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Amplitude of Dominant T–Wave Alternans assessment on ECGs obtained from a biophysical model

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Abstract— **The Amplitude of Dominant T–Wave Alternans (ADTWA) is a recently introduced index which quantifies the presence of microvolt T Wave Alternans (TWA) on surface ECG recordings. In this paper we investigate the reliability of ADTWA and its robustness against broadband noise. At this regard, we generated synthetic 12–leads ECG recordings through a forward electrophysiological model and we added TWA, at different extent, by modulating the variation of the repolarization times of transmembrane action potentials across even and odd beats. Using a stochastic model, we derived an analytical relationship between the repolarization variation injected into the model and TWA at the surface, thus offering a strategy to evaluate lead sensitivity. In terms of robustness, the results of the simulations show that ADTWA correctly measured the amplitude of synthetic TWA with an average error of $3.3\% \pm 5.8\%$ in absence of noise. When a 100 μV peak–to–peak broadband noise is present, its effects on estimation errors were kept limited by singular value decomposition on which ADTWA builds.**

I. INTRODUCTION

T–wave Alternans (TWA) is defined as a beat–to–beat alteration in the repolarization morphology that repeats every other heart beat. In many cases the size of such alterations is small (about tens of microvolts) and they are often buried into noise. Therefore signal processing methods are most often necessary to reveal microvolt TWA presence [1].

In a recent paper [2], a new technique termed Amplitude of Dominant T–Wave Alternans (ADTWA) was proposed. It quantifies TWA starting from the dominant T wave (DTW) [3] associated to a number of consecutive beats. Three strengths make it promising: i) the DTW derives directly from a physiological model [4] and reflects the repolarization stage of the myocytes transmembrane potentials. Then ADTWA is linked to the differences in the cellular repolarization times and it carries a clear physiological meaning; ii) ADTWA uses Singular Value Decomposition (SVD) to compute the DTW thus it benefits from SVD's resilience towards uncorrelated noises; iii) in pooling the various leads it implicitly overcomes one of the typical problem, that TWA magnitude may be lead–dependent [5].

The goals of this paper are two-folds. First we assessed ADTWA on synthetic 12-leads ECG recordings obtained with a electrophysiological forward model for the electrical activity of the human heart in healthy conditions. This permits an extensive test which in [2] was instead limited to part of the Computers in Cardiology 2008 challenge database.

Second, we measured the theoretical sensitivity of each lead to variation of the repolarization delays. In fact, in generating the synthetic ECGs, TWA was not added onto the signals or the vectorcardiogram as done in most simulations, but obtained modulating the repolarization delays in the physiological model. The approach we followed is shared by the works of Selvaraj *et al.* [6] and Janusek *et al.* [7], but in here, using a stochastic model, it is possible to derive an analytical relation between the standard deviation of the differences of the repolarization delays and TWA. Also we explored a much larger number of cases.

II. METHOD

A. Origin of the ADTWA metric

The shape of the T–wave observed on the surface ECG, $\psi(t)$, can be related to the repolarization phase of the transmembrane potentials at the level of the myocytes, $D_m(t)$ (with $m = 1, \ldots, M$, being M the number of sources, or "nodes", used to describe the heart), by the following

