Early Warnings of Heart Rate Deterioration

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***Abstract*— Hospitals can experience difficulty in detecting and responding to early signs of patient deterioration leading to late intensive care referrals, excess mortality and morbidity, and increased hospital costs. Our study aims to explore potential indicators of physiological deterioration by the analysis of vital-signs. The dataset used comprises heart rate (HR) measurements from MIMIC II waveform database, taken from six patients admitted to the Intensive Care Unit (ICU) and diagnosed with severe sepsis. Different indicators were considered: 1) generic early warning indicators used in ecosystems analysis (autocorrelation at-1-lag (ACF1), standard deviation (SD), skewness, kurtosis and heteroskedasticity) and 2) entropy analysis (kernel entropy and multi scale entropy). Our preliminary findings suggest that when a critical transition is approaching, the equilibrium state changes what is visible in the ACF1 and SD values, but also by the analysis of the entropy. Entropy allows to characterize the complexity of the time series during the hospital stay and can be used as an indicator of regime shifts in a patient's condition. One of the main problems is its dependency of the scale used. Our results demonstrate that different entropy scales should be used depending of the level of entropy verified.**

I. Introduction

Hospitals can experience difficulty in detecting and responding to early signs of patient deterioration, leading to late intensive care referrals, excess mortality and morbidity, and increased hospital costs. Critical illness in hospitalised patients are preceded by physiological abnormalities that can be observed, detected and acted upon: some examples include changes in respiratory rate (RR), heart rate (HR) and blood pressure [1-3]. In clinical practise, the early detection of patient deterioration is supported by regular bedside observations, but research has suggested that monitoring and charting of patients' vital signs may not be satisfactory on hospital wards [4]. A landmark study in patient safety, the Harvard Medical Practice Study, estimated that adverse events such as cardiac and respiratory arrests occurred in 3.7% of hospitalisations, and that over a quarter of the events were caused by medical management rather than by disease or the original condition itself [5]. Other studies suggest that ward staff can miss, misinterpret or mismanage the signs [6], partly due to overloaded work schedules [7]. In addition, 'regular' observations are measured relatively infrequently (e.g. at 4-hour intervals) and do not support analysis of patterns in vital signs.

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Nowadays, with the emergence of mobile health, new challenges are focused on how effectively use vital-sign monitoring to improve health outcomes, [8]. Wearable devices such as SensiumVitals® patches [9] can provide long-term monitoring allowing with increased frequency and accuracy compared to bedside observations, providing a better decision-support system capable to improve the detection of, and response to, early signs of deterioration.

In spite of the increasing importance of personalised health care systems, progress in the development of models dedicated to early warning of clinical deterioration is still slow [10]. The goal is to identify regime shifts in a patient's condition. Such transitions, commonly called tipping points, can result from an external factor, but also result from a stepwise change in the patient's health [11]. Recent studies of generic warning signals in other domains suggests a range of novel approaches capable of bringing new insight to this field. There is ample evidence that climate or ecosystems when approaching a tipping point tend to be dominated by a phenomenon known as critical slowing down [11-14]. Other studies have also provided evidence that biological systems are subject to similar types of tipping points, such as the onset of an epileptic episode or the onset and remission of clinical depression [15].

This work aims to explore different indicators capable to identify regime shifts in a patient's condition that can be correlated with a process of physiological deterioration, by the analysis of HR measurements. There are an enormous range of methods available that can be used to assess critical transitions, as reviewed by Dakos et. al. [14]. We implemented some of these methods according to Early Warnings Signals Toolbox (http://www.early-warning-signals.org/). Additionally, entropy measures were computed, namely Kernel Entropy (KerEnt) and Multi Scale Entropy (MSE), to model signal complexity. This paper is organised as follows. An overview of the methodology followed is presented in Section II. Results are presented and discussed in Section III and conclusions are presented in Section IV.

