Assessing Nonlinear Properties in Breathing Signals from Preterm Infants

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Abstract. Breathing signals from preterm infants are studied with the noise titration technique and surrogate-data analysis using nonlinear indexes from correlation dimension and sample entropy. We verify that most analyzed breathing time-series contains nonlinear dynamics, and their strengths become more significant as maturational aspects (weight and post-conceptional age) increase. This behavior is partially followed in variability-series extracted from five-minute breathing signals. We also observe that entropy and titration based tests were more robust than correlation dimension in short and noisy signals.

Keywords: Preterm infants; Breathing; Nonlinear; Surrogate-data test; Noise titration

1. Introduction

Although it has been observed that adult human breathing shows chaotic dynamics under certain conditions, it remains still unclear whether the rhythm generated by respiratory control centers is governed by deterministic chaos [Fiamma et al., 2007]. One of the reasons contributing to this uncertainty is that experimental conditions, as the presence of noise, or an insufficient series length makes detection of chaos quite arduous. So, quantifying underlying nonlinear dynamics rather than chaos in physiological data seems more realistic and reliable.

Breathing dynamics in preterm infants have not been explored extensively. [Engoren et al., 2009] studied the complexity in the respiratory rate concluding that while some entropy measures increased significantly with age and weight, others did not. Concerning healthy term infants, the works of [Small et al., 1999; Small and Judd, 1998] confirmed the presence of nonlinearity in ventilation, proposed some modeling methods, and stated that chaos was probably present during quiet sleep by examining the correlation dimension.

This communication shows the results of analyzing short regular breathing signals from premature newborns with two different approaches: the surrogate-data test and the noise titration, still unexplored in this concern. We studied the presence of nonlinearity by means of several nonlinear indexes and its eventual relationship with maturity in preterm infants.

2. Methods

Surrogates test [Theiler et al., 1992] has been classically employed to reveal the presence of nonlinear processes, but more recently noise titration [Poon and Barahona, 2001] arose as a more robust strategy to this purpose in noisy and short time-series. In this section both methods are introduced, then we describe how nonlinear indexes are derived from surrogates.

2.1. Surrogate-data test

The surrogate-data based test consists of computing a statistic from the empirical data and the family of series (surrogates) originated by removing nonlinearity and preserving the spectrum [Theiler et al., 1992]. If the data under test is generated by a nonlinear process, the computed statistic is significantly different from the surrogate set and the null hypothesis, that a linear method characterizes the original data, can be rejected. We generated the ensemble of surrogates using the iterated Amplitude Adjusted Fourier Transform (iAAFT) method [Schreiber and Schmitz, 1996]. The statistics, chosen by their ability to evidence nonlinearity, were correlation dimension (*D*) and sample entropy (*SpEn*).

Correlation dimension is a parameter describing the characteristics of the chaotic attractor of a dynamical system, and the first step to compute it relies on reconstructing the phase space with the

appropriate lag and embedding dimension (*d*). *D* was estimated by the Gaussian Kernel Algorithm (GKA) [Yu et al., 2000] with *d* from 3 to 15 as was suggested by the nearest neighbor technique, and a lag equal to the first zero of the autocorrelation function.

Sample entropy is a well-known robust measure of pattern regularity in short data-series [Richman and Moorman, 2000]. Here, *SpEn* was computed by introducing time delays (τ) between templates (*m*) as shown in the following equation:

$$SpEn(\tau) = -ln \frac{\sum_{i=1}^{N-m} A_i^m(\tau, r)}{\sum_{i=1}^{N-m} B_i^m(\tau, r)} \quad (1)$$

where *N* is the number of points of the series, *r* is the tolerance, and $A_i^m(\tau,r)$ and $B_i^m(\tau,r)$ are the probabilities that two (*m*+1)-point sequences and two *m*-point sequences match, respectively. Computing *SpEn* across several time delays (see Fig. 1-D) allows to better capture nonlinear contributions than using a single sample delay (τ =1) as done traditionally [Kaffashi et al., 2008].

