

Stochastic Dynamics of Anaesthesia

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Abstract.

Recent developments in the analysis of synchronization and directionality of couplings for noisy nonlinear oscillators are being applied to study the complex interactions between cardiac and respiratory oscillations, and brain waves (especially delta and gamma), during anaesthesia. It is found that marked changes occur in the inter-oscillator interactions during anaesthesia in both rats and humans. These could form a new basis for measurement of depth of anaesthesia. The new EC programme BRACCIA will explore and quantify causal relationships between the oscillatory processes for the different stages of anaesthesia and consciousness.

Keywords: Synchronization, noise, nonlinear oscillator, directionality, anaesthesia, cardiovascular system, phase transition

INTRODUCTION

There is abundant evidence favouring the perception of the cardiovascular system as a *noisy* dynamical system that behaves much like a collection of coupled oscillators [1]. The inter-oscillator couplings give rise to many of the complex and emergent phenomena seen in classical oscillator systems, including chaos [2, 3], modulation [1] and episodes of synchronization [4, 5, 6]. Numerical modelling of the cardiovascular system [7] has shown that the role of noise in facilitating these phenomena can be crucial. Yet the physiological origin of the oscillators is not yet fully established, nor the nature of the interactions between them, nor the origins or character of the noise itself. The nonlinear dynamics of anaesthesia therefore represents *par excellence* an unsolved problem of noise.

It has become clear that the oscillatory processes – their amplitudes, frequencies and especially their mutual couplings – can be used to characterise the state of the system. It is known, for example, that marked changes in cardio-respiratory synchronisation occur in anaesthesia [8]; furthermore, recent work by two of us [9] has shown that cerebral (cortical) oscillations interact with those of the cardiac and respiratory systems and that these interactions change in anaesthesia. Although the work is in its infancy, and is extremely challenging, there is a clear opportunity for applying techniques from

stochastic nonlinear dynamics, information theory and control theory to illuminate the underlying physiological processes.

Application of the techniques of nonlinear science to rhythmic signals of biological origin [10] has already illuminated many fundamental processes, especially those connected with cardiac function. These include fractal dynamics [11], deterministic chaos [3] in heart rate variability (HRV) data and the fact (see above) that the blood circulatory system behaves in many respects like a collection of five coupled oscillators [1] with frequencies ranging from 1 Hz (cardiac) down to 0.01 Hz (endothelial/metabolic [12]). Episodes of cardio-respiratory synchronization are known [4, 8] to occur in humans; synchronization phenomena involving a 0.1 Hz blood flow component, believed to be of myogenic origin, can also occur [13, 14]. Pomfrett suggested [15] that HRV or a bispectral index could be used to quantify depth of anaesthesia but that, in practice, it will probably be better to use several indicators rather than to rely on any particular technology; Larson and Galletly have commented [16] that the standard methods used for HRV analysis are limited in their ability to detect the presence of cardioventilatory coupling in heart rate time series, although there are some graphical methods [17, 18] that seem promising. A different approach, based on synchronization indices and synchronograms, has recently been used to reveal an unexpected and very marked increase of cardio-respiratory synchronization during anaesthesia [8] in rats.

ANÆSTHESIA

In anaesthesia a chemical perturbation of the organism leads to a temporary loss of consciousness, but just how this happens remains to a large extent a mystery. Perhaps on account of this lack of deep understanding, there are not yet any reliable markers for depth of anaesthesia. Consequently, as Pomfrett [15] puts it –

“...the anaesthetist is still unable to measure the depth of anaesthesia in order to prevent inadvertent awakening during anaesthesia.”

It is perhaps not surprising, therefore, that the incidence of awareness among patients undergoing surgery is nonzero: see Table 1. Note that even the *lowest* estimate of 0.2% is unacceptably high. The problem can be particularly severe in cases where for clinical reasons the anaesthesia is kept as light as possible (e.g. Cæsarian section), and where a mechanically ventilated curarised patient is unable to give any voluntary indication of awareness.

A well advertised approach to assessment of depth of anaesthesia is the bispectral index technique known as BIS [20]. Its use is controversial, however, and it is certainly not 100% accurate [21, 19]. Other promising approaches involves measurements of changes in heart rate variability (HRV) [15] and cardio-respiratory coupling [8, 17]. What we propose in this project takes such ideas much further, partly by adopting a more sophisticated mathematical analysis of the data, and partly by including consideration of the neural (cortical) oscillations.

