Time-Varying Surrogate Data to Assess Nonlinearity in Nonstationary Time Series: Application to Heart Rate Variability

Luca Faes*, *Member, IEEE*, He Zhao, Ki H. Chon, *Senior Member, IEEE*, and Giandomenico Nollo, *Member, IEEE*

***Abstract*—We propose a method to extend to time-varying (TV) systems the procedure for generating typical surrogate time series, in order to test the presence of nonlinear dynamics in potentially nonstationary signals. The method is based on fitting a TV autoregressive (AR) model to the original series and then regressing the model coefficients with random replacements of the model residuals to generate TV AR surrogate series. The proposed surrogate series were used in combination with a TV sample entropy (SE) discriminating statistic to assess nonlinearity in both simulated and experimental time series, in comparison with traditional time-invariant (TIV) surrogates combined with the TIV SE discriminating statistic. Analysis of simulated time series showed that using TIV surrogates, linear nonstationary time series may be erroneously regarded as nonlinear and weak TV nonlinearities may remain unrevealed, while the use of TV AR surrogates markedly increases the probability of a correct interpretation. Application to short (500 beats) heart rate variability (HRV) time series recorded at rest (R), after head-up tilt (T), and during paced breathing (PB) showed: 1) modifications of the SE statistic that were well interpretable with the known cardiovascular physiology; 2) significant contribution of nonlinear dynamics to HRV in all conditions, with significant increase during PB at 0.2 Hz respiration rate; and 3) a disagreement between TV AR surrogates and TIV surrogates in about a quarter of the series, suggesting that nonstationarity may affect HRV recordings and bias the outcome of the traditional surrogate-based nonlinearity test.**

***Index Terms*—Complexity, heart rate variability (HRV), nonlinear dynamics, nonstationarity, surrogate data, time-varying (TV) autoregressive (AR) models.**

I. Introduction

THE METHOD of surrogate data belongs to the family of statistical tests known as *hypothesis testing*, which nowadays is the most popular test used in nonlinear time series analysis to investigate the existence of nonlinear dynamics underlying experimental data. Since its original formulation by Theiler *et al.* [1], this method has received great attention by researchers involved in the field of heart rate variability (HRV) analysis. It is indeed acknowledged that nonlinear dynamics are involved in the genesis of HRV, as a result of the interactions among hemodynamic, electrophysiological, and humoral variables as well as by autonomic and central regulations [2]. As a consequence, a large number of nonlinear analysis techniques have been proposed as tools for HRV assessment, and the method of surrogate was widely exploited for assessing the capability of nonlinear indexes to test the presence of nonlinearity in HRV series [3]–[7].

The method of surrogate data applied on a single time series is based on: 1) establishing a statistical hypothesis (the *null hypothesis*) against which observations are tested; 2) generating a set of time series (the *surrogate series*) that, in accordance with the null hypothesis, shares given properties of the original series but lacks the property that is under investigation; 3) calculating a certain index (the *discriminating statistic*) from the original series and from each surrogate series; and 4) performing a statistical test that, if the discriminating statistic computed for the original series results significantly different from the values obtained for the surrogate set, allows to reject—with some predetermined confidence level—the null hypothesis. Different types of surrogate data can be generated in accordance with different null hypotheses, and different discriminating statistics can be used (for recent reviews, see [8] and [9]). When the method is used for testing nonlinearity, a nonlinear index is used as discriminating statistic, and the null hypothesis of linear stochastic process is assumed for the investigated time series. Two main approaches have been identified to generate surrogate series according to this null hypothesis [10]: one is to fit a linear model to the original series and then feed the estimated model by independent noise realizations, generating "typical realizations" of the linear stochastic process; the second is to take a Fourier transform (FT) of the data, randomize the phases, and then invert the FT to generate "constrained realizations" of the process. Both these approaches generate surrogate series that have the same linear correlation function of the original series, but are otherwise random as specified by the null hypothesis.

In its classical formulation, the method of surrogate data investigates the presence of nonlinear dynamics assuming that the observed time series is stationary [1]. Due to this assumption, the surrogate series generated by the method is time-invariant (TIV), i.e., has statistical properties that are invariant to

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*L. Faes is with the Biophysics and Biosignals Laboratory, Department of Physics, University of Trento, Trent 12 I-38100, Italy (e-mail: luca.faes@unitn.it).

H. Zhao was with the Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, NY 11794-8181 USA. He is now with Mathworks, Inc., Natick, MA 01760-2098 USA (e-mail: hezhao@ic.sunysb.edu).

K. H. Chon is with the Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, NY 11794-8181 USA (e-mail: ki.chon@sunysb.edu).

G. Nollo is with the Biophysics and Biosignals Laboratory, Department of Physics, University of Trento, Trent 12 I-38100, Italy (e-mail: nollo@science.unitn.it).

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translation of the time origin. However, it is well known that nonstationarity may affect cardiovascular variability [11], and stationary HRV sequences to be analyzed are often impossible to find even in short-term recordings and during well-controlled experimental settings [12], [13]. In fact, stationarity is not usually checked in a systematic way before performing HRV analysis, and HRV series are commonly regarded as stationary on the basis of simple but imprecise visual inspection criteria. These considerations evidence the need for evaluating to what extent the presence of nonstationarities affects the application of time series analysis methods to HRV recordings. With regard to the method of surrogate data, ambiguities between nonstationarity and nonlinearity might arise when the null hypothesis of having a TIV linear process is rejected by using a nonlinear discriminating statistic.

In this study, we propose a method for generating time-varying (TV) surrogate data in order to test the presence of nonlinear dynamics in potentially nonstationary time series, according to the null hypothesis of TV linear stochastic process. The method is based on fitting a TV autoregressive (AR) model to the original series and then regressing the estimated model coefficients with random replacements of the model residuals to generate the TV surrogate series. Model identification is performed by expansion of the TV model coefficients onto a set of predefined basis functions, while a classical nonlinear index (i.e., the sample entropy (SE) [14]) is used as a discriminating statistic. To provide a comparison with traditional approaches, we consider traditional TIV surrogates generated either as typical realizations through the residual-based AR bootstrap [15], [16], and as constrained realizations through the phase-randomization procedure [1], [17]. The comparison is first performed on simulations reproducing both linear and nonlinear processes, in which TIV and TV features are imposed. The performance of TIV and TV surrogates is then assessed on real HRV data measured during common experimental protocols, in order to address the influence of possible nonstationarities on the detection of nonlinear dynamics in standard short-term HRV recordings.

II. Methods

A. TIV AR Surrogates

Given the time series $x(n), n = 1, \ldots, N$, TIV AR surrogates were generated by performing AR prediction of the series

$$x(n) = a(0) + \sum_{i=1}^{P} a(i)x(n-i) + e(n) \tag{1}$$

where $e(n)$ is the prediction error and the coefficients $a(0)$ and $a(1), \ldots, a(P)$ describe, respectively, constant and linear contributions to the dynamics of x. The AR model of (1) was identified by the least squares method, yielding estimates of the model coefficients, $\hat{a}(0), \hat{a}(1), \ldots, \hat{a}(P)$, and of the residuals $\hat{e}(1), \ldots, \hat{e}(N)$ as well. A surrogate of the series x was then generated according to the typical residual-based bootstrap approach [15], i.e., by resampling the residuals and feeding them into the estimated AR model

$$x_{s\mathrm{TIV}}(n) = \hat{a}(0) + \sum_{i=1}^{P} \hat{a}(i)x_{s\mathrm{TIV}}(n-i) + \hat{e}(\mathrm{rnd}(N)), \quad n = 1, \ldots, N \tag{2}$$

where rnd(N) is a random number drawn from the discrete uniform distribution with maximum equal to N. The model order P was selected using the Akaike criterion [18].

