Use of complexity modeling of physiology signals in real time to predict cardiorespiratory instability

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Monitoring Truth
No monitoring device, no matter how accurate or insightful its data will improve outcome,
Unless coupled to a treatment, which itself improves outcome

Three Primary Clinical Problems
• How to identify patients who are becoming hemodynamically unstable before they progress too far?
• How to determine the most appropriate therapy to reverse the primary cause for impending circulatory shock?
• How to implement the most appropriate therapy when individual training of care givers and responses of patients vary?

Circulatory Shock in Phase Space
• Shock represents the expression of inadequate tissue perfusion
• Four primary mechanisms result in shock
  – Hypovolemic, cardiogenic, inflammatory, neurogenic
• The measured physiological variables reflect the interaction between the primary dysfunction and the host’s adaptive responses

Medical Issues
• Identify circulatory insufficiency before secondary tissue injury occurs
• Assess disease severity
• Accurately predict response to treatment
• Gauge adequacy of specific therapies
• Estimate improved predictions of disease severity by additional biological measures (biosensors)
• Need to develop metrics to assess these challenges

Effect of Hemorrhage on Bladder Mucosal Blood Flow and Mitochondrial Function in the Pig

Measuring Mean Systemic Pressure at the Bedside


Calculating Pms at the Bedside

Effective Circulating Blood Volume

Navigator 1

Applied Physiology

Pms = (Vs + Vus)/(Cvs + Cas)

assuming Cas/Cvs = 1/24 and Ras/Rvs = 25/1

Pms = 0.96Pra + 0.04Pa + 0.96 x c x CO

Eh = Pms-Pra

Pra

Parkin. Crit Care Resusc 1: 311-21, 1999

Why Blood Pressure Does Not Define Cardiovascular Status

Heart failure

Hypovolemia

MAP = 80 surfaces

Pms

Eh

SVR

Why Cardiac Output Does Not Define Cardiovascular Status

Heart failure

Hypovolemia or Sepsis

CO = 5 L/min surface

Pms

Eh

SVR

Combining pressure and flow helps

Heart failure

Hypovolemia

MAP=80 & CO=5 line for Eh

Pms

Eh

SVR

Separating Pms, Eh and SVR for Hypovolemia, Heart Failure and Sepsis

Navigator 3-D Display

Hypovolemia

Septic Shock

Cardiogenic Shock

Hemorrhagic Shock
Health and Disease Defined as a Time-Space Continuum

- In a static field of single point-in-time data health and disease can be separated in stochastic fashion using Neuronet approach to create a probabilistic equation.
- In a dynamic field of continuously changing but inter-related variables, health and disease can be defined by the differences their Lorenz Attractors ($\rho$) independent of the actual physiological variables raw values.

Chaos Theory and Biology

- Non-linearity
  - Chaotic Behavior
  - Fractal appearance
- Non-linear thinking can result in solutions to otherwise unsolvable problems
  - Benoit Mandelbrot & James A. Yorke

Natural Non-Linear Systems

- Fractal Structure
  - Self similarity at all levels
  - Defined by minimal organizational rules
- Deterministic
- Self-organizing
- Adapt to external stress

Complexity Theory

- Self-Organizing Behavior

Health and Disease Defined as a Time-Space Continuum

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Three Primary Clinical Problems

- How to identify patients who are becoming hemodynamically unstable before they progress too far?
- How to determine the most appropriate therapy to reverse the primary cause for impending circulatory shock?
- How to you implement the most appropriate therapy with non-physician when individual responses of patients and care givers vary?

Background

Early discharge from ICUs to lower acuity monitoring units (step-down units or SDUs) is increasing, placing sicker patients in less well staffed units. Minimally invasive monitoring devices are used to assess stability outside the ICU. MET activation is grouped around morning and afternoon rounds, suggesting instability was missed at other times.


An electronic integrated monitoring systems (BioSigns) was developed to identify cardio-respiratory instability using Neuronet analysis of existing ICU patient behavior.