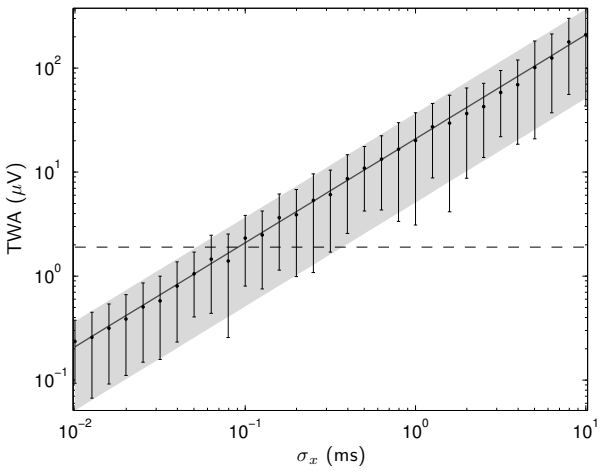

Fig. 1. Value of TWA, as measured on ECGs obtained from the model in equation (1) for lead V1, as a function of the standard deviation of the repolarization times' variations σ_δ across even and odd beats. The mean value obtained from 64 different computations performed for each values of σ_δ are reported as well as their standard deviation (dots with errorbars). The thick line is the expected mean TWA value predicted by equation (8), while the gray area is the span of the expected standard deviation (68.4% of the distribution is contained in the gray area). The sketched horizontal line evidences the TWA value of 1.9 μV sometimes used as a threshold for a positive TWA test.

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approximate relationship

$$\boldsymbol{\psi}(t) = \begin{bmatrix} \psi_1(t) \\ \cdots \\ \psi_L(t) \end{bmatrix} = \mathbf{A} \begin{bmatrix} D_1(t) \\ \cdots \\ D_M(t) \end{bmatrix}, \quad (1)$$

where $\psi_l(t)$ is the potential recorded in one of the L leads considered and $\mathbf{A}$ is a transfer matrix. Matrix $\mathbf{A}$ has size $[L \times M]$, it is patient–dependent and depends on the specific leads configuration. It accounts for both the volume conductor (geometry and conductivity) and the solid angle under which the single source contributes to the potentials in $\boldsymbol{\psi}(t)$. In first approximation, the decay of the transmembrane potential during repolarization is very similar across nodes. Therefore, in equation (1) the functions $D_m(t)$ can be approximated by a common function $D(t-\rho_m)$, where ρ_m is the repolarization time, different for each node. Expanding the function $D\,(t)$ around $\bar{\rho} = \frac{1}{M}\sum_{m=1}^{M} \rho_m$ leads to the following model [4]

$$\boldsymbol{\psi}(t) \approx -\mathbf{A} \begin{bmatrix} \Delta\rho_1 \\ \cdots \\ \Delta\rho_M \end{bmatrix} \dot{D}(t-\bar{\rho}), \quad (2)$$

where $\Delta\rho_m = \rho_m - \bar{\rho}$. Its discrete-time equivalent is

$$\boldsymbol{\Psi} \approx \mathbf{w}\mathbf{T}_{\mathrm{d}}, \quad (3)$$

with $\mathbf{w} = -\mathbf{A}\boldsymbol{\Delta\rho}$ is the vector of lead factors and $\boldsymbol{\Delta\rho} = [\Delta\rho_1, \ldots, \Delta\rho_M]^T$. $\mathbf{T}_{\mathrm{d}}$, the sampled first derivative of the repolarization curve $\dot{D}(t-\bar{\rho})$, was termed by Van Oosterom [3], [8] *dominant* T–wave.

The utility of equation (3) relies on the fact that both $\mathbf{T}_{\mathrm{d}}$ and $\mathbf{w}$ can be computed from the surface ECG. In particular, minimizing the Frobenius norm of the quadratic error $\epsilon = \|\boldsymbol{\Psi} - \mathbf{w}\mathbf{T}_{\mathrm{d}}\|_F$, leads to

$$\mathbf{T}_{\mathrm{d}} = c_2\lambda_1\mathbf{v}_1^T \qquad \mathbf{w} = \frac{\mathbf{u}_1}{c_2}.$$

where $\mathbf{u}_1$ and $\mathbf{v}_1$ are the unit-norm, first columns of the matrixes $\mathbf{U}$ and $\mathbf{V}$ obtained by SVD of $\boldsymbol{\Psi} = \mathbf{U}\mathbf{S}\mathbf{V}^T$ and where λ_1 is the corresponding largest singular value.

