# ICCAI 2012

11th International Conference on Complexity in Acute Illness

## Ottawa, Ontario

## Canada

## September 6-9th 2012

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Dear ICCAI attendees,

As the chair of the 11th annual International Conference on Complexity in Acute Illness (ICCAI), I would like to welcome you all to Ottawa, Canada's capital city. We welcome many new attendees to the ICCAI this year, and hope that this will lead to insightful discussion throughout the meeting.

The theme of this year's meeting, "quantitative, innovative, transdisciplinary, and clinically relevant research" focuses on ground breaking research from leaders in the field of complexity and acute illness. The meeting will highlight research focused on innovative quantitative methods that make use of high-fidelity bedside monitoring, as well as advanced mathematical modeling, both applying the paradigm and technologies derived from complexity science for the benefit of patients at the bedside. We welcome speakers from around the world to this meeting, and hope that you all enjoy the variety of perspectives to be presented here in the next four days.

This year's ICCAI involves a special focus on attendee interaction and live feedback through the app created specifically for the meeting (for use on smartphones and computers). I am excited to see the results of this new method of feedback and participation. It is our objective that the interactive technology used in this meeting will promote discussion and networking among attendees. I hope that this meeting will be instructive, and thought-provoking and that you will leave here with new insights and connections.

There are several groups I would like to thank, for their efforts and contributions to this year's meeting. Thank you to all of our sponsors for supporting the ICCAI. This meeting would not be possible without your support. Thank you to the J*ournal of Critical Care* for their continued support of ICCAI through abstract publication.

I am very grateful to the ICCAI 2012 organizing committee for their suggestions, feedback, and assistance in planning this meeting. I would also like to thank the "CKaitlyins" for dedicating much of their time to make this meeting a success. Thank you to Kaitlyn Chambers, our meeting coordinator for her organization, communication, and for ensuring all of you have breakfast and coffee breaks throughout the meeting. Thank you to Caitlin Anstee for her creativity and talent in developing the ICCAI 2012 website and the innovative app to be used in this meeting.

I would also like to acknowledge those of you who submitted an abstract to this year's ICCAI. It is always exciting to have new research presented, and I am impressed by the high-quality of abstracts and podium presentations this year.

Whether this is your first ICCAI meeting, or you have attended in the past, I would like to welcome you all to Ottawa for great discussion and sharing of perspectives among new and old friends.

Warm regards,

**Andrew JE Seely**
**Chair, ICCAI 2012**

Dear ICCAI participants,

On behalf of the Society for Complexity in Acute Illness (SCAI), I would like to extend my warm welcome to all of the attendees of the 11th International Conference on Complexity in Acute Illness (ICCAI). I thank all of our sponsors as well as the Journal of Critical Care for their support; we could not put on the ICCAI or expand our reach as we have in the past decade without you. Our Society is the only one dedicated to the application of complex systems methods to the direct, urgent needs of critical care while also fostering novel basic and pre-clinical studies. This year's meeting continues our tradition of presenting cutting-edge interdisciplinary research from both academia and industry. This meeting promises to be wide-ranging in both scope of material and methods of presentation, including for the first time an extensive social networking / online component which we hope you will find innovative and engaging. In this spirit of interaction, I welcome both old friends and new attendees to Ottawa, Canada.

**Yoram Vodovotz**
**President, Society for Complexity in Acute Illness**

Dear attendees of ICCAI 2012,

It gives me great pleasure to welcome you all to Ottawa on behalf of the Ottawa Hospital Research Institute (OHRI) and our local health sciences community. Over the next few days, I look forward to hearing about all the exciting research taking place in this area of complexity related to acute illness. It's impressive to see such a large number of international participants who share in the overarching goal of improving patient care at the bedside; a simple ambition with a complex path. It is my hope that we can make progress through gatherings like this one, which provides a unique opportunity to share new insights and foster new collaborations here in Ottawa and around the world. I look forward to the discussions over the coming days and hope to connect with many of you during the course of the conference.

Given the ambitious and wide-ranging program, I also hope you manage to find a bit of time to enjoy Canada's capital city.

Dr. Duncan J. Stewart
CEO and Scientific Director, Ottawa Hospital Research Institute

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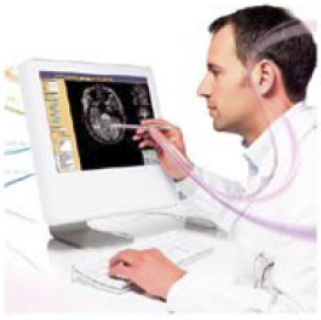


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# PROGRAM OF EVENTS

| Thursday September 6th 2012 | | | | |
|---|---|---|---|---|
| **Presentation section** | **Speaker** | **Title** | **Start** | **End** |
| **Workshop 1** Part 1 | A. Seely & A. Batchinsky | Experiments in variability analysis over time | 10:00 | 12:00 |
| **Workshop 1** Part 2 | J. Doyle | Modeling and analytical tools for physiological data | 10:00 | 12:00 |
| **Lunch** | | | 12:00 | 13:00 |
| **Workshop 2** Part 1 | S. Zenker | Creating mathematical models for biomedical scenarios: from model design to model application | 13:00 | 15:00 |
| **Workshop 2** Part 2 | A. Johnson | Machine learning methods for clinical prediction systems: understanding and extracting clinical relevance | 13:00 | 15:00 |
| **Break** | | | 15:00 | 15:30 |
| **Session 1** Welcome and introduction Chairs: A. Seely | A. Seely | Welcome | 15:30 | 15:45 |
| | D. Stewart | OHRI Welcome | 15:45 | 16:00 |
| | Y. Vodovotz | SCAI Welcome | 16:00 | 16:15 |
| | C. Neylon | Plenary: Open access networked science | 16:15 | 17:00 |
| | | **Discussion** | 17:00 | 17:30 |
| **Coffee** | | | 17:30 | 18:00 |
| **Session 2** Insights in Complexity and Health Care Chairs: C. Arce | C. Lindberg | Embracing Uncertainty: Complexity inspired innovations at Billings Clinic | 18:00 | 18:20 |
| | J. Scott | Healing relationships as an emergent pattern of complex responsive processes of relating | 18:20 | 18:40 |
| | T. Buchman | Value-based restructuring of the critical care workforce | 18:40 | 19:00 |
| | | **Discussion** | 19:00 | 19:30 |
| **Break** | | | 19:30 | 20:00 |
| **Speakers' and sponsors' welcome dinner** | | | 20:00 | 22:00 |

# Friday September 7th 2012

| Presentation section | Speaker | Title | Start | End |
|---|---|---|---|---|
| **Breakfast** | | | 7:00 | 7:30 |
| **Session 3**<br><br>Mechanistic Models in Vivo and in Silico<br><br>Chairs: J. Day & S. Zenker | Y. Vodovotz | Measurement, modeling, and modulation of the inflammatory response in shock states | 7:30 | 7:50 |
| | C. DosSantos | Application of Microarray meta-analysis in the identification of Clinically Relevant Acute Lung Injury Gene Expression Profiles | 7:50 | 8:10 |
| | C. Ziraldo | Abstract podium : A computational tissue-realistic model of pressure ulcer formation in spinal cord injury patients | 8:10 | 8:30 |
| | F. Jacono | Insights into central mechanisms responsible for breathing pattern changes following acute lung injury | 8:30 | 8:50 |
| | S. Hollenberg | Bench to bedside and back again : Non-linear hemodynamics in the lab and the ICU | 8:50 | 9:10 |
| | | **Discussion** | 9:10 | 9:40 |
| **Coffee Break and Poster Session 1** | | | 9:40 | 10:10 |
| **Session 4**<br><br>Transdisciplinary Exploration of Complexity<br><br>Chairs: A. Longtin & G. Kenny | M.E. Harper | Plasticity of mitochondrial energetics: Cellular and whole body implications | 10:10 | 10:30 |
| | W. Haddad | Multi-stability, bifurcations, and biological neural networks | 10:30 | 10:50 |
| | H. Mattila | Building healthier and more productive honey bee colonies through complexity | 10:50 | 11:10 |
| | R. Lorenz | The principle of maximum entropy production | 11:10 | 11:30 |
| | C. Arce | **Discussion, feedback, and questionnaire** | 11:30 | 12:00 |
| **Poster session 2** | | | 12:00 | 12:30 |
| **Lunch and break** | | | 12:30 | 15:00 |
| **Poster Session 3** | | | 15:00 | 15:30 |
| **Session 5**<br><br>Origins of Complex Variability<br><br>Chairs: R. Moorman & A. Flower | J. Zebrowski | Complexity of sinus rhythm combined with arrhythmia | 15:30 | 15:50 |
| | N. Wessel | Cardiovascular physics: Assessment of autonomic tone around the operation theatre | 15:50 | 16:10 |
| | G. Baselli | Intra-operative monitoring of cardiovascular variability: From blood pressure waves to mathematical models of baroreflex function | 16:10 | 16:30 |
| | M. Soehle | Abstract podium : Intracranial hypertension following head injury is associated with a loss of ICP-complexity | 16:30 | 16:50 |
| | M. Petelczyc | Randomness, determinism, and complexity of heart rate variability : Measurement and description based on stochastic analysis | 16:50 | 17:10 |
| | | **Discussion** | 17:10 | 17:40 |
| **Coffee Break and Poster Session 4** | | | 17:40 | 18:10 |
| **Session 6**<br><br>Redefining the characterization and treatment of acute illness<br><br>Chairs: T. Buchman | M. Cohen / A. Menezes | Modeling Coagulation Activation in Trauma Patients | 18:10 | 18:30 |
| | G.An | Abstract podium: Examination of differential fitness domains and a paradoxical effect of antibiotic culling with an agent-based model of evolutionary dynamics in host-microbe interactions | 18:30 | 18:50 |
| | M. Csete | Regenerative medicine in the ICU | 18:50 | 19:10 |
| | D. Stewart | Multi-tiered systems biology approach to pulmonary hypertension | 19:10 | 19:30 |
| | J. Marshall | Towards a stratification system for severe acute illness | 19:30 | 19:50 |
| | | **Discussion** | 19:50 | 20:20 |

# Saturday September 8th 2012

| Presentation section | Speaker | Title | Start | End |
|---|---|---|---|---|
| **ICCAI Run** | | | 6:30 | 7:30 |
| **Breakfast** | | | 7:30 | 8:00 |
| **Session 7**<br><br>Advanced Quantitative and Complexity Analysis<br><br>Chairs: S. Zenker | D. McNair | Non-invasive assessment of acute deterioration likelihood in in-patients | 8:00 | 8:20 |
| | G. An | The road to translation: Paved with knowledge rather than data | 8:20 | 8:40 |
| | A. Hubbard | A statistical roadmap for prediction and variable importance/causal inference in medical informatics | 8:40 | 9:00 |
| | D. McNair | **Discussion, feedback, and questionnaire** | 9:00 | 9:30 |
| **Coffee Break and Poster Session 5** | | | 9:30 | 10:00 |
| **Session 8**<br><br>Respiratory Failure & Ventilator-Human Interaction<br><br>Chairs: M. Cohen | A. Seely | Heart and respiratory variability monitoring in the ICU : Update from WAVE and other studies. | 10:00 | 10:20 |
| | S. Rees | Measurement of pulmonary gas exchange in the ICU | 10:20 | 10:40 |
| | A. Batchinsky | Monitoring signal- and systems-based cardiovascular and respiratory complexity during respiratory failure of different origin | 10:40 | 11:00 |
| | D. King | Abstract podium : Real-time heart rate complexity on hospital arrival predicts the need for life-saving intervention in trauma activation patients | 11:00 | 11:20 |
| | T. Buchman | **Discussion, feedback, and questionnaire** | 11:20 | 12:00 |
| **Poster Session 6** | | | 12:00 | 12:30 |
| **Lunch and break** | | | 12:30 | 15:00 |
| **Poster Session 7** | | | 15:00 | 15:30 |
| **Session 9**<br><br>Gathering & Analyzing High-Dimensional Data at the Bedside<br><br>Chairs: M. Csete | J. Salinas | Development of a prospective study using the wireless vital signs monitor for capturing heart rate complexity and variability in trauma patients | 15:30 | 15:50 |
| | D. Sow | Exploration in intensive care | 15:50 | 16:10 |
| | Y. Vodovotz & M.Csete | **Panel discussion : Data collection challenges** | 16:10 | 17:30 |
| **Coffee Break and Poster Session 8** | | | 17:30 | 18:00 |
| **Session 10**<br><br>Network Structure in Complex Systems<br><br>Chairs: B. Suki | B. Suki | Variable stretch patterns alter mitochondrial network formation and ATP supply in cells | 18:00 | 18:20 |
| | J. Doyle | What are power laws really telling us? | 18:20 | 18:40 |
| | J. Bates | Complex disease as an aberrant network phenomenon | 18:40 | 19:00 |
| | | **Discussion** | 19:00 | 19:30 |
| **Break** | | | 19:30 | 20:00 |
| **Gala dinner** | | | 20:00 | 22:00 |

| Sunday September 9th 2012 | | | | |
|---|---|---|---|---|
| **Presentation section** | **Speaker** | **Title** | **Start** | **End** |
| **Breakfast & ICCAI Business Meeting** | | | 7:00 | 8:30 |
| **Session 11**<br><br>Variability Monitoring at the Bedside<br><br>Chairs: A. Batchinsky | R. Moorman | Predictive monitoring for subacute potentially catastrophic illnesses in adults | 8:30 | 8:50 |
| | L. Cancio | New ways of envisioning critical care medicine : recent progress | 8:50 | 9:10 |
| | R. Arnold | Differentiating sepsis and predicting disease progression in the emergency department using heart rate variability | 9:10 | 9:30 |
| | M. Frasch | Abstract podium: The timing and degree of fetal systemic and cerebral inflammatory responses correlate with a subset of heart rate variability measures: Evidence of cholinergic anti-inflammatory pathway activation in sepsis | 9:30 | 9:50 |
| | | **Discussion** | 9:50 | 10:20 |
| **Coffee** | | | 10:20 | 10:50 |
| **Session 12**<br><br>Future Challenges and Feedback<br><br>Chairs: A. Seely & E. Neugebauer | A. Seely | Review of feedback and ICCAI Awards | 10:50 | 11:20 |
| | Open discussion | Unanswered questions/Future challenges | 11:20 | 12:30 |