Study Design

<table>
<thead>
<tr>
<th>Pre</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
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<tbody>
<tr>
<td>8 weeks</td>
<td>13 weeks</td>
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<th>Train Staff</th>
<th>Implement display</th>
<th>Implement use rules</th>
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<td>Collect Data, Bedside display inactive</td>
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<td>Implement Clinical Decision Rules for VSI trigger evaluate and Condition C</td>
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**Efferent Arm:**

**Medical Emergency Teams (MET) Improve Acute Care**

- System-wide ICU-based MET activation to evaluate and treat patients at risk to develop adverse events.
- Pre-defined MET activation criteria by non-MD staff.
- Reduces adverse events Relative Risk Reduction:
  - Stroke: 78%, Severe Sepsis: 74%, Respiratory failure: 79%
- Saves lives: post-op death decreased 37%
- Decreases costs: less ICU transfers, decreased LOS
  - But first one must identify these unstable patients

**Explanation BioSign Neural Network**

- An early warning system that may alert when all individually measured variables are still in their “normal” ranges.
- The score is weighted and automated through neural networking, data fusion algorithmic processes.
- Able to recognize changes from normality (defined by a training set).
- Alerts for a single parameter deviating by >3 SD from “normal” value in the training set, or 2-3 parameters moving away from normality by a smaller amount.
- Filtered for noise; requirement for temporal persistence (i.e. 4 out of previous 5 minutes).


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Phase 1 Results

333 patient admissions representing all patients, reflecting 18,692 hours continuous monitoring.

All 7 MET activation events of respiratory and/or cardiac cause were detected by BSI in advance of MET activation.

Mean advanced detection time prior to MET activation was 6.3h.

78% of MET did not result in MET activation and <1/2 were commented on in nursing notes.

Cardio-respiratory deterioration was generally characterized by progressive increases in BSI over time rather than step increases.

Most patients were stable during their SDU stay: 75%

Unstable patients were only unstable at most 20% of the time.


Phase 3: Process Improvement

Application and impact of an integrated monitoring system to identify cardio-respiratory insufficiency and activate Medical Emergency Treatment (MET)

Alert threshold for Phase 3 based on the MET criteria from Phase 1 data was increased from 3.0 to 3.2 based on analysis of Phase 1 data sensitivity and specificity.
Instability Classification

- **MET hit** - any time in which the monitored variables deviated from normal enough to minimally fulfill our MET activation criteria, including artifacts.

- **MET min** - any time in which the monitored variables deviated from normal enough to minimally fulfill our MET activation criteria, even if occurring for very brief intervals and of questionable clinical significance (e.g., isolated brief tachycardia or hypotension).

- **MET full** - those MET min events which also fulfilled our MET activation criteria and should have caused MET activation.

- Determined blindly by a senior critical care medicine physician familiar with MET activation criteria.

Example of Chart Judged as Met min

Patient has baseline hypertension but with normal HR, RR, and SpO2. BP further elevated at 04:00 with VSI alert but then reverts to baseline.

Example of Chart Judged as Met full

Progressive and interactive increase in both HR and RR, and finally hypertension.

Summary Phase 1 to Phase 3 Comparisons

- Patient admissions: 333 patient Phase 1 vs. 313 Phase 3
- Continuous monitoring:
  - 18,692 hr Phase 1 vs. 18,314 hr Phase 3
  - Phase 1, SpO2 monitoring data were absent in 38.5% of monitored hours, despite SpO2 monitoring being mandatory; sub-QI project initiated to improve compliance
- Most patients both phases were stable throughout their SDU stay:
  - 75% Phase 1 vs. 76% Phase 3
- The duration of MET min decreased in Phase 3.
- Both the incidence and duration of MET full decreased in Phase 3.
- The percentage of MET full patients who had a MET activation increased in Phase 3.
Summary Phase 1 to Phase 3 Comparisons

