Evaluation of a Nonlinear Prediction Algorithm Quantifying Regularity, Synchronization and Directionality in Short Cardiovascular Variability Series

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Abstract

An unifying approach evaluating complex dynamics and dynamical interactions in short bivariate time series is presented. The method performs nearest neighbor local linear prediction to estimate regularity, synchronization and directionality of two interacting time series. It was implemented through a specific cross-validation procedure which allowed an unconstrained embedding of the series and a full exploitation of the available data to maximize the accuracy of prediction. The approach was evaluated by simulations of stochastic (autoregressive processes) and deterministic (Henon maps) models in which uncoupled, unidirectionally coupled and bidirectionally coupled dynamics were generated. The method was then applied to representative examples of heart period and systolic pressure variability series, showing its ability to describe complexity and interactions in short term cardiovascular variability.

1. Introduction

Regularity, synchronization and causality are concepts playing an important role in the study of complex physiological systems. In particular, these concepts are fundamental to investigate the short-term regulation of the cardiovascular system, that is the result of the interaction among several regulatory subsystems (e.g., central and peripheral oscillators and reflex loops). This complex regulation is indeed reflected in the beat-to-beat variability of the heart period (RR interval) and the systolic arterial pressure (SAP) [1], in a way such that modifications of the reciprocal activity of the interacting subsystems (e.g., due to pathology or experimental conditions) could be captured by measuring regularity, synchronization and causality.

Up to now, several tools have been proposed to quantify the complexity of single time series, the strength of coupling in bivariate time series, and the direction of interaction in coupled time series [2-5]. While these tools have been proven useful to detect both linear and nonlinear dynamics and to assess complex cardiovascular modulations in several experimental and/or pathological conditions, some methodological issues are often not addressed. Most of these methods are indeed not suitable to deal with short time series, and their application to finite data sets usually poses serious constraints on the embedding of the series. Moreover, methods determining regularity, synchronization and causality usually are not carried out according to a common framework, thus limiting the possibility to infer complementary information from these different measures.

In this study we propose an unifying approach, based on nonlinear prediction of short bivariate time series, to investigate together the concepts of regularity, synchronization and causality. With this approach, these concepts are evaluated by measuring respectively the predictability of a series given its own past (self-prediction), the predictability of a series given the other series (cross-prediction), and the improvement in predictability of a series given both its own past and the past of the other series (mixed-prediction). Nonlinear prediction is performed by nearest-neighbor local linear approximation [6], and a specific cross-validation approach [7] is followed to let the embedding of the series unconstrained and to maximize the accuracy of prediction on short (few hundred samples) data sequences. The approach is validated on simulations of stochastic and deterministic models reproducing uncoupled, unidirectionally coupled and bidirectionally coupled dynamics. An example of application to real RR interval and SAP series is then given to illustrate the potentiality of the approach in describing complex cardiovascular dynamics and interactions in different experimental conditions.

2. Methods

Given two normalized time series x and y, the evaluation of regularity, synchronization and directionality, in the unifying framework of nonlinear prediction, was performed by means of self-prediction, cross-prediction, and mixed-prediction, respectively. In all these prediction schemes the current value of a series was estimated as a linear combination of the values of a suitably chosen reference vector containing past values of either one or both the two series. Specifically, the current value of x, $x(i)$, was predicted from the reference vector formed by the past Lx values of x, $[x(i-1),\dots,x(i-Lx)]$, in self prediction, by the past Ly values of y, $[y(i-1),\dots,y(i-Ly)]$ in cross-prediction, and by both the past Lx values of x and the past Ly values of y, $[x(i-1),\dots,x(i-Lx), y(i-1),\dots,y(i-Ly)]$, in mixed prediction. Specularly, to estimate $y(i)$ by self-, cross-, and mixed-prediction, the roles of the two series were switched in the construction of reference vectors.

For each prediction scheme, the coefficients used as weights of the samples of the reference vector to predict $x(i)$ (or $y(i)$) were estimated through standard least squares optimization starting from the K nearest neighbors of the reference vector, where neighborhood was assessed by the Euclidean distance. The prediction error series was then obtained as the difference between the estimated and the actual values of the series to be predicted, and its variance was estimated as mean squared prediction error (MSPE). As the MSPEs correspondent to different prediction schemes are functions of the parameters Lx, Ly, and K, predictions were repeated for different combinations of values of these parameters. Finally, the minimum MSPEs were considered as indexes of unpredictability of the investigated series. Specifically, the self-, cross-, and mixed-prediction of x and y yielded the minimum MSPEs $E_{x|x}$ and $E_{y|y}$, $E_{x|y}$ and $E_{y|x}$, and $E_{x|x,y}$ and $E_{y|x,y}$, respectively.