## Invited Speakers

**Gary An, MD**

**Talk title:** *The road to translation: Paved with knowledge rather than data*

Dr. Gary An is a graduate of the University of Miami, Florida School of Medicine, and did his surgical residency at Cook County Hospital/University of Illinois, Chicago. He is currently an Associate Professor of Surgery at the University of Chicago, and is the Co-director of the Surgical Intensive Care Unit. He previously worked as a Trauma Surgeon at Cook County Hospital from 1997 to 2003, was the Director of the Burn Intensive Care Unit at Cook County Hospital from 2003-2006, and was a Trauma/Critical Care Surgeon at Northwestern Memorial Hospital in Chicago, IL from 2006 to July of 2010. He has worked on the application of complex systems analysis to sepsis and inflammation since 1999, using primarily agent based modeling to create mechanistic models of various aspects of the acute inflammatory response. He is a founding member of the Society of Complexity in Acute Illness (SCAI). He is a faculty member of the Center for Inflammation and Regenerative Modeling at the McGowan Institute of Regenerative Medicine at the University of Pittsburgh. He is very active in the agent based modeling community, participating in the Swarm simulation community since 1999. He is the current president of the Swarm Development Group, and was the host of the Group's annual meetings from 2008-2011. He is currently working on the use of agent-based models as a means of dynamic knowledge representation to integrate multiple scales of biological phenomenon. His research involves bioinformatics/ontology development to facilitate mechanism-based computer simulation/agent-based modeling, investigation of mathematical descriptions of fundamental aspects of biological systems and high-performance/parallel computing architectures for agent-based models.

**Carlos Arce, M. Ed**

**Talk title:** *Discussion facilitator*

Carlos R. Arce is the Chief Learning Officer at Billings Clinic - a non-profit multi-specialty clinic practice based in Billings, Montana. In his role he has contributed to the national recognition Billings Clinic has received in areas of service, quality, and safety.

With an extensive background in both process improvement and education, Carlos has worked with organizations throughout North America successfully developing and implementing leadership and learning strategies aimed at improving organizational efficiency, customer and patient satisfaction and employee engagement.

Carlos holds a Bachelors of Political Science Degree from Santa Clara University and a Masters in Education from the University of California, Los Angeles. He has facilitated both undergraduate and graduate courses in management, certificate programs in quality management and team problem solving, and has served as an Athletic Head Coach in the NCAA. He is a student of Complex Systems Theory and its application within healthcare and leadership development.

**Ryan Arnold, MD**
**Talk title:** *Differentiating sepsis and predicting disease progression in the emergency department using heart rate variability*

**Giuseppe Baselli, M.Sc**

**Talk title:** *Intra-operative monitoring of cardiovascular variability: From blood pressure waves to mathematical models of baroreflex function*

Giuseppe Baselli, MSc, Milano 1958, achieved his degree in Electronic Engineering at the Politecnico di Milano cum laude, in 1983, with a thesis on parametric spectral analysis of heart rate variability. Since 1986 was assistant professor at the Università di Brescia. Since 1998 was associate professor at Politecnico di Milano, Bioengineering Department; full professor since 2001. He was chair of the Biomedical Engineering program (2004- 2009). Since 2010 he is head of the Department of Bioengineering member of the Academic Senate. His teaching activity is in the fields of bioengineering for physiological control systems and neurosensory systems, biomedical signal processing and modeling, advanced medical imaging. His research interests are in the field of biomedical signal processing and in its relationships with the linear and non-linear modeling of cardiovascular regulation, image reconstruction in oncology, molecular imaging and neuro-imaging.

**Andriy Batchinksy, MD**

**Talk title:** *Monitoring signal- and systems-based cardiovascular and respiratory complexity during respiratory failure of different origin*

Dr. Batchinsky is a general surgeon who received his M.D. degree from Uzhgorod State University in the Ukraine. He completed his general surgery specialty training in the Lviv State Medical Institute Faculty for Postgraduate Education and worked as a staff surgeon in the Uzhgorod Municipal Clinical Hospital rendering general surgery as well as emergency/trauma surgery services. In addition to his general surgical practice, he completed cardiac pacing and endoscopic specializations.

Since 2001, Dr. Batchinsky works at the U.S. Army Institute of Surgical Research and at present is a senior research scientist at the Combat Critical Care Engineering Task Area within the USA ISR. He leads a transdisciplinary research team engaged in clinical and laboratory research.

Dr. Batchinsky pioneered application of nonlinear analysis techniques to investigation of cardiovascular regulatory complexity during hemorrhagic shock, burn shock and resuscitation, combined trauma animal models, as well as for non-invasive assessment of trauma patients. He is currently developing real-time signal-level (heart rate complexity sampled from EKG), as well as systems level (cumulative assessment of all sensor and monitor data from subjects), monitoring tools for assessment of changes in the state of the critically injured. His other research interests are cardiovascular and pulmonary physiology as applicable to trauma, hemorrhagic shock, lung injury and acute respiratory distress syndrome and other critical states. Dr. Batchinsky has a special interest in minimally invasive

extracorporeal life-support systems for treatment of lung failure and multiorgan failure. Dr. Batchinsky is a reviewer for multiple scientific journals and a member of the Society for Experimental Biology in Medicine, American Physiologic Society, Shock Society, and Society for Critical Care Medicine. He is a member of the Board of Directors of the Society for Complexity in Acute Illness. Dr. Batchinsky has authored and co-authored multiple publications and peer-reviewed presentations featured both nationally and internationally.

**Jason H.T. Bates, PhD, DSc**

**Talk title:** *Complex disease as an aberrant network phenomenon*

Jason Bates has been at the University of Vermont since 1999, where he is currently a Professor of Medicine and the Interim Director of the School of Engineering. He spent the earlier part of his career at the Meakins-Christie Laboratories of McGill University, becoming Professor of Medicine and Biomedical Engineering. He has published over 220 papers focusing mostly in the area of lung physiology and biomechanics. Dr. Bates' interest in complex biomedical systems grew out of his research into how to link structure to function in the lung. These interests have recently expanded to include emergent behavior in cardiac electrophysiology as well as nonlinear network theory in general.

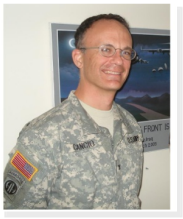
**Timothy G. Buchman, Ph.D., M.D., FACS, FCCM**

**Talk title:** *Value-based restructuring of the critical care workforce*

Tim Buchman joined Emory Healthcare in 2009. He graduated from the University of Chicago with degrees in chemistry, organic chemistry, virology and medicine. In 1980 he moved to Baltimore to join the Halsted surgical residency at John Hopkins. He went on to train in trauma and critical care in Baltimore's ShockTrauma Center at the University of Maryland. He returned to Hopkins in 1987 to join the faculties of Surgery, Molecular Biology and Emergency Medicine. In 1994, he was appointed to the Washington University in Saint Louis as the Edison Professor of Surgery, Professor of Anesthesiology and of Medicine. There, he formed and led the Section of Acute and Critical C are Surgery. While in Saint Louis, Dr. Buchman built the region's only nationally verified Level I trauma center.

Dr. Buchman is past President of the Society of Critical Care Medicine, the largest organization of critical care medicine professionals in the world. He is a Past President of the Society of Complexity in Acute Illness, and is currently President of the Shock Society. He was named one of Saint Louis "Top Doctors" 2005-2009, and one of Atlanta's "Best Doctors" 2010-2011. A member of Sigma Xi, Phi Beta Kappa and Alpha Omega Alpha, Dr. Buchman was named Teacher of the Year by the Senior Class of the Washington University School of Medicine and also by the surgical residents at Johns Hopkins and at Washington University.

Dr. Buchman's research activities include the genetic predisposition to sepsis, end-of-life care in the ICU, and the application of fundamental laws of biology to predictive medicine. His research is supported by NIH. He also holds Airline Transport Pilot and Flight Instructor certificates.



**Colonel Leopoldo C. Cancio, MD, FACS**

**Talk title:** *New ways of envisioning critical care medicine: recent progress*

Dr. Lee Cancio is a surgeon at the U.S. Army Institute of Surgical Research (Army Burn Center), Fort Sam Houston, Texas. He is a graduate of Amherst College, of Catholic University of America, and of Georgetown University School of Medicine. He completed a residency in General Surgery at Brooke Army Medical Center, and fellowships in Burns at the U.S. Army Institute of Surgical Research and in Surgical Critical Care at the National Trauma Institute, San Antonio, TX. He is board-certified in Surgery and Surgical Critical Care.

He served as a Regimental Surgeon during combat operations with the 82d Airborne Division in Panama (1989-90) and during the Gulf War in Iraq (1990-1). He deployed to Iraq 3 times during Operation Iraqi Freedom. His duties there included trauma and burn surgery, Deputy Commander for Clinical Services at the hospital in Baghdad, deployed Principal Investigator for the Special Operations Command protocol to investigate the Hemostatic Dressing, and Central Command Burns Consultant.

Dr. Cancio served as the Chief, Clinical Division (1998-2001) and as the Director of the Army Burn Center (2003-4). In 2006 he established Combat Critical Care Engineering, a research Task Area within the U.S. Army Medical Research and Materiel Command concerned with new vital signs, decision support, and extracorporeal life support. Dr. Cancio is a member of 13 academic societies including the Society for Complexity in Acute Illness. He is a Clinical Professor of Surgery at the University of Texas Health Science Center at San Antonio and is the author/coauthor of over 125 chapters and articles.

**Mitch Cohen, MD, FACS**

**Talk title:** *Modeling Coagulation Activation in Trauma Patients*

Dr. Cohen is an Associate Professor in the Department of Surgery, UCSF School of Medicine based primarily at San Francisco General Hospital. Additionally, he is the Director of Acute Care for the San Francisco Injury Center. After completing his undergraduate studies at Brandeis University, he attended Mt Sinai School of Medicine in New York. He completed his residency at Rush University/Cook County Hospital in Chicago and then came to San Francisco where he completed the Surgical Critical Care and Trauma Fellowships. Dr. Cohen is actively engaged in research on hypoperfusion and perturbations in coagulation and inflammation in trauma.

**Marie Csete, MD PhD**
**Talk title:** *Regenerative medicine in the ICU*

Marie Csete is the Division Director for Cell Therapy at AABB in Bethesda. She received her MD from Columbia University after undergraduate work at Princeton University in music. After residency training at Harvard and Tufts, she was on the faculty of the medical schools at UCSF, UCLA, and Michigan leading the liver transplant anesthesiology teams at those institutions. Her clinical research work focused on methods to optimize the perioperative care of liver transplant patients. Dr. Csete received a PhD in developmental biology from the California Institute of Technology, where she worked on the role of physiologic gases in stem cell fate. She extended this work into the study of stem cell aging as the John E. Steinhaus Professor of Anesthesiology at Emory University where she also directed the liver transplant anesthesia team and was co-Director of the MD/PhD Program and founding director of the Emory/GaTech Human Embryonic Stem Cell Core facility. Past positions also include Chief Scientific Officer of the California Institute for Regenerative Medicine, the state's stem cell agency, and significant industry/academic consulting experience in regenerative medicine. She is on the editorial boards of Stem Cells Translational Medicine, Anesthesia & Analgesia, and the Encyclopedia of Human Biology, several study sections, and is the holder of three U.S. patents. Dr. Csete is board certified in Anesthesiology and Critical Care and continues clinical work on the UCSD liver transplant team.

**Judy Day, PhD**

**Talk title:** *Session Chair*

Judy's primary research is focused on the development and analysis of mathematical models relating to the immune response to various stimuli and the application of control methodologies to modulate the immune response with therapeutic inputs. Her interests are motivated by the potential of mathematical and engineering techniques to assist in answering vital questions in the medical field. Her main objective is to conduct research within an interdisciplinary group to promote a symbiotic relationship among the various areas of expertise in hopes of acquiring results and developing tools of clinical relevance and academic significance.

Judy holds a joint appointment with the Department of Mathematics and the Electrical Engineering & Computer Science (EECS) Department at the University of Tennessee. She is currently collaborating with an EECS colleague on adaptive control methodologies to improve theoretical work aimed at determining optimal dosing strategies in critically ill patients. In addition, Judy is exploring strategies for modeling low dose chronic exposure to inhalation anthrax. This work is in collaboration with a team of researchers from diverse institutions (i.e. Academia, EPA, Battelle-PNNL) to determine how to best model this disease and integrate available data to inform response decisions in the event of a bio-terror attack.