B. TV AR Surrogates

TV AR surrogates of the series x were generated through a TV AR prediction model

$$x(n) = a(0,n) + \sum_{i=1}^{P} a(i,n)x(n-i) + e(n) \tag{3}$$

where the TV coefficients $a(i,n), i = 0, \ldots, P$, are functions of time. To identify the TV AR model (3), the TV coefficients were expanded onto a set of basis functions $\pi_m(n)$ [19]

$$a(i,n) = \sum_{m=0}^{M} \alpha(i,m)\pi_m(n) \tag{4}$$

where $\alpha(i,m)$ represent the expansion parameters with $M+1$ as the maximum number of basis sequences. Substituting (4) into (3), we have

$$x(n) = \sum_{m=0}^{M} \alpha(0,m)\pi_m(n) + \sum_{i=1}^{P}\sum_{m=0}^{M} \alpha(i,m)\pi_m(n)x(n-i) + e(n). \tag{5}$$

The linear system (5) is now TIV, since the $(P+1)(M+1)$ coefficients $\alpha(i,m)$ are not functions of time. Hence, it can be solved by least squares optimization, yielding estimates of the expansion parameters $\hat{\alpha}(i,m),\ i = 0, \ldots, P, m = 0, \ldots, M$, and of the model residuals $\hat{e}(1), \ldots, \hat{e}(N)$. The estimated parameters were then regressed with the resampled residuals to yield the TV surrogate of the series x

$$x_{s\mathrm{TV}}(n) = \sum_{m=0}^{M} \hat{\alpha}(0,m)\pi_m(n) + \sum_{i=1}^{P}\sum_{m=0}^{M} \hat{\alpha}(i,m)\pi_m(n)x_{s\mathrm{TV}}(n-i) + \hat{e}(\mathrm{rnd}(N)). \tag{6}$$

To perform model order selection for the TV case, we exploited the fact that expansion onto the basis functions led to a TIV system. Hence, we used a modified version of the Akaike information criterion accounting for the increased number of TIV coefficients for the system (5). Specifically, the parameters P and M in (5) were optimized by letting them vary within a prescribed range and selecting the values that minimized the

figure of merit

$$\mathrm{AIC}(P, M) = N \log \hat{\sigma}_e^2 + 2\left[P\left(M+1\right)\right]. \tag{7}$$

This modified criterion allowed us not only to select the optimal model order, but also to choose the proper number of basis functions onto which the TV AR coefficients are expanded.

The selection of the basis functions that characterize the time variation of the model coefficients is crucial to obtain a proper description of the TV dynamics under analysis. The first basis function is the unitary constant function $[\pi_0(n) = 1]$, representing the stationary portion of the model. The TV features are described by the basis functions $\pi_m(n)$, with $m > 0$. Different types of basis functions, each showing its own unique tractability and accuracy, can be chosen to describe TV dynamics. In this study, we implemented as basis functions both Legendre polynomials, which are appropriate for smoothly changing dynamics, and Walsh functions, which behave well for dynamics exhibiting fast transients and/or burst-like behavior [19].

C. Nonparametric Surrogates

Contrary to AR surrogates, nonparametric surrogates do not assume a linear model to reproduce the linear autocorrelation present in the original series, but operate in the frequency domain according to a constrained realization approach. In this study, we considered the two types of constrained surrogates used in HRV studies [5]: 1) the Fourier transform (FT) surrogates [1], generated by computing the FT of the series x, substituting the Fourier phases with random numbers uniformly distributed between 0 and 2π, and finally, performing the inverse FT; 2) the iteratively refined amplitude-adjusted FT (IAAFT) surrogates [17], generated with an iterative procedure that alternatively constrains the surrogate series to have the same power spectrum (by replacing the squared Fourier amplitudes of the candidate surrogate series with those of the original series) and to have the same amplitude distribution (by a rank ordering procedure) of the original series.

D. Testing for Nonlinearity

The existence of nonlinear dynamics in the considered time series was investigated in accordance with the well-known method of surrogate data [1]. This approach is based on a null hypothesis to be rejected, a surrogate dataset constructed in accordance with the null hypothesis, a discriminating statistic that has to be calculated on original and surrogate series, and a statistical test allowing it to reject (if it is the case) the null hypothesis.

The general null hypothesis assumed in nonlinearity tests is that the investigated time series is a realization of a linear stochastic process. However, a more specific null hypothesis is often required to be set, depending on the ability of the surrogates to preserve the statistical properties of the original series. Being conceived to test for nonlinearity, all the four algorithms considered here preserve, though with a different degree of approximation [16], the linear autocorrelation of the original series. Whereas FT surrogates have a Gaussian distribution by construction, IAAFT surrogates preserve the marginal distribution of the original series, regardless of whether it is Gaussian or not. Typical realizations, generated either by the TIV AR or the TV AR approach, do not preserve closely the original marginal distribution, but do assume Gaussianity of such a distribution. The three TIV algorithms (i.e., FT, IAAFT, and TIV AR) generate stationary surrogate series, while the TV AR method attempts to reproduce nonstationary behaviors of the original series. In view of these considerations, FT, IAAFT, TIV AR, and TV AR surrogates were used to test the null hypotheses of a TIV Gaussian linear process, a TIV linear process, a TIV linear AR process, and a TV linear AR process, respectively.

As a discriminating nonlinear statistic, we utilized the SE [14], a measure based on comparing patterns within a time series to estimate its complexity through estimation of entropy rates. The SE has been originally devised to overcome some known shortcomings associated to the most common nonlinear measure of complexity used in cardiovascular variability analysis, i.e., approximate entropy (ApEn) [20]. It has been fully characterized in the context of physiological time series analysis and has been successfully used as complexity measure in short-term HRV studies [21]–[24]. Moreover, the evaluation of SE over multiple time scales, performed by the multiscale entropy method, has been proposed as a diagnostic tool to detect HRV complexity in conditions of normal and impaired cardiac efficiency [25]. For SE calculation, the series x was first partitioned in patterns of length L, obtained as sequences of L consecutive samples, i.e., $x_L(i) = [x(i), x(i+1), \ldots, x(i+L-1)]$. The SE statistic was then computed as

$$\mathrm{SE}\left(L, r\right) = -\log \frac{\sum_{i=1}^{N-L} N_i\left(L+1, r\right)}{\sum_{i=1}^{N-L} N_i\left(L, r\right)} \tag{8}$$

where $N_i(L, r)$ is the number of patterns of length L found at a distance smaller than the threshold r from $x_L(i)$ and $N_i(L+1, r)$ is the number of patterns of length $L+1$ found at a distance smaller than r from $x_{L+1}(i)$. The sums in (8) were extended to all the patterns of length $L+1$, and the distance was evaluated by the Euclidean norm. Since the SampEn requires stationary data segments to be calculated, its TIV version of (8) was used as discriminating statistic only in nonlinearity tests including stationarity into the null hypothesis, i.e., those using the FT, IAAFT, and TIV AR algorithms for surrogate generation. Differently, as the proposed TV AR surrogates inherently allow nonstationarity, we used them in conjunction with a TV version of the SampEn (TV-SampEn). TV-SampEn was computed adaptively, segmenting the time series of N samples in Q subwindows of W samples, with a partial overlap, and calculating within each subwindow the TIV SampEn of (8).

As a statistical test, we performed a nonparametric test based on percentiles. The test compared the SampEn statistic calculated for the original series (SE_O) with a threshold for significance ($\mathrm{SE}_{\mathrm{TH}}$) given by the $100 \times \alpha$th percentile of the empirical SampEn distribution estimated from 100 surrogate series. If $\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$, the null hypothesis was rejected and nonlinear dynamics was detected. If, on the contrary, $\mathrm{SE}_O \geq \mathrm{SE}_{\mathrm{TH}}$, surrogates were interpreted as consistent with their corresponding null hypotheses. While for TIV nonlinearity tests, a single

