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Continuous Multiorgan Variability Monitoring in Critically Ill Patients – Complexity Science at the Bedside

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Abstract—**Complex systems science has led to valuable insights regarding the care and understanding of critical illness, but has not led to fundamental improvements to care to date. Realizing the fact that there is inherent uncertainty in patient trajectory, we have developed Continuous Individual Multiorgan Variability Analysis (CIMVA) as a tool theoretically and practically designed to track the systemic emergent properties of the host response to injury or infection. We present an overview of CIMVA software, and discuss four separate potential clinical applications that we are evaluating; including early detection of infection, better prediction of extubation failure, continuous monitoring of severity of illness in the ICU, and the evaluation of cardiopulmonary fitness. Future challenges are discussed in conclusion.**

I. Introduction

THE science of complex systems has been a formal subject of study for over five decades [1], yet with roots that date at least a century ago when Poincaré uncovered the irreducible uncertainty associated with the three body problem. Numerous individuals have built pillars of this large yet still incomplete theoretical framework, including Shannon [2], von Bertalanffy [3], Kauffman [4], Mandelbrot [5], Bak [6], Capra [7], Glass [8], Prigogine [9], Goldberger [10], and many more. Despite a rich theoretical framework, the clinical impact of complexity science currently in use to directly improve patient care is inconsequential in comparison to the enormous impact of analytical science (basic science) and population science (epidemiology). The overall aim of this research program is to contribute to addressing this deficit, aiming to deliver complexity science at the bedside for the direct benefit of the individual patient.

A fundamental problem facing clinicians caring for patients at risk for or with existing critical illness is the inherent uncertainties and inefficiencies associated with their care. For clinicians caring for patients admitted to an emergency room (ER), hospital ward or intensive care unit (ICU), there is a great deal of uncertainty regarding if a patient will subsequently deteriorate requiring life support, in particular during the early stages following significant injury, operation or infection. Often, the recognition of patient deterioration is made late, well after illness and organ dysfunction have progressed. Clinicians then face uncertainty regarding timing of removal of mechanical ventilation life support (i.e. extubation) so as not to cause harm to their patients if they should fail requiring emergency re-institution of ventilation (i.e. re-intubation). All of this uncertainty leads to significant inefficiency, with patients admitted unnecessarily to the ICU, kept on life support or in the ICU longer than necessary. Complexity science teaches us that this uncertainty has an irreducible component (i.e. infinite knowledge of the present still cannot predict the future); thus, embracing the reality of uncertainty as well as of emergence, it is logical to attempt to track the complex system as a whole, and do so continuously over time. Seemingly paradoxically, accepting uncertainty leading to systematic tracking a complex system's trajectory may then help reduce uncertainty, at least in the short term.

Within the science of complex systems, scientists have focused on the patterns inherent to the time series created by complex systems. Variability analysis provides a measure of the patterns of fluctuation occurring over an *interval-in-time*, in contrast to a *point-in-time* assessment. Variability analysis describes the means by which a time series is comprehensively characterized in terms of its overall fluctuation, high and low frequency variation, irregularity, scale invariant correlation, and more. Both cardiac variation [11] and respiratory variation [12-14] were discovered not to be random, but rather correlated and contain information. Numerous investigators have developed a broad and increasing array of analysis techniques that are grouped empirically into "domains" of analysis.[15] Research has focused on the development of algorithms that optimally characterize healthy (physiologic) variability, and the study of how illness and aging are associated with deterioration into unhealthy (pathologic) variability. Hypothesizing that multiorgan variability reflects system-level integrity, then monitoring multiorgan variability offers a means to track the emergent properties of a complex system.

The aim of this paper is to introduce Continuous Individualized Multiorgan Variability Analysis (CIMVA^{TM}) software to enable standardized transparent comprehensive multiorgan variability analysis derived from standard continuously monitored waveforms (e.g. electrocardiogram (ECG), end-tidal capnography ($EtCO_2$), chest impedance, oxygen saturation, etc.). The following is a general description of the methodology and potential clinical utility of CIMVA.