II. Experiments

A. Dataset

HR measurements from the MIMIC II waveform dataset [16, 17], taken from six patients (P1-P6) admitted to the Intensive Care Unit (ICU) and diagnosed with severe sepsis (ICD9 code – 995.92). The data analysis focuses on the computation of generic early warning signals and entropy measures for HR segments subject to tipping points, clearly identifiable by visual inspection. To access the research data see http://dx.doi.org/10.17036/ae7f18ce-a8d8-4c6d-a0b5-f5916dde49bc.

B. *Generic early warning signals*

A 'critical slowing down', in other words a slower rate of return to equilibrium following a disturbance is a generic risk marker of a critical transition [14]. A lower return rate can be detected by different methods (Table I): 1) changes in its correlation structure, as the state of the system become increasingly similar due to an increase in the 'short-term memory' prior to a transition; 2) changes in the pattern of variability, namely its increase prior to a complete transition and the increase of the conditional heteroskedasticity – a positive relationship with the previous time steps; 3) the dynamics at the boundary between two states become slow and as result the time series become asymmetric (skewness) and reach extreme values (kurtosis).

C. *Entropy*

Entropy is a family of metrics that allow the quantification of the complexity of time series. It can be computed in many ways [18]. Over the last years there have been many applications of entropy for evaluating physiological and biological signals. There is clinical evidence that healthy systems are more complex in comparison to pathologic systems, e.g. disease, aging, drug toxicities contribute to degrade the physiologic information content [19]. In this study, two distinct measures were computed: KerEnt and MSE. The first one [20] was developed in the context of electrocardiogram analysis. It also demonstrated its value as a measure of irregularity in other domains, such as in nocturnal oxygen saturation (SaO_2) analysis [21]. MSE analysis was introduced by Costa et. al. to separate healthy and pathologic groups at different scales [22, 23].

- **KerEnt**

KerEnt is obtained by incorporating the Renyi entropy [24], computed by Eq. 1 of order 2 (α=2), into the concept of entropy rate (Eq. 2), as presented in Table I.

TABLE I. LIST OF PARAMETERS USED IN THE HR ANALYSIS.

Effect	*Indicator*	*Method used to compute*
Correlation	Increase in the autocorrelation at-lag-1	Autocorrelation function (ACF1))
Variance	Increase variability	Standard deviation (SD)
	Increase conditional heteroskedasticity	Langrange multiplier test
Dynamics at the boundary	Increase Skewness	Standardized third moment around the mean of a distribution
	Increase Kurtosis	Standardized fourth moment around the mean of a distribution
Entropy	KerEnt	$H_{R_\alpha} = \frac{1}{1-\alpha} log \int p(x)^\alpha dx$ (1) $KerEnt(m,\sigma,N) = H_{R_2}^{m+1}(\alpha) - H_{R_2}^{m}(\alpha)$ (2)
	MSE	1) Multiple coarse-grained time series $y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i$ (3) 2) SampEn computed according to [25]

The values are computed using Gaussian kernels for specific time scales (m) and distribution width (σ). The choice of m is similar to other entropy measures, where m=1 or m=2 are common values [19]. Different methods can be used for choosing appropriate σ: Bayesian inference using the Metropolis-Hastings algorithm is the most rigorous [20].

- **MSE**

MSE method evaluates the entropy of a signal on different scales. Firstly, according to Eq (3) - Table I- multiple coarse-grained time series (y_j) are constructed by averaging the data points$\{x_1,x_2,\ldots x_i\}$ within non-overlapping windows of increasing length, for different scale factors (τ), where the length of each coarse-grained time series is N/τ and $1 \leq j \leq N/\tau$. The Sample Entropy (SampEn), proposed originally by Richman and Moorman [25], is then calculated for each coarse-grained time series.