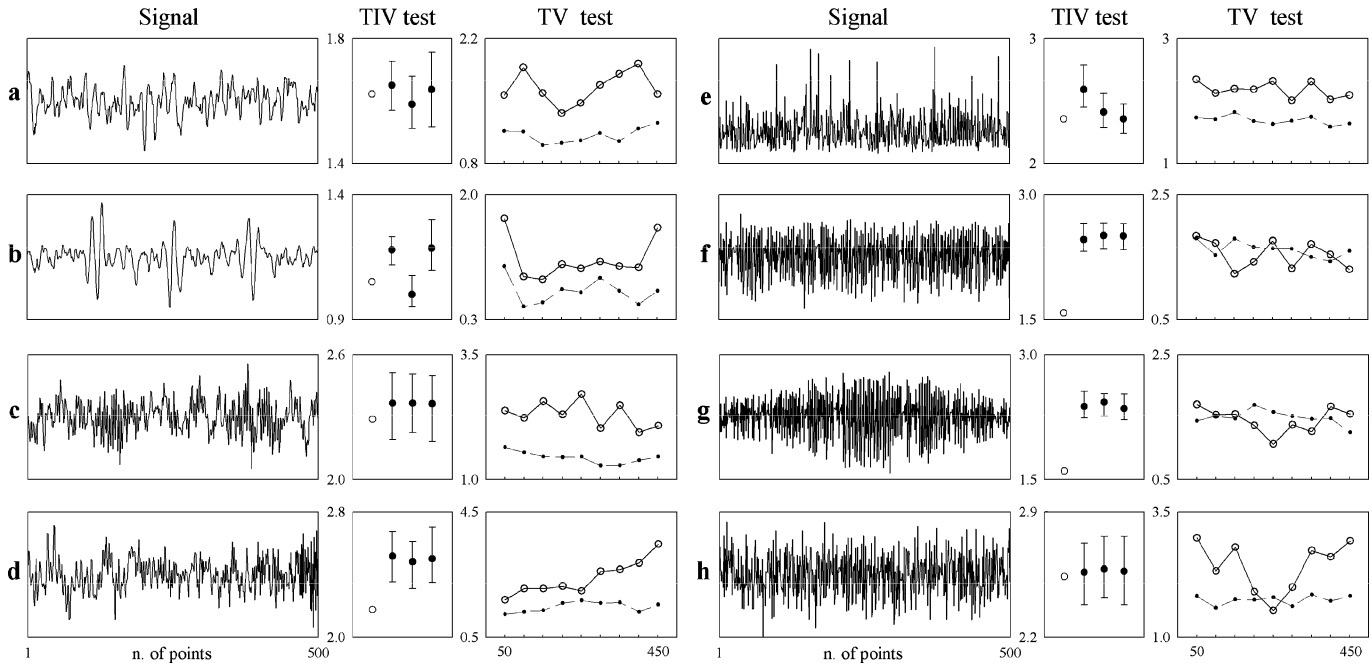

Fig. 1. Example of nonlinearity test performed on simulated signals. (a) Stationary AR2 process. (b) Nonstationary AR2 process with amplitude modulations. (c) Stationary AR5 process. (d) Nonstationary AR5 process with frequency drifts. (e) Stationary non-Gaussian AR2 process. (f) Stationary noisy Tent map. (g) Nonstationary noisy Tent map with varying control parameter. (h) Nonstationary noisy Tent map with varying additive noise variance. Middle panels depict the SampEn statistic calculated for the original series (SE_O, empty circles) along with its distributions (5th, 50th (filled circles), and 95th percentiles) over 100 surrogate series generated using FT, IAAFT, and TIV AR approaches (from left to right); the lower 5th percentile is the threshold for significance $\mathrm{SE}_{\mathrm{TH}}$ of each TIV nonlinearity test. Right panels depict the TV-SampEn calculated for the original series ($\mathrm{SE}_O(i)$, empty circles) along with the threshold for significance of the TV nonlinearity test ($\mathrm{SE}_{\mathrm{TH}}(i)$, dots) derived from 100 TV AR surrogate series; values are calculated over subwindows of 100 samples, overlapped by half.

comparison with nominal significance level α was performed, in the TV test involving the proposed TV AR surrogates, a multiple testing strategy was implemented [26]. Specifically, $\mathrm{SE}_O(i)$ and $\mathrm{SE}_{\mathrm{TH}}(i)$ were calculated, respectively, as the SampEn of the original series and the $(100 \times \alpha(i))$th percentile of the SampEn surrogate distribution within each subwindow selected for TV-SampEn analysis, $i = 1, \ldots, Q$; then, the overall null hypothesis was rejected if rejection was achieved in at least one subwindow, i.e., $\mathrm{SE}_O(i) < \mathrm{SE}_{\mathrm{TH}}(i)$ for at least one i. In multiple testing procedures, a Bonferroni correction reducing the significance level of the single tests [i.e., imposing $\alpha(i) < \alpha$] is required to achieve an overall nominal significance level equal to α [26]. In this study, we adopted the improved Bonferroni method introduced in [27], which is based on sorting the Q subwindows according to an ascending order of the p-values of the corresponding single hypothesis test, and then assigning to the ith sorted subwindow a significance level $\alpha(i) = i\alpha/Q$. With respect to the classical Bonferroni correction that sets constant significance levels $\alpha(i) = a/Q$, this approach is less conservative in the presence of dependent comparisons (as is our case in which the subwindows overlap) and is associated with an increased power of the statistical test [27].

III. Simulations

To evaluate the ability of the proposed TV AR surrogates to detect nonlinearity in comparison with the traditional TIV surrogates during different conditions, we simulated time series containing linear and nonlinear dynamics, reproducing in both cases either stationary behaviors or nonstationary behaviors with different types of nonstationarity. As linear time series, we considered: 1) second-order AR (AR2) processes given by

$$x(n) = 2\rho \cos(2\pi f(n))\, x(n-1) - \rho^2 x(n-2) + w(n) \tag{9}$$

where ρ and $2\pi f$ are the modulus and phase of the complex conjugate poles of the process and w is a Gaussian white noise with zero mean and unit variance; 2) fifth-order AR processes (AR5) generated by adding the series yielded by (9) with different pole modulus ρ and phase $2\pi f$, with parameters set to render the power spectrum of the AR5 process similar to that of the short-term HRV series (i.e., with peaks in low frequency (LF $\sim$ 0.1 Hz) and high frequency (HF $\sim$ 0.25 Hz) bands, superimposed to very slow fluctuations at about 0 Hz [11]). As a nonlinear time series, we considered the Tent map with control parameter k, defined as

$$x(n+1) = \begin{cases} 2k(n)x(n), & \text{if } 0 < x(n) \le 0.5 \\ 2k(n)(1-x(n)), & \text{if } 0.5 < x(n) \le 1. \end{cases} \tag{10}$$

We considered eight different processes for which realization examples are shown in Fig. 1: a) a stationary AR2 process with $\rho = 0.8$ and $f = 0.06$; b) a nonstationary AR2 process in which nonstationarity was obtained imposing three steps in the values over time of the pole modulus [$\rho(n) = 1$ for $3N/15 \le n < 4N/15, 7N/15 \le n < 8N/15$, and $11N/15 \le n < 12N/15$; $\rho(n) = 0.8$ elsewhere] with constant $f = 0.06$;

c) a stationary AR5 process with one real pole ($\rho_0 = 0.7$, $f_0 = 0$), and two pairs of complex conjugate poles corresponding to LF ($\rho_1 = 0.84$, $f_1 = 0.1$) and HF ($\rho_2 = 0.98$, $f_2 = 0.25$) oscillations; d) a nonstationary AR5 process with the same stationary parameters of (c) ($\rho_0 = 0.7$, $f_0 = 0$; $\rho_1 = 0.84$, $f_1 = 0.1$; $\rho_2 = 0.98$) except for the HF oscillation that was linearly increased in frequency from 0.15 to 0.4 Hz: $f_2(n) = 0.15 + 0.25(n-1)/(N-1)$; e) a stationary AR2 process with $\rho = 0.8$ and $f = 0.06$, amplitude-transformed (by a rank-order procedure) according to a chi-squared distribution with 4 DOF in order to distort from Gaussianity its marginal distribution; f) a stationary noisy Tent map with $k = 0.9$, generated rescaling (10) to zero mean and then adding zero-mean Gaussian white noise with 5% variance; g) a nonstationary noisy Tent map, generated as in (f) but with control parameter linearly increasing from 0.7 to 0.9 in the first half of the series [$k(n) = 0.7 + 0.2(n-1)/(N/2-1),\ n = 1, \ldots, N/2$] and then decreasing back to 0.7 in the second half [$k(n) = 0.9 - 0.2(n - N/2 - 1)/(N/2-1)$, $n = N/2+1, \ldots, N$]; (h) a nonstationary noisy Tent map, generated as in (f) ($k = 0.9$) but with a step in the variance of the additive noise (variance = 5% for $2N/5 \leq n < 3N/5$, variance = 150% elsewhere).

In all cases, 100 different realizations of the simulated series, each lasting $N = 500$ points, were considered for the analysis. The maximum model order investigated by the Akaike criteria for the generation of parametric surrogates was $P_{\max} = 20$, and the maximum number of basis functions used for generating TV AR surrogates was $M_{\max} = 20$. As basis functions, we used Legendre polynomials for the simulations (a), (d), (f), and (g), and Walsh functions for the simulations (b), (c), (e), and (h). Before SampEn calculation, the series were rescaled to have zero mean and unit variance. SampEn and TV-SampEn were calculated setting $L = 2$ and $r = 0.2$ in (8). TV-SampEn was computed on windows of $W = 100$ samples, with 50% overlap. The length $W = 100$ was chosen to satisfy the recommended minimum sample size for reliably calculating SampEn [14], [20]. The overall nominal significance level associated to the hypothesis tests was $\alpha = 0.05$.

