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Monitoring Heartbeat Nonlinear Dynamics during General Anesthesia by using the Instantaneous Dominant Lyapunov Exponent

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***Abstract*— We present a novel methodology for instantaneous estimation of quantitative correlates of depth of Anaesthesia from noninvasive electrocardiographic recordings. The analysis is based on a point process model of heartbeat dynamics that allows for continuous tracking of linear and nonlinear HRV indices, including a novel instantaneous assessment of the Lyapunov Spectrum by using a cubic autoregressive formulation. The effective estimation of the model parameters is ensured by the Laguerre expansion of the Wiener-Volterra kernels along with the maximum local log-likelihood procedure. We apply the proposed assessment to experimental recordings from healthy subjects during propofol anesthesia. The new assessment reveals novel time-varying complex heartbeat dynamics that underlie the quasi-periodic heartbeat fluctuations elicited by the sympatho-vagal balance. Results suggest that such quantification provides important information which is independent from the standard autonomic assessment and significantly correlated with loss of consciousness. Further investigation will focus on evolving our mathematical approach towards a promising monitoring tool for an accurate, noninvasive assessment of general anesthesia.**

I. Introduction

Accurate assessment of depth of anesthesia based on analysis of noninvasive physiological recordings may lead to important advances in clinical anesthesia monitoring and patient safety. In particular, analyses of recordings during anesthesia based on the electrocardiogram (ECG), recorded in every operating room, have been recently the subject of research investigation. Focusing on autonomic quantification, it has been shown that frequency-domain parameters are able to indirectly assess depth of anesthesia [1]–[4]. Multivariate point process heart rate variability (HRV) analysis has been also proposed to track the cardiovascular control dynamics during anesthesia [5]. All this research is aware of the still existing significant limitations of ECG-based anesthesia monitoring, mainly due to confounding effects from necessary compensatory maneuvers and drug administrations, as well as from the nociceptive stimuli to the central nervous system occurring during surgery. To this extent, the assessment of the intrinsic higher dimensional heartbeat generation dynamics (due to the complexity of the sinus node activity modulation system) may provide important complementary information in addition to the measures associated with short term autonomic control.

It has been shown that the electrical properties of the human heart undergo many complex transitions as important quantifiers of complexity of cardiovascular control in normal and diseased states [6]–[10]. The Lyapunov exponents (LEs) [11] have been proven to be a useful measure for the characterization of complex dynamics in a nonlinear system. Chon et.al. [12], and later Armoundas et.al. [13], have suggested that biological systems such as the one generating heartbeat dynamics should be considered as both chaotic and stochastic. This concept is in agreement with current physiological knowledge, since the normal heartbeat is originated by intrinsic nonlinear mechanisms within the pacemaker cells of the sinus node, and is modulated at the same time by a high-dimensional input, i.e. the influence of the autonomic nerves innervating the sinus node. In this context, we do not address the issue related on the chaotic behavior of HRV, focusing instead on the time-varying changes in its complexity by taking advantage of the ability of our techniques to provide an instantaneous estimation of the LE spectrum. According to current literature, we associate negative LE values with simpler, possibly predominantly linear, HRV dynamics (i.e. predictability, lower complexity), whether an increasingly positive LE points at more complex and less stable dynamics (i.e. unpredictability, higher complexity).

In this work, we propose a novel approach which allows to track the underlying heartbeat complex dynamics during anesthesia. This is achieved through the inclusion of the Fast Orthogonal Search (FOS) algorithm [14] and consequent LEs estimation [13] within an Inverse-Gaussian (IG) point-process framework having a cubic autoregressive Wiener-Volterra representing the IG first order moment. The point process parametric formulation of the probability function allows for a systematic, parsimonious estimation of the parameter vector in a recursive way and at any desired time resolution. Instantaneous indices, including the instantaneous dominant Lyapunov exponent (IDLE), can then be derived from the parameters in order to track both autonomic dynamics due to short-term cardiovascular control and the underlying heartbeat complexity modulation during induction of anesthesia.