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II. Overview of CIMVA Software

CIMVA is structured as a library of software routines that: a) performs a continuous measurement of the degree of variation and complexity in a patient's biosignals over time and b) generates reports and output files that clinicians and researchers can use to investigate the clinical utility of these measurements in their own patient populations. A simplified block diagram of the overall CIMVA system is shown in Fig. 1, followed by a brief description of each component.

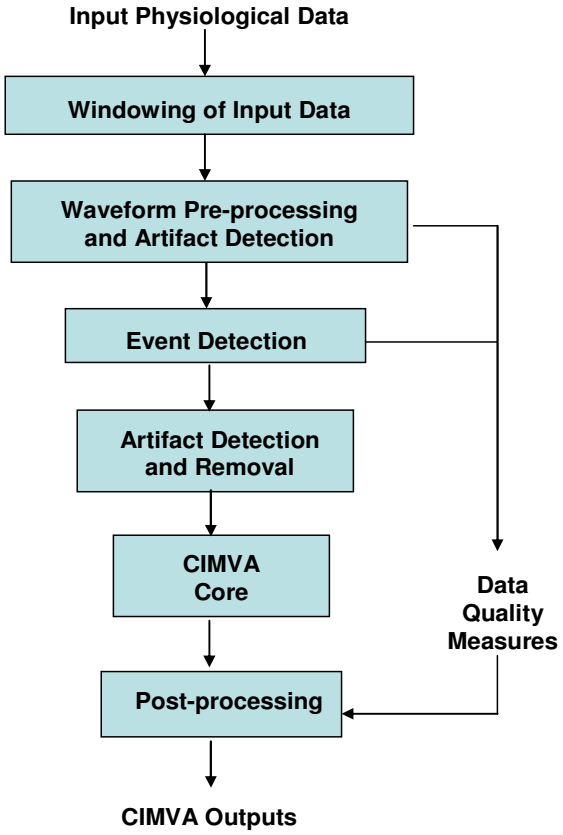

Fig. 1. Overall CIMVA system. Data flow shown is for the case where the input data is a regularly sampled waveform.

A. Input Physiological Data

The inputs to the CIMVA system are time-varying biomedical signals that have been acquired from a patient. In general, these fall into three categories:

1. Regularly sampled waveforms, e.g. ECG (500Hz typical) or $EtCO_2$ (125 Hz typical)
2. Regularly sampled numerics, e.g heart rate or respiratory rate (1 Hz typical)
3. Irregularly sampled time series, e.g. tachogram (one per heartbeat) or tidal volume (one per breath), possibly annotated with additional information (e.g. sinus rhythm)

CIMVA software can harvest this data from the major intensive care unit (ICU) monitoring vendors as well as several ambulatory physiological monitors.

B. Windowing of Input Data

CIMVA is designed to calculate measures of physiological signal complexity and variability as a *continuous* output. This is done with a sliding window approach, defined by the *CIMVA analysis window size* (that defines the portion of the input signal used in the current window) and the *CIMVA step size* (that defines by how much the window is shifted from one iteration to the next). The CIMVA output measures are calculated using the input signal values at each step, a process that results in a new set of CIMVA outputs at a rate determined by the CIMVA step size [16].

C. Waveform Pre-processing and Waveform Artifact Detection (if required)

Pre-processing is applied to waveform inputs to condition the signal for subsequent analysis. These operations may include noise reduction, filtering and re-sampling. Certain artifacts (e.g. leads disconnected) are detected in the waveform and stored as a data quality measure for future processing.

D. Event Detection (if required)

For waveform inputs, a time series of events is extracted for subsequent analysis. For example, heart rate variability (HRV) studies typically operate on the R-R interval time series (or *tachogram*), which requires accurate determination of R-wave locations. Other examples of event detection include extraction of inter-breath intervals from respiratory waveforms (for calculation of respiratory rate variability, RRV).

E. Artifact Detection and Removal

Physiological signals (and time series derived from these) are frequently contaminated by artifact, which can be due to pathological conditions or issues with instrumentation (spurious noise). Detection and elimination of artifact is performed by the CIMVA system (using published, validated algorithms for measurement of, for example, atrial fibrillation [17] and ECG signal quality index [18]) so as not to confound the downstream variability analysis. Data quality measures from this stage include measurements of the degree to which artifact removal was required.