**Claudia dos Santos, MD, M.Sc.**

**Claudia dos Santos, MD, M.Sc.**

**Talk title:** *Application of Microarray meta-analysis in the identification of Clinically Relevant Acute Lung Injury Gene Expression Profiles*

Claudia dos Santos is a scientist at the Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's hospital as well as a scientist and assistant professor at the University of Toronto. Her major research interest is acute lung injury. This can be caused by either biomolecular or biophysical insults to the lungs, such as an infection or the mechanical injury resulting from mechanical ventilation itself. Claudia's lab is dedicated to understanding the interaction between patients and the breathing machine and finding new ways to identify individuals, who are at higher risk for developing lung injury, diagnose, treat and monitor improvement from injury. To accomplish their goals, they have developed various model systems from basic epithelial cell stretch models to animal models of lung injury. They exploit whole genome approaches, such as microarray technology, to identify novel molecular targets and use various computational strategies to analyze our data. They are also interested in understanding how and why critically ill patients develop multi-organ failure. To answer some of the more complex questions Claudia's lab also collaborates actively with clinical researchers involved in state of the art clinical trials related to novel mechanical ventilation strategies.

**John Doyle, MS, PhD**

**Talk title:** *What are power laws really telling us?*

John Doyle is the John G Braun Professor of Control and Dynamical Systems, Electrical Engineer, and BioEngineering at Caltech. He has a BS and MS in EE, MIT (1977), and a PhD, Math, UC Berkeley (1984). Current research interests are in theoretical foundations for complex networks in engineering and biology, focusing on architecture, and for multiscale physics. Early work was in the mathematics of robust control, including extensions to nonlinear and networked systems. Related software projects include the Robust Control Toolbox (muTools), SOSTOOLS, SBML (Systems Biology Markup Language), and FAST (Fast AQM, Scalable TCP). Prize papers include IEEE Baker, IEEE Automatic Control Transactions Axelby (twice), and best conference papers in ACM Sigcomm and AACC American Control Conference. Individual awards include AACC Eckman, and IEEE Control Systems Field and Centennial Outstanding Young Engineer Awards. He has held national and world records and championships in various sports. He is best known for having excellent co-authors, students, friends, and colleagues.

**Abigail Flower, PhD**

**Talk title:** *Session Chair*

Abigail Acton Flower, Ph.D. received her B.S. in Physics in 1999 at the College of William and Mary, also receiving the Don E. Harrison Award for Excellence in Physics for the Class of 1999. From 1999 to 2001, she was an NSF Optics Fellow in the physics graduate program at State University of New York at Stony Brook, where she graduated with a Masters degree in physics. After this, Abigail was a researcher at the Kennedy Krieger Institute of Johns Hopkins Hospital, using functional MRI to study the neural function of autistic children when performing tasks involving the use of inhibition. In 2003, Abigail began her doctoral work at the University of Virginia as a student of J. Randall Moorman, M.D., studying heart rate variability in neonates. She received her doctorate in Biophysics in 2009. In 2010, Abigail was awarded the Andy Ford Award for Innovation in the Field of Pediatric Cardiovascular Disease from the University of Virginia School of Medicine. Abigail is currently a member of the research staff at Philips Research Briarcliff Manor, where her area of focus is clinical decision support in the intensive care unit.

**Wassim M. Haddad MS, PhD**

**Talk title:** *Multi-stability,* bifurcations, and biological neural networks

*Wassim M. Haddad received the B.S., M.S., and Ph.D. degrees in mechanical engineering from Florida Institute of Technology, Melbourne, FL in 1983, 1984, and 1987, respectively, with specialization in dynamical systems and control. From 1987 to 1994 he served as a consultant for the Structural Controls Group of the Government Aerospace Systems Division, Harris Corporation, Melbourne, FL. In 1988 he joined the faculty of the Mechanical and Aerospace Engineering Department at Florida Institute of Technology, where he founded and developed the Systems and Control Option within the graduate program. Since 1994 he has been a member of the faculty in the School of Aerospace Engineering at Georgia Institute of Technology where he holds the rank of Professor and Chair of the Flight Mechanics and Control Discipline. Dr. Haddad's research contributions in linear and nonlinear dynamical systems and control are documented in over 540 archival journal and conference publications. He is a coauthor of the 8 books in the areas of science, mathematics, medicine, and engineering including Hierarchical Nonlinear Switching Control Design with Applications to Propulsion Systems (Springer-Verlag, 2000), Thermodynamics: A Dynamical Systems Approach (Princeton, 2005), Impulsive and Hybrid Dynamical Systems: Stability, Dissipativity, and Control (Princeton, 2006), Nonlinear Dynamical Systems and Control: A Lyapunov-Based Approach (Princeton, 2008), Nonnegative and Compartmental Dynamical Systems (Princeton, 2010), Stability, Control of Large-Scale Systems (Princeton, 2011), and Decision Support and Feedback Control in Clinical Pharmacology (Springer-Verlag, to appear). His recent research is*

*concentrated on nonlinear robust and adaptive control, nonlinear dynamical system theory, large-scale systems, hierarchical nonlinear switching control, analysis and control of nonlinear impulsive and hybrid systems, adaptive and neuroadaptive control, system thermodynamics, thermodynamic modeling of mechanical and aerospace systems, network systems, expert systems, nonlinear analysis and control for biological and physiological systems, and active control for clinical pharmacology. Dr. Haddad has received numerous outstanding research and teaching awards, and is an NSF Presidential Faculty Fellow, a member of the Academy of Nonlinear Sciences, and an IEEE Fellow.*

**Mary-Ellen Harper, PhD**

**Talk title:** *Plasticity of mitochondrial energetics: Cellular and whole body implications*

Dr. Mary-Ellen Harper is a Full Professor of Biochemistry in the Faculty of Medicine at the University of Ottawa, Canada. She completed her undergraduate degree at University of Guelph, followed by a PhD at the University of Ottawa under the supervision of Drs. John Patrick and Jean Himms-Hagen. Her thesis focused on mechanisms of facultative energy expenditure, including Na/K transport mechanisms and brown fat thermogenesis. Thereafter she held a postdoctoral fellowship at Cambridge University in the U.K. where she trained under the supervision of Dr. Martin Brand, and studied the effects of thyroid hormone status on the uncoupling of mitochondrial oxidative phosphorylation. Current research interests are mitochondrial energetics, redox, proton leaks and the role of the uncoupling proteins; fundamental mechanistic aspects are studied, and the processes are also examined in the contexts of obesity, type 2 diabetes mellitus, cancer cell metabolism and oxidative stress. In collaboration with Ottawa Hospital and Heart Institute clinicians and researchers, Drs. Bob Dent and Ruth McPherson, investigations have focused on metabolic and genetic factors contributing in inter-individual variation in weight loss. She has published 93 peer-reviewed papers, as well as many invited reviews and book chapters.

Her research has been acknowledged by awards including several postdoctoral fellowship awards, a Polanyi Award (Physiology and Medicine), a Premier's Research Excellence Award, an Endowed Summer Research Fellowship (Marine Biological Lab, Woods Hole, MA), a Canadian Foundation for Innovation New Investigator's Award, and the national Centrum Award for excellence in nutrition and metabolism research. Demand for her unique expertise is exemplified by many international invitations to collaborate and to lecture. Dr. Harper serves on various teaching and research committees at the University of Ottawa and in scientific societies nationally and internationally.

**Steve Hollenberg, MD**

**Talk title:** *Bench to bedside and back again: Non-linear hemodynamics in the lab and the ICU*

Steve Hollenberg is a professor of medicine at Robert Wood Johnson Medical School/UMDNJ and Cooper Medical School of Rowan University, and director of the coronary care unit at Cooper University Hospital in Camden, NJ. He was educated at Amherst College and Emory University School of Medicine, and then training in internal medicine at The New York Hospital-Cornell Medical College, in critical care medicine at the National Institutes of Health, and in cardiovascular diseases at Johns Hopkins Hospital.

Research interests relate to microvascular and myocardial function, with emphasis on the pathophysiology of shock. Clinical interests include septic and cardiogenic shock, acute heart failure, and acute coronary syndromes. Current laboratory investigations include analysis of blood pressure and heart rate variability in a murine model of sepsis, with translation into clinical projects measuring similar parameters in critically ill patients by acquiring hemodynamic data from bedside monitors.

**Alan Hubbard, PhD**

**Talk title:** *A statistical roadmap for prediction and variable importance/causal inference in medical informatics*

Alan Hubbard received his undergraduate degree in Geology at UC Santa Barbara (1985), his MA in Geology/Paleontology from Virginia Tech (1990) and his PhD in Biostatistics from UC Berkeley (1998). He has been a member of the faculty at UC Berkeley since 1998, currently as Associate Professor in Biostatistics. His research focuses on the theory and application of mathematics statistics to population studies, with particular expertise in semi-parametric models in causal inference, as well as methods in computational biology. He has worked on applied projects ranging from molecular biology, wildlife biology, epidemiology, and climate, but has recently focused on molecular studies of aging, infectious disease, social epidemiology and trauma research. He has taught courses in Epidemiological Statistics, Categorical Data Analysis, Causal Inference, Longitudinal Data and Methods in Social Epidemiology. He is an adjunct professor at the Buck Institute for Aging Research, statistical consultant for California Department of Fish and Game, as well and a member of the American Statistical Association.

**Frank Jacono, MD**

**Talk title:** Insights into central mechanisms responsible for breathing pattern changes following acute lung injury

Frank Jacono, MD is Assistant Professor of Medicine at Case Western Reserve University School of Medicine, Louis Stokes Cleveland VA Medical Center, and University Hospitals Case Medical Center. Dr. Jacono's major research interests include the development and testing of computational approaches to quantify biologically determined heart rate and ventilatory pattern variability with an emphasis on waveform analysis as a novel tool for investigating mechanisms responsible for breathing behaviors and providing predicative insight into prognosis and reversible pathophysiology leading to recovery, survival and rehabilitation. Ongoing work in acute lung injury, pulmonary fibrosis and respiratory failure has been
funded by the VA Research Service, the NIH and the American Heart Association. Dr. Jacono graduated summa cum laude with a B.S in hysics from Case Western Reserve University (1994), earned his medical degree at Washington University School of Medicine (1998), followed by training in internal medicine (2001) and pulmonary & critical care medicine (2004) at University Hospitals Case Medical Center.

**Alistair Johnson, B.Eng, PhD Candidate**

**Talk title:** *Workshop 4: Machine learning methods for clinical prediction systems: understanding and extracting clinical relevance*

Alistair Johnson is a PhD Candidate at Oxford University supervised by Gari Clifford. He has a B.Eng in Biomedical and Electrical Engineering from McMaster University (2006) where he designed and constructed a prototype scanning array for breast tumour detection using millimetre wave antenna. The current focus of his PhD is in the application of advanced artificial intelligence techniques in the intensive care unit to improve current risk-adjustment techniques and develop new models for patient-specific predictions for mortality, length of stay, and readmission. His current research interests include ensemble models, pattern recognition, feature generation including measures of time series complexity, and feature selection. Earlier work was in the application of non-convex optimization algorithms, such as particle swarm optimization, to develop interpretable clinical severity scores. His research group has collaborated in many applications of artificial intelligence to medical data, including mobile health technologies, signal quality indices of ECG recordings, and kalman filtering approaches to noise rejection.

**Glen Kenny, PhD**
**Talk title:** *Session Chair*

**Curt Lindberg, Dman, MHA**

**Talk title:** *Embracing Uncertainty: Complexity inspired innovations at Billings Clinic*

Curt Lindberg is director of the Billings Clinic Partnership for Complex Systems and Healthcare Innovation and health scientist at the Center for Disease Control and Prevention. Prior to this current work he founded and served as president and chief learning and science officer of Plexus Institute, an organization devoted to helping people use concepts from the complexity to improve the health of individuals, families, communities, organizations and the natural environment. His work to understand complexity science concepts and their relevance to healthcare began in the mid 1990s. Lindberg has played an important role in bringing complexity science concepts into healthcare and management. He has written numerous articles and coauthored several books, including *Edgeware: Lessons From Complexity Science for Health Care Leaders* and *On the Edge: Nursing in the Age of Complexity*.

In 2004 he helped introduce the social and behavioral change process Positive Deviance (PD) into healthcare and served as principal investigator on the first significant multi-hospital application. He has served as an advisor on PD projects in the US, Canada and Colombia South America on such issues as infection prevention, palliative care and pain management. Lindberg has written and spoken extensively about PD and coauthored *Inviting Everyone: Healing Healthcare through Positive Deviance.*

Lindberg holds a masters degree in healthcare administration and a doctorate in complexity and organizational change from University of Hertfordshire, United Kingdom. Ralph Stacey was his doctoral dissertation advisor.

**Andre Longtin, PhD**

**Talk title:** *Session Chair*

André Longtin works at the interface of physics, applied mathematics, biology and medicine. He runs the Neurophysics and Nonlinear Dynamics Group at the University of Ottawa. His main interests lie in the physical principles of brain function, and the interaction of deterministic systems with noise.

