Noise in Interacting Biological Systems

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***Abstract*—Biological systems are never isolated, usually oscillatory, and invariably subject to noise and fluctuations that may be of either internal or external origin. We present a methodological framework for studying the deterministic interactions of biological oscillatory systems, while at the same time decomposing and evaluating the noise strength. Based on dynamical Bayesian inference, the method models coupled phase oscillators in the presence of dynamical noise. We demonstrate first the potential and the precision of the method on a predefined numerical system. Then we illustrate its usefulness in detecting how the noise strengths from three human physiological systems – the heart, the lungs and the brain – are affected by general anæsthesia. The results demonstrate the potential of the method for detecting and quantifying noise from biological dynamical systems, quite generally.**

***Index Terms*—dynamical Bayesian inference, noise, interactions, coupling functions, biological systems**

I. Introduction

Biological systems are never isolated, usually oscillatory in nature, and invariably subject to many different perturbing influences [1]–[4], often resulting in fluctuations and variability around their dynamical states. Some of these influences are of known deterministic origin; others are of currently unknown, seemingly random, origin and may be treated as stochastic noise [5]. The noise can act at many different levels, ranging from the most basic molecular, sub-cellular processes up to the dynamics of tissues, organs, organisms, populations and their interactions.

Often, oscillatory biological systems mutually interact, with the noisy perturbations in addition. Here, we focus on such systems – studying their deterministic interactions while, at the same time, decomposing and quantifying the noise.

In particular we will study oscillatory interactions through their phase dynamics [6], subject to white noise, described by bivariate stochastic differential equations. We will use the method of dynamical Bayesian inference to model the coupled phase oscillators in the presence of noise [7], based on real biological data. The modeling will yield the deterministic interactions and the coupling functions [8] between the systems, as well as the stochastic noise strength. The deterministic interactions described by the coupling functions have recently been studied intensively [8]–[14]. Here we will instead focus primarily on the stochastic part of the inference, i.e. on the inferred noise strength, and will discuss how it changes in different states of the biological system.

After first presenting the inference method, we will demonstrate its usefulness in a numerical example of a predefined model of coupled phase oscillators. The stochastic model will be inferred from the numerically generated time-series. The results of the inference will provide an insight into the properties and precision of the inference on the deterministic dynamics, as well as on the noise strength.

The approach will then be used to illustrate its usefulness in detecting how the noise strengths in human subjects are affected by general anæsthesia. We will study three states: awake resting, anæsthesia with propofol, and anæsthesia with sevoflurane anæsthetic [15], [16]. We will study three human physiological systems – the heart, the lungs and the brain. The recordings include the electrocardiogram (ECG), the respiration signal and the electroencephalogram (EEG), all measured simultaneously in individual subjects. We will be interested in three groups of noise strengths: (i) for the heart; (ii) for respiration; and (iii) for different brainwaves (including delta, theta, alpha and gamma brainwaves), noting how they are affected by general anæsthesia with the two different anæsthetics.

II. Dynamical Bayesian Inference

In order to tackle the problem in hand – to infer the noise from the data of interacting biological systems – we will use a method based on dynamical Bayesian inference [7], [17]. The method is able to infer separately the deterministic part of the model, and the stochastic part of the dynamics. Considering such a model defined by stochastic differential equations (SDEs), we will infer the noise as a residual part of the dynamics that is complementary to the deterministic part of the model.

So we consider oscillating biological systems that mutually interact. Their self and interacting dynamics will constitute the deterministic part of the model. Moreover, due to their oscillatory nature we will concentrate on the phase dynamics reduction approach [6], leaving a single time-series for the instantaneous phase of each system. Having these as input, we will then apply the method of dynamical Bayesian inference to find the coupling functions between the systems and the

This work was supported by EU NEST Project, no. 517133, 'Brain, Respiratory and Cardiac Causalities in Anæsthesia' (BRACCIA), by the EPSRC, UK (grant no. EP/100999X1) and in part by the ARRS Slovenia (no. P20232).

noise perturbing them. Our focus here will be on the strength of the noise.

We therefore consider a model pair of coupled phase oscillators [6] described by the stochastic differential equation:

$$\dot{\phi}_i(t) = \omega_i(t) + q_i(\phi_i, \phi_j, t) + \xi_i(t), \tag{1}$$

with $i \neq j$ for $i, j = \{1, 2\}$ and where $\omega_i(t)$ is the parameter for the natural frequency. The deterministic part given by the base functions $q_i(\phi_i, \phi_j, t)$ describes the self and the interacting dynamics. The external stochastic dynamics $\xi_i(t)$ is considered to be Gaussian white noise $\langle \xi_i(t)\xi_j(\tau)\rangle = \delta(t-\tau)D_{ij}$. Due to the periodic nature of the deterministic dynamics, the base functions can be decomposed into infinite Fourier series:

$$q_i(\phi_i, \phi_j, t) = \sum_{s=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} \tilde{c}(t)_{i;r,s}\, e^{i2\pi r\phi_i(t)} e^{i2\pi s\phi_j(t)}.$$