F. CIMVA Core

CIMVA Core calculates a diverse panel of complexity and variability measurements (called CIMVA output measures) based on the event data in the analysis window. The CIMVA Core is composed of 96 measures belonging to five *domains of variability*: Time, Frequency, Scale-Invariant, Entropy and Nonlinear [15]. Each domain defines the type of information content that the variability measure extracts, and it is used to investigate specific properties characterizing the system under study.

G. Post-processing based on Quality Measures

The preceding stages provide quality measures associated with a given analysis window's input data. In certain instances, however, the data quality may be so corrupted, that the CIMVA Core outputs would be untrustworthy. CIMVA has been designed in a manner which allows the

user to select his/her own thresholds which would cause the rejection of a window.

H. CIMVA Outputs

The following are available at the end of a CIMVA analysis:

1. Report with summary (in .pdf format)
2. Matrix of numerical results, with one row per CIMVA analysis window (in .csv format). The columns of the matrix are structured in groups: a) properties of the CIMVA analysis window, b) data quality measures, c) CIMVA Core outputs.

III. Clinical Applications

In this section we briefly introduce and discuss some of the results achieved by applying CIMVA analysis in various clinical scenarios.

A. Predicting Extubation Failure

Expeditious yet safe extubation is critically important in the care of mechanically ventilated ICU patients. Failed extubation (defined as re-intubation within 48 hrs) is associated with increased morbidity, mortality and costs. Spontaneous breathing trials (SBTs), whereupon patients are subjected to brief periods of reduced ventilatory support (taking on a greater workload of breathing as a simulation of breathing after extubation) are the current gold standard of care to predict failed extubation. Nonetheless, several studies have determined that 15% patients who are extubated subsequently fail [19].

We performed continuous HRV and RRV monitoring during 125 SBTs in 60 patients. Twelve of these patients were excluded for missing data and protocol violations, leaving a total of 48 patients – 41 of these passed extubation and 7 of these failed extubation. Restricting analysis to the last SBT performed prior to extubation, patients who subsequently failed extubation had a greater absolute loss of RRV compared to patients who passed extubation as measured by several CIMVA Core output measures ($p<0.005$). There were non-significant reduction in the change in HRV associated with failed extubation. No correlation was found between measures of variability and standard measures of readiness for extubation (submitted for publication). A multi-center observational study, supported by the Canadian Critical Care Trials Group, is underway to evaluate the added value of CIMVA (compared to standard of care) and determine thresholds of HRV and RRV that predict extubation failure.

B. Early Detection of Infection

Early diagnosis of sepsis leading to aggressive resuscitation involving antibiotic administration is vital to recovery and survival. Patients undergoing bone marrow transplantation (BMT) for the treatment of acute leukemia become neutropenic (abnormally low white blood cell count) as a side effect of the BMT. These neutropenic patients comprise a group at a high risk of sepsis (approximately 80%) and mortality (approximately 5%). Current clinical approaches for diagnosing sepsis are based on an increased absolute value of one or more vital signs (e.g. fever) in addition to laboratory tests such as blood cultures to look for evidence of a pathogen.

We performed HRV analysis on continuously recorded heart rate waveforms of 21 ambulatory outpatients as they underwent BMT. Of the 21 patients enrolled, 4 patients withdrew, leaving 17 patients who completed the study (12±4 days of continuous Holter monitoring). Fourteen patients developed sepsis requiring antibiotic therapy, whereas 3 did not. On average, for 12 out of 14 infected patients (86%), a significant (25%) reduction in several CIMVA Core output measures were observed prior to the clinical diagnosis and treatment of sepsis. For infected patients, wavelet AUC [20] demonstrated on average a 25% drop from baseline 35 hours prior to sepsis. For non-infected patients, all measures except two showed no significant reduction. For further details refer to [21].