He received an honours B.Sc. Physics in 1983 and M.Sc. Physics in 1985 from the Université de Montréal, and his Ph.D. in Physics from McGill University in 1989. His thesis was a theoretical and experimental study of nonlinear oscillations, noise and chaos in neural delayed feedback systems. He then joined Los Alamos National Laboratory for two years, both as a Natural Sciences and Engineering Research Council of Canada Postdoctoral Fellow and a Los Alamos Director's Funded Postdoctoral Fellow. He held a joint position in the Theoretical Division T13 (Complex Systems) and the Center for Nonlinear Studies. He began as assistant professor of Physics in 1992 at the University of Ottawa.

He is now Professor since 2002, and cross-appointed to the Department of Cellular and Molecular Medicine in the Faculty of Medicine, and Mathematics and Statistics. He is founding co-director of the University of Ottawa Center for Neural Dynamics. He is a Fellow of the American Physical Society since 2003, and on the editorial board of Biological Cybernetics, Cognitive Neurodynamics, Bulletin of Mathematical Biology Journal of Mathematical Neuroscience, Frontiers in Computational Neuroscience and Frontiers in Systems Physiology. He was awarded a Government of Ontario Premiers Research Award in 1999, the inaugural award for Interdisciplinary research at U. Ottawa in 2004 (with Len Maler), and a senior Humboldt Research Prize in 2010, to which was associated a Hans Fischer Senior Fellowship at the Institute for Advanced Study, Technical University of Munich. He was also awarded a special NSERC Discovery Accelerator Grant in 2009. He was invited visiting professor at the EPFL in Lausanne January to March 2006.

**Ralph Lorenz, B.Eng, PhD**

**Talk title:** *The principle of maximum entropy production*

Ralph D. Lorenz has a B.Eng. in Aerospace Systems Engineering from the University of Southampton in the UK and a Ph.D. in Physics in 1994 from the University of Kent at Canterbury. He worked 1990-1991 for the European Space Agency on the design of the Huygens probe to Saturn's moon Titan. His research interests at the University of Arizona (1994-2006) and now at the Johns Hopkins University Applied Physics Laboratory in Laurel, MD include aerospace vehicles and instrumentation and their application to the exploration of planetary bodies, in particular Titan and Mars. Through studies of the climate of those worlds he developed an interest in nonequilibrium thermodynamics and self-organization in complex systems. He is the recipient of 5 NASA Group Achievement Awards and has over 180 publications in refereed journals. He is author or co-author of several books including 'Titan Unveiled', 'Spinning Flight' and 'Space Systems Failures' : he co-edited 'NonEqulibrium Thermodynamics and the Production of Entropy'.

**John C. Marshall, MD, FRCSC, FACS**
**Talk title:** *Towards a stratification system for severe acute illness*

John Marshall is a Professor of Surgery at the University of Toronto, and a trauma surgeon and intensivist at St. Michael's Hospital in Toronto, Canada. His academic interests are sepsis and the innate immune response. His laboratory, funded by the Canadian Institutes of Health Research, studies the cellular mechanisms that prolong neutrophil survival in critical illness by preventing neutrophil programmed cell death, or apoptosis. Professor Marshall has also been active in clinical research in sepsis and ICU-acquired infection, and in the design of clinical trials and outcome measures. He has published more than 250 manuscripts and more than 70 chapters, and is the editor of 2 books. He is the past-chair of the International Sepsis Forum and past-President of the Surgical Infection Society, and currently serves as chair of the Canadian Critical Care Trials Group. He is also the founding chair of the International Forum of Acute Care Trialists – a global network of investigator-led critical care clinical research groups. He is a member of the editorial boards of seven journals.

**Heather Mattila, PhD**

**Talk title:** *Building healthier and more productive honey bee colonies through complexity*

Heather Mattila completed her Ph.D. at the University of Guelph in 2005, where her research focused on the effects of nutritional stress on colony health and growth. After receiving her doctorate, she began a 4-year postdoctoral fellowship at Cornell University. At Cornell, Heather's research shifted to an examination of the effects of promiscuous mating behavior by honey bees queens on the productivity and strength of the genetically diverse colonies that they produce. Heather continues this line of research at Wellesley College, where she moved in 2009 to begin a position as the Knafel Assistant Professor of Natural Sciences in the Department of Biological Sciences. At Wellesley, she has established a program in Animal Behavior with the help many undergraduate students and over 40 colonies of bees

**Douglas McNair, MD, PhD**

**Talk title:** *Non-invasive assessment of acute deterioration likelihood in in-patients*

Douglas McNair is one of three Cerner Engineering Fellows and is responsible for innovations in mathematical modeling, decision support, and very-large-scale datamining. McNair joined Cerner in 1986, first as head of Cerner's Knowledge Systems engineering department; then as vice president of Regulatory Affairs, responsible for both submissions and compliance; then as General Manager for Cerner's Detroit and Kansas City branch offices. Subsequently, he was Chief Research Officer, responsible for overseeing Cerner research operations. In 1987, McNair was co-inventor and co-developer of *Discern Expert* ®, a decision-support engine that today is used in more than 2,000 health care facilities around the world. Between 1977 and 1986, McNair was a faculty member of Baylor College of Medicine, in the Departments of Medicine and Pathology.

McNair came to Cerner from Select Therapeutics, Inc., where he was Senior Vice President for Research and Development. Prior to this role, McNair was Vice President for Clinical Development at Abiomed, where he authored investigational plans and protocols for all products and was responsible for clinical trials of VAD and artificial heart devices, both in North America and in Europe. Between 1977 and 1986, McNair was a faculty member of Baylor College of Medicine, in the Departments of Medicine and Pathology, and co-directed the biostatistics and Design & Analysis Unit under Drs. Tony Gotto and Michael Debakey. McNair received his bachelor's and graduate degrees from the University of Minnesota. He also was a fellow in laboratory medicine and pathology at the Mayo Graduate School of Medicine. He is certified by the American Board of Pathology and the American Board of Internal Medicine.

**J. Randall Moorman, MD**

**Talk title:** *Predictive monitoring for subacute potentially catastrophic illnesses in adults*

Dr. J. Randall Moorman is Professor of Medicine, Physiology, and Biomedical Engineering at the University of Virginia. He completed his undergraduate and medical degrees from the University of Mississippi, and his basic science research training was in membrane biophysics. His work focuses on bedside prediction of subacute, potentially catastrophic illnesses using advanced mathematical and statistical analyses of time series data from clinical monitors. The effort initially centered on neonatal sepsis, a life-threatening infection of the bloodstream and a major cause of morbidity and mortality in premature infants. His group developed a new strategy for early diagnosis based on the finding that signs of illness are preceded by abnormal heart rate characteristics (HRC) of reduced variability and transient decelerations. Using a validated predictive algorithm for continuous HRC monitoring, he and his colleagues at 8 medical centers completed the largest RCT ever conducted in premature infants, and found that display of the HRC index, or HeRO score, reduced NICU mortality by more than 20%. The group now works on early detection of neonatal apnea, and respiratory decompensation leading to urgent unplanned intubation in infants and adults.

**Edmund Neugebauer, PhD**

**Talk title:** *Session chair*

Edmund A. M. Neugebauer Born: Nov.18, 1949 in Kleinalmerode (Hessia) Current Position: Professor and Chairman of Surgical Research, Director: Institute for Research in Operative Medicine (IFOM) Faculty of Health, University Witten/Herdecke, Campus Köln (Cologne), Dean for Research, Faculty of Health,University Witten/Herdecke Education •Studies as Chemical Engineer, University Aachen (1971 – 1974)•Position as Chemical Engineer, Chemie Grünenthal (1974 – 1975), .1975 change to University Marburg/Hessia, Studies in Chemistry,Diploma Chemistry 1979 •PhD in Chemistry/ Biochemistry 1982 •Start of Education in Experimental/Theoretical Surgery (Prof. Lorenz),Institute of Theoretical Surgery•Vice Chairman Institute of Theoretical Surgery 1983, Team leader shock 1982 •Study of Medicine 1982 - 1988 at University Marburg (cand. med.)•Habilitation (Assistant Professor) Nov. 1988 •1989 change to University of Cologne, Head of Biochemical and Experimental Department, Surgical Clinic II, University of Cologne •Full Professor of Experimental Surgery, University Cologne 1995 •2004 offer of University Cologne as Chairman of Surgical Research (declined)•2005 offer of University Witten/Herdecke as Chairman of Surgical Research and Director of the Institute for Research in Operative Medicine (accepted) Funding German Research Council (DFG), Ministry of Research and Education (BMBF), Foundations and Industry by a total of 3.5 Mio. Euro/ yearScientific Achievements 750 scientific publications, more than 250 original articles, Editor of 10 scientific books,Lectures > 650 Awards •Diefenbach bust for excellence in science in Traumatology by the German Society of Traumatology (DGU) (2005) •Prof. hc. of Southern Medical School, Kanton (China) (2005) •Rudolph-Zenker Prize of the German Surgical Society (2004) •Müller-Osten Prize of the German Association of Surgery (2001) •Singapore Totalisator Board, Visiting Professor, National University of Singapore (2000)•Scientific award for Research in Surgical Intensive Care of the German Surgical Society (1992) I have been one of the founding members of SCAI(first president) and organized several international ICCAI congresses as well as the International Shock congress of the IFSS in 2008 in Cologne, Germany, and continue to serve this organization and its development as vice president.

**Cameron Neylon, PhD**

**Talk title:** *Plenary: Open access networked science*

Cameron Neylon is practicing experimental scientist with an interest in how the web can be effectively applied to the practice of science. He is in demand as a speaker and writer on the technical and social opportunities and issues that the Internet brings to scholarly communication in general and the ways in which the detail of scientific process can be recorded and communicated in particular. His research work in this area has focused on the design and development of systems for capturing the research process at source and making it directly available on the web. He writes regularly on these issues as well as the challenges the web brings to traditional scientific practice at his blog, Science in the Open.

**Monika Petelczyc, PhD**

**Talk title:** *Randomness, determinism, and complexity of heart rate variability : Measurement and description based on stochastic analysis*

My scientific interests focus on heart rate variability analysis and its modeling. I obtained a Master of Science at the Faculty of Physics at Warsaw University of Technology specializing in physics of complex systems. My doctoral thesis was dedicated to develop the method of Kramers-Moyal expansion for heart rate variability analysis. Now, I am developing this method for data  which specifically contains large fluctuations (such due to arrhythmias) – to show the role of such behavior in cardiovascular disease. The main purpose is to measure and compare fluctuations of the heart rate occurring in healthy persons and in different groups of patients (predominantly aortic valve stenosis and hypertrophic cardiomyopathy) in order to development risk assessment techniques. Another goal is to relate heart rate variability properties with the development stage of the cardiovascular disease. I am married and a very happy mother of a two-year-old daughter.

**Stephen Rees, Ph.D, Dr.Tech**

**Talk title:** *Measurement of pulmonary gas exchange in the ICU*

Stephen Rees is Professor of Respiratory and Critical Care Technology at Aalborg University, Denmark. His research interests include development, validation, and application of physiological models to solve medical problems. Modeling activities include pulmonary gas exchange, the acid-base chemistry of blood and pulmonary mechanics. These models have been applied in computer systems and hardware for measurement of pulmonary gas exchange, mathematical arterialization of peripheral venous blood and automatic control of mechanical ventilation.

Stephen Rees is currently Chairman of the European Society for Computing and Technology in Anaesthesia and Intensive Care, and Editor-in-Chief of the Journal of Clinical Monitoring and Computing.

**José Salinas, PhD**

**Talk title:** *Development of a prospective study using the wireless vital signs monitor for capturing heart rate complexity and variability in trauma patients*

Dr. Salinas currently works at the U.S. Army Institute of Surgical Research (USAISR) as Research Task Area Manager and Computer Scientist for the Combat Critical Care Engineering group supporting and leading the research and development of new critical care medical information technologies and systems for all echelons of patient care. Responsibilities include oversight and concept development, prototyping, deployment, and support of new hardware and software projects in support of the Army's Combat Casualty Care programs. Projects include the support and management of the U.S. Army Institute of Surgical Research decision support systems and prehospital/hospital patient database and warehousing systems. Other research and interests include statistical modeling of patient injuries and outcomes for development of new triage and patient diagnosis tools in support of the Army's remote triage projects within the Combat Critical Care Engineering research task area. Development of new remote triage and patient sorting algorithms for prehospital civilian and military medics based on invasive/non invasive patient sensor data streams. Development of new real time processing approaches for prediction of patient outcome using real time wireless data. Data warehousing of high frequency waveform and numeric vital signs in a web enabled environment. Use of data mining approaches for pattern identification and pattern recognition of dense physiologic signals. Development of new database management systems for querying of real time high frequency vital sign waveforms.

**John Scott, M.D., PhD**

**Talk title:** *Healing relationships as an emergent pattern of complex responsive processes of relating*

John Scott received his M.D. and Ph.D in the Medical Scientist Training Program at Duke University Medical School, after which he completed family medicine residency training at the Medical University of South Carolina. He was in private practice in rural Arkansas for 21 years and during that time served as a clinical professor of family medicine at the University of Arkansas for Medical Sciences. He participated in practice-based research through the ASPN network for many years.

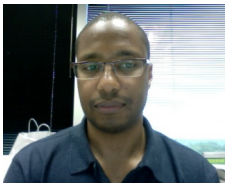
He was an assistant professor in the Robert Wood Johnson Medical School Department of Family Medicine from 2002-2010, working with Benjamin Crabtree who uses concepts of complexity science as a way to understand primary care practices as complex adaptive systems. He did qualitative and quantitative research focused on the doctor-patient relationship as well as teaching residents and medical students. In 2003, he received a Robert Wood Johnson Generalist Physician Faculty Scholar Award to do research on doctor-patient healing relationships.