<table>
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<th>Phase 1</th>
<th>Phase 3</th>
<th>% Change P1 to P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>% total admissions MET&lt;sub&gt;all&lt;/sub&gt; during stay</td>
<td>24.9%</td>
<td>23.1%</td>
<td>-7.2%</td>
</tr>
<tr>
<td>% total admissions MET&lt;sub&gt;full&lt;/sub&gt; during stay</td>
<td>17.7%</td>
<td>5.7%</td>
<td>-72.8%</td>
</tr>
<tr>
<td>Ratio MET&lt;sub&gt;full&lt;/sub&gt;/MET&lt;sub&gt;min&lt;/sub&gt;</td>
<td>1:2.12</td>
<td>1:4.86</td>
<td></td>
</tr>
<tr>
<td>% pts. with MET&lt;sub&gt;full&lt;/sub&gt; had MET&lt;sub&gt;actual&lt;/sub&gt; called</td>
<td>17%</td>
<td>61%</td>
<td>258.8%</td>
</tr>
<tr>
<td>Ratio MET&lt;sub&gt;actual&lt;/sub&gt;/MET&lt;sub&gt;full&lt;/sub&gt;</td>
<td>1:11.2</td>
<td>1:3.27</td>
<td></td>
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VSI Episodes and Events

VSI Event = Any red VSI until no red VSI

VSI Episode = All Time from start of initial VSI episode to end of final VSI episodes that occur within 30 min of each other

Red VSI duration = Σ all VSI episode time/VSI event time
Qualifying VSI Events and MET Criteria Achieved

Visensia Alert Activity

<table>
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<tr>
<th>Event</th>
<th>Phase 1</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>VSI Episodes</td>
<td>2050</td>
<td>917</td>
</tr>
<tr>
<td>VSI Events</td>
<td>1047</td>
<td>653</td>
</tr>
<tr>
<td>Pts with VSI</td>
<td>159</td>
<td>141</td>
</tr>
<tr>
<td>VSI Duration/unstable</td>
<td>151 min/pt</td>
<td>5.6 min/pt</td>
</tr>
<tr>
<td>VSI Episodes/unstable</td>
<td>12.9 /pt</td>
<td>6.5 /pt</td>
</tr>
<tr>
<td>MET but no VSI</td>
<td>359</td>
<td>378</td>
</tr>
<tr>
<td>MET but no VSI duration</td>
<td>6343 min</td>
<td>3652 min</td>
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Total duration 18,600 hr = 1,116,000 min = 0.3% false negatives

Using Neuronet Modeling to Look into the Future

- Using the VSI fusion parameter to quantify instability
- Compared blinded 8 week data collection (Phase 1) with 8 week nurse alerted monitoring (Phase 3)
  - To identify Medical Emergency Team (MET) need
  - To reduce time and incidence of instability
- $V_{SI_{\text{min}}}$ occurred before $MET_{\text{min}}$ 80% of the time with a mean advance time $9.4 \pm 9.2$ minutes and correlated well ($r=0.815, p < 0.001$)
- $V_{SI_{\text{full}}}$ occurred $6.4 \pm 1.5$h before CODE called


Implications

Does care improve?

Much smaller % of patients progressed from $MET_{\text{min}}$ to $MET_{\text{full}}$ in Phase 3, suggesting that instability was presumably addressed earlier before it progressed

In Phase 1, only 17% of patients with $MET_{\text{full}}$ had a MET Activation, this increased to 61% Phase 3.

Suggests that although fewer patients progressed to $MET_{\text{full}}$, those who did were more likely to have a Condition called

Limitations

The OBS Visensia monitor reports point-in-time status. The monitor displays trends but does not use these data in calculations

The VSI signal needs to be calibrated for each patient subgroup and is dependent of the vital sign input parameters

If data are collected at differing intervals the reliability of the predictive model degrades

Need a predictive tool to identify deterioration before overt cardio-respiratory failure develops

Health and Disease Defined as a Time-Space Continuum

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- In a dynamic field of continuously changing but inter-related variables, health and disease can be defined by the differences their Lorenz Attractors ($\rho$) and dynamical analysis independent of the actual physiological variable raw values
Natural Non-Linear Systems

Predicting Behavior: What things do and When
- The existing state is highly dependent of initial condition
  - The Butterfly effect
- How things interact
  - Deterministic
    - Periodic
    - Chaotic
  - Non-deterministic
    - Random