IV. Application to HRV

A. Experimental Protocols

In the two considered experimental protocols, the surface ECG (lead II) was acquired in young healthy subjects during the morning in quiet ambience conditions. In the type-1 protocol, 18 subjects (25 $\pm$ 2.7 years old) underwent recordings during the resting supine position and during the 60° upright position. The transition from supine to upright position was achieved by the passive head-up tilt manoeuver through the progressive sloping of a motorized tilt table. In each body position, subjects were given 10 min of acclimatizing before data were collected. In the type-2 protocol, 16 subjects (26 $\pm$ 2.4 years old) underwent recordings in the resisting supine position, during spontaneous breathing, paced breathing (PB) with frequency of 0.2 Hz, and PB with frequency of 0.3 Hz. To achieve controlled respiration, subjects were instructed to inhale and exhale in time with a metronome acting at 12 and 18 cycles/min.

In both experimental protocols, the recorded ECG was digitized with 1 kHz sampling rate and 12-bit precision. After that, the QRS peaks were detected by threshold crossing of the first derivative of the signal and the R peaks were located by using a parabolic interpolation. The RR interval series was then measured as the sequence of the temporal distances occurring between each pair of consecutive R peaks. In each experimental condition (i.e., supine position (Su) and upright position (Up) for the type-1 protocol; spontaneous breathing (Sp), paced respiration at 0.2 Hz (R1) and 0.3 Hz (R2) for the type-2 protocol), a time window consisting of 500 heartbeats was selected from the RR interval series. The only manipulation of the measured RR series was the removal, when necessary, of cardiac artifacts. Attention was paid that the selected sequence was stationary and free from measurement artifacts. Stationarity was checked according to common visual inspection criteria.

B. Data Analysis

AR TIV surrogates were generated with $P_{\max} = 20$ as maximum model order for the Akaike criterion. AR TV surrogates were generated with $P_{\max} = 20$ and $M_{\max} = 20$ as maximum model order and number of basis functions to include in the modified Akaike criterion of (7). As in real data applications, the behavior of possible TV dynamics is not known *a priori*, so we combined together both Legendre and Walsh basis functions for the generation of AR TV surrogates according to the method described in [28]. This method provides a set of orthogonal basis functions from multiple sets of original basis functions, using the Gram–Schmidt orthogonalization procedure to eliminate the possible linear dependence between the original functions. The advantage of the approach is that, without scarifying accuracy, the criticality of choosing a suitable type function is minimized even without any prior knowledge of the characteristics of the nonstationary system under analysis.

The SampEn statistic was calculated with the typical pattern length and threshold distance suggested for short data sequences, i.e., $L = 2$ and $r = 20\%$ of the standard deviation of the considered RR interval series [14], [22]. As for simulations, nine subwindows of $W = 100$ samples, with 50% overlap, were set to compute TV-SampEn, and the nominal significance level of the hypothesis tests was $\alpha = 0.05$. The Student's t-test for paired data was used to test the statistical significance of the difference between the SampEn distributions evaluated in the different experimental conditions. A $p < 0.05$ was considered statistically significant.

V. Results

A. Simulation Results

Fig. 1 reports an example of the nonlinearity test performed by the three TIV approaches using FT, IAAFT, and TIV AR surrogates, and by the proposed approach using TV AR surrogates, on a single realization of the eight simulated processes described in Section III. In the presence of stationary linear dynamics generated by the AR2 and AR5 processes with constant parameters [Fig. 1(a) and (c)], the TIV approaches and

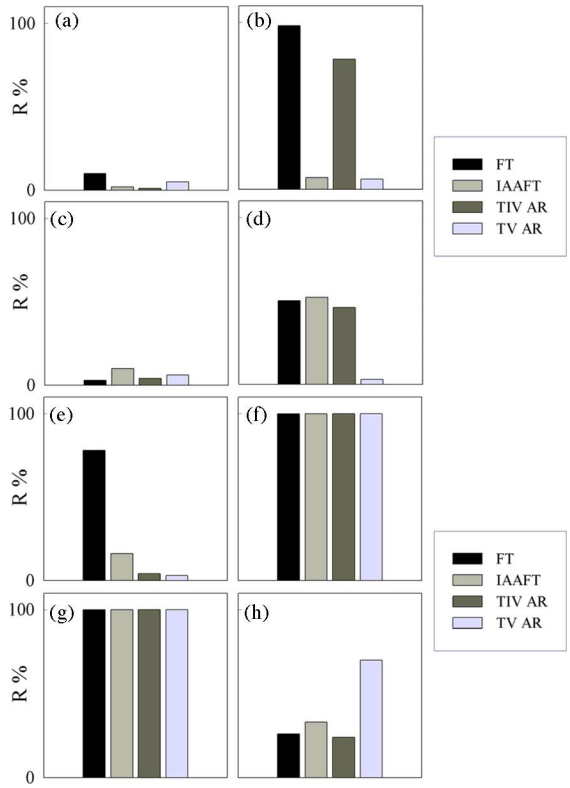

Fig. 2. Percentage of rejections of the null hypothesis ($R\%$) revealed by the considered surrogate data methods (FT, IAAFT, TIV AR, and TV AR) on 100 realizations of the eight simulated processes described in Fig. 1.

the TV AR approach did not reject the null hypothesis, as the SampEn and TV-SampEn statistics calculated for the original series were above their corresponding threshold for significance ($\mathrm{SE}_O > \mathrm{SE}_{\mathrm{TH}}$). When the AR2 series was amplitude-transformed to have a skewed marginal distribution, a rejection of the null hypothesis ($\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$) was observed using the FT approach [Fig. 1(e)]. In the presence of the linear nonstationary behaviors due to pole modulus variations of the AR2 process [Fig. 1(b)] and frequency drifts in the AR5 process [Fig. 1(d)], TIV and TV nonlinearity tests gave opposite results, as $\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$ for TIV surrogates [except for IAAFT surrogates in Fig. 1(b)] and $\mathrm{SE}_O \geq \mathrm{SE}_{\mathrm{TH}}$ in all subwindows for TIV AR surrogates. For the stationary Tent map [Fig. 1(f)] and the Tent map with nonstationary control parameter [Fig. 1(g)], rejection of the nonlinearity test was achieved for all surrogate methods. Finally, the weak nonlinearity obtained blurring 80% of the samples of a Tent map with high variance noise [Fig. 1(h)] was detected only by combining TV AR surrogates with the TV-SampEn statistic [$\mathrm{SE}_O(5) < \mathrm{SE}_{\mathrm{TH}}(5)$], while the TIV approaches did not reject the null hypothesis ($\mathrm{SE}_O > \mathrm{SE}_{\mathrm{TH}}$).

Fig. 2 summarizes the results of the nonlinearity test extended to the 100 realizations generated for each system, expressed in terms of percentage of rejection of the null hypothesis. During stationary conditions imposed in linear dynamics [Fig. 2(a), (c), and (e)], the four approaches to surrogate data generation performed comparably, returning a very low rejection rate and thus correctly detecting the dynamics as linear; the only exception was the considerable number of false rejections obtained using FT surrogates in the analysis of the non-Gaussian process modeled by skewing the marginal distribution of the AR2 process [Fig. 2(e)]. In case of nonstationary linear dynamics produced by amplitude modulations in the AR2 process [Fig. 2(b)], the percentages of erroneous rejections were very high (>80%) for FT and TIV AR surrogates and very low (<7%) for IAAFT and TV AR surrogates. The TV AR method performed better than TIV approaches in the presence of nonstationarities also due to frequency drifts, as documented in Fig. 2(d), where the rejection rate was about 50% for FT, IAAFT, and TIV AR surrogates, and was very low for TV AR surrogates. Stationary nonlinear dynamics generated by the Tent map [Fig. 2(f)] as well as nonstationary nonlinear dynamics generated by the Tent map with variable control parameter [Fig. 2(g)] were correctly addressed as nonlinear by all methods. When nonstationarity was due to modulation of the quantity of the additive noise used to blur the tent map [Fig. 2(h)], the three TIV approaches were unable to detect the weak nonlinearity, and thus returned a low rejection rate, while the TV nonlinearity test returned a higher percentage of rejections.