The minimum MSPEs were related to regularity, synchronization and causality of the two series by means of the following relationships:

$$R_x = 1 - E_{x|x} \ , \quad R_y = 1 - E_{y|y} \tag{1}$$

$$S_{xy} = 1 - \min\left(E_{x|y}, E_{y|x}\right) \tag{2}$$

$$\begin{gathered}\delta_{x|y} = \frac{E_{x|x} - E_{x|x,y}}{E_{x|x}} \ , \quad \delta_{y|x} = \frac{E_{y|y} - E_{y|x,y}}{E_{y|y}} \\ \Delta_{xy} = \frac{\delta_{y|x} - \delta_{x|y}}{\delta_{y|x} + \delta_{x|y}}\end{gathered} \tag{3}$$

Eq. (1) defines the regularity of a series as the fraction of variance of the series that can be described by its own past, and ranges from 0 (for fully unpredictable series) to 1 (for fully predictable series). Eq. (2) defines the synchronization between x and y as the fraction of the variance of a series that can be described by the other series. By taking the minimum between $E_{x|y}$ and $E_{y|x}$, the synchronization was defined as the maximum of the two cross-predictabilities, so that S_{xy} is 1 when x and y are fully coupled, while it is 0 when x and y are independent. Eq. (3) defines the causal coupling indexes $\delta_{x|y}$ and $\delta_{y|x}$ as the relative improvements in predictability brought by mixed-prediction with respect to self-prediction, and the directionality index Δ_{xy} indicating the preferential causal direction of interaction ($\Delta_{xy}>0$: predominance of interaction from x to y; $\Delta_{xy}<0$: predominance of interaction from y to x).

To avoid overfitting and waste of data, each prediction was performed according to a specific cross-validation approach [7]. Specifically, the prediction of the i-th sample of a series was performed by excluding from the ensemble of possible neighbors all vectors containing $x(i)$ and/or $y(i)$. In this way, an out-of-sample prediction was performed, as at each prediction step the tested sample was not considered for the definition of the predictor.

3. Simulations

The proposed approach was evaluated by simulations reproducing different types and degrees of interactions between two short time series. Calculations were performed on 300 point realizations.

In the first set of simulations, the series x and y were generated as realizations of the stochastic bivariate autoregressive (AR) process:

$$\begin{aligned}x(n) &= \sqrt{2}r\left[(1-c_2)x(n-1) + c_2 y(n-1)\right] - r^2 x(n-2) + w_1(n) \\ y(n) &= \sqrt{2}r\left[(1-c_1)y(n-1) + c_1 x(n-1)\right] - r^2 y(n-2) + w_2(n)\end{aligned}$$

where r is the modulus of the poles of the AR process, which is inversely related to the regularity of the series, c_1 and c_2 are the degrees of coupling from x to y and from y to x, and w_1 and w_2 are white noises with zero mean and unit variance.

In the second set of simulations, x and y were deterministic chaotic signals (Henon maps) corrupted by the stochastic noises w_1 and w_2:

$$\begin{aligned}x(n) &= 1.4 - x^2(n-1) + 0.3x(n-2) + \\ &\quad d_2\left[x^2(n-1) + y^2(n-1)\right] + \alpha w_1(n) \\ y(n) &= 1.4 + d_2\left[y^2(n-1) - x^2(n-1)\right] + 0.1y(n-2) \\ &\quad - \left[d_1 x(n-1) + (1-d_1)y(n-1)\right]y(n-1) + \alpha w_2(n)\end{aligned}$$

where the regularity of the series is inversely related to the variance α^2 of the additive noises, d_1 is the degree of unidirectional coupling from x to y, and d_2 is the degree of bidirectional coupling between x and y.

As shown in Table 1, the parameters of the simulations were set to reproduce uncoupled dynamics (A,B,G,H), unidirectionally coupled dynamics from x to y (C,D,I,K), and bidirectionally coupled dynamics (E,F,L,M). Results indicate that self-prediction was able to distinguish regular from irregular dynamics, as R_x and R_y resulted high when r=0.9 or α=0, and low when r=0.2 or α=1. Cross-prediction was useful to distinguish uncoupled (A,B,G,H, low S_{xy}) from coupled (C,D,E,F; I,K,L,M, high S_{xy}) dynamics. The directionality index was not defined (ND) in case of uncoupled dynamics (as $\delta_{x|y}=\delta_{x|y}=0$), was close to 1 in case of unidirectional interaction, and was close to 0 in case of bidirectional interaction.

