RUNNING ON EMPTY?
THE COMPENSATORY RESERVE INDEX

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Disclosures

• Co-inventor
  – All IP assigned to Regents of the University of Colorado

• Consultant at Flashback Technologies, Inc.
  – Co-founder; licensed technology from CU; CU start-up

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Technology under discussion is not approved by the FDA
Introduction

• Acute hemorrhage
  – Cascade of physiological responses
  – Wide array of cardiopulmonary changes
  – Many changes can be measured

• Hypotension
  – Beginning of circulatory compromise?
  – Signals the onset of decompensation

• Definition
  – “Compensatory phase” of acute volume loss extends from normovolemia to decompensation
Compensatory Reserve Index (CRI)

Normovolemic

"Compensatory Phase" of Acute Volume Loss

Point of Decompensation (Class III Shock)

Death

CR = Compensatory Reserve

DR = De-compensatory Reserve

Time
Background

Machine learning algorithms developed under DARPA* program “Learning Applied to Ground Robots” (LAGR)

Background

• Machine Learning

• Subfield of artificial intelligence
  – Design and development of algorithms and techniques that allow computers to “learn”
  – Extract information from massive data sets using computational and statistical methods
    • Expose hidden relationships in data
    • Build predictive models of the condition
    • Determine the accuracy of the models
    • No human intervention is needed!
Background

• Autonomous robot navigation
  – Identify safe, navigable terrain
  – Smooth trajectories
  – Tight integration of learning platform + memory
  – Navigation algorithms grew increasingly more accurate with greater experience in the field

• Similar problem in medicine
  – Rely on experience to “know” clinical trajectory
  – Anticipate patient needs
  – Intervene early when physiology less complex
Hypotheses

State-of-the-art feature extraction and machine learning techniques can:

1) Reveal subtle waveform features that trend and correspond with the compensatory phase of central volume loss (hemorrhage)

2) Learn to **identify and track** pt. types
   - Low tolerant versus high tolerant
   - Before any significant change in vital signs
LBNP Model of Blood Loss

• Ethical constraints limit human modeling

• Lower body negative pressure (LBNP)
  – Simulate significant human hemorrhage
  – Healthy males and females, 18 – 55 years old
  – Lower body in LBNP chamber
  – Stepwise decompression at:
    - -15, -30, -45, -60, -70, -80, -90, -100 mmHg
  – Waveform data collected at 500 Hz
  – > 200 LBNP experiments have been performed
Stop experiment for:
- Grey out
- SBP < 80 mmHg
- Completion of -100 mmHg level
  or
- Voluntary Subject termination
Initial Data Analysis

• Do vital sign waveforms from LBNP subjects contain info on physiology of compensation?
  – Which features of waveforms important?
  – Some more important than others?
  – More important at different levels of volume loss?

**Feature extraction**: dimensionality reduction

**Machine learning**: extract information

Unbiased analytical tools worked independently in an iterative fashion, analyzing thousands of features within each waveform
Initial Data Analysis

• In 2008 used archived LBNP data from 28 subjects:
  – Built models using 27 subjects, tested on 28th
  – Repeated process 28 times

• First model:
  – Investigated cNIBP, pulse ox and IPG waveforms
  – Chose continuous non-invasive BP waveform data
  – Sample size = 64 beats (now 30 beats)
  – New prediction made w/ each subsequent beat

• Initial Results:
  – Estimated vs. actual LBNP = 0.96
  – Predicted vs. actual LBNP at CV collapse = .89
Results

First Naïve Subject

Low Tolerant (-45 mmHg)

- Need more training data
- Need to look at shape of entire waveform to maximize computational model accuracy
Mean square difference between actual and estimated CRI is 0.032 (130 subjects)

Every patient collapses at a different time, volume of blood loss or LBNP
High Tolerant vs. Low Tolerant

- **High tolerant subjects have greater elevation in HR**
  - Greater vagal withdrawal vs. higher sympathetic n. activity
  - Greater oscillations in arterial blood pressure

**Low Tolerant** (max LBNP = -30 mmHg)

- Av. SBP = 116 mmHg, DBP = 70 mmHg, MAP = 87 mmHg

**High Tolerant** (max LBNP = -80 mmHg)

- Av. SBP = 104 mmHg, DBP = 83 mmHg, MAP = 91 mmHg

Feature extraction and advanced statistical methods can detect subtle beat-to-beat changes; humans cannot.