B. Real Data Results

Fig. 3 reports an example of application of the nonlinearity test on the RR interval series measured during type-1 protocol for a representative subject. In the supine position, all the considered approaches detected the presence of nonlinear dynamics, since $\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$ for the three TIV methods [Fig. 3(b)] and $\mathrm{SE}_O(i) < \mathrm{SE}_{\mathrm{TH}}(i)$ for $i = 7$ for the TV method [Fig. 3(c)]. In the upright position, where modulations over time in the amplitude of the RR series are evident [Fig. 3(d)], FT, IAAFT, and AR TIV surrogates indicated the series as nonlinear [$\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$, Fig. 3(e)], while TV AR surrogates gave the opposite result as $\mathrm{SE}_O(i) > \mathrm{SE}_{\mathrm{TH}}(i)$ for each $i = 1, \ldots, 9$ [Fig. 3(f)]. Fig. 4 shows the application on RR interval series measured for a subject enrolled in the type-2 protocol. During spontaneous breathing, an increase of the respiratory frequency with time seems to occur [Fig. 4(a)]. In correspondence, FT, IAAFT, and TIV AR surrogates found nonlinear dynamics [$\mathrm{SE}_O < \mathrm{SE}_{\mathrm{TH}}$, Fig. 4(b)], while TV AR surrogates did not detect any nonlinearity [$\mathrm{SE}_O(i) > \mathrm{SE}_{\mathrm{TH}}(i)$ for each $i = 1, \ldots, 9$, Fig. 4(c)]. On the contrary, the three TIV methods and the TV AR method were in agreement during 0.2 Hz paced respiration, where the null hypothesis was rejected and nonlinearity was detected [Fig. 4(e) and (f)], and during 0.3 Hz paced respiration, where the RR series was found consistent with the null hypothesis [Fig. 4(h) and (i)].

Fig. 5 summarizes the results obtained during the two protocols, in terms of complexity values, either measured by the SampEn statistic or by the average over successive subwindows of the TV-SampEn statistic, and of percentage of nonlinear dynamics detected by the four considered surrogate approaches. During type-1 protocol, SampEn and mean TV-SampEn decreased significantly moving from the supine to the upright position [Fig. 5(a)]. During type-2 protocol, SampEn and mean TV-SampEn decreased significantly with PB at 0.2 Hz, and

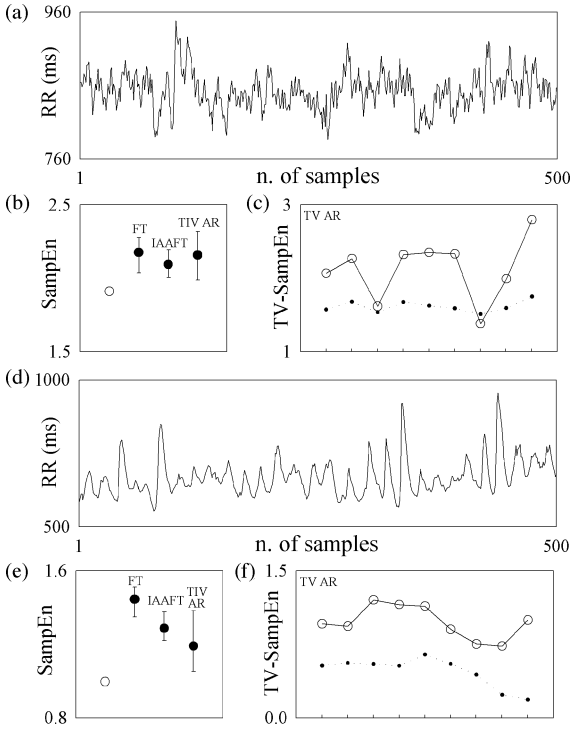

Fig. 3. RR interval variability series measured for a healthy subject in (a) the resting supine position, and in (d) the upright position during head-up tilt. (b) and (e) Corresponding SampEn statistic calculated for the original series (SE_O, empty circles) along with its distributions (5th, 50th (filled circles) and 95th percentiles) over 100 surrogate series generated using FT, IAAFT, and TIV AR approaches (from left to right); the lower 5th percentile is the threshold for significance $\mathrm{SE}_{\mathrm{TH}}$ of each TIV nonlinearity test. (c) and (f) TV-SampEn calculated for the original series ($\mathrm{SE}_O\,(i)$, empty circles) along with the threshold for significance of the TV nonlinearity test ($\mathrm{SE}_{\mathrm{TH}}\,(i)$, dots) derived from 100 TV AR surrogate series; values are calculated over subwindows of 100 samples, overlapped by half.

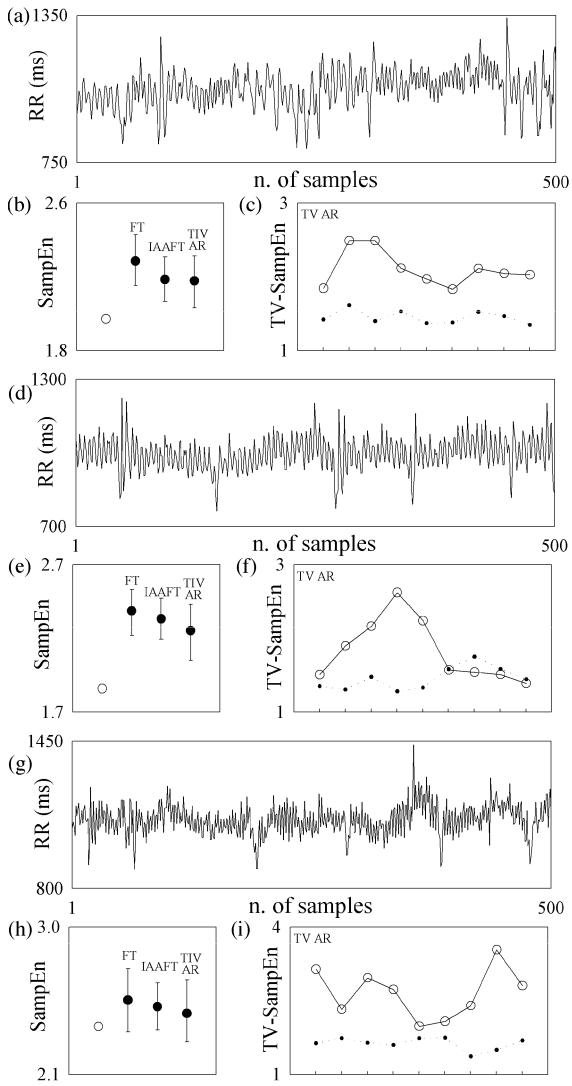

Fig. 4. RR interval variability series measured for a healthy subject in the supine position during (a) spontaneous breathing and during (d) PB at 0.2 Hz and (g) at 0.3 Hz. Panels (b), (e), and (h) and panels (c), (f), and (i) depict the results of TIV and TV nonlinearity tests, respectively; symbols are as in Fig. 3.

increased significantly with PB at 0.3 Hz, returning to average values comparable to those measured during spontaneous breathing. As shown in Fig. 5(b)–(e), regardless of the method used to generate surrogate data, the percentage of rejection of the null hypothesis increased from the supine to the upright position during type-1 protocol and from spontaneous respiration to paced respiration at 0.2 Hz breathing rate during the type-2 protocol; the number of rejections decreased when the rhythm of the paced respiration was increased to 0.3 Hz . Using TV AR surrogates, a lower percentage of nonlinear dynamics was detected in all conditions [Fig. 5(e)]; with this approach, the increase in the percentage of nonlinear dynamics was slight with assumption of the upright position, and was considerable moving from spontaneous to 0.2 Hz paced respiration.

Besides detection of nonlinear dynamics, complementary information can be deduced from the analysis of the agreement/disagreement among the four surrogate data approaches regarding the outcome of the nonlinearity test. Table I lists the different combinations of the test outcomes (rejection or not rejection of the null hypothesis) encountered in HRV analysis during the two protocols. Of the 84 analyzed RR interval series, in 51 cases (60.7%, patterns a and b in Table I), there was complete agreement among the four surrogate types in rejecting or not rejecting the null hypothesis. A disagreement between TIV and TV AR surrogates (patterns c, d, and e) was revealed in 22 cases (26.2%). According to simulation results, patterns of types c and d (22.6%) might indicate false rejections of the null hypothesis using TIV surrogates induced by nonstationarities, while patterns of type e (3.6%) might reflect weak nonlinearities detected by the TV approach but not TIV approaches. The disagreement between TIV and TV AR surrogates was larger during spontaneous breathing in supine or upright positions (16 out of 22 cases) than during 0.2 or 0.3 Hz PB (6 cases). Patterns of type f (7.1%) may indicate the presence of non-Gaussianity in the marginal distribution of HRV, leading FT surrogates to false rejections of the null hypothesis. Finally, patterns of type g (6%) evidenced a disagreement between constrained and typical surrogate realizations.