III. RESULTS AND DISCUSSION

KerEnt, ACF1, SD, heteroscedasticity, skewness and kurtosis were computed for segments with the same length (approx. 4h) where HR changes are identifiable by visual inspection. Boxplots presented in Figure 1 show that KerEnt mean values are higher for P1, P5 and P6 (1.29±0.18, 1.52±0.14 and 1.32±0.12; respectively) compared to P2 and P4 (0.66±0.09, 0.66±0.06; respectively) leading to the conclusion that P2 and P4 time series are less complex. P3 values are in the middle of both groups (1.02±0.13). Spearman rank correlation was used to explore correlations between indicators. We observed that the KerEnt is most (anti-) correlated with ACF1 for P1 (ρ=-0.43, p<0.05) and P5 (ρ =-0.48, p<0.05), both characterized by high entropy values. In opposition, KerEnt is most correlated with SD when the KerEnt is low: strong/moderate values were observed (ρ=0.76, p<0.05 and ρ=0.46, p<0.05; for P2 and P4 respectively). Between ACF1-SD, it was observed ρ=0.35 p<0.05, taking into account all the subjects. Heteroskedasticity, kurtosis and skewness values are less variable among subjects than ACF1, SD and KerEnt (excluding P4). However, strong correlations were observed among them, namely between kurtosis and skewness (ρ=0.71, p<0.05). Heteroskedasticity is most correlated with kurtosis (ρ=0.38, p<0.05).

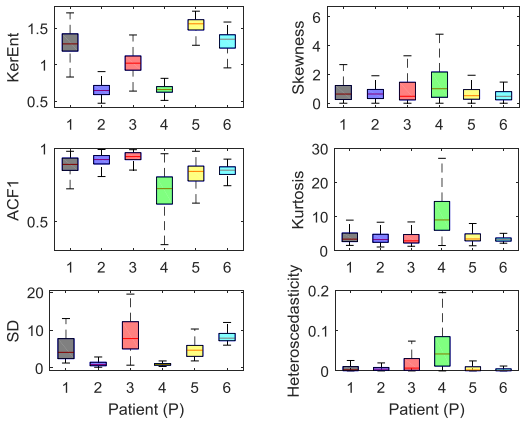

Figure 1. Boxplots for each patient and indicator,including the median. box edges represent the 25th and 75th percentiles, and box whiskers indicate the 5th and 95th percentiles.

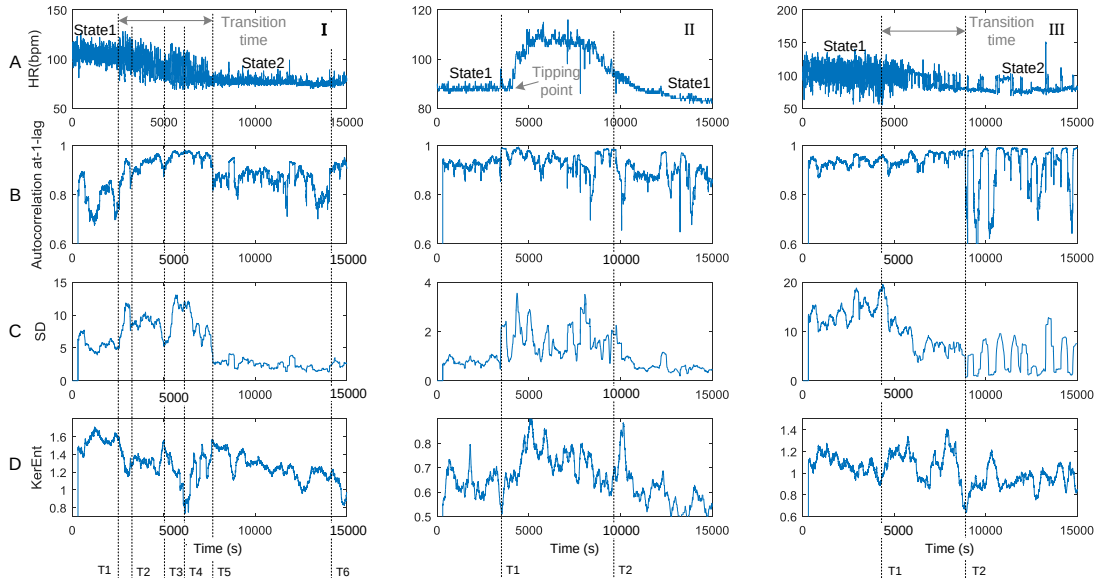

Figure 2. HR segments analysed in detail (A): ACF1 (B), SD (C) and KerEnt (D) for P1, P2 and P3, respectively.