Compensatory Reserve Index (CRI) in 2010 - 11

- CRI Scale 0 to 1
  - 1: Normovolemic
  - 0: CV collapse point

- 30 sec initialization, then outputs CRI with every beat

- > 95% accurate when applied at any stage of bleeding or volume loss

- Real-time implementation tested at USAISR in July 2011
  - PPG and cNIBP versions
Results from 184 LBNP Studies Using cNIBP

- **Red Line:** Reference CRI
- **Green Line:** CRI Monitor Output

- **Low tolerance to reduced central volume**
- **High tolerance to reduced central volume**
Results from 184 LBNP Studies Using cNIBP

- Correlation between reference CRI (red) and the CRI monitor output (green) is $r^2 = 0.94$

- Mean absolute difference between reference CRI (red) and the CRI monitor output (green) is 0.1 with std. dev. of 0.09

- For all 184, the CRI monitor output fell below 0.3 before the subject entered presyncope
  - Signaling presyncope before it occurred
Ethical constraints limit modeling severe human blood loss

Direct comparisons between LBNP and human hemorrhage are not possible

Models based on healthy subjects 18 - 55 years old

Might injury/pain alter waveform features?

Striking similarity between physiologic responses to LBNP and severe hemorrhage
Limitations

- MAP and Stroke volume (SV) are early indicators of blood loss\(^1\)
- MAP and stroke volume (SV) are key variables to target during resuscitation\(^2,3\)
- To validate LBNP as a model of human hemorrhage
  – Compared changes in SV in 14 adult male baboons (hemorrhage versus LBNP)\(^4\)

\(^3\)Sinclair S, et al. BMJ. 1997;315:909-912
\(^4\)Convertino et al. Unpublished data.
True Hemorrhage versus LBNP

Adult Male Baboons
- N = 14
- Age: 11 ± 0.5 years
- Weight: 32 ± 2 kg
- Blood Volume: 71 ml/kg
- Ketamine/Valium sedation

Lead II ECG:
- Heart Rate

Vascular Catheters
- Arterial Blood Pressure
- Central Venous

Hemorrhage Procedure

Total 25% Hemorrhage  4 steps (7 min/step)

LBNP Procedure

Set LBNP to match CVP and/or PP during previous hemorrhage steps
17.8/71 ml/kg = 25% blood volume loss
Use cNIBP or PPG Waveforms

- Applied modeling technique to pulse ox PPG
- CRI accuracy results for 30 HT/LT
- CRI models for both pulse oximeters are similarly accurate
- CRI accuracy ± 0.1 w/ std. dev. 0.09
Genesis of the Concept: Compensatory Reserve Index (CRI)

2009

2010

2011

2012

2013
Case

15 y/o M unhelmeted bicyclist vs auto, dragged 250 ft

- Transported to OSH
  - 15:22: RR 18 HR 120 BP 147/82 100% sat
  - 15:30: CT head, chest, abd/pelvis
  - 16:41: Cystogram, left shoulder and knee films

- Injuries identified:
  - Lt pulmonary contusions w/ small apical PTX
  - Lt humerus fx w/ Lt brachial plexus inj, open Rt AC joint w/ scapula fx
  - Rt sup/inf pubic rami fxs; bilat obturator ring fxs; widening Lt SI joint
  - Pelvic hematoma; trace free fluid in peritoneal cavity
  - Hematuria, no urinary extravasation on cystogram
  - Extensive road rash, multiple deep lacerations to fascia and bone

- Received IV Fentanyl x 6 and 4 liters IV crystalloid
  - 19:00: T 96.9 P 128 BP 106/59 RR 16

- Transferred to CHCO
Case

• Arrives CHCO at 19:52 w/ O2 by mask on BB w/ c-collar, bilateral PIVs, Lt arm splint and foley
  – Vitals: T 35.6  RR 20  P 146  BP 99/61
  – O/E: pale, extensive road rash, normal BS, RRR w/ delayed cap refill (3 sec) and diminished distal pulses, flat abdomen, tender pelvis, open left AC, GCS=15

• Labs
  – FAST exam negative
  – VBG pH=7.14  pCO₂=65  pO₂=26  HCO₃=23  BD= -6
  – Hgb/Hct = 8.6/25.5
  – All OSH films reviewed
  – X-rays: Rt shoulder, Rt elbow, Rt hand, Lt knee
Case

• Patient persistently tachycardic
  – Attributed to pain
  – Dilutional anemia

• 23:04: Arrives in OR
  – Irrigation and closure open left AC joint
  – Cleanse and dress multiple deep abrasions
  – Close multiple facial and extremity lacerations
  – Discussed CVC placement; decided against
  – **Total ED + OR fluids = 1200 ml’s nl saline**

• 0148: Arrives in PICU
Case

- 05:30: Patient weaned to room air
- 08:00: Nurse charts “tender abd, decreased BS”
  - Abdominal pain attributed to road rash (“CT negative”)
  - PCA ordered
- 11:00: CT face per ENT request
- 14:00: Urine output falls
- 20:00: Patient c/o abdominal pain
  - Abdomen firm, tender, distended
  - Rising base deficit (-7.3)
  - Senior surgical resident informed; no changes
Case