We recently noticed [2] that physiological studies suggest that the shape of the myocytes' action potentials during repolarization, in first approximation, does not vary during TWA. Therefore throughout TWA, $\mathbf{T}_{\mathrm{d}}$ should be approximately fixed, with the variations embedded in the lead factors $\mathbf{w}$. The TWA, computed simply as the maximum absolute differences in the T–waves of even ($\boldsymbol{\Psi}^{\mathrm{e}}$) and odd ($\boldsymbol{\Psi}^{\mathrm{o}}$) beats in the i^{th} lead, is then

$$\mathrm{TWA}_i = \max_t |\boldsymbol{\Psi}_i^{\mathrm{e}} - \boldsymbol{\Psi}_i^{\mathrm{o}}| \approx |w^{\mathrm{e}}[i] - w^{\mathrm{o}}[i]| \max_t |\mathbf{T}_{\mathrm{d}}|. \quad (4)$$

This justifies why we termed *Amplitude of Dominant T–Wave Alternans* (ADTWA) the index

$$I = \mathrm{ADTWA} = \max_i |w^{\mathrm{e}}[i] - w^{\mathrm{o}}[i]| \max_t |\mathbf{T}_{\mathrm{d}}|. \quad (5)$$

TABLE I

SMALLER VALUE OF σ_δ FOR WHICH A GIVEN *reference* TWA LEVEL IS DETECTED IN THE SURFACE ECG.

Lead	σ_δ (ms)		
	TWA= 1.9 μV	TWA= 4 μV	TWA= 10 μV
V1	0.091	0.191	0.478
V2	0.075	0.159	0.396
V3	0.112	0.235	0.588
V4	0.166	0.349	0.873
V5	0.230	0.484	1.209
V6	0.297	0.625	1.563
aVR	0.376	0.792	1.981
aVL	0.247	0.519	1.298
aVF	0.245	0.517	1.292
I	0.272	0.573	1.432
II	0.270	0.568	1.421
III	0.195	0.411	1.028

ADTWA and T–Wave Alternans

Two main models have been set forth to explain TWA [9], [10]. Both link to modifications at the cellular level to explain the phenomenon and, basically, support the theory that changes in the dispersions of the repolarization times of myocytes in turn modify the shape of the surface T–wave. The link between dispersion of repolarization and T–wave shape was implied by di Bernardo & Murray [11] and formalized by Van Oosterom (see equation (2)), but never referred explicitly to TWA. In here, we show that changes in the dispersion of the repolarization times in equation (1) lead to synthetic ECGs displaying TWA.

We start modeling the vector of repolarization times in two consecutive beats with

$$\begin{aligned} \boldsymbol{\rho}^{\mathrm{e}} &= \bar{\rho}^{\mathrm{e}} + \boldsymbol{\Delta\rho}^{\mathrm{e}} = \bar{\rho}^{\mathrm{e}} + \boldsymbol{\vartheta} + \boldsymbol{\delta}/2 \\ \boldsymbol{\rho}^{\mathrm{o}} &= \bar{\rho}^{\mathrm{o}} + \boldsymbol{\Delta\rho}^{\mathrm{o}} = \bar{\rho}^{\mathrm{o}} + \boldsymbol{\vartheta} - \boldsymbol{\delta}/2 \end{aligned} \quad (6)$$

where $\boldsymbol{\vartheta} = (\boldsymbol{\Delta\rho}^{\mathrm{e}} + \boldsymbol{\Delta\rho}^{\mathrm{o}})/2$, $\boldsymbol{\delta} = (\boldsymbol{\Delta\rho}^{\mathrm{e}} - \boldsymbol{\Delta\rho}^{\mathrm{o}})$ and the exponents relate to even ($^{\mathrm{e}}$) or odd ($^{\mathrm{o}}$) beats. The first term, $\bar{\rho}^{\mathrm{e}}$ or $\bar{\rho}^{\mathrm{o}}$, is the average value in each beat. The second one, $\boldsymbol{\vartheta}$, embeds the dispersion around the mean and the fact that repolarization times are not random but do follow largely a physical time–sequence, set forth by the functioning of the cardiac pump. Finally, $\boldsymbol{\delta}$ models the (recurrent) changes in the repolarization delays which give rise to TWA.

