Phase shifts of synchronized oscillators and the systolic/diastolic blood pressure relation

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We study the phase-synchronization properties of systolic and diastolic arterial pressure in healthy subjects. We find that delays in the oscillatory components of the time series depend on the frequency bands that are considered, in particular we find a change of sign in the phase shift going from the Very Low Frequency band to the High Frequency band. This behavior should reflect a collective behavior of a system of nonlinear interacting elementary oscillators. We prove that some models describing such systems, e.g. the Winfree and the Kuramoto models offer a clue to this phenomenon. For these theoretical models there is a linear relationship between phase shifts and the difference of natural frequencies of oscillators and a change of sign in the phase shift naturally emerges.

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I. INTRODUCTION

Time series of physiological origin very often display synchronous behavior. Most likely, this is the result of collective behavior of a huge number of nonlinearly interacting elementary oscillators. Different examples of this phenomenon, as well as models of it, can be found for example in [1]. In the present paper we address a further example, i.e. the relation between diastolic (DAP) and systolic (SAP) blood pressure signals in healthy subjects. The analysis of blood pressure fluctuations may provide significant information on the physiology and pathophysiology of the autonomic control of the cardiovascular function [2], [3]. The synchronization of these signals is expected, though a detailed study of its features is apparently still lacking. In a previous paper [4] it was noticed that DAP and SAP are characterized by a phase lag in the very low frequency band (VLF). The analysis of [4] uses Fourier analysis, which is not particularly useful when non-stationary effects play a relevant role. In the present work we address two questions about the DAP/SAP relationship: Is the phase lag depending on the frequency band? Is the phase lag connected to a causal relation between SAP and DAP? To address these questions, we measured DAP and SAP signal in a number of healthy subject. Studying the mutual interdependency between the two time series, we conclude that there is not a causal relationship between DAP and SAP time series, i.e. none of the two is driver for the other. Moreover, a significant phase delay is found, for healthy subjects, in the VLF band and in the high frequency (HF) band. The phase shift between DAP and SAP is positive in VLF band and negative in the HF band. This change of sign in the phase shift has its origin in the regulatory mechanisms of blood circulation. A physiological interpretation of these mechanisms is beyond the scope of our work; however the hypothesis that synchronization results from the collective behavior of elementary nonlinear oscillators may offer a clue to its understanding. To exploit this idea we use below two well known models of coupled oscillators, the Winfree model [5] and the Kuramoto model [6].

Winfree's paper [5] on coupled oscillators provided one of the first tractable examples of a self-organizing system. Winfree introduced an approximation that has become the standard approach to the study of ensembles of biological oscillators: In the weak coupling limit, amplitude variations could be neglected and the oscillators could be described only by their phases along their limit cycles. Winfree also discovered that systems of oscillators with randomly distributed frequencies exhibit a remarkable cooperative phenomenon, reminiscent of a thermodynamic phase transition, as the variance of the frequencies is reduced. The oscillators remain incoherent, each running near its natural frequency, until a certain threshold is crossed. Then the oscillators begin to synchronize spontaneously. Winfree model was subsequently modified by Kuramoto who provided an analytically solvable version of it [6]. This field of study has been very active all along and the analysis of synchronization phenomena remains a thriving area of research, see [7] for a review. Having in mind our experimental findings on the SAP/DAP relation, we first examine in Section II the phase shift between coupled oscillators in these models, once synchronization has been reached. We observe that there

phase shift between coupled oscillators in these models, once synchronization has been reached. We observe that there exists a simple linear dependence between phase shifts of synchronized oscillators and the difference between their natural frequencies. This phenomenon, to our knowledge never noticed before, offers a simple mechanism to describe the change of sign in the phase lag as the frequency band is changed. In Section III we describe the experimental data and analyze them using the theoretical approach of Section II. Moreover we discuss the problem of the causal relation between the DAP/SAP time series. Finally in Section IV we draw our conclusions.