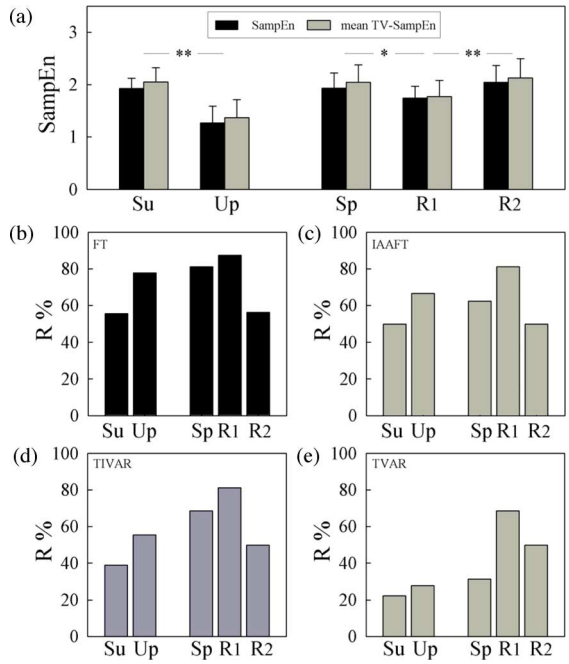

Fig. 5. (a) Mean + SD over subjects of the SampEn (black bars) and the average TV-SampEn (gray bars) calculated during type-1 protocol (Su: supine position; Up: upright position) and type-2 protocol (Sp: spontaneous respiration; R1: paced respiration at 0.2 Hz; R2: paced respiration at 0.3 Hz); $^{*}p < 0.05$, Sp versus R1; $^{**}p < 0.005$, Su versus Up and R1 versus R2 (paired Student t-test). (b)–(e) Percentage of rejections of the null hypothesis ($R\%$) revealed in RR interval series by the considered surrogate data methods (FT, IAAFT, TIV AR, and TV AR) over subjects during the five conditions.

TABLE I
PATTERNS OF COMBINED OUTCOME OF NONLINEARITY TEST PERFORMED WITH CONSIDERED SURROGATE DATA APPROACHES ON HRV TIME SERIES

Pattern	FT	IAAFT	TIV AR	TV AR	Occurrence (%)
a	*R*	*R*	*R*	*R*	35.7 %
b	*NR*	*NR*	*NR*	*NR*	25.0 %
c	*R*	*R*	*R*	*NR*	20.2 %
d	*R*	*NR*	*R*	*NR*	2.4 %
e	*NR*	*NR*	*NR*	*R*	3.6 %
f	*R*	*NR*	*NR*	*NR*	7.1 %
g	*R*	*R*	*NR*	*NR*	6.0 %

R: rejection and NR: non-rejection of the null hypothesis

VI. DISCUSSION

While in its traditional formulation [1] the method of surrogate data is applicable only under the assumption of stationarity, most biological signals are not stationary due to the inherent TV characteristics of the biological systems that produce them. As a consequence, the null hypothesis commonly set by the surrogate-based test for nonlinearity, i.e., that the investigated time series is a realization of a TIV linear process [1], should be relaxed in order to account for possible TV behaviors. To agree with a more general null hypothesis, surrogate series that mimic the possible nonstationary behaviors present in the original series have to be generated. In this study, we addressed this issue by extending the "typical realizations" approach to the generation of surrogate data, originally designed for testing nonlinearity in TIV processes, to be applicable to TV systems. Typical realizations of the TV surrogates were obtained using a TV AR model, instead of a TIV model, to fit the original time series. Hence, contributions to the complexity of the original series due to nonstationary behaviors that could be modeled by the TV AR approach were also present in the surrogate series. This led us to rule out nonstationarity as a possible explanation for the rejection of the null hypothesis, thus making more robust the detection of nonlinearity.

It should be remarked that the proposed procedure depends on the capability of the method to track linear TV behaviors present in the analyzed time series. We dealt with this problem by using basis functions to model the TV AR coefficients, an approach that ensures an efficient identification of various types of nonstationary processes [19]. In particular, the use of a multiple set of basis functions [28] made our method able to simultaneously capture different TV behaviors (including together both slowly changing dynamics and fast transients), without the need of having any prior knowledge about the kind of nonstationarity that may be present in real data applications.

A. Comparison Among Different Approaches for Surrogate Data Generation

We compared, on both simulations and real HRV data, the novel approach to generate TV surrogate data based on TV AR model identification with the main TIV approaches proposed to test for nonlinearity in time series, i.e., the AR method [10], the FT method [1], and the IAAFT method [17]. Consistency in the outcome of the nonlinearity test among the four methods was interpreted as an indication of the linearity of the investigated time series, when all approaches did not reject the null hypothesis, or as a marker of the presence of nonlinear dynamics, when all approaches rejected the null hypothesis. These situations were successfully reproduced by the simulations [see Figs. 1(a), (c), (f), (g) and 2(a), (c), (f), (g)], and were encountered in a considerable part of the experimental data ($\sim$60%).

On the other side, different outcomes of the nonlinearity test observed using the different surrogate approaches may give important information about the nature of the investigated time series. In particular, a disagreement between the TIV approaches on one side, and the TV AR approach on the other, may suggest a role of nonstationarity on the detection of nonlinear dynamics. Our simulations showed that, in the presence of nonstationary behaviors like amplitude modulations or frequency drifts imposed on linear time series, TIV surrogates tend to reject the null hypothesis, thus erroneously indicating nonlinearity, while TV AR surrogates are correctly consistent with the null hypothesis [see Figs. 1(b), (d) and 2(b), (d)]. Moreover, in the presence of weak nonlinearities confined to a short epoch, TIV surrogates tend to accept the null hypothesis, while only TV AR surrogates show a high rejection rate [see Figs. 1(h) and 2(h)]. Our experimental results suggest that these situations are quite common in HRV analysis, especially during spontaneous breathing either in the supine or in the upright position. We ascribe the possible presence of nonstationarities during spontaneous breathing to important modulations of the LF rhythm of HRV, which is

predominant over other rhythms especially after head-up tilt [2] and to spontaneous variations of the respiratory frequency. On the contrary, the enhancement of the respiratory-related HF oscillation that occurs in PB protocols, as well as its entrainment on a stable frequency, are likely to favor the establishment of stationary conditions.

Two other situations of disagreement in the outcome of the nonlinearity test were those evidencing a difference between FT surrogates and other surrogate types, and a difference between "constrained" (FT and IAAFT) and "typical" (TIV AR and TV AR) surrogate realizations (patterns f and g in Table I). The first situation might reflect the fact that FT surrogates are forced to have Gaussian marginal distribution, and thus departures from Gaussianity of the distribution of the observed time series may induce false rejections when FT surrogates are used [see also Figs. 1(e) and 2(e)]. The second situation might be due to the strict adherence of the power spectrum of constrained surrogates to the spectrum of the original series, which can favor false rejections [9], [29], combined with the larger variance in power spectrum replication obtained by typical surrogates, which can lead to a misleading consistency with the null hypothesis. More generally, it is worth remarking that discrepancies among the outcomes of the nonlinearity test performed with the various surrogate approaches could be caused by subtle differences between the distribution (and/or the linear correlation) of the original series and of the surrogate series. Indeed, FT, IAAFT, AR TIV, and AR TV surrogates all have different distributions, which, in turn, differ from that of the original series. Hence, some care has to be taken in interpreting differences in the detection of nonlinear dynamics among the various surrogate approaches.

B. Nonlinearity in Short-Term HRV

A major result of this study is that even when the approach setting the most general null hypothesis (i.e., the TV AR method) was used to test for nonlinearity in HRV series, nonlinear dynamics were detected in a significant number of subjects in all experimental conditions. Previous studies revealed the existence of nonlinear dynamics underlying HRV signals [3], [6], [7], [30]. Such nonlinearities may be the result of the activity of several nonlinear physiological mechanisms, like nonlinear interactions between sympathetic and parasympathetic branches of the autonomic nervous system, respiratory modulations, saturation of receptors, and others [2], [31].