II. Methods

In this section we provide an overview of the methods that are discussed in greater detail in the companion paper [15]. Let $(0, T]$ denote the observation interval, $\{u_j\}_{j=1}^{J}$ the

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ordered set of times of the R-wave events recorded in $(0,T]$, $RR_j = u_j - u_{j-1} > 0$ the j^{th} R–R interval. We can assume the probability distribution of the waiting time until the next R-wave event follows an inverse-Gaussian (IG) model [16]:

$$f(t|\mathcal{H}_t,\xi(t)) = \left[\frac{\xi_0(t)}{2\pi(t-u_{\widetilde{N}(t)})^3}\right]^{\frac{1}{2}} \times \exp\left\{-\frac{1}{2}\frac{\xi_0(t)[t-u_{\widetilde{N}(t)}-\mu_{RR}(t,\mathcal{H}_t,\xi(t))]^2}{\mu_{RR}(t,\mathcal{H}_t,\xi(t))^2(t-u_{\widetilde{N}(t)})}\right\} \quad (1)$$

where $\widetilde{N}(t) = \max\{k : u_k < t\}$ is a left continuous function denoting the index of the previous R-wave event occurred before time t, $\mathcal{H}_t = (u_j, RR_j, RR_{j-1}, ...)$ is the history of events, $\xi(t)$ is the vector of the time-varing parameters, $\xi_0(t) = \theta > 0$ denotes the shape parameter of the IG distribution, and $\mu_{RR}(t,\mathcal{H}_t,\xi(t))$ represents the first-moment statistic (mean) of the distribution.

Let us consider the Taylor expansion of a generic Nonlinear Autoregressive Model (NAR):

$$y(n) = F(y_{n-n}, y_{n-2}, ...) = \gamma_0 + \sum_{i=1}^{M}\gamma_1(i)\,y(n-i) + \sum_{K=1}^{\infty}\sum_{i_1=1}^{M}...\sum_{i_K=1}^{M}\gamma_K(i_1,...,i_K)\prod_{j=1}^{K}y(n-i_j) + \epsilon(n) \quad (2)$$

where $\epsilon(n)$ are independent, identically distributed Gaussian random variables. If we represent a nonlinear physiological system by taking into account up to the cubic nonlinear term, the NAR system retains an important part of the non-linearity of the system and gives robustness against the presence of measurement noise in the data [12].

We use a noiseless version of the NAR framework in (2), $y(n) - \epsilon(n)$, to model the first moment of the IG distribution, $\mu_{RR}(t,\mathcal{H}_t,\xi(t))$. Rather than regressing directly on the previous R-R interval, we use the Laguerre functions [17] to expand the kernels and reduce the number of unknown parameters in (2) that need be estimated. Given the Laguerre function, $\phi_j(n)$ (see [17]), and the input $RR_{\widetilde{N}(t)}$, the j^{th}-order Laguerre filter output is:

$$l_i(t) = \sum_{n=1}^{\widetilde{N}(t)}\phi_i(n)(RR_{\widetilde{N}(t)-n} - RR_{\widetilde{N}(t)-n-1}). \quad (3)$$

The choice of the derivative series improves the achievement of stationarity within the sliding time window W (here $W =$ 90 s) [18]. By using the Laguerre expansion of the kernels (NARL model), the instantaneous RR mean becomes:

$$\mu_{RR}(t,\mathcal{H}_t,\xi(t)) = g_0(t) + \sum_{i=0}^{P}g_1(i,t)\,l_i(t) + \sum_{i=0}^{Q}\sum_{j=0}^{Q}g_2(i,j,t)\,l_i(t)\,l_j(t) + \sum_{i=0}^{K}\sum_{j=0}^{K}\sum_{k=0}^{K}g_3(i,j,k,t)\,l_i(t)\,l_j(t)l_k(t)$$

where $g_k(...)$ are the regression coefficients of the model.

Given the proposed point process statistical model (1), the nonlinear indices of the HR and HRV will be defined as time-varying functions of the parameters $\xi(t) = [\theta(t), g_0(t), g_1(0,t), ..., g_1(P,t), g_2(0,0,t), ..., g_2(Q,Q,t), g_3(0,0,0,t), ..., g_3(K,K,K,t)]$. Concerning the parameter estimation, a local maximum likelihood method is used to estimate the unknown time-varying parameter set $\xi(t)$. The goodness-of-fit of the point process model is based on the KS test. Autocorrelation plots are also considered to test the independence of the model-transformed intervals [16]. Using (3) the NAR representation (2) corresponding to the fitted NARL model can be easily obtained.