• 22:45: Copious bloody emesis
• 22:51: HR 39  O₂ sat. 70%
  – Patient unresponsive
• **22:52:** Code called
  – BVM ventilation
• 22:58: Unable to get pulse ox reading
• 23:10: ETT; HR 108  BP 154/122  O₂ sat. 83
• 23:30: HR 155  BP 86/59
Post-intubation CXR

- To OR for Ex-lap
  - Gross contamination, two jejunal perforations
  - Resected 20 cm SB, jejunojejunostomy, washout
CRI vs Time

4000 mL @ OSH, 1200 ml in ED/OR
No pulse ox recorded

BD -10.2
Hct 23

BD -4.5
Hct 21

BD -5.6

BD -7.3

BD -11.2
Hct 18

Intubated
BVM/RRT
Pressors

Suctioning?

1 Liter LR
MIVF 90 ml/hr
220 ml PRBCs
500 ml NS
450 ml LR
500 ml NS

IVF

SBP
DBP
HR
UOP

ml/Kg/hr UOP

0 0.5 1 1.5 2 2.5 3

0 50 100 150 200 250 300
How It Works

• Computational engine constructs models
  – Autonomously identifies relevant information in data
  – Autonomously identifies clean data
  – Efficiently builds models from **VERY LARGE** data sets
    • Terabytes of waveform data can be analyzed in a few days
    • 1 terabyte is 1000000000000 bytes, or 1 trillion bytes
    • 1 terabyte of audio recorded at CD quality = 2,000 hrs of audio

• Models
  – Only predict/estimate/control when vital signs are valid
  – Identify what is *new* versus *not known*

• Learning algorithm
Many thousands of features may be extracted from a single waveform.

Feature selection algorithms:
- Construct linear regression models:
  \[ \text{prediction} = \sum_{j=1}^{d} a_j x_j + a_0 \]
- Construct nonlinear density models:
  \[ \Pr(H_2 \leq H \leq H_1) = f(s_1, \ldots, s_k) \]

Example: \( \text{SpO}_2 \) waveform
- Pulse height (amplitude), width and area under the curve (AUC)

Sample waveform data at 500 Hz (500 times/sec)

Extract 1000’s of features from every waveform; find the most estimative or predictive of events and compare/time.
Beat-to-Beat CRI Estimate

CRI Model + Library of Waveform Features

Features CRI=1

Features CRI=0.5

Features CRI=0

Input 30 noninvasive PPG waveforms

This process takes 28 milliseconds and follows each heartbeat

How It Works

Beat-to-Beat CRI Estimate
Ongoing/Pending Clinical Trials

- Blood Bank Study at CHCO
  - Verification of CRI w/ low volume (500ml) blood loss
- Hemodialysis
  - CRI tracks volume loss to dry weight
- Dengue shock syndrome
  - Diagnosis of volume loss and monitoring fluid resuscitation in children
    - Queen Sirikit National Institute of Child Health, Bangkok, Thailand
- Mayo human blood loss study
  - Validate CRI for larger volume blood loss (1000ml)
- CRI in trauma setting
  - Denver Health, CHCO and San Antonio Military Medical Center (BAMC)
- Acute appendicitis at CHCO
- Sepsis in children at CHCO
- Intra-operative at CHCO
  - Children w/ and w/o congenital heart disease
- Major burns at CHCO and University Hospital
- Dehydration
  - USAISR and Boulder athletes
CRI During Blood Donation

CRI is NOT absolute volume loss:
CRI is a measure of compensation for volume loss.
CRI 90% Accurate Detecting 500 ml Blood Loss: Drop is Subject Specific

90 +/- 4 percent detection at alpha 0.05
Dengue Shock Syndrome

7 year old male with DSS

Treatment begins 27-Jul-2011

Blood transfusion on 29-Jul-2011

Accurately detects volume loss; tracks recovery.
Early results suggest CRI is applicable in children
Preliminary Dehydration Data

CRI Before Exercise (Dehydration)

CRI After Exercise (Dehydration – 700ml of fluids lost during a 44 min jog in 86F weather):

CRI During Rehydration

Fluid Intake Profile During Rehydration
Summary

• Applying advanced, feature extraction and state-of-the-art machine-based data modeling strategies to continuous, physiological waveform data

• Finding hidden features within the waveform data, indicative of real-time changes in the physiology of various organ systems

• Fundamentally change vital sign monitoring
  – Current monitors are “dumb”
  – Future monitors will interpret raw waveform data
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Questions?