The nonlinearity test detected the largest number of subjects exhibiting nonlinear HRV dynamics during PB at 0.2 Hz (about 70% of the subjects using TV AR surrogates). This result confirms previous findings, suggesting that a voluntary periodic forced input like paced respiration, mainly at slow breathing rates, enhances nonlinear dynamics in the RR interval [4], [5], [32]. The nature of these nonlinear dynamics has been explained in terms of possible nonlinear interactions between the external forcing input given by voluntary periodic respiration and endogenous oscillators determining spontaneous HRV [5]. Results of the TV nonlinearity test suggest that head-up tilt is less effective than periodic breathing at low breathing rates in increasing the percentage of nonlinearities in RR interval series. Thus, it seems that the activation of the sympathetic nervous system occurring after transition to the upright position does not favor the rise of nonlinear HRV dynamics. This finding is in agreement with previous studies [5], [32], showing that head-up tilt as well as other experimental conditions shifting the sympatho-vagal balance toward a sympathetic predominance do not evoke nonlinear dynamics in HRV time series.

C. Complexity in Short-Term HRV

Besides evaluating the presence of nonlinear dynamics in HRV by means of the surrogate data, we also quantified, through the absolute values of the SampEn statistic or the values of the TV-SampEn statistic averaged over successive epochs, the complexity of the RR interval series in the different experimental conditions. In general, indexes of complexity and nonlinearity are not redundant, as high complexity does not necessarily indicate the presence of important nonlinear dynamics (or vice versa). This is, for example, the case of our simulated series, where linear stochastic processes were found in some cases to exhibit higher SampEn than nonlinear Tent maps [e.g., compare Fig. 1(c) and (d) with Fig. 1(f) and (g)], and of the considered real HRV data, where the transition from the supine to the upright position was associated with a decrease in the SampEn measure and an increase of the percentage of nonlinear dynamics (Fig. 5).

Overall, we found that the SampEn values: 1) decreased significantly moving from the supine to the upright position; 2) decreased significantly moving from spontaneous breathing to PB at 0.2 Hz; and 3) were substantially unchanged during 0.3 Hz PB compared to spontaneous breathing. These results agree completely with those previously obtained in the same experimental conditions using complexity measures based on conditional entropy [22], [33] and nonlinear predictability [5], [32], [34]. The decreased complexity of RR interval series in the upright position is explained by the sympathetic activation induced by head-up tilt, which causes the rise of LF oscillations and the drop of HF oscillations, ultimately simplifying the dynamics of HRV [35]. During paced respiration at low breathing rates, the decrease of complexity can be related to limited LF oscillations and the presence of strong HF oscillations associated to an important respiratory sinus arrhythmia [36]. On the contrary, the RR interval complexity is not reduced during paced respiration at 0.3 Hz, since higher breathing rates are less effective in strengthening HF oscillations and inhibiting LF oscillations of heart rate due to mechanical effects related to a reduced tidal volume [36].

Our findings about HRV complexity and nonlinearity observed during the PB protocol may be discussed also in terms of cardiorespiratory synchronization (CRS). CRS is a phenomenon that manifests itself through the entrainment between the cardiac and the respiratory oscillatory systems [37] and has been revealed either during spontaneous breathing [37], [38] or during PB [39]. We suggest that CRS is more likely to occur in correspondence of instances of high complexity of the HRV signal and that its appearance might mask nonlinear HRV

dynamics. For instance, 0.2 Hz PB induces a respiratory sinus arrhythmia [36] that is associated in this study to a decrease of SampEn and an increase of nonlinear dynamics in the HRV series (Fig. 5); previous studies showed that respiratory sinus arrhythmia and CRS are competing phenomena, with weakened CRS corresponding to important sinus arrhythmia [37], [38]. Moreover, increasing the frequency of the PB from 0.2 to 0.3 Hz led to HRV dynamics with higher SampEn and reduced nonlinearity; rapid paced respiration (frequency > 0.3 Hz) was also associated to more prolonged and effective CRS regimes [39].

VII. Conclusion

The approach proposed in this study is able to provide, thanks to the use of an efficient procedure to identify TV linear models [19], [28], TV surrogate data that mimic possible changes through time in the properties of a given time series. This approach permits application of the surrogate-based test for nonlinearity to a wider class of null hypotheses, including nonstationary behaviors. While we improved the parametric approach for the generation of typical surrogate realizations, recent studies [40], [41] proposed wavelet-based methods to generate constrained surrogate series preserving the average local properties of the original data, and are thus also suitable to track time-dependent signal features. A comparative analysis of these two approaches regarding nonlinearity tests in time series with TV features could constitute an interesting extension of this study.

Utilization of TV surrogates extends the applicability of the nonlinearity test to biological systems from which stationary signals cannot be extracted. This situation is likely to occur in spontaneous HRV analysis, where stationarity may be difficult to attain even in short epochs and during well-controlled experimental settings. This is the case, according to our results, of widely studied protocols such as supine resting and passive head-up tilt. Hence, we suggest the utilization of TV approaches in the generation of surrogate data to investigate the existence of nonlinear dynamics underlying experimental time series. The optimization of the method of surrogate data seems to be of particular importance in short-term cardiovascular variability analysis, as our results confirm that nonlinear dynamics are significantly involved in the genesis of spontaneous HRV during different experimental conditions.

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References

[1] J. Theiler, S. Eubank, A. Longtin, B. Galdrikian, and J. D. Farmer, "Testing for nonlinearity in time series: The method of surrogate data," *Physica D*, vol. 58, pp. 77–94, 1992.

[2] A. Malliani, *Principles of Cardiovascular Neural Regulation in Health and Disease*. Norwell, MA: Kluwer, 2000.

[3] J. K. Kanters, N. H. Holstein-Rathlou, and E. Agner, "Lack of evidence for low-dimensional chaos in heart rate variability," *J. Cardiovasc. Electrophysiol.*, vol. 5, pp. 591–601, 1994.

[4] J. O. Fortrat, Y. Yamamoto, and R. L. Hughson, "Respiratory influences on non-linear dynamics of heart rate variability in humans," *Biol. Cybern.*, vol. 77, pp. 1–10, 1997.

[5] A. Porta, S. Guzzetti, R. Furlan, T. Gnecchi-Ruscone, N. Montano, and A. Malliani, "Complexity and nonlinearity in short-term heart period variability: Comparison of methods based on local nonlinear prediction," *IEEE Trans. Biomed. Eng.*, vol. 54, no. 1, pp. 94–106, Jan. 2007.

[6] J. J. Gonzalez, J. J. Cordero, M. Feria, and E. Pereda, "Detection and sources of nonlinearity in the variability of cardiac R–R intervals and blood pressure in rats," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 279, pp. H3040–H3046, 2000.

[7] C. Braun, P. Kowallik, A. Freking, D. Hadeler, K. D. Kniffki, and M. Meesmann, "Demonstration of nonlinear components in heart rate variability of healthy persons," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 275, pp. H1577–H1584, 1998.

[8] T. Schreiber and A. Schmitz, "Surrogate time series," *Physica D*, vol. 142, pp. 346–382, 2000.

[9] K. T. Dolan and M. L. Spano, "Surrogate for nonlinear time series analysis," *Phys. Rev. E*, vol. 64, pp. 046128-1–046128-6, 2001.

[10] J. Theiler and D. Prichard, "Constrained-realization Monte Carlo method for hypothesis testing," *Physica D*, vol. 94, pp. 221–235, 1996.

[11] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability: Standards of measurement, physiological interpretation, and clinical use," *Eur. Heart J.*, vol. 17, pp. 354–381, 1996.

[12] A. Porta, G. D'Addio, S. Guzzetti, D. Lucini, and M. Pagani, "Testing the presence of non stationarities in short heart rate variability series," *Comput. Cardiol.*, vol. 31, pp. 645–648, 2004.

[13] Y. Zhong, Y. Bai, B. Yang, K. Ju, K. Shin, M. Lee, K. M. Jan, and K. H. Chon, "Autonomic nervous nonlinear interactions lead to frequency modulation between low- and high-frequency bands of the heart rate variability spectrum," *Amer. J. Physiol. Regul. Integr. Comput. Physiol.*, vol. 293, pp. R1961–R1968, 2007.

[14] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 278, pp. H2039–H2049, 2000.

[15] D. N. Politis, "The impact of bootstrap methods on time series analysis," *Stat. Sci.*, vol. 18, pp. 219–230, 2003.

[16] D. Kugiumtzis, "Evaluation of surrogate and bootstrap tests for nonlinearity in time series," *Stud. Nonlinear Dyn. Econometrics*, vol. 12, no. 1, 2008.

[17] T. Schreiber and A. Schmitz, "Improved surrogate data for nonlinearity tests," *Phys. Rev. Lett.*, vol. 77, pp. 635–638, 1996.