II. PHASE SHIFTS OF SYNCHRONIZED OSCILLATORS

A. Winfree model

The Winfree model is defined by the set of equations (i = 1, ..., N)

$$\dot{\theta}_i(t) = \omega_i + \frac{1}{N} \sum_{j=1}^N \kappa P(\theta_j) R(\theta_i), \tag{1}$$

It describes a set of $N \gg 1$ coupled non linear oscillators, with coupling constant proportional to κ . $\theta_i(t)$ is the phase of the *i*-th oscillator; $\{\omega_i\}$ describes a set of natural frequencies taken randomly from a distribution $g(\omega)$. $P(\theta_j)$ is the influence function of the *j*-th; $R(\theta_i)$ is the sensitivity function giving the response of the *i*-th oscillator. We shall assume below : $g(\omega) = 1/2\gamma$ for $\gamma \in [\omega_0 - \gamma, \omega_0 + \gamma]$, $g(\omega) = 0$ otherwise. In the previous equation $P(\theta) = 1 + \cos \theta$, $R(\theta) = -\sin \theta$. The phase diagram of the Winfree model has been recently discussed [8]. In particular the long-time behavior of the system is characterized by a synchronous dynamics for κ and γ not very large. For $\omega_0 = 1$ synchronization occurs for $\kappa < 0.77$ and $\gamma < h(\kappa)$, where the function $h(\kappa)$ can be found in Fig. 3 of Ref. [8]; in any case $\gamma < 0.2$. This means that all the oscillators are characterized by a common average frequency (or rotation number) $\rho_i = \lim_{t\to\infty} \theta_i(t)/t$. The Winfree model can describe different sets of pulse-coupled biological oscillators, see e.g. [9, 10, 11].

We now wish to study the relation between the phase shift $\delta\theta$ of a pair of oscillators and the difference of their natural frequencies $\delta\omega$. We have performed numerical simulations with N = 500 oscillators with different values of κ and $\gamma = 0.10$ corresponding to the synchronization phase. We have considered times as large as t = 1,000. As expected there is no dependence on the initial conditions. On the contrary $\delta\theta$ is linearly related to $\delta\omega$ as shown in Fig. 1, where we plot ρ_i versus ω_i for various values of κ (on the left) and $\delta\theta$ versus $\delta\omega$ (on the right). This dependence



FIG. 1: On the left: the rotation number ρ plotted versus ω for $\gamma = 0.10$ and $\kappa = 0.35$, 0.45, 0.65 (from top to bottom). On the right: $\delta\theta$ versus $\delta\omega$ for the same values of γ and κ (larger slopes correspond to smaller values of κ).

can be understood as follows. As $N \to \infty$, the sum over all oscillators in (1) can be replaced by an integral, yielding

$$v(\theta, t, \omega) = \omega - \sigma(t) \sin \theta \tag{2}$$

where

$$\sigma(t) = \kappa \int_0^{2\pi} \int_{1-\gamma}^{1+\gamma} \left(1 + \cos\theta\right) p\left(\theta, t, \omega\right) g(\omega) d\omega d\theta .$$
(3)

Here $p(\theta, t, \omega)$ denotes the density of oscillators with phase θ at time t. We consider the large t behavior to allow for synchronization; moreover we take a temporal averaging over the common period T to get rid of local fluctuations. We get

$$v = \omega - \frac{1}{T} \int_{t}^{t+T} dt \,\sigma(t) \sin \theta(t) \tag{4}$$

and consider variations in ω :

$$0 = \delta\omega - \frac{1}{T} \int_{t}^{t+T} dt \,\sigma(t) \,\delta\theta(t) \cos\theta(t) \,.$$
(5)

Since the oscillators are synchronized $\delta\theta(t)$ is time-independent for t large enough. Therefore

$$\delta\omega = \frac{\kappa\delta\theta}{T} \int_{t}^{t+T} dt \int d\omega g(\omega) \int_{0}^{2\pi} d\hat{\theta} \left(1 + \cos\hat{\theta}\right) p(\hat{\theta}, t, \omega) \cos\theta(t) = \\ = \frac{\kappa\delta\theta}{T} \int_{t}^{t+T} dt \cos\theta(t) + \frac{\kappa\delta\theta}{2T} \int_{t}^{t+T} dt \int d\omega g(\omega) \int_{0}^{2\pi} d\hat{\theta} p(\hat{\theta}, t, \omega) \cos[\hat{\theta} + \theta(t)] + \\ + \frac{\kappa\delta\theta}{2T} \int_{t}^{t+T} dt \int d\omega g(\omega) \int_{0}^{2\pi} d\hat{\theta} p(\hat{\theta}, t, \omega) \cos[\hat{\theta} - \theta(t)] .$$
(6)