TABLE 1. Incidence of awareness during surgery (after Pomfrett [15] and Myles et al [19]).

Author	Date	Sample	Awareness %
Hutchinson	1960	656	1.2
Harris	1971	120	1.6
McKenna	1973	200	1.5
Wilson	1975	490	0.8
Liu et al	1990	1000	0.2
Myles et al	2004	1238	0.9

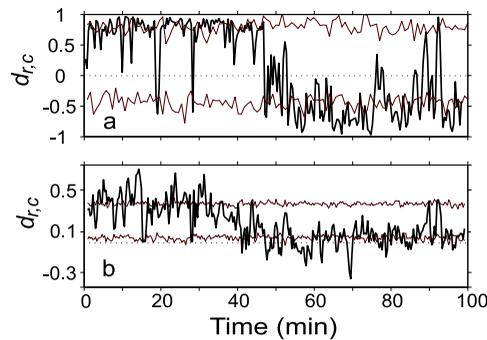


FIGURE 1. Direction of the cardio-respiratory interaction measured for a rat during anaesthesia. Top: calculated from the data according to the method proposed by Rosenblum et al [22]. Bottom: calculated from the same data using mutual information as proposed by Paluš et al [23]. The nearly horizontal thin lines are plotted ± 2 standard deviations outside a set of surrogate data. If $d_{r,c} > 0$ it means that respiration drives cardiac function, and *vice versa* if $d_{r,c} < 0$. In each case the directionality index exhibits a change of sign at a time that coincides approximately with the end of deep anaesthesia ([24]).

Anaesthesia in rats

The first simultaneous studies of the neural and cardio-respiratory phenomena associated with anaesthesia were carried out on rats, revealing a number of interesting effects. Rats exhibit similar cardiovascular dynamics to humans, except that the oscillatory components are 3–4 times faster [25], with heart beat at ~ 3 Hz and respiration at ~ 1 Hz. Analyses based on techniques drawn from nonlinear science [22] and information theory [23, 26] are being used to reveal and quantify *causal* relationships between the cardiac, respiratory and neural oscillations, and how these change during anaesthesia. Several important results have emerged, and show that the more systematic study now proposed is likely to yield important results. As one example, we show in Fig. 1 how the cardio-respiratory directionality index evolves as deep anaesthesia gives way to lighter anaesthesia. There is a dramatic change of sign showing that, during the lighter anaesthesia, the heart is predominantly driving respiration rather than *vice versa* as is observed in the conscious state or in deep anaesthesia.

Computation of the cardio-respiratory directionality index and how it evolves with

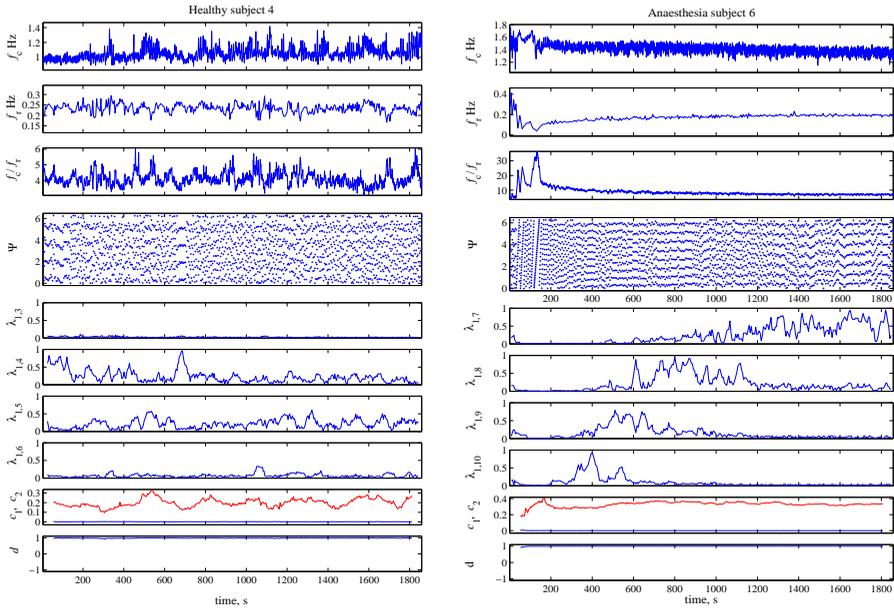


FIGURE 2. Typical analysis of cardiorespiratory data from human volunteers in the wakeful state (left) and under anaesthesia (right). From the top in each case, the plots show as functions of time: cardiac f_c and respiratory f_r frequencies and their ratio f_r/f_c ; synchrogramme Ψ ; synchronization indices $\lambda_{1,n}$; coupling coefficients c_1 and c_2 ; and directionality index d .