C. Monitoring Severity of Illness in the ICU

Severity of illness is determined by clinical judgment and is never certain in critically ill patients. Although illness and injury severity scores and organ dysfunction scores exist, they represent population-based measures and are not well suited to evaluate the prognosis or severity of illness in individual patients over time.

Continuous data collection was performed for 35 patients by harvesting the ECG and $EtCO_2$ waveforms (already monitored as per standard practice). These data were collected continuously for 24 hours a day (the enrollment in the study lasted on average 11 days per patient). In this pilot study we demonstrated feasibility of continuous HRV and RRV analysis in critically ill patients. First, we observed correlation between increasing organ failure and reduced variability. Patients with low levels of organ failure had preservation of HRV and RRV, while patients with increasing degree of organ failure had progressively lower levels of variability. Decreasing HRV was observed in patients (n=6) as they progressed towards the onset of shock (as defined by initiation of vasopressor and/or inotrope therapy). Increasing RRV was observed in patients as the progressed towards resolution of respiratory failure and extubation (n=15) (submitted for publication).

D. Evaluation of Cardiopulmonary Fitness

Since the 1970s, staged exercise testing has been increasingly employed in the outpatient or ambulatory care setting, providing an assessment of cardiac and respiratory functioning, determining an individual's pre-, peri-, and postoperative risk assessment, and measuring fitness level. Although cardiopulmonary exercise testing is a well-justified assessment tool, its major limitations include physical incapability, a lack of motivation and desire, reluctance to repeatedly perform exercise testing to exhaustion, and invasive and expensive test equipment.

Alternative measures that are noninvasive, inexpensive and require minimal exertion should be explored.

39 healthy and physically active (Group 1: ≤25 years of age, n=12; Group 2: ≥40 years of age, n=12) or unhealthy and less physically active (Group 3: ≤25 years of age, n=3 or Group 4: ≥40 years of age, n=12) subjects had R-R interval data recorded from a portable Holter monitor which participants wore for 24 hrs prior to maximal aerobic capacity (VO2max) test using a metabolic cart.

The average Day 1 awake HRV was found strongly correlated with cardiopulmonary fitness; such that both wavelet AUC ($r=0.83$, $p<0.001$) and detrended fluctuation analysis (DFA) ($r=0.83$, $p<0.001$) accounted for approximately 80% of the variation in cardiopulmonary fitness. Furthermore, a paired t-test demonstrated significant differences between young healthy and older unhealthy ($p<0.05$) and older healthy and older unhealthy ($p<0.05$) for measures of standard deviation and DFA (submitted for publication).

IV. Discussion

In the introduction, we have seen how the science of complex systems as grown of interest since 1980. During the following three decades many researchers have successfully applied this paradigm to solve problems in medicine. Some recent works include the assessment of ICU patients' mortality through HRV [22], the prediction of neonatal sepsis through HRV [23] and the characterization of RRV during spontaneous breath trials [24]. These results motivate a further characterization of variability analysis, shifting current research towards two principal future challenges.

The first challenge is to characterize multi-organ variability. This type of analysis focuses in the mutual information exchanged between coupled physiological systems. Examples in the literature are the evaluation of interactions between the cardiac and respiratory systems through spectral analysis [25], or the evaluation of the differences between heart rate variability and blood pressure [26]. Despite the clear relevance of these analyses, the research in this area still needs to take advantage of novel multivariate methods and multi-signal comparison. Indeed, few studies compare two signals at one time, and rarely more than two signals are simultaneously considered.

The second challenge corresponds to the exploration of the nature and meaning behind variability and its domains. Even if inaccurate in categorizing all the measures today available, a classification is needed to better understand the meaning and the nature of variability. For instance, it is well known that the measures belonging to the frequency domain, if applied to heart rate variability, are capable to estimate the sympathetic and parasympathetic activity of the brain [27]. However, the link between physiology and other domains of variability, so as the link with single measures of variability, still remains to be discovered.

Including a variety of up-to-date techniques of nonlinear time series analysis, and incorporating in its core multivariate techniques for multi-organ analysis, CIMVA represents a tool to face these challenges and improve healthcare at the bedside.

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