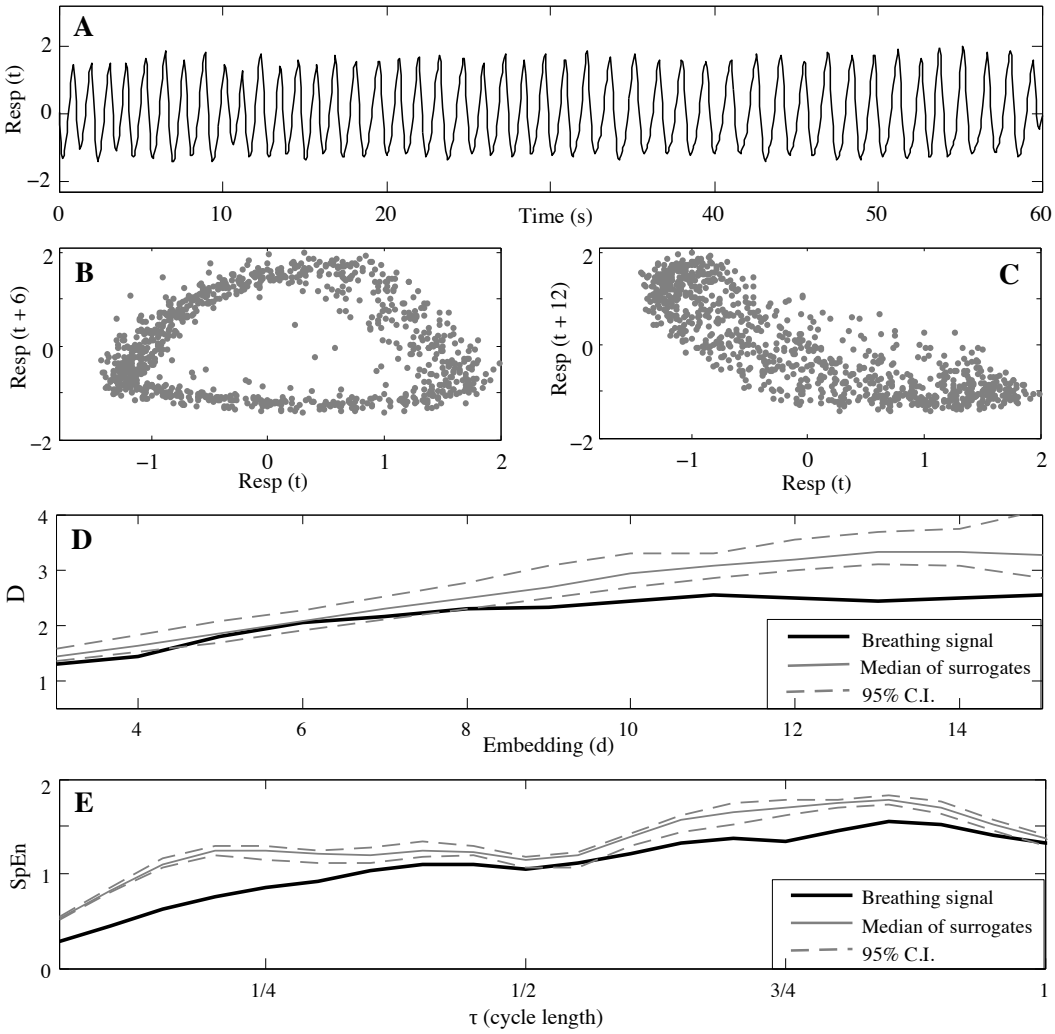

Figure 1. *Example of one-minute breathing signal (A). Return maps plotted from the original and time-delayed data sets: 6 points (B) and 12 points (C). Estimated D with embeddings from 3 to 15 (D). SpEn of breathing signal (E) calculated with τ from 1 to 20 points (1-cycle length).*

2.2. Noise titration

Noise titration was proposed by [Poon and Barahona, 2001] to provide a robust measure of chaos intensity even in the presence of noise and with short data series. Despite noise titration was found later to have some pitfalls detecting deterministic chaos confidently, this test can still be used as an efficient

tool to detect nonlinearity in time series [Freitas et al., 2009]. Briefly, the noise titration technique (Fig. 2) begins by fitting a family of polynomial autoregressive Volterra-Wiener models, both linear and nonlinear, with different degrees of nonlinearity (d) and embedding dimension (κ). If the best model, chosen according to the Akaike information theoretic criterion is nonlinear, titration can be applied. Then, white noise is added to the series increasing its standard deviation until nonlinearity is not detected. The level of noise, called noise limit (NL) denotes the relative intensity of nonlinearity, so $NL = 0$ can be interpreted as the neutralization of nonlinear dynamics by the background noise in the data.