He is now in part-time practice at Corner Medical in Lyndonville, Vermont, a primary care practice owned by Northeastern Vermont Regional Hospital. He is working on a book about clinician-patient healing relationships and how to create healing environments in health care.

**Andrew J.E. Seely, MD PhD FRCSC**

**Talk title:** *Heart and respiratory variability monitoring in the ICU : Update from WAVE and other studies*

Andrew JE Seely is Associate Professor of Surgery within the Divisions of Thoracic Surgery and Critical Care Medicine at the University of Ottawa, Associate Scientist with the Ottawa Hospital Research Institute, Chair of Research for the Canadian Association of Thoracic Surgeons, Director of Research for the Ottawa Division of Thoracic Surgery, as well as Founder and Chief Science Officer of Therapeutic Monitoring Systems Inc. Education includes an undergraduate honours physics at Carleton University, followed by medical school, general surgery training, and a doctoral degree in basic science from McGill University, and thoracic surgery and critical care medicine training at the University of Ottawa. Scholarly interests include theoretical research exploring the clinical insights of complex systems science, experimental research applying continuous variability analysis at the bedside, and development of means to continuously monitor quality of surgical care. Dr Seely has published over 45 peer-reviewed papers, presented at numerous international meetings, and was awarded a "New Investigator" Award by the Canadian Institutes of Health Research in 2005. He shares his family life with Kathy Patterson and their daughters Phoebe and Ruby in Ottawa.



**Daby Sow, PhD**

**Talk title:** *Exploration in intensive care*

Dr. Daby Sow is a research staff member at IBM T.J. Watson Research Center. His research interests are at the intersection of several fields of computer science and electrical engineering, including stream computing, complex event processing, applied machine learning, signal processing, and information theory, with applications to medical informatics problems. He received his bachelor of science in electrical engineering from the Universite Laval, Quebec, Canada, and his master of science and Ph.D. degrees in electrical engineering from Columbia University in 2000.

**Duncan Stewart, MD, FRCPC**

**Talk title:** *Multi-tiered systems biology approach to pulmonary hypertension*

Dr. Duncan Stewart is the CEO and Scientific Director of the Ottawa Hospital Research Institute (OHRI), as well as an active cardiologist and scientist focusing on developing new regenerative therapies for cardiovascular disease. Dr. Stewart has made a number of important discoveries about the endothelial cells that line our blood vessels, including elucidating the important roles of the endothelial factors endothelin-1 and nitric oxide in vascular disease. He has also initiated Canada's first clinical trials using gene therapy for therapeutic angiogenesis in patients with advanced coronary artery disease and gene-enhanced progenitor cell therapy for pulmonary hypertension. More recently, he is investigating gene and cell therapy approaches for myocardial infarction and acute respiratory distress syndrome, with clinical trials expected to start in the near future.

**Béla Suki, PhD**

**Talk title :** *Variable stretch patterns alter mitochondrial network formation and ATP supply in cells*

Dr. Béla Suki graduated with a Masters in Physics and a PhD in Biomechanics from Jozsef Attila University, Szeged (Hungary). Dr. Suki is currently a Professor at Department of Biomedical Engineering. Previous work of Dr. Suki was related to the mechanical characterization of soft biological tissues, respiratory physiology in diseases such emphysema and asthma and nonlinear and network modeling of physiological processes. Dr. Suki's current research involves evaluating the effects of variability in mechanical stretch on cell function. Specifically, mechanotransduction in the laboratory is always studied using sinusoidal stretching. However, in the body, cells are never exposed to strictly monotonous mechanical perturbations. Variability itself appears to influence essential cell functions such as ATP production. His other fields of interest are variability in physiological signals, the coupling between enzyme activity and mechanical forces in the extracellular matrix as well as applying statistical mechanical concepts to large biological networks.

**Yoram Vodovotz, PhD**

**Talk title:** *Measurement, modeling, and modulation of the inflammatory response in shock states*

Yoram Vodovotz, Ph.D., is a Professor of Surgery, Immunology, Computational and Systems Biology, Bioengineering, Clinical and Translational Science, and Communication Science and Disorders at the University of Pittsburgh. His research interests include the biology of acute inflammation in shock states, chronic inflammatory diseases, wound healing, malaria, and restenosis. His work utilizes mathematical modeling to unify and gain insight into the biological interactions that characterize these inflammatory conditions. As the Director of the Center for Inflammation and Regenerative Modeling (CIRM; www.mirm.pitt.edu/cirm) at the University of Pittsburgh's McGowan Institute for Regenerative Medicine, he has been involved in the mathematical modeling of acute inflammatory states (e.g. septic or hemorrhagic shock, wound healing), including cellular and physiological elements, as part of a large, interdisciplinary collaborative team. He is also a co-founder of Immunetrics, Inc., a company that is commercializing this mathematical modeling work. He is currently the President of the Society for Complexity in Acute Illness (www.scai-med.org).

**Niels Wessel, PhD**

**Talk title:** *Cardiovascular physics: Assessment of autonomic tone around the operation theatre*

Niels Wessel is head of the Cardiovascular Physics Group at the Department of Physics of Humboldt-Universität zu Berlin. He has been working in the field of nonlinear time series analysis and modelling and its applications to medical data and risk stratification since 1993. His group aims to improve clinical diagnostics via model-based nonlinear dynamic data analysis of non-invasively measured biosignals. The use of modern nonlinear methods in multivariate analysis enhances our understanding of the neurocardiovascular regulation and allows improved answers to clinically relevant questions. Wessel has longstanding scientific interaction with collaborators in many relevant medical disciplines such as: cardiology, obstetrics, hypertensiology, heart surgery, pharmacology, sports medicine, electrophysiology, sleep medicine, and molecular medicine. He has more than 200 publications, which were collectively cited more than 2200 times.

**Jan Zebrowski, PhD**

**Talk title:** *Complexity of sinus rhythm combined with arrhythmia*

Prof. Jan J. Żebrowski was born in 1951 in Warszawa, Poland and graduated with a MSEE at the Warsaw University of Technology in 1974. He was a graduate student (Special Status) at the California Institute of Technology in 1977-1979 where he did experimental research on magnetic bubbles. He obtained the doctorate in physics degree at the Institute of Physics of the Warsaw University of Technology in 1981 specializing in the theory of solid state magnetism. Since 1983 his main interest has been nonlinear dynamics (chaos theory) initially in solid state magnetism and since 1991 in physiology and medicine. He obtained his PhD in physics in 1989. He is now a full professor at the Faculty of Physics at WUT and head of the Cardiovascular Physics Group. His current main interests are nonlinear methods of time series analysis and modeling in cardiovascular physics.

**Dr. med. Sven Zenker**
**Talk title:** *Workshop 3: Creating mathematical models for biomedical scenarios: from model design to model application*

Dr. Zenker is currently employed as a physician/scientist at the Dpt. of Anesthesiology and Intensive Care Medicine, University of Bonn Medical Center, Bonn, Germany. Previously, after completing his medical education, working clinically in medical intensive care, and receiving formal training in physics at the University of Bonn, he joined the Dpt. of Critical Care Medicine and the Dpt. of Mathematics at the University of Pittsburgh for three years of postdoctoral work. His research group (http://www.amp.uni-bonn.de/front-page?set_language=en) focuses on utilizing mathematical models of physiology and pathopyhsiology to quantitatively interpret monitoring data from acute care settings, with the mid-term goal of achieving fully individualized quantitative prediction and optimized therapeutic control of critical illness trajectories exploiting all quantitative data available for a patient. In addition to developing mathematical models optimized for these application scenarios, he focuses on the complete quantification of uncertainty in the solutions of the practically relevant parameter and state estimation problems and the resulting predictions arising in this context by applying probabilistic solution techniques to the underlying inverse problems. His work is supported by by the German-Israeli Foundation (GIF) and the Deutsche Forschungsgemeinschaft (DFG).

## ABSTRACT 1

# SYNCHRONY IN BROAD-BAND FLUCTUATION AND APPLICATION TO EEG ANALYSIS OF TRAUMATIC BRAIN INJURED PATIENTS

DER CHYAN LIN[1] , JOSE L. PEREZ VELAZQUEZ[2] , VERA NENADOVIC[3]

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**Objectives:** The objective of this work is to introduce the idea of fluctuation of synchrony (FIS) in broad-band processes and use the approach to study the EEG of TBI patients.

**Methods:** We propose to use the modulus maxima line (MML) from the wavelet transform to track the timing of fluctuation. These geometrical objects are known to emerge from the small scale in the wavelet time scale plane and mark the event of the singular change in the signal fluctuation. Since no assumption is made on the frequency band of the signal, the proposed method is applicable to the broad band process. Once the MML locations are found, we estimated the distance, d, between the nearest MML and use its distribution p(d) to measure the difference in the timing of fluctuation between time series. For complete FIS, p(d) is a Dirac delta function, which implies the fluctuation of one time series always follow/precede the other. It applies to the trivial case of identical processes and, more generally, processes with dependent fluctuation. In general, FIS results in a unimodal p(d). When FIS fails to exist, p(d) either takes an exponential form since the "arrival" of the MML becomes a Poisson event, or is uniformly distributed for completely independent processes.

**Results:** Via artificial multifractal processes and artificial neural network, we found that FIS can effectively capture the "coincidence" of the fluctuation among complex signals and reveal the underlying complex dynamics. The application of our approach to TBI patients reveals a rather localized and less dynamic spatio-temporal FIS pattern, wherein the synchrony appear to coincide with the injured areas of the patient.

**Conclusions:** In this work, a novel approach is introduced to capture the timing of the fluctuation using wavelet transform. It is applicable to broad band processes and provides a new paradigm of synchrony that does not appear to have been studied before. We believe FIS is an intrinsic property in the complex dynamical system and the proposed could lead to useful application in treating patients with acute brain injury.

# ABSTRACT 2

## Relation Between Health and Life

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***Objectives:*** In 2010 PT Macklem and A Seely (1) presented a new definition of life. Among other features it describes a self-regulating, open thermodynamic system that performs work and combines stability and adaptability in a phase transition between order and chaos. The objectives of this presentation are to pursue the question, how this description of life is related to a recent definition of health (2).

***Methods:*** The use of terms and relationships given by Maklem and Seely are analysed and compared with the rationale of the definition of health.

***Results:*** In analogy to life human health also is a dynamic state. It results from resources, which are produced in the above open thermodynamic system. These must be sufficient to fully meet the specific internal and external requirements for survival. In particular, performance of work and adaptability must remain within the capacities for homeokinesis. Since the capabilities needed for this purpose are relevant not only for the present, but also for the future lifetime of the system, they are better expressed as potentials. There are a biologically given and a personally acquired potential. The former is mainly determined by genetics and has a finite value at the time of birth. Thereafter it is continuously reduced to reach zero at the time of death. The personally acquired potential, predominantly expressing epigenetics, is quite small at the time of birth, increases rapidly thereafter and may rise continuously as long as an individual is concerned with its development. That is why personal responsibility and culture are important features of health. Analysis of the time course of the two potentials shows that their relative contribution to the system varies with age. Based on these considerations the nature of health may be described as a dynamic state of wellbeing characterized by a potential, which satisfies the demands of a life commensurate with age, culture, and personal responsibility. Life based on a potential that does not fully meet the internal and external requirements for survival means disease.

***Conclusions:*** Not all the features of the definition of life are needed to discuss human health. The description of health focuses on several other specific relationships and properties, such as the balance between resources and requirements of life, the double nature of the resources, and its orientation toward the future. Thus, both models are consistent with each other, yet their descriptions overlap only in part.

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## ABSTRACT 3

# TEMPERATURE CURVE COMPLEXITY ESTIMATED WITH TSALLIS ENTROPY IS RELATED WITH SOFA SCORE OF SEVERITY OF ILLNESS IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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**Objectives:** Different studies estimating complexity of temperature curves in critically ill patients have found decreased entropy during severe stress. In this study, a nonextensive entropy measure, Tsallis entropy (TsEn), was undertaken to assess temperature complexity, in a cohort of septic patients and predict severity of illness, estimated with Sequential Organ Failure Assessment Score (SOFA).

**Methods:** Twenty-one patients were enrolled in the study. There were 13 who suffered from sepsis (group 1) and 8 from septic shock (group 2). All temperature curves were analyzed during the first 24 hours of an inflammatory state. A wavelet transformation was applied, decomposing the signal in different frequency components (scales) that have been found to reflect neurogenic and metabolic inputs upon temperature oscillations. Tsallis entropy of the whole signal, per different scales and frequency bands derived from wavelet transformation was calculated. Statistical significant differences of entropy features were tested between the two groups of patients and correlated with SOFA. A regression model after exhaustive regression and many bootstrapping repetitions was built for predicting severity of illness. Finally, a Bland Altman plot was used for estimating agreement between the two methods.

**Results:** Patients from group 2 exhibited reduced TsEn values in relation with group 1. TsEn measurements per different scales were proven to correlate with SOFA in the whole group of patients. The regression model built included a triple combination of entropy features per high scales, indicating an association between clinical deterioration and reduced metabolic inputs upon temperature oscillations. The R2 was 0.6171 ($p = 0.0008$), whereas bias (mean of differences between SOFA measured and SOFA predicted) was 0.0397; SD of bias was 2.0964 and 95% limits of agreement (LA) were $0.0397 \pm 4.19$. Moreover, spearman correlation coefficient between model and measured SOFA was found to be 0.785 ($p < 0.005$).