time from measured data could therefore provide one way of assessing depth of anaesthesia. There are several others: from the original research [8] it appears that strength of synchronization, synchronization index, and respiratory rate variability are good indicators; the latest results show that, in addition to the cardio-respiratory directionality index (Fig. 1), characteristic changes occur in the brain, especially δ and γ waves, and in the interactions and causalities with the cardiac and respiratory oscillations.

An initial modelling of coupled oscillators within both the micro and macroscopic worlds and has been undertaken [27]. A large number of oscillators acting on a similar time scale has been represented as an ensemble that, on the macroscopic scale, may be taken as a single oscillator. Furthermore, their interaction on the macroscopic scale with other similar type of oscillators has been described, but acting on widely different time scales.

Anaesthesia in humans

The crucially important question of “Does what applies to rats also apply to humans?”, i.e. whether anaesthetised humans display similar phenomena to those seen earlier in rats, is being addressed. The preliminary investigation [28] has involved studies of ten healthy

men aged between 20 and 40 undergoing elective surgery. Standard clinical monitoring was supplemented by forehead BIS Quatro electrodes (Aspect Medical Systems, Leiden) for EEG capture and a TSD201 respiratory effort transducer (BIOPAC Systems Inc, Goleta, CA) for respiratory frequency (f). A standard anaesthetic (midazolam 2mg, fentanyl $1.5\mu\text{gkg}^{-1}$, sleep-dose propofol and isoflurane 1% in 40% oxygen in air) was administered by the same anaesthetist. Recordings were made for 30 minutes in the anaesthetic room prior to surgery. Waveforms were digitised at 1000 Hz and stored on a PC for later analysis.

A typical set of results is shown in Fig. 2 for healthy subjects in the waking (left) and anaesthetised (right) states. The synchrogramme Ψ plots points of fixed phase of the cardiac oscillator as a function of the phase of the respiratory oscillator, and therefore yields n horizontal lines where there is $1:n$ synchronisation; the synchronisation index $\lambda_{1,n}$, calculated from the data, is equal to unity for perfect $1:n$ synchronisation, but is zero in its absence; the coupling coefficients c_1, c_2 provide measures of the cardiac-to-respiratory (lower lines) and respiratory-to-cardiac (upper lines) couplings; and the directionality index d specifies the direction of coupling, being $+1$ for exclusively respiratory-to-cardiac coupling, and -1 for the opposite extreme. In all cases the idealised behaviour is to some extent modified by noise. In the waking state, the synchrogramme reveals two *brief* episodes of 1:4 synchronisation starting at 0 and 650 s into the measurements. Under anaesthesia, in marked contrast, there is a virtually continuous state of synchronization as shown by the horizontal lines in the synchrogramme and finite values of the synchronization indices. As time evolves, the system passes through 1:10, 1:9, 1:8 and 1:7 synchronized states – very similar to the behaviour seen earlier in rats [8]. The directionality index d , calculated from the two unidirectional coupling coefficients c_1, c_2 , shows that during deep anaesthesia, as in the waking state, respiration tends to drive the cardiac oscillator. In rats, d changes sign during emergence from anaesthesia (Fig. 1); it is not yet known what happens for humans.

We now plan to monitor patients throughout surgery and into recovery to explore how synchronisation and directionality alter with changing depth of anaesthesia.

CONCLUSION

Many problems remain to be solved. In particular it will be necessary to develop algorithms for calculation of the directionality indices that are robust in the presence of physiological noise. It is also highly desirable to reach an understanding of the underlying processes giving rise to interactions between the oscillatory processes. If such problems can be solved, the potential impact of the work is high, in both specific and general terms. Specifically in relation to anaesthesia, we note that: anaesthesia is universally employed throughout the world for all but the simplest surgery; awareness during anaesthesia is not as uncommon as it should be (Table 1) and, as already mentioned, a better way of measuring depth of anaesthesia would be widely welcomed. More generally, we note that: coupled oscillators are widespread in nature, at all levels; and causal relationships between such oscillators are of great interest because they shed light on the underlying mechanisms of coupling. Improved techniques for establishing causalities based on measured noisy time series will be applicable in many areas.

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