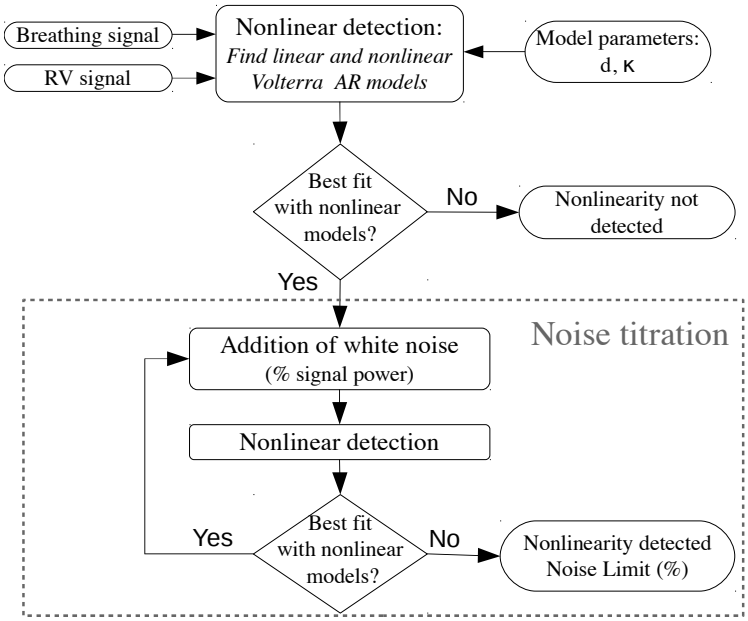

Figure 2. *Illustration of the noise titration technique.*

2.3. Nonlinear indexes

Nonlinear indexes were derived from the surrogate analysis of breathing signals as follows:

- Estimate D_0, the correlation dimension on the original signal across the range of embeddings, and $SpEn_0$, the sample entropy across the delays τ, also on the original breathing signal.
- Similarly, estimate $\tilde{D}_s$ and $Sp\tilde{E}n_s$, the medians of D and $SpEn$ on the set of surrogates, respectively.
- Obtain nonlinear indexes, NI_D = mean($\tilde{D}_s$ - D_0) and NI_{SpEn} = mean($Sp\tilde{E}n_s$ - $SpEn_0$).

3. Results

3.1. Database and study protocol

Data, collected at the neonatal intensive care unit of the University Hospital Center of Rennes (France), consisted of 1-hour electrocardiograms and respiratory signals (recorded with abdominal strain gauges) sampled at 400 Hz. We removed baseline and high frequency noise and subsampled signals to 16 Hz before performing calculations. From our database of 47 preterm infants between 27 and 35 weeks of post-conceptional age, we formed three groups of 1, 2 and 5-minute excerpts of the steadiest and least noisy breathing traces in quiet sleep. The infants could be included in several groups (with different excerpts), but only once in the same group. We chose such a short sample duration due to the limitation of finding highly regular patterns without amplitude modulations and apnea. In group 1, it was possible to select signals with a low envelope variation (the standard deviation of the magnitude of the Hilbert transform), but this feature increased in longer excerpts from second and third groups, where regularity was sparser (see Table 1). Respiratory variability (RV) signals were extracted from the 5-minute set applying a peak detector. Inhalation time (*ti*) was measured as the time elapsed between a valid minimum and its consecutive time, and exhalation time (*te*) as the time between a maximum and its consecutive minimum. Used RV signals (Fig. 3) were *ttot* series, containing the inter-breath times (*ti* to *ti*), and *tite* series containing the time between minima and maxima (half-cycle

times). Data relative to newborns was post-conceptional (PCA) and post-natal age (PNA), gender and weight. There were not significant statistical differences between them.

Table 1. *Number of infants (N_i), length (L) and mean ± std of number of cycles (N_c), main frequency (M_f) and envelope variation (EV) of groups. M_f was estimated as the maximum of the power spectral density (Burg method, order 30).*

Group	N_i	*L (s)*	N_c	M_f *(Hz)*	*EV*
1	29	60	61.2 ± 17.9	1.04 ± 0.28	0.29 ± 0.07
2	23	120	105.6 ± 30.3	0.89 ± 0.27	0.35 ± 0.09
3	23	300	287.5 ± 76.0	1.03 ± 0.27	0.92 ± 1.50