**Conclusions:** We suggest that reduced nonextensive Tsallis entropy values may reflect severity of illness in septic patients, capturing inherent thermoregulatory dynamics.

## ABSTRACT 4

# COEFFICIENT OF VARIATION OF COARSELY SAMPLED HEART RATE PREDICTS EARLY VASOPRESSOR INDEPENDENCE IN EARLY SEVERE SEPSIS AND SEPTIC SHOCK

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**Objectives:** Early resuscitation of severe sepsis and septic shock is important, but hemodynamic predictors of response to therapy and outcome are uncertain. We sought to determine whether variability in heart rate, measure at 30-second intervals, early in the course of severe sepsis and septic shock predicts successful resuscitation.

**Methods:** We sampled heart rate every 30-seconds over the first six hours of ICU admission and calculated variability of those measurements. Primary outcome was vasopressor independence at 24 hours; secondary outcome was 28-day mortality.

**Results:** We studied 165 patients. Of them 97 (59%) achieved vasopressor independence at 24 hours. Overall 28-day mortality was 15%. Significant multivariate predictors of vasopressor independence at 24 hours included the coefficient of variation of heart rate, age, Acute Physiology and Chronic Health Evaluation (APACHE II), the number of increases in vasopressor dose, mean vasopressin dose, mean blood pressure, and time-pressure integral of mean blood pressure below 60mm Hg. Lower sampling frequencies (up to once every 5 minutes) did not affect the findings.

**Conclusions:** Increased variability of heart rate was predictive of vasopressor independence at 24 hours after controlling confounders. Further work should clarify the reason for this finding. The optimal sampling frequency for coarsely granular physiological data may be as infrequent as every 5 minutes, depending on the clinical setting.

## ABSTRACT 5

## THE PRINCIPLE OF MAXIMUM ENTROPY PRODUCTION (MEP OR MAXEP)

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**Objectives:** Initially a methodology was sought for predicting the equator-to-pole temperature gradient on an arbitrary planet.

**Methods:** Work in the 1970s suggested that the heat flows in the Earth's oceans and atmosphere might conspire to produce entropy at the maximum rate. In steady state there is a temperature gradient enforced by the uneven distribution of sunlight on a spherical planetary surface. If the heat flow is not too large (leading to an isothermal planet that has a zero Carnot efficiency) nor too small (where no heat flow means no work can be produced), there may be an optimum with maximum mechanical work output or maximum rate of production of entropy. This notion has been explored more generally.

**Results:** It has been found that the gross climates of Mars and Titan seem better-predicted by this principle as any of comparable succinctness and universality. The idea is in essence a generalization of the 2nd law to nonequilibrium steady-states, but relies on the system having adequate degrees of freedom. While evolutionary mechanisms can be postulated, the most general interpretation is that for complex systems with many possible internal configurations, those that maximize the production of entropy may simply be the most probable ones to be encountered.

**Conclusions:** A selection principle in complex systems is suggested, namely that they may maximize their production of entropy. There is an interesting association of systems with high entropy production and low internal configurational entropy. High-performance systems are more ordered, and export entropy to maintain that internal order.

## ABSTRACT 6

# DETERMINANTS OF VENTILATION STRATEGIES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME AND CONCURRENT COPD OR OBESITY-HYPOVENTILATION SYNDROME

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**Objectives:** Nasal continuous positive airway pressure (CPAP) is the current treatment of obstructive sleep apnea syndrome (OSAS). Despite general efficacy of, oxygen desaturation persists in some high-risk groups of patients such as those with concurrent chronic obstructive pulmonary disease (COPD) or obesity-hypoventilation syndrome (OHS). In such patients, bilevel positive airway pressure ventilation (BiPAP) represents a treatment modality with the highest efficacy. In addition, BiPAP is used in severely hypercapnic COPD patients with acute exacerbations. Nevertheless, little data is available on the determinants of CPAP versus BiPAP indication at the time of diagnostic polysomnography and establishment of OSAS. Our aim was to investigate factors related to the need to use BiPAP ventilation strategy in patients with OSAS and concurrent COPD or OHS.

**Methods:** 69 patients with OSAS [mean apnea-hypopnea index (AHI) 55.2±4.6 events/hour, mean sleep transcutanous oxygen saturation (SpO2) 84.8±8.3%] and comorbid COPD (n=41) or OHS (n=28) were consecutively recruited. Overnight polysomnography (Alice 4 System; Respironics, Murrysville, Pennsylvania, USA), bodyplethysmography (Ganshorn, Germany). anthropometric variables and standard biochemical analyses were analysed. Noninvasive ventilation was introduced using either CPAP or BiPAP ventilation strategy.

**Results:** Thirty-four patients required CPAP and 35 patients required BiPAP ventilation strategy for their OSAS. No differences were observed between the two groups in mean age or body mass index. Indices of the OSAS severity including intermittent hypoxia during sleep were similar between patients requiring BiPAP vs CPAP therapy (AHI: 50.8±23.3 vs 58.2±27.6 events/hour, p=0.432; oxygen desaturation index: 64.2±21.4 vs 55.7±26.6 /hour, p=0.337). In contrast, patients requiring BiPAP had significantly more profound sustained nocturnal hypoxemia (mean SpO2 during non-rapid eye movement sleep: 80.6±8.2 versus 88.5±6.5%, p<0.001; mean SpO2 during rapid eye-movement sleep: 75.6±12.9 versus 82.9±8.5%, p=0.02; time asleep at SpO2<90%: 178±145 versus 385±154 min, p<0.001). The need for BiPAP therapy was predicted by sustained hypoxemia while asleep (SpO2<90%) (p=0.011) independently of age, gender, body mass index, AHI, and severity of pulmonary function impairment (R2=0.478, p=0.002).

**Conclusions:** Our results suggest that sustained hypoxemia is the main determinant of the need for BiPAP therapy in patients with OSAS and concurrent COPD or OHS. Support: APVV-0134-11 and VEGA 1/0111/12 of the Ministry of Education, Slovakia.

## ABSTRACT 7

# ASSESSMENT OF FLUID RESPONSIVENESS IN LIVER SURGERY: COMPARISON OF DIFFERENT CARDIAC OUTPUT ESTIMATORS AND HEMODYNAMIC INDICES

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**Objectives:** The majority of studies on fluid responsiveness is focused on volume expansion maneuvers in the intensive care unit (ICU), while fewer studies have analyzed the same problem during major surgery. The aims of this work are to compare the performance of different hemodynamic indices in the prediction of cardiac output variations following fast fluid infusion, as well as to compare different cardiac output estimators.

**Methods:** The inclusion criteria were: no persistent arrhythmias, no arteriosclerosis, tidal volume higher than 8ml/(kg of ideal weight). We analyzed rapid infusion events, i.e. boluses of 100ml or 500ml administered within 30 sec or 1 minute, respectively. Pulse contour cardiac output (PCCO) and stroke volume (SV) estimated by Pulsion PiCCO© were recorded and analyzed. Invasive arterial blood pressure (ABP) was measured via an arterial catheter inserted in the brachial artery and placed in the aortic arch. ABP was recorded at a sample frequency of 100 Hz, while air flow (AF) and air pressure (AP) were recorded at 25 Hz by GE S/5 Avance Carestation©. For each maneuver, time intervals were selected beginning 20 sec before the start of infusion and including the following 3 minutes. Beat-to-beat pulse pressure (PP) series were obtained from the continuous ABP waveform. Heart rate was calculated after R peak detection on the ECG waveform. Beat-to-beat cardiac output (CO) and SV were estimated by the Lijestrand and Zander method (LM) and the systolic area method (SA) [J. X, Sun et al., Critical Care Medicine, 2009] and compared to PCCO estimated by Pulsion PiCCO®. Pulse pressure variation (PPV) and stroke volume variation (SVV) were estimated according to their definitions, as percentage variation in each respiratory cycle [F. Michard and J-L. Teboul, Chest, 2002].

**Results:** A total of 25 maneuvers were analyzed. All maneuvers were retrospectively classified according to CO variations measured by the PiCCO monitor (ΔPCCO values). A maneuver was considered responsive if ΔPCCO resulted larger than 10% after infusion. The variation of CO estimated with the proposed indices was positively correlated to ΔPCCO (ΔCOSA: $r=0.56$ $p\text{-val}<0.05$; ΔCOLM: $r=0.60$ $p\text{-val}<0.05$). Bland-Altman analysis showed that the PPV values estimated by the monitor (PPV_PiCCO) were consistent with the indices computed according to the definition. The average value of the differences was close to zero and the standard deviation of the differences was less than 5% Both PPV and SVV indices, provided by the PiCCO monitor as well as calculated by the proposed algorithms, resulted significantly different in the maneuvers classified as responsive (R) as compared to the ones classified as non responsive (NR). As expected, lower values of the indices corresponded to lower or no increase of CO. PPV_PiCCO and PPV were significantly correlated to ΔPCCO ($p\text{-value}<0.05$), and the correlation coefficients were $r = 0.54$ and $r = 0.44$, respectively.

**Conclusions:** Our results showed that PPV estimated according to its definition, i.e. taking into account the respiratory cycle, and PPV estimated by PiCCO, without employing respiratory information, are coherent and very similar. Moreover, PPV and SVV produced good values of sensitivity and specificity in separating the maneuvers.

## ABSTRACT 8

# DESIGN OF TEMPORAL ANALYSIS FOR A NOVEL PREMATURE INFANT PAIN PROFILE USING ARTEMIS

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**Objective:**
The main objective of this research work was to assess physiological data streams and nociceptive events from the Artemis Project database for translating into rules to describe a novel pain profile. The Artemis platform is a framework for concurrent multi-patient and multi-stream temporal analysis in real-time for prospective clinical management and retrospective clinical research.[1] This novel Artemis Premature Infant Pain Profile (APIPP) would then act as an efficient pain detection tool in newborn infants for health care professionals.
In our previous work, we have correlated physiological data streams with pain response using an Artificial Neural Network (ANN). [4] Noxious stimuli were defined when HR≥160, MAP≥55, RR≥40 and SpO2< 90 occurred concurrently. The study demonstrated a positive correlation between nociceptive response and non-invasive physiological response. With the elimination of increased heart rate variability caused by nociceptive events, it should be possible to better classify reduced heart rate variability as a pathophysiological indicator of late onset neonatal sepsis (LONS).

**Methods:**
Pain management in newborn infants is a constantly challenging task that has been extensively investigated in this unique population. Research states that premature infants have the neurological capacity to experience pain and that they are more vulnerable to pain than older infants, children and adults. [2] Pain that is not treated may cause significant morbidity and mortality in new-born infants. [3]
The novel APIPP will be deployed within the Artemis platform using gestational age and four physiological variables (heart rate, blood pressure, respiratory rate, and blood oxygen saturation) to identify nociceptive stimulus in real-time. [2, 5]
The absolute and the relative values of the multiple physiological data stream presented in this study (HR, MAP, RR and SpO2) will be used to correlate differing gestational ages to access and validate a reliable APIPP score. The use of APIPP based on physiological data streams should increase the sensitivity and specificity for the detection of LONS. [1]

**Significance:**
Using various physiological data streams, the novel scale will be deployed into the Artemis platform to predict nociceptive events. With this informatics tool, it should be possible to better identify nociceptive stimuli, and therefore, improve the use of drugs and non-pharmacological interventions for pain relief. The use of APIPP with Artemis may reduce the rates of morbidity in neonates as well as the prolonged pain exposure, which has shown to have negative effects that lead to serious conditions such as LONS and intraventricular haemorrhage. [2, 5]

**Conclusion:**
In the future, work will be carried out to deploy this novel pain scale utilising physiological data streams within the Artemis platform to evaluate the detection of nociceptive stimuli, as well as, a more ambitious algorithm will be deployed in Artemis which should then enable not only detection but also quantification of pain in neonates as mild, moderate or severe.

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## ABSTRACT 9

# DESIGN OF TEMPORAL ANALYSIS OF NEONATAL VAGAL SPELLS AT DIFFERENT GESTATIONAL AGES USING THE ARTEMIS' FRAMEWORK

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**Objectives**: The objective of this project is to conduct an analysis of the incidences of neonatal vagal spells at different gestational ages. This study uses Artemis's capabilities to automatically detect vagal spells.

Artemis is a framework for concurrent multi-patient, multi-diagnosis and multi-stream temporal analysis in real-time for clinical management and research.

Apnoea is defined as a pause in breathing for more than twenty seconds or a pause in breathing of any duration that is associated with cyanosis, pallor, bradycardia, or marked hypotonia [1]. The most common cause of spells in preterm infants results from immaturity although infection, lung collapse and seizures are other causes. A spell can occur as the result of one of three types of apnoea, central, obstructive, or mixed apnoea. In studies of infants who are experiencing spells, mixed apnoea is the most common (49.6%) followed by central (39.9%) and obstructive (10.5%) of apnoeic events [2].