Let's now consider the corresponding ECG. Similarly to equation (3), we have

$$\begin{aligned} \boldsymbol{\Psi}^{\mathrm{e}} &\approx -\mathbf{A}\left\{\boldsymbol{\vartheta} + \boldsymbol{\delta}/2\right\}\mathbf{T}_{\mathrm{d}}^{\mathrm{e}} \\ \boldsymbol{\Psi}^{\mathrm{o}} &\approx -\mathbf{A}\left\{\boldsymbol{\vartheta} - \boldsymbol{\delta}/2\right\}\mathbf{T}_{\mathrm{d}}^{\mathrm{o}}. \end{aligned}$$

Considering that, during TWA, $\mathbf{T}_{\mathrm{d}}^{\mathrm{e}} \approx \mathbf{T}_{\mathrm{d}}^{\mathrm{o}} \approx \mathbf{T}_{\mathrm{d}}$ hence

$$\boldsymbol{\Psi}^{\mathrm{e}} - \boldsymbol{\Psi}^{\mathrm{o}} \approx -\mathbf{A}\boldsymbol{\delta}\mathbf{T}_{\mathrm{d}}$$

and following equation (4)

$$\mathrm{TWA}_i \approx |\mathbf{A}_i\boldsymbol{\delta}| \max_t |\mathbf{T}_{\mathrm{d}}|, \quad (7)$$

where $\mathbf{A}_i$ is the i^{th} line of the matrix $\mathbf{A}$.

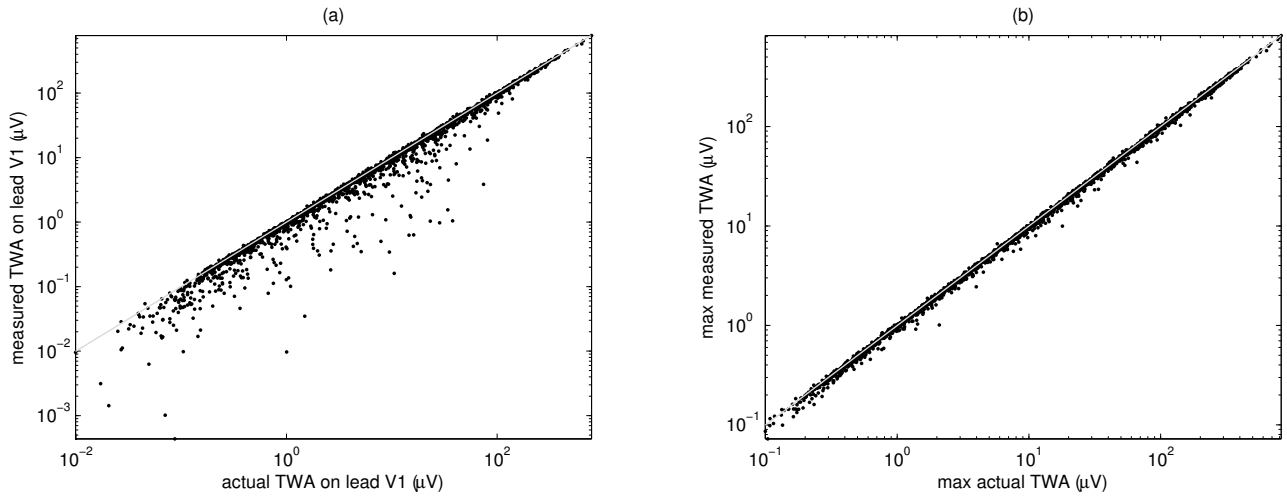

Fig. 2. Estimated TWA as a function of *reference* TWA values. Panel (a) contains values limited to lead V1 – computed using equation (7). Panel (b) displays the ADTWA index, i.e. the maximum values across the leads considered as in equation (5).