The first two terms on the r.h.s. of (6) vanish since the integrand functions have zero temporal average. We get therefore

$$\delta\omega = \frac{\kappa\lambda}{2}\,\delta\theta,\tag{7}$$

which is the desired linear relation between $\delta \omega$ and $\delta \theta$. The factor λ is evaluated as follows:

$$\lambda = \frac{1}{T} \int_{t}^{t+T} dt \int_{1-\gamma}^{1+\gamma} d\omega g(\omega) \int_{0}^{2\pi} d\hat{\theta} \, p\left(\hat{\theta}, t, \omega\right) \cos[\hat{\theta} - \theta(t)] =$$

$$= \frac{1}{N} \sum_{j=1}^{N} \frac{1}{T} \int_{t}^{t+T} dt \cos[\theta_{j}(t) - \theta(t)] = \frac{1}{N} \sum_{j=1}^{N} \cos[\delta\theta_{j}] =$$

$$= \frac{4\gamma}{\kappa\lambda} \int_{-1}^{+1} dy \, \tilde{g}\left(\frac{4\gamma y}{\kappa\lambda}\right) \cos\left(\frac{4\gamma y}{\kappa\lambda}\right) .$$
(8)

Here $\tilde{g}(\delta\theta)$ is probability distribution of $\delta\theta$. It is related to the probability distribution of $\delta\omega$ by (7). Both the $\delta\omega$ and the $\delta\theta$ distribution functions are derived from the ω density $g(\omega)$. If this density is flat, as assumed here, then $\tilde{g} = g \star g$, i.e.

$$\tilde{g}(\delta\theta) = \frac{\kappa\lambda}{4\gamma} - \left(\frac{\kappa\lambda}{4\gamma}\right)^2 |\delta\theta| .$$
(9)

In conclusion λ is given by solving the equation

$$\frac{4\gamma^2}{\kappa^2} = \lambda \sin^2\left(\frac{2\gamma}{\kappa\lambda}\right) \,. \tag{10}$$

We notice that in (7) there is no dependence on ω_0 ; this dependence is in the first two terms of (6) since they vanish only in the large N, large t limit.

In Fig. 2 we report the slope $\delta\theta/\delta\omega$ as computed by (10), as a function of κ (with $\gamma = 0.1$) on the left and as a function of γ (with $\kappa = 0.45$) on the right. This curve is independent of ω_0 . We also report results of the numerical analysis for two values of ω_0 These data show a small dependence on ω_0 [12].



FIG. 2: The slope $\frac{\delta\theta}{\delta\omega}$ in the Winfree model. On the left: $\frac{\delta\theta}{\delta\omega}$ as a function of κ for two values of ω_0 and $\gamma = 0.1$. On the right: $\frac{\delta\theta}{\delta\omega}$ as a function of γ for two values of ω_0 and $\kappa = 0.45$. The curves are independent of ω_0 .

B. Kuramoto model

The analysis of the Kuramoto model produces comparable results. The Kuramoto model is based on the set of equations (i = 1, ... N)

$$\dot{\theta}_i(t) = \omega_i + \frac{\kappa}{N} \sum_{j=1}^N \sin(\theta_i - \theta_j) .$$
(11)

The numerical results one gets are similar to those of fig. 1, with a linear dependence of $\delta\theta$ on $\delta\omega$ and the rotational frequency $\rho_i = \omega_0$ (we use the same distribution function $g(\omega)$ as before). The latter results follows from the fact that the phases θ_i are dynamically pulled toward the the mean phase [7]. These results can be compared with an analytical treatment by observing that, in this case, instead of (6) one gets

$$\delta\omega = \frac{\kappa\delta\theta}{T} \int_{t}^{t+T} dt \int d\omega g(\omega) \int_{0}^{2\pi} d\hat{\theta} \, p(\hat{\theta}, t, \omega) \cos[\hat{\theta} - \theta(t)] \,. \tag{12}$$

Due to the absence of terms analogous to the first and second terms on the r.h.s. of (6), we expect a better agreement between numerical simulations and analytical evaluation. From (12) we get, instead of (7):

$$\delta\omega = \kappa\lambda\,\delta\theta\,.\tag{13}$$

with λ given by

$$\frac{2\gamma^2}{\kappa^2} = \lambda \left(1 - \cos \frac{2\gamma}{\kappa\lambda} \right) \,. \tag{14}$$

These results are reported in fig. 3 together with the results of the numerical simulations.