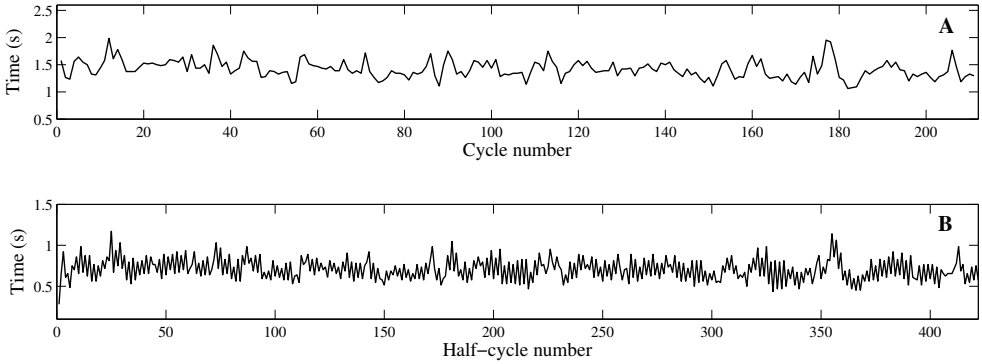

Figure 3. *Examples of extracted variability signals from group 3: ttot (A) and tite (B).*

3.2. Surrogate analysis

We generated an ensemble of 20 surrogates for each signal to obtain the nonlinear indexes. NI_D was not computed in RV series due to its lack of periodicity, which prevents a reliable phase space reconstruction.

Since randomized signals have higher chaos dimension, $\tilde{D}_s > D_0$, hence $NI_D > 0$ when nonlinearity is detected. Likewise, $NI_{SpEn} > 0$ because surrogates exhibit higher entropy than the original signal.

A linear regression of the indexes as a function of age and weight was performed to describe the relationship between maturation and nonlinearity. The Pearson's linear correlation coefficient (ρ) was inserted in the figures as a measure of fit. Results from PCA and weight manifested consistent trends whereas PNA (not shown) did not.

NI_D was computed on first and second group. A few samples failed the nonlinearity test ($NI_D < 0$) and hence not taken in account to calculate the linear regressions. As it can be observed in Fig. 4-A1, A2, NI_D increases slightly with PCA and weight in group 1, but not in group 2 (Fig. 5-A1, A2). This disagreement may be explained by the high sensitivity of the correlation dimension with irregularities, more present in two-minute samples.

NI_{SpEn} was obtained from all signals with $r = 0.2$ and $m = 2$. For groups 1 and 2, τ ranged from 1 to the average cycle length of each series, and for group 3, τ was fixed to 1 due to the absence of short-term correlations in RV signals. All signals passed the nonlinear test with entropy ($NI_{SpEn} > 0$). In temporal signals, a positive slope was also observed within PCA and weight regression lines, being the 2-minute group (Fig. 5-B1, B2) better fitted than results from group 1 (Fig. 4-B1, B2).

On the other hand, opposed patterns were observed in variability signals. According to the regression lines from *ttot* series, nonlinearity decreases with maturity (see Fig. 6-A1, A2), whereas in *tite* it grows (Fig. 6-B1, B2). Since *SpEn* could be estimated inaccurately in signals with a small number samples as *ttot*, and indexes from *tite* follows the generalized behavior, it can be stated that the latter are more reliable.