The Lyapunov exponent (LE) of a real valued function $f(t)$ defined for $t > 0$ is defined as:

$$\lambda = \limsup_{t\to\infty}\frac{1}{t}\log(|f(t)|)$$

Let us consider a generic n-dimensional linear system in the form $y_i = Y(t)\,p_i$, where $Y(t)$ is a time-varying fundamental solution matrix with $Y(0)$ orthogonal, and $\{p_i\}$ is an orthonormal basis of $\mathbb{R}^n$. Then, the corresponding λ_i are straightforward defined. When the sum of the λ_i is minimized, the orthonormal basis $\{p_i\}$ is called "normal" and the λ_i are called the Lyapunov exponents [19]. One of the key theoretical tools for determining LEs is the continuous QR factorization of $Y(t)$ [20], [21]:

$$Y(t) = Q(t)R(t)$$

where $Q(t)$ is orthogonal and $R(t)$ is upper triangular with positive diagonal elements R_{ii}, $1 \le i \le n$, leading to an easier formulation of the LEs, i.e. [19]–[21]:

$$\lambda_i = \lim_{t\to\infty}\frac{1}{t}\log\|Y(t)p_i\| = \lim_{t\to\infty}\frac{1}{t}\log\|R(t)p_i\| = \lim_{t\to\infty}\frac{1}{t}\log\|R_{ii}(t)\|\,.$$

The NAR model (2) can be rewritten in an M-dimensional state space canonical representation:

$$r_n^{(k)} = \begin{cases} r_{n-1}^{(k+1)} & \text{if } k < M \\ F\left(r_{n-1}^{(M)}, r_{n-1}^{(M-1)}, \cdots, r_{n-1}^{(2)}, r_{n-1}^{(1)}\right) & \text{if } k = M \end{cases}$$

By evaluating the Jacobian $J(n)$ over the time series, the LE can be determined using the QR decomposition:

$$J(n)Q_{(n-1)} = Q_{(n)}R_{(n)}$$

This decomposition is unique except in the case of zero diagonal elements. Then the LEs λ_i are given by

$$\lambda_i = \frac{1}{\tau H}\sum_{j=0}^{H-1}\ln R_{(j)ii}$$

where H is the available number of matrices within the local likelihood window of duration W, and τ the sampling time step. The estimation of the LEs is performed at each time t from the corresponding time-varying vector of parameters, $\xi(t)$. This provides us with a time-varying vector, $\lambda_i(t)$,

TABLE I

SPEARMAN CORRELATION COEFFICIENT ρ_{sp} DURING LOSS OF CONSCIOUSNESS

ρ_{sp}	μ_{RR}	σ_{RR}	LF	HF	LF/HF	IDLE
σ_{RR}	0.2825	1	0.6689	0.7721	0.0177	-0.0233
LF/HF	-0.1699	0.0177	0.5702	-0.4330	1	-0.5550
IDLE	0.1776	-0.0233	-0.2022	0.3676	-0.5550	1

able to track the Lyapunov spectrum in continuous time. We set forth the first LE, $\lambda_1(t)$, as the instantaneous dominant Lyapunov exponent (IDLE).

III. EXPERIMENTAL RESULTS

In order to validate the proposed algorithms' ability to track pharmacological interventions in the OR or ICU, we have considered experimental RR datasets from healthy volunteer subjects participating in a study approved by the Massachusetts General Hospital (MGH). Intravenous and arterial lines were placed in each subject. Propofol was infused intravenously using a previously validated computer-controlled delivery system running STANPUMP connected to a Harvard 22 syringe pump (Harvard Apparatus, Holliston, MA). Five effect-site target levels (L1 to L5, step Propofol concentration increase of 5 mcg/ml) were each maintained for 15 minutes respectively, and then step-wise decreased by 5 mcg/ml per epoch during E6, E7 and E8 before full emergence from anesthesia. Along the experiment, subjects listen to pre-recorded auditory stimuli and are instructed to press a button to differentiate between sounds. We use the loss of button responses as a marker of loss of consciousness (LOC). Capnography, pulse oximetry, ECG, and arterial BP were recorded and monitored continuously throughout the study. Bag-mask ventilation with 30% oxygen was administered as needed in the event of propofol-induced apnea. Because propofol is a potent peripheral vasodilator, phenylephrine was administered intravenously to maintain mean arterial BP within 20% of baseline.