ACF1, SD and KerEnt are analysed in detail for P1, P2 and P3 in Figure 2. Three different situations are depicted: I) it is presented a continuous transition, while the segment presented in II) suffers an abrupt increase, and III) represents a system that switches back and forth between alternative states – a phenomenon termed flickering. A sliding window (6 min) was used to compute ACF1 (B) and SD (C). The values were estimated within each rolling window. A similar process was used to compute KerEnt using m=2 and σ=0.2 (D). In the case I, the first evidence of a transition occurs during T1-T2. During this period, the KerEnt decreases, while the ACF1 and SD values increase. During T3-T4 all the indicators imply that the system is about to move to a new state (KerEnt at minimum, ACF1 and SD at maximum). The KerEnt values observed before T5 are highly variable (T4-T5). At the end, new evidence of instability appears. For the case presented in II, it is visible that both ACF1 and SD increase at T1. During T1-T2 both decrease, but these increase again just prior to T2. KerEnt increased slightly at T1, which would not be expected a priori. We assumed that this occurred as a consequence of the low entropy values. This is consistent with the positive correlation between KerEnt and SD observed for P2 and P4. The segment presented in III exemplifies a flickering transition that confounded both ACF1 and SD. KerEnt starts to increase at T1, and then to decrease at T2. From the comparison of the states before T1 and after T2, it is possible to point out the KerEnt decrease. These three examples suggest that a patient can experience different transitions and the analysis of a single indicator is not enough to the identification (as verified in III). In the case of a continuous transition, entropy analysis can be used as an indicator of the progressive stages. Additionally, it allows to follow and identify low physiological complexity in time series.

KerEnt analysis lacks a thorough analysis of entropy values at different scales. We evaluated MSE analysis considering a maximum scale of 20, as presented in Figure 3. Results are presented using a sliding window of 1 h which means that e.g. at scale 20 the entropy is computed using the last 20 non-overlapping windows of 3 min. A longer segment collected after the segment presented in III is presented in the Figure 3 (a). We concluded that the flickering behaviour is common for this patient (e.g. a similar transition was observed at T1). The entropy decreases at all scales (during approx. 20 h), what lead us to identify this as a case of physiological deterioration. The signal presented in b) lasts for approx. 30 h enclosing the segment II presented in Figure 2. At its beginning the entropy values observed are quite low for all scales (different colour scales are used for a) and b)), but during the monitoring time, the patient is subject to abrupt HR changes that increase the entropy values at high scales. This conclusion justifies the KerEnt results discussed before for the patients P2 and P4. We were not able to identify relevant KerEnt changes due to the inappropriate time scale used. This case is an example of normal changes in HR that can occur to any patient during a long acquisition, and cannot be considered as part of a degradation process.

IV. Conclusion and Future Work

This study was a preliminary work to explore potential indicators of vital signs deterioration in clinical wards. We explored some indicators used in other domains and also introduced new indicators based on entropy-based measures. Our findings suggest that when a transition is approaching, the equilibrium state changes and early warning of the new state is identifiable by both ACF1 and SD but also by the entropy analysis. Entropy values are intrinsically related to the time series complexity of the time series, providing additional information that can be used as an indicator of the pathological state. We concluded also that different entropy scales should be used depending of the level of complexity verified. We agree with Dakos et. al that there was no single best indicator or method capable of identifying an upcoming change [14]. One of the main limitations that we will address in future studies will be the evaluation of the effect of non-stationarities.