Vagal spells, are a subtype of central apnoea and are the result of stimulation of the vagal nerve. The pattern of events that occur with a vagal spell is a rapid fall in HR accompanied by a simultaneous pause in respiration followed shortly by a decrease in blood oxygen saturation. Neonatal respiratory physiologists have demonstrated this pattern of vagal spell by stimulating the vagal nerve of preterm lambs with an acid solution sprayed on the larynx. Many neonatologists consider that infants have spells as a result of gastroesophageal acid reflux [3]. This has been difficult to prove in vivo. The polyvagal theory describes an autonomic nervous system (ANS) that is influenced by the central nervous system (CNS). As the CNS matures the output of the ANS is modified and it has been hypothesized that the nature of vagal spells changes with increasing maturity [4]. The modification of vagal tone described in this theory may explain why apnoea is rare in term infants with severe gastroesophageal acid reflux.

**Methods**: The Artemis project has high fidelity physiological data stored from over 300 neonates. We have developed a streams based algorithm to detect vagal spells and plan to use this analysis to examine the frequency of events at the various gestational ages.

**Conclusions:** This analysis will allow us to determine if gestational age does affect the incidence of vagal spells. It will also provide the first in-depth analysis of the frequency of vagal spells in neonates.

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## ABSTRACT 10

# CONTINUOUS MULTIVARIATE ELECTRONIC FETAL MONITORING DURING LABOUR DETECTS EARLY ONSET OF ACIDEMIA: PROSPECTIVE STUDY IN FETAL SHEEP MODEL

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***Objectives:*** There is an urgent need to identify early signs of fetal acidemia because it confers a risk of lasting neurological deficits. Changes in root mean square of successive differences in R-R intervals of ECG (RMSSD) reflect modulation of fetal heart rate (FHR) variability (fHRV) by vagal activity on a beat-to-beat time scale and are more precise than the current clinical short-term FHR variation measures used in electronic fetal monitoring (EFM). EFM samples FHR at ~4 Hz. An augmented bedside fetal monitoring would have to perform reliably even at this low sampling rate. We have shown that with fHRV sampled at 1000 Hz, RMSSD increases ~70min (range, 17min – 1h39min) prior to the onset of severe acidemia (pH<7.00). When measured at a fHRV sampling rate of 4 Hz, RMSSD increase was delayed by 40 min and so missed the onset of severe acidemia in 2 out of 7 fetuses. In the remaining 5 fetuses, RMSSD increased at ~50min (range, 40- 60min) prior to the pH falling < 7.00. Sample Entropy (SampEn), a measure of fHRV complexity, has shown promise in early detection of neonatal sepsis and may also reflect alterations in the autonomic nervous system during acidemia, complementary to the linear time domain fHRV measure RMSSD. Amplitude of the fetal sheep electroenkephalogram (EEG) is predictably altered with worsening acidemia, as it shows temporal correlation with the accompanying FHR decelerations. It might hence prove useful for EFM during labour. We found that such EEG-FHR pattern alerts to the pH drop < 7.00 emerging ~58min in advance (range, 19min – 1h52min). Thus, there is considerable interindividual variability of changes in RMSSD and EEG-FHR pattern in advance of severe acidemia. We hypothesized that a continuous multivariate fHRV – EEG – FHR EFM during labour will better detect incipient severe fetal acidemia than each of these modalities alone.

***Methods:*** Seven near term fetal sheep were chronically prepared with arterial catheters, ECG, EEG electrodes and an umbilical cord occluder. For 1 min every 2.5 min, animals underwent mild then moderate partial umbilical cord occlusions (UCO) each over a 1 hour period, and then severe complete UCO over a 1-2 hour period, until arterial pH reached < 7.00. This timing was chosen to model human labour. Arterial blood samples were drawn at baseline and every 20 min during the UCO period. We tested the performance of RMSSD and SampEn when determined with 1000 Hz and 4 Hz sampling rates using the automated and standardized CIMVA (Continuous Individualized Multiorgan Variability Analysis) system.

***Results:*** Repetitive fetal UCO resulted in marked acidemia (pH 7.36±0.01 decreasing to 6.99±0.01, mean±SEM). We found individual differences in the timing of increase in RMSSD and SampEn compared to EEG-FHR pattern onset. At the 1000 Hz fHRV sampling rate, in two animals RMSSD increased ~1h06min before the onset of the EEG–FHR pattern at ~23min prior to pH<7.00 drop. With SampEn, this time was

increased by another hour for all seven fetuses at ~2h11min (range, 1h17min – 2h40min) prior to pH<7.00. At the 4 Hz fHRV sampling rate, the same two out of seven fetuses were missed with SampEn as with RMSSD. SampEn decreased at ~44 min (range, 22min – 1h39min) prior to pH<7.00. In six out of seven fetuses EEG–FHR pattern emerged ~34 min earlier than SampEn increase (range, 6min – 1h). In contrast, in one fetus the increase of SampEn was found 20min and of RMSSD - 40min earlier than EEG–FHR pattern onset. Moreover, RMSSD increased ~26 min earlier than EEG–FHR pattern onset in two out of seven fetuses.

***Conclusions:*** At 1000 Hz, SampEn extends our ability to detect fetal acidemia. At 4 Hz, EEG–FHR monitoring is augmented by the addition of fHRV RMSSD monitoring, but not by SampEn. Our findings support the hypothesis that multivariate EEG–FHR–fHRV EFM is more likely to detect fetal acidemia early than any of these modalities alone. That is true even at the low fHRV sampling rate of 4 Hz used clinically.

## ABSTRACT 11

# HOW CAN BLOOD PRESSURE AND DEPTH OF NARCOSIS PREDICTION BENEFIT FROM A NETWORKED OPERATING ROOM?

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## Objectives

During standard surgical interventions, the anesthesiologist controls the depth of anesthesia (DoA) using several drugs. Currently, decisions are made based on vital signs like heart rate and blood pressure from patient monitor, anesthesia machine, and furthermore by observing visual events like sweating or patient movement. The anesthesiologist must regard information displayed on each of these devices in context to the current state of the intervention in order to react to events like pain stimuli or CO2 insufflation. For an optimal anesthesia, not only the current situation and context is relevant but also the further procedures. Moreover, in some cases heart rate and blood pressure follow a certain trend due to the pharmacokinetic (PK) and pharmacodynamic (PD) properties of applied drugs and therefore are potentially predictable. This fact is already in use for some commercially available projects like SmartPilot View (Draeger, Luebeck, Germany).

The smart operating room (smartOR) research project aims to build a manufacturer independent standard which networks all medical devices used in the operating room (OR). Consolidated information about the patient condition and relevant parameters from networked devices are collected and shown on central displays optimized for the surgical and anesthesiological workplace, respectively. As an application example, we present an approach to estimate and predict blood pressure and DoA based on a PK/PD model together with information gathered from the networked OR. In particular, we focus on intravenous anesthesia (TIVA) using Propofol and Remifentanil.

## Methods

The PK modeling uses standard models and parameters which are already in use in target controlled infusion (TCI) pumps. Blood pressure is estimated using a linear combination of the concentrations of Propofol and Remifentanil. Additionally, the Bateman function models the influence of manually applied drugs. Finally, the influence of pain stimuli is modelled using a simple proportional time delay in combination with information about the event.

Vital signs and information about applied drugs are automatically obtained from devices within the smartOR network in real-time. Information about further events like pain stimuli are currently obtained post-hoc. In future, these events will be provided by a combination of an expert system and a workflow engine.

## Results

Using the described PK/PD model, blood pressure can be estimated and predicted during neutral conditions, depending on parameters like patient weight, age, size, and sex. The influence of pain stimuli can currently only be simulated post-hoc, because of a high inter-patient variation. Once the parameters have been estimated for a specific patient, the influence of pain stimuli can be considered during the prediction of blood

pressure. Unfortunately, since such a calibration would require forced pain stimuli, it is not feasible due to practical and ethical reasons.

## Conclusions

Blood pressure can be predicted during normal conditions. As a matter of fact, DoA cannot be assessed and predicted reasonably using only the blood pressure. Therefore, further vital signs and other clinical observations must be considered. Nevertheless, the aim of the prediction is to assist and not to replace the anesthetist by means of a combination of a PK/PD model and a workflow-supported expert system in particular in critical situations.

## ABSTRACT 12

# THERMOREGULATORY RESPONSES OF CORONARY BYPASS PATIENTS TO A REMOVAL OF THE HEATING BLANKET

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**Objectives:** The control and regulation of body temperature is one of the key homeostatic functions of the body. In response to internal or external stimuli (such as thermal disturbances of the environment, invading pathogens, medications, surgical trauma, psychological stress, etc.) these complex control mechanisms are continuously adjusted in order to maintain an optimal internal micro-environment. After a cardiac surgery, the thermoregulation is often highly disturbed. In this study, we hypothesized that insight in the dynamics of the thermoregulatory responses of coronary bypass patients can provide critical information about the health status of the patients. Previous studies showed that thermoregulatory responses are related to the extubation time. This study had two main objectives: i) To quantify the dynamics of the relation between body (Tbo) and skin (Ts) temperature of coronary bypass patients in response to removal of the heating blanket. ii) To relate these dynamics with the length of stay (LOS) at ICU.

**Methods:** For this preliminary study, seven coronary bypass patients were followed after surgery starting from the moment they arrived at the ICU. During the first 30 minutes at ICU, the patients were warmed by a forced-air heating blanket. The LOS of the patients ranged from 25 hours to 410 hours. Skin temperature (toe), core body temperature (blood), heart rate (bpm), medication (mg and ml), forced-air warming by heating blanket (etc.) were measured for a period of eight hours. The sampling interval of the recorded temperature time-series was 1 min. A data-based transfer function modelling approach was used to determine the dynamics of the temperature profiles. The models described the relation between the blanket temperature (Tbl), the core body temperature (model inputs) and the skin temperature (model output).

**Results:** The developed models were very accurate ($R2 > 0.93$). For every patient, second order models were found representing the relations between the model inputs (Tbo and Tbl) and the model output (Ts). Based on the preliminary experiments, the model results suggested that the feedback gain between Tbo and Ts is related to the length of stay (hours) at ICU. More specifically, patients with a larger LOS showed smaller feedback gain values.

**Conclusions:** To conclude, this study suggests that the dynamics of the thermoregulatory response to surgery of coronary bypass patients can reveal information of the patients' postoperative recovery.

## ABSTRACT 13

# COMBINED NETWORK AND MATHEMATICAL MODELING SUGGESTS NOVEL INFLAMMATION POSITIVE FEEDBACK CIRCUIT AND ROLE FOR IL-1A IN EXPERIMENTAL TRAUMA/HEMORRHAGE AND HEPATOCYTE HYPOXIA

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**Objectives:** Trauma/hemorrhagic shock (T/HS) is the most common cause of death for young people in the U.S., costing over $400 billion annually. Most deaths from T/HS occur due to the Multiple Organ Dysfunction Syndrome (MODS). MODS is thought to be due, in part, to dysregulated inflammation. We have employed computational modeling to define key networks and mechanisms of post-T/HS acute inflammation. We utilized a Dynamic Bayesian Network (DBN) algorithm (adapted from Grzegorczyk & Husmeier, Bioinformatics 27:693 [2010]). Given time-series data, DBNs provide a way of inferring causal relationships based on probabilistic measures. This approximation helps to suggest the overall network structure, including central nodes that exhibit feedback.

**Methods:** C57Bl/6 mice were subjected to T/HS for 0-4 h. Separately, C57Bl/6 hepatocytes were subjected to an in vitro surrogate of T/HS, namely hypoxia (culture at 1% O2 for 1-72 h). Cytokines/chemokines were assayed in the plasma (in vivo T/HS) as well as supernatants and lysates (in vitro hypoxia) by Luminex™, and the data were subjected to DBN analysis.

**Results:** DBN analysis suggested a core network that involves the cytokines IL-10 and IL-1α, as well as the chemokines IP-10 and MIG. Assigning biologically plausible functions to directed edges of the network resulted in a so-called incoherent type I feed forward loop that predicted pulsatile, "gatekeeper" behavior for the cytokine IL-1α - a behavior that was indeed observed in preliminary studies in mice subjected to T/HS. An initial ordinary differential equation (ODE) model was constructed to analyze this behavior in further detail. Simulated trajectories of cytokines and chemokines in the ODE model corresponded closely with the data.

**Conclusions:** Data-driven (DBN) and mechanistic (ODE) analyses suggest a novel inflammatory circuit with a central role for IL-1α in T/HS and hepatocyte hypoxia.

## ABSTRACT 14

# SENSITIVITY OF HUMAN IMMUNE RESPONSE TO INFLUENZA A VIRUS INFECTION AND ITS DEPENDENCE ON VIRUS AND HOST PHENOTYPES

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**Objectives:** Design of a phenotype-based abstraction of host immune response to influenza A infection and its application in an agent based population-level model of a pandemic

**Methods:** We developed a novel deterministic differential-equations model of a host-level response to influenza A virus (IAV) in which systemic and respiratory symptoms are mapped to interferon levels and the extent of damage to epithelial cells of the respiratory tract, respectively. We use an ensemble model approach to generate a distribution of parameters that represents the likelihood of the model fitting experimental data consisting of viral titers and symptoms. The resulting ensemble of models reflects patient and virus strain variability, identifiability and sensitivity of the model, and uncertainty in the data. The ensemble is computed using MCMC sampling enhanced by parallel tempering. We use the model to predict the variability of clinical factors, such as onset and severity of symptoms, across the ensemble. We further employ sensitivity analysis across the ensemble to relate population-scale clinical phenotypes (severity of infection, immunocenicity) to model parameters.

