWA} radians. That is, it corresponds to the rightmost passband centered at ω_{TWA}. Similarly, the magnitude of the second term corresponds to the leftmost passband centered at ω_{TWA}. Thus, we can conclude that the filter, whose frequency response is represented in eq. A3, can be used to implement our AMF:

$$H_{BP}(\omega) = H(\omega) \quad \text{(A4)}$$