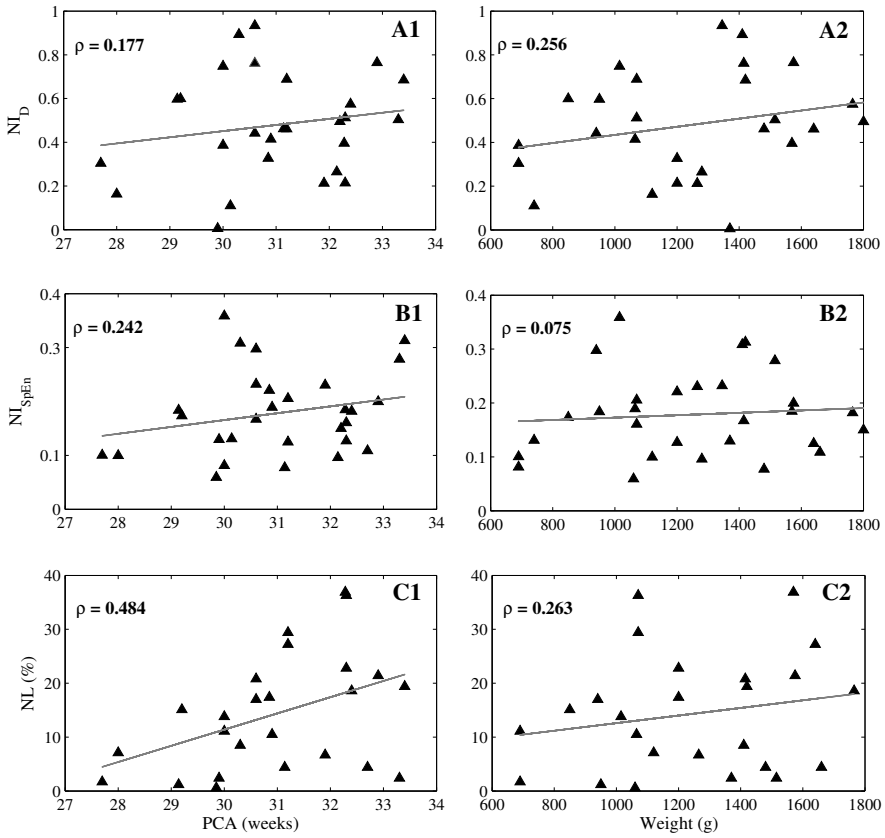

Figure 4. *Results of 1-minute breathing signal analysis. Indexes from correlation dimension (A), from sample entropy (B) and from titration (C) with regression lines.*

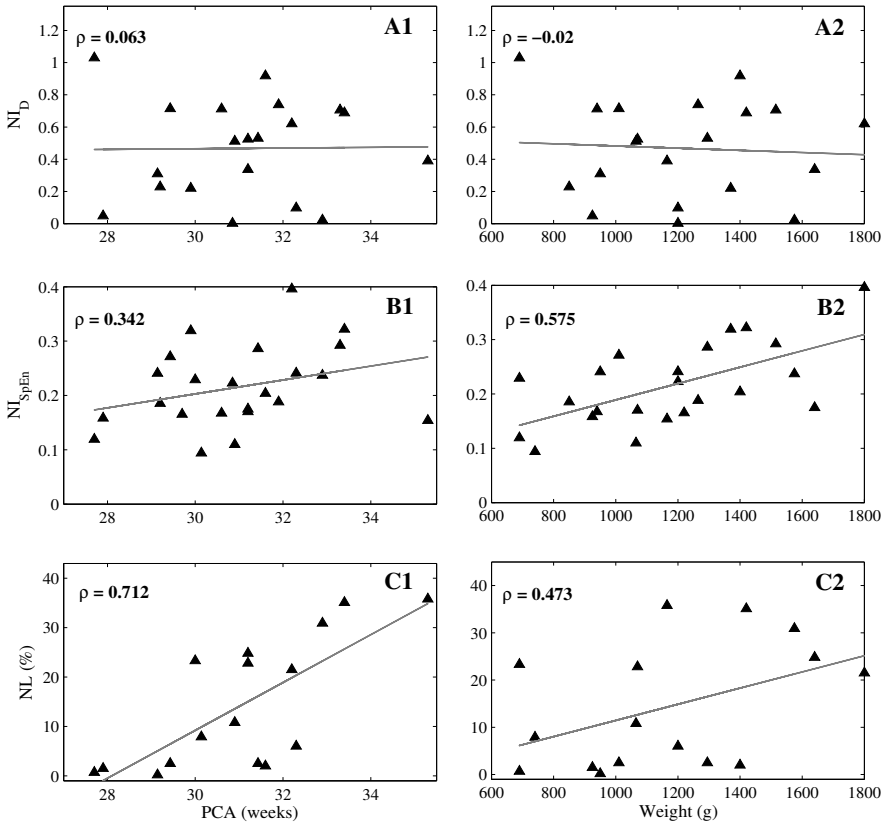

Figure 5. *The same nonlinear indexes of Fig. 4 computed in 2-minute breathing signals.*