III. SYSTOLIC/DIASTOLIC ARTERIAL PRESSURE RELATION

A. Phase shifts from arterial pressure data

Let us consider two time series: $x_S(t)$ and $x_D(t)$, representing systolic and diastolic arterial pressure. Data are from a population of 47 normal subjects (mean age+/-SD: 54+/-8 years) who underwent a 10 minutes supine resting recording of ECG and noninvasive arterial blood pressure (by the Finapres device), in the laboratory for the assessment



FIG. 3: The slope $\frac{\delta\theta}{\delta\omega}$ in the Kuramoto model. On the left: $\frac{\delta\theta}{\delta\omega}$ as a function of κ for two values of ω_0 and $\gamma = 0.1$. On the right: $\frac{\delta\theta}{\delta\omega}$ as a function of γ for two values of ω_0 and $\kappa = 0.45$.

of Autonomic Nervous Sytem, S. Maugeri Foundation, Scientific Institute of Montescano, Italy. For each cardiac cycle, corresponding values of SAP and DAP were computed and resampled at a frequency of 2 Hz using a cubic spline interpolation. In Fig. 4 we report the time series of the systolic arterial pressure $x_S(t)$ for one of the subjects examined in this study.



FIG. 4: The time series $x_S(t)$ (on the left) and $x_D(t)$ (on the right) of the systolic and diastolic arterial pressures for one of the subjects examined.

These data are analyzed by filtering in appropriate frequency bands. We consider here three bands: Very Low Frequency (VLF) band: (0.01, 0.04) Hz; Low Frequency (LF) band: (0.04, 0.15) Hz; High Frequency (HF) band: (0.15, 0.45) Hz. In a previous paper [4], using Fourier transform methods, occurrence of delays between SAP and DAP was investigated, and it was found that DAP anticipates SAP in VLF (delay equal to 2.5 sec)and in LF (0.6 secs); no significant delay was found in HF. Here we enlarge the statistical population with respect to [4], and evaluate the phases of signals by the analytic signal technique, which allows a better estimate. As well known SAP and DAP are highly synchronized and our data confirm this expectation. We have used the Hilbert transform method that allows to detect phase synchronization in noisy scalar signals [13]. To extract a phase from the signal one considers the Hilbert transform of the original time series

$$y(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{+\infty} \frac{x(\tau)}{t - \tau} d\tau , \qquad (15)$$

where P.V. denotes Cauchy principal value. Then one forms the analytic signal $z(t) = x(t) + iy(t) = A(t)e^{i\phi(t)}$, where $A(t) = \sqrt{x^2(t) + y^2(t)}$ and $\phi(t)$ is the desired phase. To control the possible synchronization of two signals $x_1(t), x_2(t)$ the following procedure is applied: the phases $\phi_1(t)$ and $\phi_2(t)$ are computed and the so called *generalized* phase differences $\Phi_{n,m}(t) = [m\phi_1(t) - n\phi_2(t)]_{mod2\pi}$, with n, m integers, are evaluated. In the present study only 1: 1 synchronization has been examined and the two phases $\phi_1(t), \phi_2(t)$ coincide with the phases of the time series $x_D(t), x_S(t)$. Phase synchronization is characterized by the appearance of peaks in the distribution of the phase difference. To evaluate the phase shift we have considered time intervals characterized by a constant phase difference between the two series:

$$\delta\theta = \theta_D(t) - \theta_S(t) . \tag{16}$$

We find $\delta\theta > 0$ in the VLF band, i.e. in this band diastolic pressure anticipate systolic pressure. Our analysis confirm the results of [4] with a different method. On the other hand in the HF band (in basal conditions) the phase shift is negative $\delta\theta < 0$, which means that in this band the systolic pressure signal anticipates the diastolic one. These data are reported for all the 47 subjects in fig. 5 that shows on the left the VLF band and on the right the HF band (we have not reported data in the intermediate region LF band, as they are compatible with $\delta\theta = 0$). We estimated 1.76×10^{-6} to be the probability that the phase shifts in the VLF band are sampled from a distribution whose mean is less than or equal to zero; analogously 3.0×10^{-2} is the probability that the phase shifts in the HF band are sampled from a distribution whose mean is greater than or equal to zero.