Population Phase Portraits for the Individual-Based Predator-Prey System

Plant Population
Herbivore Population
Carnivore Population

Solving common Solutions for Three Variables: Plants, Herbivores, Carnivores

Dependence on the Initial State

Initial states differ by only 1^-5 in x value. Difference starts at t=23 and by t=30
The two trajectories vary by as much as their limits allow

Improving Diagnosis Using Two Separate Complexity Modeling Approaches
- Complexity modeling of phase-time planes (p)
  - Define the relation between physiological variables as either healthy or not
  - Identifies the “value” of adding additional measures (monitoring) or extending lead time
    - Shlomo Ta’asan, Carnegie Mellon University
    - Gilles Clermont, University of Pittsburgh
- Linguistic modeling to define Biosignatures
  - Pattern recognition of transitions from health to disease
    - John Hotchkiss, University of Pittsburgh
Can Complexity Modeling Define Health and Disease in Phase Space?

Mathematical Solution to Defining Health and Disease in a Time-Physiological Variable Space

- Essential elements in defining state are
  - Lorenz attractor ($\rho$) location
  - Degree of variance of measured variables ($\beta$)
  - Number of variables measured over time
- Of less importance in defining state are
  - Accuracy of exact measured variables
  - Absolute value of any variable within “viability”

The Attractor and its Measure

The biologically significant quantity is the measure satisfying the equation

$$\text{div}(V(x, \alpha) \rho) - \sigma \Delta \rho = 0$$

$p(x)dx$ represent the fraction of time the trajectory spend in a small volume around $x$

Defining Physiological State

- By understanding how to characterize $\rho$ one can define the number of determinants and the duration and frequency of observation needed to characterize a state
- Health would then be defined as a series of $\rho^*$ considered by prior observation to be “good”
- Disease would then be defined as any $\rho$ not within the boundaries of any $\rho^*$

Defining Disease as $\rho$ to $\rho^*$ Distance

- Trend monitoring of inter-related variables is essential to define $\rho$
- Depending of the specific disease state, nature of the true variance ($\beta$) and error ($\sigma$) in measures, additional specific measures may be needed to increase the accuracy of estimating $\rho$
- The Wasserstein Distance ($W$) between $\rho$ and $\rho^*$

Implications for Diagnosis of Disease
Implications for Management of Disease Based on Complexity Modeling

- Experience reports that some $\rho$ are "good" in that they characterize healthy people
- Some regions in the phase space are "bad" in that they are seen with known shock states
- Biological parameters are implicit in $V(x,\alpha)$
- Thus treatment reduces to a control problem $E(\alpha) = d_{\rho^*}^2(\rho(\sigma),\rho^*)$
- Minimization of the distance between $\rho(\sigma)$ and $\rho^*$
  Conceptually, this method places within linear thinking non-linear relations

Pinsky, Crit Care Med 38:5649-55, 2010

Improving Predictions of Behavior

- Increase the duration of measured time to define chaotic behavior
  - The VSI analysis required >90 minutes to define state accurately enough to be diagnostic under most conditions
- Increase the number of measures of relevant independent variables

Pinsky, Crit Care Med 38:5649-55, 2010

System Identification Driving Questions

- How complex is the response?
  - How many variables are needed?
  - How complex is the dynamics?
- How to control it?
  - Which interventions are most effective?
  - How to apply these interventions?
  Very different from traditional approaches because it assumes no primary biological knowledge

Identifying Hemodynamically Unstable Patients

- What is the minimal data set needed to predict instability: Monitoring parsimony
  - Number of independent monitoring variable
  - Lead time
  - Sampling frequency
- What additional information will improve specificity
- Monitoring response to therapy and define end-points of resuscitation

Identifying Hemodynamically Unstable Patients

- Phase One currently available
  - Modified application of VSI input to identify better who is sick now or about to be sick
- Phase Two coming soon to a health information system near you
  - Complexity Modeling of Health and Disease
  - Identify the dynamical expression of hemodynamic stability, instability and recovery
  - Define the Architecture of instability
  - Clarify the true Picture of health
Future of Monitoring

- **Monitor the monitors**
- Scaling of monitoring devices and sampling frequency as patient specifics define
- Looking at monitors or intermittent direct patient observation unlikely to improve instability detection but very likely to increase its undetection