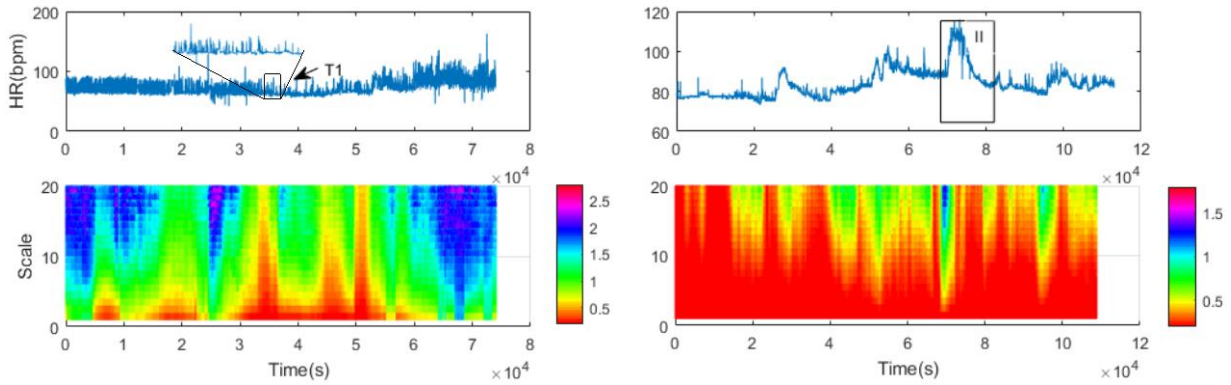

Figure 3. MSE analysis for P3 and P2, respectively: a) signal monitored after the segment III presented in Figure 2, b) signal containing the segment II presented in the same figure.

Future studies will involve controlled clinical trials to explore vital-sign deterioration (HR, RR and temperature). It is expected that the physiological variability inherent to different individuals leads to the increase of the complexity of states that can be observed. Additionally, it may depend on the patient medical condition itself (as in this case, HR values are dependent of the severe sepsis condition), as well as other comorbidities. The results can only be reliable if we are able to collect continuous data records, as the major limitation of current early warning systems is that they are based on manual checks performed by nursing staff, occurring these observations intermittently.

REFERENCES

[1] D. Goldhill and A. McNarry, "Physiological abnormalities in early warning scores are related to mortality in adult inpatients," Br J Anaesth, vol. 92, pp. 882-4, 2004.

[2] B. H. Cuthbertson, M. Boroujerdi, L. McKie, L. Aucott, and G. Prescott, "Can physiological variables and early warning scoring systems allow early recognition of the deteriorating surgical patient?*," Critical Care Medicine, vol. 35, pp. 402-409, 2007.

[3] K. M. Hillman, P. J. Bristow, T. Chey, K. Daffurn, T. Jacques, S. L. Norman, et al., "Antecedents to hospital deaths," Internal Medicine Journal, vol. 31, pp. 343-348, 2001.

[4] M. T. Chatterjee, J. C. Moon, R. Murphy, and D. McCrea, "The "OBS" chart: an evidence based approach to re-design of the patient observation chart in a district general hospital setting," Postgrad Med J, vol. 81, pp. 663-6, Oct 2005.

[5] T. A. Brennan, L. L. Leape, N. M. Laird, L. Hebert, A. R. Localio, A. G. Lawthers, et al., "Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I," N Engl J Med, vol. 324, pp. 370-6, Feb 7 1991.

[6] R. Endacott, T. Kidd, W. Chaboyer, and J. Edington, "Recognition and communication of patient deterioration in a regional hospital: a multi-methods study," Aust Crit Care, vol. 20, pp. 100-5, Aug 2007.

[7] L. A. Celi, J. D. Marshall, Y. Lai, and D. J. Stone, "Disrupting Electronic Health Records Systems: The Next Generation," JMIR Med Inform, vol. 3, p. e34, 2015.

[8] G. Appelboom, A. H. Yang, B. R. Christophe, E. M. Bruce, J. Slomian, O. Bruyere, et al., "The promise of wearable activity sensors to define patient recovery," J Clin Neurosci, vol. 21, pp. 1089-93, Jul 2014.