FIG. 5: The phase shifts $\delta\theta$ for all the 47 subjects filtered in the VLF (on the left) and HF (on the right) bands.

On a physiological basis these results mean that the different sets of oscillators producing the time series have different spectral properties. Leaving aside the task of a physiologically-based modelization we now show that the results obtained in Section II can shed light on this phenomenon. For the present application we use the Winfree model.

B. Interpretation of phase shifts between related oscillatory signals

We present here a schematic view of phase shifts $\delta\theta$ between the time series $x_S(t)$ and $x_D(t)$. This picture is only qualitative and aims to reproduce the dependence of the sign of $\delta\theta$ on the filter in frequency power spectrum. As such, the picture is not realistic and does not offer a physiologically-based model of the time series; nevertheless it can shed light on oscillator dynamics underlying them. Let us assume that the two oscillatory signals $x_S(t)$ and $x_D(t)$ are the result of the collective behavior of two sets of oscillators, sets SAP and DAP respectively. We assume that this collective behavior produces a Systolic Arterial Pressure (SAP) and Diastolic Arterial Pressure (DAP) time series. We assume that the oscillators in the set SAP have natural frequencies in the domain $\omega \in (a - \gamma, a) \bigcup (b, b + \gamma)$, while frequencies for the set DAP are in the domain $\omega \in (a, a + \gamma) \bigcup (b - \gamma, b)$. We also assume $\gamma \leq 1$. We will use as numerical values a = 1, b = 2 and $\gamma = 0.1$, see Fig.6.

On the other hand the two bands A: $1 - \gamma < \omega < 1 + \gamma$, and B: $2 - \gamma < \omega < 2 + \gamma$ would model the VLF and HF



FIG. 6: The two intervals of natural frequencies A and B. A is on the left and is centered around the value a = 1; B, on the right, is centered around b = 2. We assume that oscillators with frequencies in the band SAP (resp. DAP) produce collectively the signal $x_S(t)$ (resp. $x_D(t)$), see text.

frequency bands.

Let us assume that the coupling among the oscillators having natural frequencies in the intervals A and B is modelled by the Winfree model, i.e. by eq. (1). However we assume for the coupling

$$\kappa \to \kappa_{ij} = \kappa H \left[2\gamma - |\omega_i - \omega_j| \right] , \tag{17}$$

where *H* is the Heaviside function. By this choice there is no interaction between oscillators in the two bands, though a weak coupling would not alter the qualitative picture. We consider one value of κ ($\kappa = 0.65$ in this case). The two sets of oscillators, one centered around the natural frequency $\omega_0 = 1$ (Set *A*) and the other around $\omega_0 = 2$ (Set *B*) become synchronized around two synchronization frequencies, $\omega_{VLF} = 0.62$ Hz e $\omega_{VLF} = 1.88$ Hz see Fig.7 (left side). Correspondingly, on the right, we have two lines showing a linear dependence between $\delta\omega$ and $\delta\theta$. The two lines



FIG. 7: On the left: The oscillators of set A, with frequencies centered around a = 1 become synchronized with a frequency around $\omega_{VLF} = 0.62$ Hz; those of set B (frequencies around b = 2) have a synchronization frequency $\omega_{HF} = 1.88$ Hz. On the right: The phase shift $\delta\theta$ between any pair of oscillators as a function of the difference $\delta\omega$ between the natural frequencies of the oscillators in the pairs. The partially overlapping lines refer to the two sets of oscillators A and B, which shows a weak dependence of the slope on the natural frequencies. Numerical results refer to N = 1000 oscillators, with $\kappa = 0.65$.

are almost completely superimposed, which shows a weak dependence on the average natural frequencies of the two sets. The interesting result however is related to our definition of VLF and HF bands. The VLF band is the result of the collective behavior of oscillators in the set A. For them $\omega_D > \omega_S$ and therefore, on the basis of the results of Section II, $\delta\theta = \theta_D(t) - \theta_S(t) > 0$. On the other hand in the HF band, $\omega_S > \omega_D$ and therefore $\delta\theta < 0$. This simple mechanism implies the effect of a change of sign between the two phases when one goes from the very low frequency to the high frequency.