In practice, however, the dynamics is well-described by a finite number of Fourier terms, so that one can rewrite the phase dynamics as: $\dot{\phi}_i(t) = \sum_{k=-K}^{K} \tilde{c}_k^{(i)}(t)\, \Phi_{i,k}(\phi_i, \phi_j, t) + \xi_i(t)$, where $\tilde{c}_0^{(i)} = \omega_i$, and the rest of $\Phi_{i,k}$ and $\tilde{c}_k^{(i)}$ are the K most important Fourier components. The Fourier components $\Phi_{i,k}$ act as base functions for the dynamical Bayesian inference, through which the parameters $\tilde{c}_k^{(i)}$ are evaluated. In the analysis we used a second-order Fourier expansion ($K = 2$) because the signals come from narrow-band intervals. Two phase time-series and the order of expansion K act as inputs for the phase model which is inferred for each interaction (e.g. δ-α), from each subject.

Dynamical Bayesian inference [7], [9] enables us to evaluate the model parameters $\tilde{\mathbf{c}}$, which give the time-evolving coupling functions and coupling strength in the presence of noise. From Bayes' theorem one can derive the minus log-likelihood function, which is of quadratic form. Assuming that the parameters are represented as a multivariate normal distribution (with mean $\bar{\mathbf{c}}$, and covariance matrix $\mathbf{\Sigma} \equiv \Xi^{-1}$), and given such a distribution for the prior knowledge using the likelihood function, one can calculate recursively [7], [17] the posterior distribution of the parameters $\tilde{\mathbf{c}}_k$ using only the following four equations:

$$\begin{aligned}
\mathbf{D} &= \frac{h}{L}\left(\dot{\phi}_n - \mathbf{c}_k \mathbf{\Phi}_k(\phi^*_{\cdot,n})\right)^T \left(\dot{\phi}_n - \mathbf{c}_k \mathbf{\Phi}_k(\phi^*_{\cdot,n})\right), \\
\mathbf{r}_w &= (\mathbf{\Xi}_{\text{prior}})_{kw}\, \mathbf{c}_w + h\, \mathbf{\Phi}_k(\phi^*_{\cdot,n})\, (\mathbf{D}^{-1})\, \dot{\phi}_n + \\
&\quad - \frac{h}{2} \frac{\partial \mathbf{\Phi}_k(\phi_{\cdot,n})}{\partial \phi}, \\
\mathbf{\Xi}_{kw} &= (\mathbf{\Xi}_{\text{prior}})_{kw} + h\, \mathbf{\Phi}_k(\phi^*_{\cdot,n})\, (\mathbf{D}^{-1})\, \mathbf{\Phi}_w(\phi^*_{\cdot,n}), \\
\tilde{\mathbf{c}}_k &= (\mathbf{\Xi}^{-1})_{kw}\, \mathbf{r}_w,
\end{aligned} \tag{2}$$

where summation over $n = 1, \ldots, N$ is assumed, and summation over the repeated indices k and w is implicit. We used informative priors and a special procedure for the propagation of information between consecutive data windows [7], [18], which allowed inference parameters that varied with time (for implementation, software toolbox and usage see [19]). Given its ability to infer time-varying and noisy dynamics, the Bayesian method is especially well-fitted for applications to biological and physiological signals, like for example the EEG, ECG and respiration signals.

Once we have the inferred parameters $\tilde{\mathbf{c}}$, we can calculate the deterministic coupling quantities, including the coupling strength and the form of the coupling function. Complementary to these are the noise strengths D_i inferred for each system given with phase $\phi_i(t)$. The inference also gives the correlated noises $D_{i,j}$, between two systems given with phases $\phi_i(t)$ and $\phi_j(t)$.

III. Numerical example

Before considering applications to biological data, we first demonstrate the Bayesian inference method on a simple numerical example. We consider a pair of interacting phase oscillators subject to white noise – a numerical example of a type of dynamics we will analyse later from biological systems. The systems are given by the following stochastic differential equations:

$$\begin{aligned}
\dot{\phi}_1 &= \omega_1 + a_1 \sin(\phi_2) + a_3 \sin(\phi_2 - \phi_1) + \xi_1(t) \\
\dot{\phi}_2 &= \omega_2 + a_2 \sin(\phi_1) + a_4 \sin(\phi_1 - \phi_2) + \xi_2(t).
\end{aligned} \tag{3}$$

Each phase oscillator is described by its frequency parameter $\omega_1 = 2$, $\omega_2 = 4.53$, and the parameters for their interaction dynamics $a_1 = 0.4$, $a_2 = 0.6$, $a_3 = 0.8$ and $a_4 = 0.5$. The noises are set to be white Gaussian and mutually uncorrelated with the following noise strengths $D_1 = 0.04$ and $D_2 = 0.02$. The two oscillators are not synchronized. Fig. 1 shows samples from the resultant time series to which dynamical Bayesian inference is to be applied.