Table 1. Results of the simulation analysis.

	r	c_1	c_2	R_x	R_y	S_{xy}	Δ_{xy}
A	0.2	0	0	0.08	0.17	0.02	ND
B	0.9	0	0	0.80	0.84	0.01	ND
C	0.2	1	0	0.13	0.01	0.08	1.00
D	0.9	1	0	0.84	0.70	0.73	1.00
E	0.2	1	1	0.01	0.01	0.09	0.06
F	0.9	1	1	0.52	0.51	0.81	0.001
	α	d_1	d_2	R_x	R_y	S_{xy}	Δ_{xy}
G	1	0	0	0.13	0.21	0.03	ND
H	0	0	0	0.99	1.00	0.003	ND
I	1	0.8	0	0.12	0.02	0.15	0.67
K	0	0.8	0	0.99	0.89	0.95	1.00
L	1	0	0.2	0.15	0.06	0.21	0.38
M	0	0	0.3	0.99	0.99	0.99	-0.15

4. Real data

As representative example of application to short-term cardiovascular variability, we considered a healthy young subject (26 yrs) for which the proposed indexes were calculated in the resting supine position and during 60º head-up tilt. The analyzed series were the RR interval and SAP, measured on a beat-to-beat basis respectively from the surface ECG and the photopletismographic arterial pressure signal. Before performing nonlinear prediction, the two series were windowed to 300 samples, cleaned up from artefacts, detrended to fulfil stationarity criteria, and normalized to have zero mean and unit variance. The resulting RR and SAP variability (r and s series) were appropriately aligned so that the i-th SAP value was contained within the i-th RR interval.

The MSPEs of RR and SAP variability series, expressed as functions of the number of samples of r and s (Lr and Ls) and the number of neighbour vectors (K) used to perform self-, cross-, and mixed-prediction, are shown in Figures 1 and 2 for the supine and the upright position, respectively.

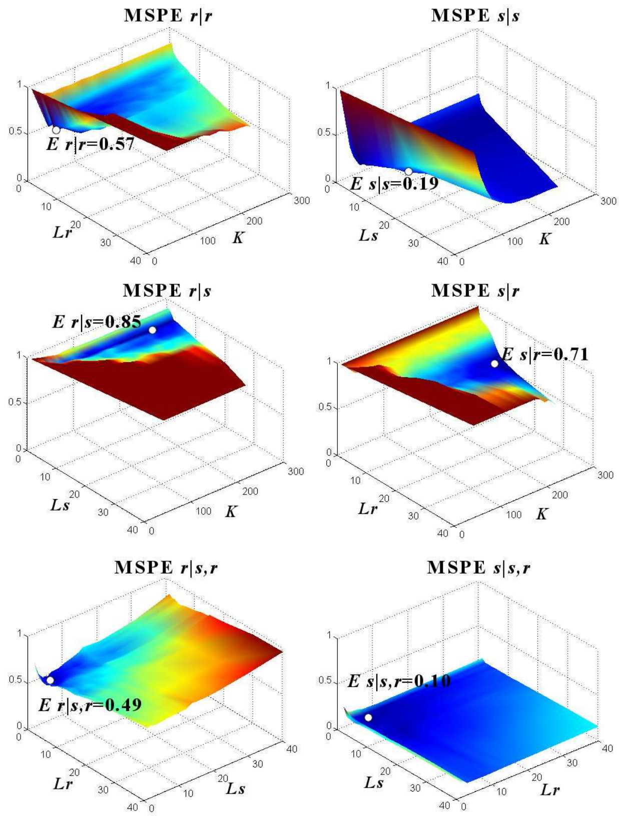

Figure 1. MSPEs obtained by self- (top), cross- (middle) and mixed- (bottom) prediction of RR interval (r, left) and SAP (s, right) variability in the resting supine position. Surface minimums are marked with circles labeled with the corresponding MSPE values.