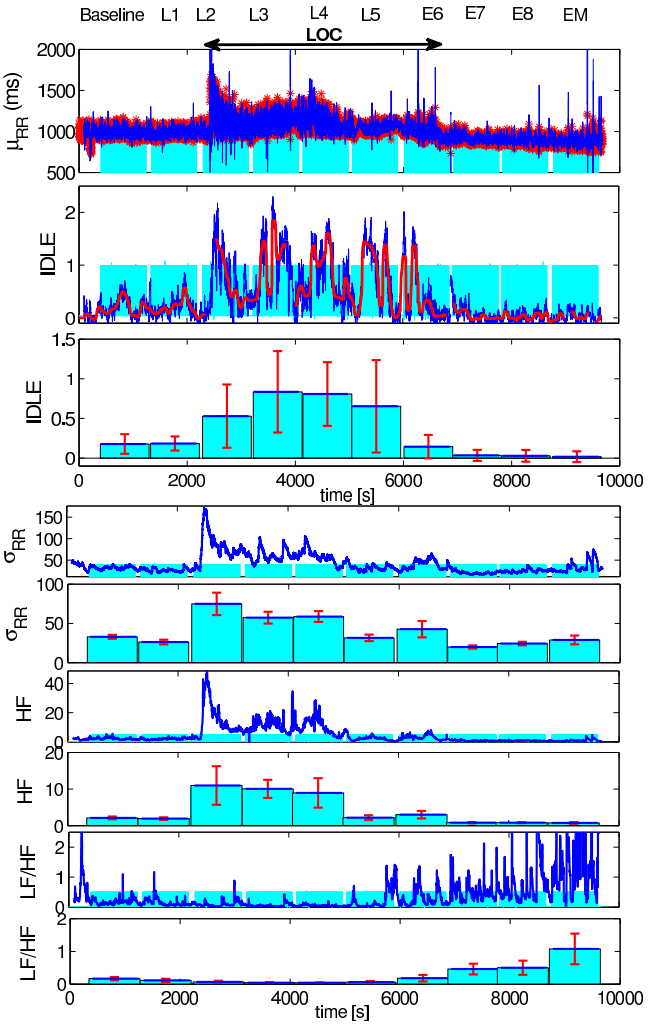

Fig. 1. Instantaneous heartbeat statistics computed from a representative subject using a cubic NARL model. High resolution dynamics (blue) are superimposed by moving averages (red). Below each index is its corresponding statistics per epoch (median and standard deviation).

To provide evidence of the potentialities of our quantification we show an exemplary application of the algorithm to a representative subject. This patient is losing his capacity to respond to auditory stimuli at the beginning of L2, and regains response capacity during the first propofol reduction step (E6). At the beginning of LOC bag-mask ventilation is started, and phenylephrine is administered with varying dosage increases all along LOC, particularly during L4 to E6. The computed HRV linear and nonlinear indices of heartbeat dynamics are shown in Fig 1. In particular, the HF power mirrors the sharp increase in instantaneous RR variability (correlation 0.66, Table I) especially when the subject starts losing his ability to respond to auditory stimuli in L2. Here the concurrent start of artificial ventilation may play a significant role, as the HF power index measures respiratory-related heartbeat variations (respiratory sinus arrhythmia). Importantly, these two indices significantly decrease in L4 and tend to return to baseline values in L5 and E6, thus loosing their correlation with both propofol administration and loss of consciousness. In this case the autonomic assessment is likely being affected by the synpathomimetic action of phenylephrine administration. The index most correlated with propofol administration is the LF/HF sympatho-vagal index, confirming previous findings. On the other hand, the IDLE index maintains a consistent fluctuating trend around higher positive values all along the epochs associated with loss of response, going back to baseline values coincidently with recovery of consciousness (in E6), and then becoming negative with sympathetic predominance during emergence from anesthesia. Of note, the IDLE index is highly uncorrelated with RR mean (0.18) and variability (-0.02) and only partially correlated with LF/HF (-0.55). IDLE and LF/HF are the two indices with highest significant difference of the epochs during LOC from baseline (see Table II). In fact, σ_{RR} and HF show a non-significative difference in L5 and, likewise, LF in L4. Moreover, LF/HF changes significantly between baseline and L1 (where the subject is still responding), whereas the IDLE maintains comparable values during