If we assume $\boldsymbol{\delta}$ to be an independent normal variable, i.e. $\delta_m \sim \mathcal{N}(0, \sigma_\delta^2)$, the quantity $\zeta = |\mathbf{A}_i \boldsymbol{\delta}|$ is also a random variable distributed as a half-normal distribution of mean $\mu_\zeta = \sigma_\delta [2/\pi \sum_{m=1}^{M} A_{i,m}^2]^{1/2}$ and standard deviation $\sigma_\zeta = \mu_\zeta [(\pi - 2)/2]^{1/2}$. This follows directly from the fact that each term in $\boldsymbol{\delta}$ is an independent normal variable. The TWA for lead i is then given by the product of a constant deterministic term, the maximum of the dominant T–wave, with a random variable and on average

$$E[\mathrm{TWA}_i] = \sigma_\delta \left[\frac{2}{\pi} \sum_{m=1}^{M} A_{i,m}^2 \right]^{1/2} \max_t |\mathbf{T}_\mathrm{d}|. \qquad (8)$$

In this model the relation between the standard deviation of the repolarization times' variations σ_δ across even and odd beats and its effect on the surface potentials is linear.

B. Synthetic TWA signals

To test the validity of equation (8), we generated body surface potentials using the forward electrophysiological model of equation (1). We used the transfer matrix $\mathbf{A}$ provided by ECGSIM (version 1.3) [12] which maps 257 nodes, each modeling the activity of a group of close-by myocytes on the epicardium and endocardium. We limited our study to the 12 standard leads. Transmembrane potentials – including depolarization and repolarization – were described with [13]

$$S(t) = \gamma \frac{1}{1 + e^{\alpha(t-\eta)}} \frac{1}{\left[1 + e^{\beta_1 (t-\rho)}\right] \left[1 + e^{\beta_2 (t-\rho)}\right]} - c,$$

where ρ is the repolarization time (which corresponds to $\rho_m = \bar{\rho} + \vartheta_m$ in equation (6)). The values of the parameters were obtained by fitting the transmembrane potential of each node provided by ECGSIM with $S(t)$.

To perform the simulations, we reimplemented the model within MATLAB (The MathWorks, Natick, MA). The vector $\boldsymbol{\delta}$ was built out of random independent normal variables with σ_δ in the range $[0.01, 10]$ ms. The potentials $\boldsymbol{\Psi}^\mathrm{e}$ and $\boldsymbol{\Psi}^\mathrm{o}$ were obtained from equation (1) with $\boldsymbol{\rho}^\mathrm{e} = \bar{\rho} + \boldsymbol{\vartheta} + \boldsymbol{\delta}/2$ and $\boldsymbol{\rho}^\mathrm{o} = \bar{\rho} + \boldsymbol{\vartheta} - \boldsymbol{\delta}/2$ modeling two consecutive beats. Synthetic TWA was directly evaluated on each lead as the maximum (over time) absolute difference among $\boldsymbol{\Psi}^\mathrm{e}$ and $\boldsymbol{\Psi}^\mathrm{o}$. The values are taken as *reference* TWA amplitude in the following of the paper. Finally a set of noisy ECG signals was generated by adding 100 μV peak–to–peak noise on the synthetic beats (noise's standard deviation $\sigma_e = 13.8$ μV).

III. RESULTS

A. Variation of repolarization and TWA

Figure (1) shows how the *reference* TWA value depends on σ_δ in lead V1. For each value of σ_δ, 64 different simulations were performed (total number of simulations: 1984). The figure contains the mean *reference* TWA value as long as its standard deviation. The prediction of equation (8) is also displayed in the same figure and matches perfectly the simulations. This suggests that the approximations which led to the equation hold reasonably well. Similar results were observed in the other leads.

Given the good match obtained, we inverted equation (8) to investigate which was the minimum value of σ_δ leading to a certain average *reference* TWA level at the surface. TWA of 1.9, 4 and 10 μV were considered and the corresponding values of σ_δ for each of the 12 standard leads are reported in table I.