One might wonder if our data also show a casual dependence between the two time series. To address this issue we have considered the index S(X|Y) that measures the nonlinear interdependency between two time series X and Y, as described in [14]. More precisely, from the time series **x** and **y**, one reconstructs delay vectors $\mathbf{x}_n = (x_n, ..., x_{n-(m-1)\tau})$ and $\mathbf{y}_n = (y_n, ..., y_{n-(m-1)\tau})$, where n = 1, ..., N is the time index, m is the embedding dimension, and τ denotes the time lag. Let $r_{n,i}$ and $\mathbf{y}_{n,j}$; j = 1, ..., k denote the time indices of the k nearest neighbors of \mathbf{x}_n and \mathbf{y}_n , respectively.

For each \mathbf{x}_n , the mean squared Euclidean distance to its k neighbors is defined as

$$R_n^{(k)}(\mathbf{X}) = \frac{1}{k} \sum_{j=1}^k (\mathbf{x}_n - \mathbf{x}_{r_{n,j}})^2,$$
(18)

while the **Y**-conditioned mean squared Euclidean distance is defined by replacing the nearest neighbors by the equal time partners of the closest neighbors of \mathbf{y}_n ,

$$R_n^{(k)}(\mathbf{X}|\mathbf{Y}) = \frac{1}{k} \sum_{j=1}^k (\mathbf{x}_n - \mathbf{x}_{s_{n,j}})^2.$$
 (19)

The interdependence measure is then defined as

$$S(\mathbf{X}|\mathbf{Y}) = \frac{1}{N} \sum_{n=1}^{N} \frac{R_n^{(k)}(\mathbf{X})}{R_n^{(k)}(\mathbf{X}|\mathbf{Y})}.$$
(20)

S(X|Y) is an asymmetric quantity and the degree of asymmetry is connected to causal relationship between the two time series, in other words if S(X|Y) is much greater than S(Y|X) then we may conclude that Y is driving X. On the other hand each of these values measures by its size the degree of interdependency, S = 0 (resp. S = 1) meaning minimal (resp. maximal) interdependency. We evaluated these indexes both on the SAP and DAP time series $x_S(t)$, $x_D(t)$ and on their phases $\theta_S(t)$, $\theta_D(t)$. In both cases the asymmetry was not significant, which means that there is no causal relationship between SAP and DAP time series; however the results obtained with the phases are always much greater than those obtained with the full signals. Quantitatively, the average values for the HF band are: $S(x_D|x_S) = 4.8 \times 10^{-3}$, $S(x_S|x_D) = 4.6 \times 10^{-3}$, which shows a very small asymmetry and, at the same time, a very small interdependency. As to the phases, we get $S(\theta_D|\theta_S) = 0.899$, $S(\theta_S|\theta_D) = 0.901$, which on the contrary shows a larger interdependency. Similar results are obtained in VLF and LF bands. Besides showing the absence of a causal relation, these results confirm that in these systems of oscillators the main source of information on the underlying structures resides in the dynamics of the phases.

IV. CONCLUSIONS

Our results represent an original analysis of the relation between systolic/diastolic blood pressure, which completes previous studies [4]. The measured delays between the oscillatory components of systolic and diastolic blood pressure time series, show a change of sign going from low to high frequencies. We have addressed it within the paradigm of coupled nonlinear synchronous oscillators. We have shown, using Winfree and Kuramoto models, that once synchronization is achieved, the phase delay between oscillators is determined by the underlying structure and we have found a linear relationship between oscillator phase shifts and the difference of their natural frequencies. We then used these results to describe our findings, that confirm that changes in the modulating factors of arterial pressure affect differently the systolic and diastolic pressure values [3].

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