At rest, the SAP series was more predictable (R_s=0.81) than the RR interval series (R_r=0.43). Cross-prediction yielded a significant coupling between the two series (S_{sr}=0.29). The combination of self- and mixed-prediction suggested a prevalence of the causal coupling from r to s ($\delta_{s|r}$=0.47) over that from s to r ($\delta_{r|s}$=0.14), that resulted in a negative directionality index (Δ_{sr}=-0.54). During head-up tilt, both series were highly predictable (R_r=0.71, R_s=0.80) and coupled (S_{sr}=0.40), while a balancing of the two causal coupling indexes ($\delta_{s|r}$=0.25, $\delta_{r|s}$=0.20) shifted towards zero the directionality index (Δ_{sr}=-0.09).

5. Discussion

The unifying approach proposed in this study aims to quantify different concepts related to the dynamical complexity of short bivariate time series: regularity, which is inversely related to the complexity of a single series; synchronization, intended as the degree of coupling between the two series; and directionality, inferring driver-response relationships in coupled series.

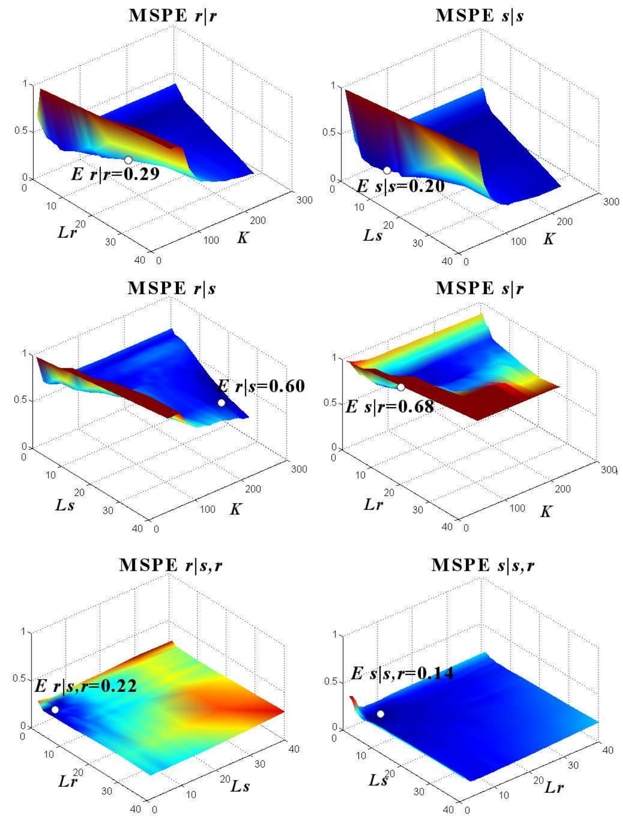

Figure 2. MSPEs obtained by self- (top), cross- (middle) and mixed- (bottom) prediction of RR interval (*r*, left) and SAP (*s*, right) variability in the head-up position. Surface minimums are marked with circles labeled with the corresponding MSPE values.

These three measures are performed by exploiting the same basic function, i.e. the prediction error. With this approach, the degree of predictability coming from self-, cross-, or mixed-prediction is related to regularity of a series, coupling strength between two series, or causality from one series to another. The main features of the approach are the sensibility to nonlinear dynamics, since nearest neighbor local linear prediction [6] is performed, the possibility to let unconstrained the embedding of the series, since overfitting is prevented by performing out-of-sample prediction [7], and the use of cross-validation that maximizes the accuracy prediction making it useful for the application to short sequences [7].

The application to synthetic time series documented the ability of the proposed approach to detect regularity, coupling and directionality even in short (300 points) realizations of the simulated dynamics. Both in linear stochastic and nonlinear deterministic processes, the method seems to be able to distinguish regular from irregular dynamics, to detect the presence of coupled dynamics, and to identify the directions of interaction in coupled dynamics. A slight ambiguity could arise detecting the synchronization of irregular but coupled dynamics (e.g., cases C and E in Table 1), but this can be settled by the use of a proper surrogate data approach.

Results concerning real cardiovascular data agree with previously observed findings, thus supporting the feasibility of our approach. Specifically, SAP variability was more regular than RR interval variability, and regularity seems larger during head-up tilt [5]. The two series were more coupled in the upright than in the supine position, suggesting a simplification of their interactions with tilt [4,7]. Finally, at rest the negative directionality suggested a prevalence of non-baroreflex mechanisms from RR interval to SAP [8], which seems to be compensated after tilt (Δ close to zero), probably as a consequence of the enhancement of the feedback regulation from SAP to RR [1].

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