B. Reliability of ADTWA

Figure (2) compares the *reference* TWA values either with the TWA measured by the approximation of equation (4) in lead V1 (panel a) or with ADTWA (panel b). The ECGs considered were free of additional noise. The results confirmed that ADTWA correctly measures the value of TWA (average estimation error $3.3\% \pm 5.8\%$). On the other hand, when the approximation of equation (4) is used to compute TWA on a single lead basis, the error introduced in the estimates might be significant (on average $11.9\% \pm 20.4\%$). The errors can be

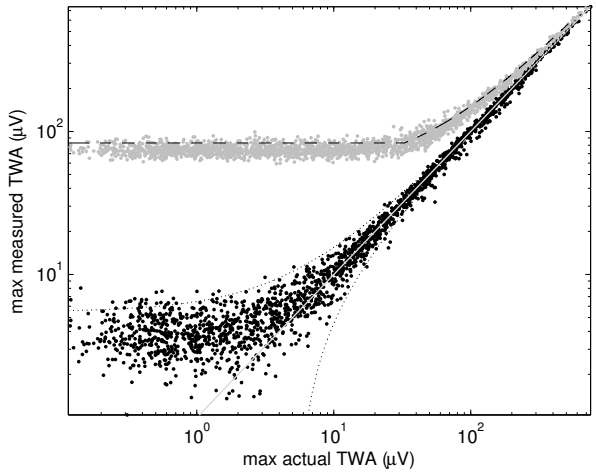

Fig. 3. As in figure (2b) but in here 100 μV peak-to-peak broadband noise was added to each beat before the analysis. Gray dots: maximum absolute difference across leads. Black dots: the ADTWA index. Dashed-lines: 99% percent confidence intervals computed extending the results in [2].

rationalized if ones considers that in a minorities of cases the TWA at the surface is, in one or more channel, orthogonal to the dominant T wave. Also, in a few cases the standard deviation σ_δ might become too large, breaking down the first order approximation implied by equation (2).

Noise effects: The influence of noise on TWA estimates is evidenced in Figure (3). The figure was obtained as figure (2b) but with a 100 μV peak-to-peak broadband noise added to each ECG synthetic beat before the analysis. For a comparison, the picture also contains (gray dots) the rough TWA estimates obtained by simply subtracting two consecutive beats and searching in time for the maximum difference (when TWA is low, this measure is dominated just by the superimposed noise). Please note that in the figure a single couple of beats is considered: in practical application several ones are taken into account. So the one proposed is a worst case scenario. Anyhow, the results of this section can be easily extended to account situations in which $2C$ beats are considered just scaling the noise level by a factor $\sqrt{C}$.

IV. CONCLUSION

In the paper we varied the repolarization times ρ_m and, using a standard electrophysiological forward model, we measured the effects on the surface ECGs between a couple of consecutive beats.

The values of *reference* TWA reported in table (I) show that when the hypothesis of the model are met, a few channel (e.g. V2, V1, V3) are more sensitive to variation of σ_δ. As reported by Bloomfield & Cohen [14], a criterium for positive TWA test is the presence of sustained alternans with an amplitude at least 1.9 μV. The results indicate that on different leads such TWA level corresponds to different variation of the repolarization times (and that a different threshold for each level should be envisioned in this perspective). Also, our findings compare well with the ones of Janusek *et al.* [15] who showed that a correlation exists between magnitude of the T–wave and sensitivity of TWA detection in a given lead (in their work leads V2 and V3 were found to be the most sensitive).

A further question we addressed is how well ADTWA captures body surface TWA. The results are positive indeed in particular when all the leads are used in the analysis. The finding is in agreement with the observation that multiple–leads analysis improves the TWA estimates [15].

A possible limit in our work is that we used the same theoretical framework for generating the data and deriving the index ADTWA. On the other hand, in generating the ECG signals with equation (1) we used a different transmembrane potential for each node. Therefore the good agreement between ADTWA and *reference* TWA was not expectable.

Finally, the use of SVD in ADTWA computation improves the robustness against noise making the estimates reliable for value of *reference* TWA $> \sigma_\delta/\sqrt{C}$ where $2C$ is the number of beats considered. In fact, the standard deviation of the error on the estimates of $\boldsymbol{T}_d$ is reduced by a factor λ_1, the largest singular value of $\boldsymbol{\Psi}$ [2]. As a result, the range of σ_δ values on which TWA can be reliably detected is enlarged.

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