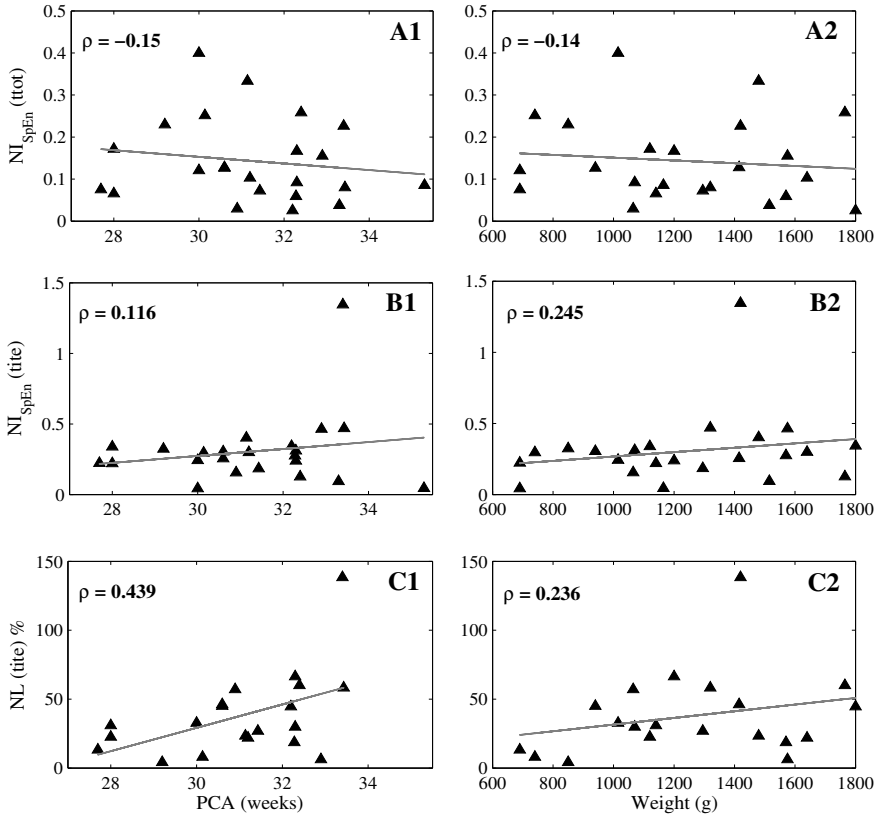

Figure 6. *Results of 5-minute variability signal analysis. SpEn indexes applied on ttot (A) and on tite series (B). C: NL applied on tite series.*

3.3. Noise titration analysis

The measure of nonlinearity given by noise titration (*NL*) was obtained in both temporal and variability signals. We chose the pair of modeling parameters (*d,* κ) equal to 3 and 5 respectively following the recommendations in [Roulin et al., 2011] to avoid false detections. Ten titrations for each sample were realized to ensure as well a reliable noise limit. In time-series, nonlinearity was undetected in 4 and 5 cases for group 1 and group 2 respectively. In RV signals, *ttot* length was often insufficient (about 300 samples) to find nonlinear models with given parameters and results are not shown here. However, *tite* series were more adequate to be analyzed with noise titration. In Fig. 6-C1 and C2, it can be observed that slopes from regression lines have a similar trend to increase with age and weight than those obtained with temporal signals. The evolution of *NL* was very similar in all analysis. Slopes, more pronounced with PCA, are even reproduced in temporal and RV signals. Furthermore, the correlation coefficients where the closest to 1, revealing that noise titration is the most reliable measure of nonlinearity studied here. A comparison of all correlation values can be seen in Table 2.

Table 2. *Correlation coefficients (ρ_{PCA} / ρ_{weight}) of the different indexes. Best results in bold.*

	Breathing signals		**Variability signals**	
Index	1 min	2 min	*ttot*	*tite*
NID	0.177 / 0.256	0.063 / -0.020	-	-
NISpEn	0.242 / 0.075	0.342 / 0.575	-0.15 / -0.14	0.12 / 0.25
NL	**0.484 / 0.263**	**0.712** / 0.473	-	**0.44** / 0.24

4. Conclusions

In this work, several indexes related to nonlinearity in preterm infants breathing were analyzed. We stated that in most of the cases nonlinear dynamics are present in temporal and RV signals, and their strength became more relevant, in qualitative terms, with maturation.

From the methodological point of view, noise titration is an interesting alternative to surrogate-data tests to evaluate nonlinearity in our breathing signals. Frequently, experimental conditions in neonatology limit the quality and length of records, hence correlation dimension based methods should be applied with caution. Indexes from sample entropy and noise titration were therefore introduced due to their robustness with noisy and short data. Indeed, observing the regression lines, trends are consistent and better fitted. The noise limit can be then considered the most reliable nonlinear index when series length is sufficient to perform noise titration. Otherwise, sample entropy based index can be used, yet being aware of its inaccuracy within very short data-series.

From a clinical point of view, the presented nonlinear indexes could be a useful tool to assess and understand maturation in neonatology. Loss (or absence) of nonlinearity in the breathing signal might be associated with underdevelopment in preterm infants, but additional tests on longitudinal databases should be done to confirm this conjecture.

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