In this example we know beforehand the phase model and the deterministic terms on the rhs of the coupled system (3) that are the actual base functions to be used for inference of the six parameters (ω_1, ω_2, a_1, a_2, a_3 and a_4). The inference results from a single block of data (40 seconds long) from the first system are presented in Table III. The agreement between the actual (intrinsic) parameters and their inferred values is good, and the method evidently works to high precision. In

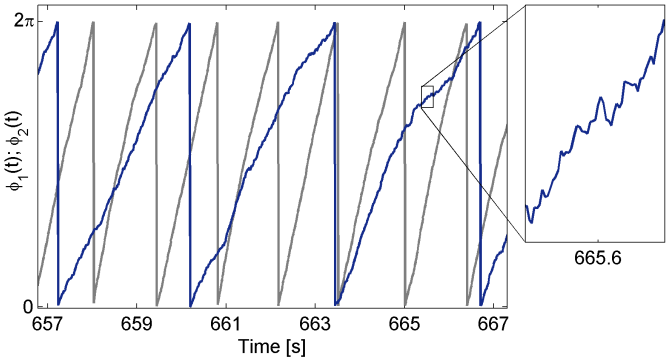

Fig. 1. The instantaneous phases $\phi_1(t)$ and $\phi_1(t)$ simulated by the mathematical model (3). The effect of noise on the phase is more clearly visible in the enlarged inset on the right. The dark line and the inset show $\phi_1(t)$, and the light line shows $\phi_2(t)$.

Parameters	ω_1	a_1	a_3	D_1	D_{12}
Intrinsic values	2	0.4	0.8	0.04	0
Inferred means	1.9826	0.4040	0.8017	0.0400	0.0005

TABLE I
RESULTS FROM INFERENCE OF THE $\phi_1(t)$ DYNAMICS OF MODEL (3).

addition, the intensity and the correlations of the noise are inferred very precisely.

IV. BIOLOGICAL EXAMPLE – NOISE IN THE PHASE DYNAMICS OF CARDIAC, RESPIRATION AND NEURAL OSCILLATIONS AS AFFECTED BY ANÆSTHESIA

In order to demonstrate the potential of this approach in tackling the noise and fluctuations in biological systems, we now consider an example of dynamical Bayesian inference applied to the phase dynamics of interacting biological oscillators. In particular, we study the phase dynamics of oscillations from the cardiac, respiration and neural activity, in each case measured simultaneously from the same subject. Moreover, this was done both in the awake state and under general anæsthesia induced by either propofol or sevoflurane i.e. three states were compared: the awake (A); anæsthetized with propofol (P); and anæsthetized with sevoflurane (S). The inference gives two outputs, the deterministic dynamics and the noise strength. The deterministic part comprises the self-dynamics of each of the cardiac-respiration-neural oscillations plus those related to the interactions described by the inter-oscillator coupling functions. The focus here is on the latter output and, in particular, on the noise strength of each oscillation.

The measurements included the electrocardiogram (ECG), the respiration signal measured with an elastic belt proportional to the thorax expansion, and an electroencephalogram (EEG) signal. There were 25 awake and 29 anæsthetized heathy subjects, aged 18 to 60 years, who were about to undergo elective surgery. Of the 29 anæsthetized subjects, 14 were given propofol and 15 sevoflurane. The oscillation intervals were estimated by standard digital filtering procedures, including a FIR filter followed by a zero-phase digital filtering procedure to ensure that no time or phase lags were introduced by the filtering. The boundaries of the intervals extracted were: $h = 0.6 - 2$Hz for the cardiac oscillations from the ECG signal, $r = 0.145 - 0.6$Hz from the respiration signal, while for the brainwaves from the EEG signal they were $\delta = 0.8 - 4$Hz, $\theta = 4 - 7.5$Hz, $\alpha = 7.5 - 14$Hz, $\beta = 14 - 22$Hz, and $\gamma = 22 - 100$Hz. Special care was taken in dealing with frequency spillage between intervals, heart artifacts, and powerline artifacts [20]. The phases of the filtered signals were estimated by use of the Hilbert transform and the protophase-to-phase transformation [21]. To determine whether the deterministic coupling relationships were genuine, or just happened by chance, we used surrogates data testing [22], [23]. From the large number of investigated relationships, only those exhibiting a statistically significant difference compared to their corresponding surrogates were retained and, similarly, the noise from the β oscillation was not presented as the couplings to this oscillation were insignificant and there were no significant noise difference. To present visually the differences between the distributions we used standard boxplots that refer to the descriptive statistics (median, quartiles, maximum and minimum). Extended technical details can be found in [15], [16].