[9] M. Hernandez-Silveira, K. Ahmed, S.-S. Ang, F. Zandari, T. Mehta, R. Weir, et al., "Assessment of the feasibility of an ultra-low power, wireless digital patch for the continuous ambulatory monitoring of vital signs," BMJ Open, vol. 5, May 1, 2015 2015.

[10] M. G. Olde Rikkert, V. Dakos, T. G. Buchman, R. de Boer, L. Glass, A. O. Cramer, et al., "Slowing Down of Recovery as Generic Risk Marker for Acute Severity Transitions in Chronic Diseases," Crit Care Med, Jan 12 2016.

[11] M. Scheffer, S. R. Carpenter, T. M. Lenton, J. Bascompte, W. Brock, V. Dakos, et al., "Anticipating Critical Transitions," Science, vol. 338, pp. 344-348, 2012-10-19 00:00:00 2012.

[12] C. Trefois, P. M. Antony, J. Goncalves, A. Skupin, and R. Balling, "Critical transitions in chronic disease: transferring concepts from ecology to systems medicine," Curr Opin Biotechnol, vol. 34, pp. 48-55, Aug 2015.

[13] M. Scheffer, J. Bascompte, W. A. Brock, V. Brovkin, S. R. Carpenter, V. Dakos, et al., "Early-warning signals for critical transitions," Nature, vol. 461, pp. 53-9, Sep 3 2009.

[14] V. Dakos, S. R. Carpenter, W. A. Brock, A. M. Ellison, V. Guttal, A. R. Ives, et al., "Methods for detecting early warnings of critical transitions in time series illustrated using simulated ecological data," PLoS One, vol. 7, p. e41010, 2012.

[15] I. A. van de Leemput, M. Wichers, A. O. Cramer, D. Borsboom, F. Tuerlinckx, P. Kuppens, et al., "Critical slowing down as early warning for the onset and termination of depression," Proc Natl Acad Sci U S A, vol. 111, pp. 87-92, Jan 7 2014.

[16] M. Saeed, M. Villarroel, A. T. Reisner, G. Clifford, L. W. Lehman, G. Moody, et al., "Multiparameter Intelligent Monitoring in Intensive Care II: a public-access intensive care unit database," Crit Care Med, vol. 39, pp. 952-60, May 2011.

[17] A. L. Goldberger, L. A. N. Amaral, L. Glass, J. M. Hausdorff, P. C. Ivanov, R. G. Mark, et al., "PhysioBank, PhysioToolkit, and PhysioNet: Components of a New Research Resource for Complex Physiologic Signals," Circulation, vol. 101, pp. e215-e220, June 13, 2000 2000.

[18] C. C. Mayer, M. Bachler, M. Hortenhuber, C. Stocker, A. Holzinger, and S. Wassertheurer, "Selection of entropy-measure parameters for knowledge discovery in heart rate variability data," BMC Bioinformatics, vol. 15 Suppl 6, p. S2, 2014.

[19] S. M. Pincus, "Assessing Serial Irregularity and Its Implications for Health," Ann N Y Acad Sci., vol. 954, pp. 245-67, 2001

[20] D. Woodcock, "A novel entropy measure for analysis of the electrocardiogram," Aston University, 2007.

[21] J. V. Marcos, R. Hornero, I. T. Nabney, D. Alvarez, and F. Del Campo, "Analysis of nocturnal oxygen saturation recordings using kernel entropy to assist in sleep apnea-hypopnea diagnosis," in Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE, 2011, pp. 1745-1748.

[22] M. Costa, A. L. Goldberger, and C. K. Peng, "Multiscale entropy analysis of biological signals," Physical Review E, vol. 71, 2005.

[23] M. Costa, A. L. Goldberger, and C. K. Peng, "Multiscale Entropy Analysis of Complex Physiologic Time Series," Physical Review Letters, vol. 89, 2002.

[24] A. Renyi, "On Measures of Entropy and Information," in Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability, Volume 1: Contributions to the Theory of Statistics, Berkeley, Calif., 1961, pp. 547-561.

[25] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," American Journal of Physiology - Heart and Circulatory Physiology, vol. 278, pp. H2039-H2049, 2000.