TABLE II

P-VALUES FROM THE RANK-SUM TEST BETWEEN L0 AND THE OTHER PROTOCOL EPOCHS

	L1	L2	L3	L4	L5	E6	E7	E8	EM
		Loss of Consciousness							
μ_{RR}	0.536	$\mathbf{1.81}\cdot10^{-5}$	$\mathbf{1.10}\cdot10^{-5}$	$\mathbf{1.80}\cdot10^{-7}$	$\mathbf{3.70}\cdot10^{-7}$	0.956	$\mathbf{1.13}\cdot10^{-9}$	$\mathbf{1.41}\cdot10^{-8}$	$\mathbf{1.65}\cdot10^{-9}$
σ_{RR}	$\mathbf{9.00}\cdot10^{-7}$	$\mathbf{4.38}\cdot10^{-9}$	$\mathbf{1.68}\cdot10^{-12}$	$\mathbf{2.60}\cdot10^{-9}$	0.985	**0.0304**	$\mathbf{6.52}\cdot10^{-11}$	$\mathbf{2.60}\cdot10^{-9}$	0.267
LF	$\mathbf{5.30}\cdot10^{-4}$	$\mathbf{1.04}\cdot10^{-4}$	**0.0277**	0.481	$\mathbf{8.90}\cdot10^{-5}$	**0.0252**	0.802	0.318	$\mathbf{9.25}\cdot10^{-6}$
HF	0.0614	$\mathbf{2.37}\cdot10^{-10}$	$\mathbf{1.41}\cdot10^{-12}$	$\mathbf{3.10}\cdot10^{-12}$	0.690	**0.0229**	$\mathbf{2.39}\cdot10^{-12}$	$\mathbf{2.61}\cdot10^{-12}$	$\mathbf{1.05}\cdot10^{-8}$
LF/HF	**0.0343**	$\mathbf{2.02}\cdot10^{-5}$	$\mathbf{5.89}\cdot10^{-9}$	$\mathbf{1.47}\cdot10^{-10}$	**0.00103**	0.898	$\mathbf{2.85}\cdot10^{-8}$	$\mathbf{2.80}\cdot10^{-9}$	$\mathbf{1.87}\cdot10^{-10}$
IDLE	0.4289	$\mathbf{1.70}\cdot10^{-4}$	$\mathbf{1.23}\cdot10^{-6}$	$\mathbf{4.04}\cdot10^{-8}$	$\mathbf{9.90}\cdot10^{-4}$	0.536	$\mathbf{1.23}\cdot10^{-3}$	$\mathbf{1.47}\cdot10^{-4}$	$\mathbf{5.60}\cdot10^{-5}$

Bold values indicate significative differences with $\alpha <= 0.05$

these two epochs, confirming its more exclusive classification power between conscious and unconscious states.

IV. DISCUSSION AND CONCLUSION

We present a novel methodology for the characterization of heartbeat nonlinear dynamics and their time-varying complexity by means of the instantaneous estimation of the Lyapunov Spectrum within a point process paradigm. The use of the discrete Laguerre expansions of a cubic autoregressive Wiener-Volterra model gives several advantages such as long-term memory and lowest complexity to the considered nonlinear system, allowing for estimation of the instantaneous dominant Lyapunov exponent (IDLE). The presented results demonstrate that our proposed point process model is able to track the autonomic-mediated short-term cardiovascular control dynamics and to characterize at the same time the inherent nonlinearity of the system. The single case study presented here demonstrates that the IDLE is independent from sympathovagal dynamics as assessed by more standard autonomic indices, and strongly associated with loss of consiousness during anesthesia. Our results suggest that the changes in autonomic tone during anesthesia are paralleled by a more preponderant presence of complex nonlinear heartbeat dynamics, which is strongly correlated with the unconscious state. Given the strong mathematical foundation of our model along with these promising findings, future works are devoted on better understanding the physiological meaning of these indices, their dependence on confounding effects from compensatory maneuvers and/or nociceptive stimuli, and their relations with central brain mechanisms as they are affected by anesthetic drugs.

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