[18] H. Akaike, "A new look at the statistical model identification," *IEEE Trans. Autom. Control*, vol. AC-19, no. 6, pp. 716–723, Dec. 1974.

[19] R. Zou, H. Wang, and K. H. Chon, "A robust time-varying identification algorithm using basis functions," *Ann. Biomed. Eng.*, vol. 31, pp. 840–853, 2003.

[20] S. M. Pincus and A. L. Goldberger, "Physiological time-series analysis: What does regularity quantify?," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 266, pp. H1643–H1656, 1994.

[21] H. M. A. Angari and A. V. Sahakian, "Use of sample entropy approach to study heart rate variability in obstructive sleep apnea syndrome," *IEEE Trans. Biomed. Eng.*, vol. 54, no. 10, pp. 1900–1904, Oct. 2007.

[22] A. Porta, T. Gnecchi-Ruscone, E. Tobaldini, S. Guzzetti, R. Furlan, and N. Montano, "Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt," *J. Appl. Physiol.*, vol. 103, pp. 1143–1149, 2007.

[23] D. E. Lake, J. S. Richman, M. P. Griffin, and J. R. Moorman, "Sample entropy analysis of neonatal heart rate variability," *Amer. J. Physiol. Regul. Integr. Comput. Physiol.*, vol. 283, pp. R789–R797, 2002.

[24] V. Vuksanovic and V. Gal, "Nonlinear and chaos characteristics of heart period time series: Healthy aging and postural change," *Auton. Neurosci.*, vol. 121, pp. 94–100, 2005.

[25] M. Costa, A. L. Goldberger, and C. K. Peng, "Multiscale entropy analysis of complex physiologic time series," *Phys. Rev. Lett.*, vol. 89, pp. 068102-1–068102-4, 2002.

[26] Y. Hochberg and A. C. Tamhane, *Multiple Comparison Procedures*. New York: Wiley, 1987.

[27] R. J. Simes, "An improved Bonferroni procedure for multiple tests of significance," *Biometrika*, vol. 73, pp. 751–754, 1986.

[28] K. H. Chon, H. Zhao, R. Zou, and K. Ju, "Multiple time-varying dynamic analysis using multiple sets of basis functions," *IEEE Trans. Biomed. Eng.*, vol. 52, no. 5, pp. 956–960, May 2005.

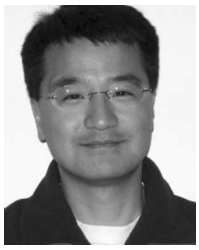
[29] D. Kugiumtzis, "Test your surrogate data before you test for nonlinearity," *Phys. Rev. E*, vol. 60, pp. 2808–2816, 1999.
[30] R. J. Storella, H. W. Wood, K. M. Mills, J. K. Kanters, M. V. Hojgaard, and N. H. Holstein-Rathlou, "Approximate entropy and point correlation dimension of heart rate variability in healthy subjects," *Integr. Physiol. Behav. Sci.*, vol. 33, pp. 315–320, 1998.
[31] Y. Bai, K. L. Siu, S. Ashraf, L. Faes, G. Nollo, and K. H. Chon, "Nonlinear coupling is absent in acute myocardial patients but not healthy subjects," *Amer. J. Physiol. Heart Circ. Physiol.*, vol. 295, pp. H578–H586, 2008.
[32] A. Porta, G. Baselli, S. Guzzetti, M. Pagani, A. Malliani, and S. Cerutti, "Prediction of short cardiovascular variability signals based on conditional distribution," *IEEE Trans. Biomed. Eng.*, vol. 47, no. 12, pp. 1555–1564, Dec. 2000.
[33] A. Porta, S. Guzzetti, N. Montano, M. Pagani, V. Somers, A. Malliani, G. Baselli, and S. Cerutti, "Information domain analysis of cardiovascular variability signals: Evaluation of regularity, synchronisation and co-ordination," *Med. Biol. Eng. Comput.*, vol. 38, pp. 180–188, 2000.
[34] L. Faes, G. Nollo, and K. H. Chon, "Assessment of Granger causality by nonlinear model identification: Application to short-term cardiovascular variability," *Ann. Biomed. Eng.*, vol. 36, pp. 381–395, 2008.
[35] N. Montano, T. Gnecchi Ruscone, A. Porta, F. Lombardi, M. Pagani, and A. Malliani, "Power spectrum analysis of heart rate variability to assess the change in sympathovagal balance during graded orthostatic tilt," *Circulation*, vol. 90, pp. 1826–1831, 1994.
[36] T. E. Brown, L. A. Beightol, J. Koh, and D. L. Eckberg, "Important influence of respiration on human R–R interval power spectra is largely ignored," *J. Appl. Physiol.*, vol. 75, pp. 2310–2317, 1993.
[37] C. Schafer, M. G. Rosenblum, J. Kurths, and H. H. Abel, "Heartbeat synchronized with ventilation," *Nature*, vol. 392, pp. 239–240, 1998.
[38] C. Schafer, M. G. Rosenblum, H. H. Abel, and J. Kurths, "Synchronization in the human cardiorespiratory system," *Phys. Rev. E*, vol. 60, pp. 857–870, 1999.
[39] S. Rzeczinski, N. B. Janson, A. G. Balanov, and P. V. McClintock, "Regions of cardiorespiratory synchronization in humans under paced respiration," *Phys. Rev. E*, vol. 66, pp. 051909-1–051909-9, 2002.
[40] C. J. Keylock, "Constrained surrogate time series with preservation of the mean and variance structure," *Phys. Rev. E*, vol. 73, pp. 036707-1–036707-4, 2006.
[41] C. J. Keylock, "A wavelet-based method for surrogate data generation," *Physica D*, vol. 225, pp. 219–228, 2007.

Luca Faes (M'07) was born in Calceranica,, Italy, in 1973. He received the Graduate degree in electronic engineering from the University of Padova, Padua, Italy, in 1998, and the Ph.D. degree in electronic devices from the University of Trento, Trent, Italy, in 2003.

Until 2000, he was a Research Fellow at the Medical Biophysics Division, Institute for Scientific and Technologies Research (ITC-irst), Trent, where he was working on system identification and modeling. He is currently with the Biosignals Laboratory, Department of Physics, University of Trento. His current research interests include time series analysis, digital signal processing, and system modeling applied to mechanisms of cardiovascular control, atrial fibrillation, and brain activity.

He Zhao received the B.S. degree in automatic control and the M.E. degree in pattern recognition from the University of Sciences and Technology of China (USTC), Hefei, China, in 1999 and 2002, respectively, and the Ph.D. degree in biomedical engineering from the State University of New York at Stony Brook, Stony Brook, in 2008.

He is currently a Senior Engineer at Mathworks, Inc., Natick, MA. His current research interests include biomedical system modeling, biomedical signal processing, and medical instrumentation.



Ki H. Chon (M'96–SM'08) received the B.S. degree in electrical engineering from the University of Connecticut, Storrs, the M.S. degree in biomedical engineering from the University of Iowa, Iowa City, and the M.S. and Ph.D. degrees in electrical engineering from the University of Southern California, Los Angeles.

He was a National Institute of Health (NIH) Post-Doctoral Fellow at the Harvard–Massachusetts Institute of Technology (MIT) Division of Health Science and Technology, Cambridge, for three years. He was a Research Assistant Professor in the Department of Molecular Pharmacology, Physiology, and Biotechnology at Brown University, Providence, RI, for one year. He was also an Assistant Professor and an Associate Professor in the Department of Electrical Engineering, City College, City University of New York, for four years. He is currently a Professor in the Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook. His current research interests include medical instrumentation, biomedical signal processing, and identification and modeling of physiological systems.

Prof. Chon is currently an Associate Editor of the IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING and the IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING LETTERS. He is an Associate Editor of the *International Journal of Bioelectromagnetism*.

Giandomenico Nollo (M'07) was born in 1960. He received the degree in physics from the University of Trento, Trent, Italy, and the Ph.D. degree in physiology from the University of Torino, Turin, Italy.

He was initially a Research Fellow in the Division of Medical Biophysics, Institute for Scientific and Technologies Research (ITC-irst), where he was a Researcher from 1989 to 1999. Since 2000, he has been with the Department of Physics, University of Trento, where he teaches biomedical instrumentation and monitoring of biosystems for the Laurea in Physics course of the Faculty of Science. His current research interests include monitoring of human biosignals and linear and nonlinear modeling of physiological data.