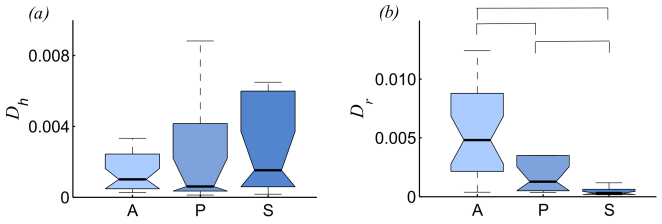

Fig. 2. Noise strength of (a) the cardiac and (b) the respiratory oscillations, evaluated from their phase dynamics. The boxplots present the subject distributions of the three states: awake (A); anæsthetized with propofol (P); and anæsthetized with sevoflurane (S). The line connectors on the tops indicate cases where there is a statistically significant difference.

In Fig. 2 we present the noise strength results from the heart and the lung activity, repesenting one of the most important parts of the cardiovascular system. The cardiac noise strength Fig. 2 (a) did not change significantly between the three states, awake and anæsthetized with propofol and sevoflurane. There was more variation (wider box plot) in the anæsthetized states, but this change was not significant. The respiration noise strength Fig. 2 (b), on the other hand, was significantly different i.e. it decreased in the two anæsthetized states in comparison to the awake state. There was also significant difference between the two anæsthetics, indicating that sevoflurane reduced the noise level more than the propofol induced anæsthesia.

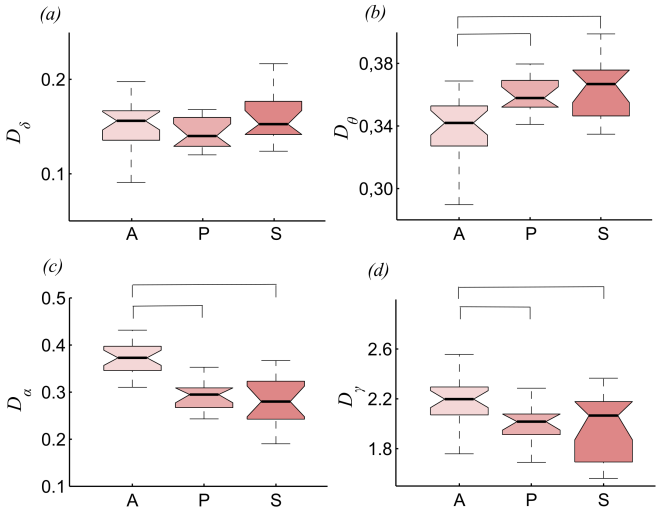

Fig. 3. Noise strength of neural brainwave oscillations in different frequency bands, including: (a) δ; (b) θ; (c) α; and (d) γ oscillations. The boxplots present the subject distributions of the three states: awake (A); anæsthetized with propofol (P); and anæsthetized with sevoflurane (S). The line connectors on the tops indicate statistically significant differences.

The effect of general anæsthesia on the noise strength of the neural cognitive brainwaves is presented in Fig. 3. There was not much difference on the noise level in the delta oscillations Fig. 3 (a). In the theta oscillation band (b) the anæsthesed state exhibited different noise strengths both for propofol and sevoflurane, the noise intensity being higher than in the awake state. In the case of the higher frequency oscillations, alpha in (c) and gamma (d), anæsthesia induced a significant decrease in noise strength compared to that in the awake state. In none of the neural oscillations (all panels in Fig. 3) was there any significant difference in noise strength dependant on anæsthetic used, propofol or sevoflurane.

V. Conclusion

This study illustrates the potential of dynamical Bayesian inference for describing the noise and fluctuations from biological oscillatory systems. Our demonstration on the numerical example showed that the method is able to infer both the deterministic and the stochastic dynamics with high precision.

The application to a biological system demonstrates that anæsthesia changes, not only the deterministic couplings, but also some of the random fluctuations acting on the oscillations. The decrease in the noise level in α, γ and respiratory oscillations might be because the processes associated with the onset of anæsthesia induce order, coupling and coherence of the oscillations [24], [25].

It is worth pointing out that, without direct observation or understanding of the processes that generated the noise, we infer it just as a residual. It remains conceivable that (some parts of) the noise are attributable to deterministic non-autonomous influences [26]–[29], e.g. from some of the other (finite number of) processes in the human body. This inherent limitation of the study is, of course, shared, with investigations of noise in other contexts. The nature and origin of biological noise raises questions of some depth and subtlety, and especially for an inverse approach they are ones that still remain largely open and unanswered in general terms.

Finally, we comment that the methodological framework described here in relation to oscillatory biological systems also carries wider implications for applications to dynamical systems, quite generally.

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