**Results:** Although marginal distributions of ensemble parameters vary over wide ranges, the sensitivities of trajectories to parameter changes are similar across the ensemble and characteristic of the model structure. Using principal component analysis, we compute linear combinations of parameters that represent predominantly virus specific (e.g. virulence) or predominantly host-specific (e.g. immunogenicity) phenotypes. By varying these phenotypes, we obtain a response surface depicting range of biologically relevant host responses to IAV infection. Applying the same methodology across the ensemble yields probabilistic response surfaces that provide a statistical representation of the time course of infection that can be efficiently integrated in a population level model.

**Conclusions:** The proposed response-surface methodology significantly increases computational efficiency over direct numerical integration, while at the same time reducing the number of variables to be varied, resulting in more realistic inputs to a population-level model of IAV.

## ABSTRACT 15

# DEVELOPMENT OF A LOW-FREQUENCY AUTOREGULATION INDEX FOR CALCULATION OF OPTIMAL CPP IN SEVERE TRAUMATIC BRAIN INJURY

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**Objectives:** Traumatic brain injury (TBI) is an important problem worldwide and a major cause of permanent disability and death in young patients. Currently there is controversy regarding the optimal cerebral perfusion pressure (CPP) thresholds required in the management of these patients. There is evidence that the critical optimal CPP threshold depends on the patient's capacity for pressure autoregulation, which is an inherent capacity to maintain cerebral blood flow constant over a broad range of CPPs. In severe TBI this capacity is frequently and dynamically disturbed. A possible tool for monitoring autoregulation is the pressure reactivity index (PRx) defined as a moving correlation coefficient between the mean arterial blood pressure (MAP) and intracranial pressure (ICP) based on signal capture at a frequency of at least 60 Hz. This need for high-frequency data has constrained the use of PRx to a few academic centers. Hinting towards the potential of an autoregulation-driven management of the individual TBI patient, recently an association was shown between outcome and the continuous calculation of an optimal CPP based on 4 hours of PRx. Here we present the novel 'Leuven autoregulation index' (LAx), developed through machine learning techniques and based on correlations between routinely available ICP and MAP signals at a standard minute-by-minute time resolution. Our main objective is a comparison between LAx and PRx in their role to determine continuous optimal CPPs for individual patients.

**Methods:** 19 TBI patients admitted to the University Hospital of Tubingen, Germany and with length-of-stays ranging from 7 hours to 19 days, were continuously monitored at the bedside using ICM+ software (Cambridge Enterprise) allowing for continuous PRx calculation. Autoregulation index vs. CPP plots for PRx and LAx, were computed to determine an optimal CPP every minute. The two indices were compared with respect to the optimal CPP values and the percentage of time for which they could be computed.

**Results:** The PRx produced on average an optimal CPP for 42% of the patient's length of stay. Two instantiations of the LAx computed on moving windows of either 4 or 8 hours were considered. The 4-hour and 8-hour LAx produced on average optimal CPPs on 57% and 64% of the stays respectively. The optimal CPPs of the 4-hour LAx were more similar to those of the PRx with an average rmse of 7.6 mmHg, while the 8-hour LAx had an average rmse of 10mmHg.

**Conclusions:** This study shows first, a small difference in continuous optimal CPPs derived from PRx and LAx, especially considering that differences of approximately 5 mmHg in CPP are not significant from a clinical perspective. Second, the LAx appears to be computable for longer periods of the patient's length-of-stay. Further studies are required to verify associations between outcome and LAx as well as to determine which version of the LAx should be used to guide CPP treatment. If however, the LAx is thus validated, it will be immediately applicable in all centers treating traumatic head injury without additional investments in software or additional invasive monitoring.

## ABSTRACT 16

# PATIENT ORIENTED CLOSED LOOP CONTROL OF EXTRACORPOREAL LUNG ASSIST

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**Objectives:** In cases of severe lung failure, long term extracorporeal membrane oxygenation has become a relevant treatment option in the ICU. With the availability of small and long term stable oxygenation circuits and dedicated drive units, it is now possible to apply ECLA in the intensive care unit on a routine basis. However, when comparing with the operating theater, were supervision and optimal setting of an extracorporeal circulation requires permanent attention of a specially trained cardio-technician/perfusionist the situation in the ICU less satisfactory. Machine operation is limited to less frequent care intervals or reaction to machine alarms. In order to provide similar levels of control performance, reliability and safety, ICU devices should provide advanced autonomous functions. In our interdisciplinary project “smart ECLA” we developed patient oriented control strategies to address this issue. Other project partners focused on dedicated safety mechanisms.

**Methods:** Our proposed ECMO system consists of two femoral venous cannulaes where venous blood is collected, a centrifugal blood pump (Medos DP3), an oxygenator (Medos Hilite 7000) as well as a jugular vein cannula for blood reinfusion. As a central processing and control prototyping unit we use a DSpace MicroAutoBox system. Actuators are a self designed electronical gas blender and a self designed pump control unit. Sensor components are pressure sensors (at pump inlet, pre oxygenator and return cannula), online blood gas measuring system (Terumo CDI500, pre and post oxygenator), a blood flow meter in the external circuit (Transsonic) as well as a fully equipped patient monitor (A/S3 Datex Ohmeda including ventilator gas monitoring and continuous cardiac output monitor). Each actuator and sensor component is connected to the CAN based data bus via microcontroller based network nodes, which implement data protocol translation. As a control concept we designed a dedicated cascaded control structure. The inner cascade controls oxygenator output blood gas partial pressure of O2 and CO2 respectively. Thus we were able to decouple the control inputs to the outer patient oriented cascade, where we control physiological target values for arterial oxygen saturation and venous CO2. The outmost cascade controls blood flow as to operate the oxygenator at an optimal operating point with least flow as possible.

**Results:** To validate the designed control structure, we performed a series of 10 animal experiments with 45-65 kg domestic pigs. After instrumentation and connection to the extracorporeal circuit, varying degrees of ventilatory insufficiency were simulated by applying a hypoxic gas mixture as well as using hypoventilation. Under normal operating conditions the controller was able to reach the desired physiological target concentrations within 20 Minutes for CO2 and 3-5 Minutes for O2. Even with extreme disturbances hypoxic episodes with SaO2<85 could be prevented. Only in cases where venous wall suction at the inlet cannulae prevented further increase of blood flow control targets could not be met.

**Conclusions:** Our experiments could prove efficacy and performance of the designed control system. Combined with advanced safety functions (not presented here) we show the feasibility of next generation ECLA devices enabling routine application in demanding hospital situations.

**ABSTRACT 17**

# CLASSIFYING NEONATAL SPELLS USING REAL-TIME TEMPORAL ANALYSIS OF PHYSIOLOGICAL DATA STREAMS – ALGORITHM DEVELOPMENT

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## Objectives

The term neonatal spell has become a common euphemism in contemporary neonatal intensive care units (NICU) for cardiorespiratory events that present with variable combinations of cessation of breathing, decrease in blood oxygen saturation and decreased heart rate. There are five main types of neonatal spell — central, mixed and obstructive apnea, isolated bradycardia and isolated desaturation. Spells may occur in the preterm infant as a consequence of physiological immaturity or as a clinical sign of more serious conditions such as lung collapse, infection and brain haemorrhage. At present, the need to determine the cause of neonatal spells frequently leads to invasive investigations and interventions, many of which may be unnecessary.

The Artemis platform enables real-time, multi-stream temporal analysis of multi-patient, high fidelity physiological data from bedside monitoring devices to provide meaningful clinical decision support. Our research goal is to develop precise, robust computational algorithms for the Artemis platform to accurately identify and classify spells that occur in the preterm population.

## Methods

Algorithms representing each type of neonatal spell are being developed based on the classical patterns described in the medical literature. The Artemis platform enables the capture and analysis in real-time of physiological data at the speed generated by the bedside medical device. In our research we are sampling heart rate, blood oxygen saturation at a rate of 1Hz together with impedance respiratory wave data at a sampling rate of 62.5Hz and ECG data at a sampling rate of 1000 Hz. As part of the algorithm development we have developed the ability to detect absolute falls in all parameters below set values. We have also developed algorithms to detect fixed percentage fall of parameters from a continuously assessed baseline. We have made a comparison of the output for relative and absolute heart rate and saturation falls for one patient over an entire day and compared both to manual data interpretation.

## Results

The manual comparison shows that there is good concordance between relative falls and clinically significant falls in heart rate and blood oxygen saturation. The absolute method detected 1117 falls in heart rate compared to 484 relative falls in one day. There were 92 absolute falls in blood oxygen saturation, compared to only 52 relative falls in the same day.

**Conclusions**

The ability to automatically detect clinically significant changes in heart rate and saturation using relative change rather than threshold values will pave the way for a unique system for detecting spells. In addition an alert system driven by relative falls may help in the future to reduce alarm fatigue in busy NICUs.

Following this initial development of the detection algorithms we will perform a comparison study of the Artemis algorithms with the only available current gold standard of manually interpreted polysomnography in infants breathing without respiratory support.

This study will lead to the development of precise, robust algorithms that enable detailed and accurate reports of spells occurring in infants breathing without respiratory support in the NICU.

**ABSTRACT 18**

# SCALE-FREE METABOLIC NETWORKS IN A PORCINE MODEL OF TRAUMA AND HEMORRHAGIC SHOCK

ER LUSCZEK PHD, DR LEXCEN PHD, NE WITOWSKI PHD, KE MULIER MBS, G BEILMAN MD

**Objectives:** Metabolic rate has been shown to possess scale-free properties under the assumption that oxygen is transported to the organism through the fractal-like vascular system. Cellular metabolic networks have been shown to possess scale-invariant properties via power law behavior of the network's degree distribution with a slope of $\gamma$, where $-2 < \gamma < -3$. Changes in oxygen delivery as a result of trauma and hemorrhage induce profound changes in cellular metabolism. We have previously evaluated scale-free metabolic networks of urine and skeletal muscle in an interim data set from our porcine model of trauma and hemorrhagic shock. In muscle metabolic networks, scale invariance is not present at any experimental timepoint until post-resuscitation. We wished to evaluate liver networks in this context and compare them to the muscle networks. We hypothesize that a lack of scale invariance in these networks is related to disruptions in oxygen delivery and utilization.

**Methods**: Nineteen fasted male Yorkshire pigs were subjected to a standardized protocol consisting of instrumentation and laparotomy, pulmonary contusion, liver crush injury, and 35% controlled bleed. Liver samples were collected at six timepoints reflective of baseline (post-laparotomy), shock, early, mid, and late resuscitation, and post-resuscitation. Nuclear magnetic resonance spectroscopy and Chenomx software were used to identify and quantify the concentrations of 48 metabolites in each liver sample. Networks were constructed for each timepoint using the Weighted Gene Correlation Network Analysis package for R software. The degree distribution of each network was evaluated for scale invariance.

**Results:** According to the parameters defined above, liver metabolic networks demonstrated scale invariance at early resuscitation and at post-resuscitation. This was in contrast to the muscle metabolic networks, which only displayed scale invariance at the post-resuscitation timepoint. Limitations include that networks were constructed from an incomplete set of liver metabolites, that tissue sampling was relatively infrequent, and that a limited number of animals were included in the study. Nineteen animals comprised the data set for the baseline network. Deaths over the course of the experiments reduced the data set to eight animals at the post-resuscitation timepoint.

**Conclusions:** The lack of scale invariance at baseline indicates that midline laparotomy constitutes trauma severe enough to have implications for the underlying scale-free structure of metabolic networks. This is supported by analysis of both the muscle and urine metabolic networks. The scale invariance observed during early resuscitation in the liver contrasts with the lack of scale invariance observed at this timepoint in the muscle. Further testing and analysis of post-interim data is required to confirm this observation. If it continues to hold, this result implies that the liver responds to trauma and hemorrhage differently than skeletal muscle, and that the organism prioritizes maintenance of homeostasis in the liver over that of skeletal muscle. Additional evaluation of a host of data related to oxygen delivery and consumption as well as analysis of metabolic networks from non-hemorrhaged controls is required to confirm our hypothesis that loss of scale-free properties in metabolic networks is related to dysfunction in oxygen availability and use in trauma and shock.

**ABSTRACT 19**

# NONLINEAR VARIABILITY IN A COMPUTATIONAL MODEL OF RESPIRATORY RHYTHM GENERATION

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Excessive variability in neurally generated rhythms may indicate an instability while insufficient variability could result from an inability to adapt to environmental stressors. Previous studies have addressed the presence of variability of the neural control of respiration in both the clinical context as well as the experimental context. It remains unknown whether variability is a cause or merely a symptom of respiratory dysfunctions such as apneas, period breathing in infants, and Cheyne-Stokes breathing in adults. A fundamental source of respiratory pattern generation is the preBötzinger complex (preBötC) which is part of the ventral respiratory column located in the brainstem. Here we use a computational model of the preBötC to analyze the variability of motor output patterns. In particular, we look at the relationship between sensory input and the resulting variability in the motor output pattern.

Our model utilizes Hodgkin-Huxley style neurons that are divided into three cell types: hypoglossal motoneurons, premotoneurons, and preBötC cells that are configured for bursting by means of a persistent sodium current. The architecture consists of a feedforward hierarchy such that motoneurons are driven by premotoneurons and premotoneurons are driven by preBötC cells. The preBötC cells receive inputs from each other and also receive random tonic drive in the form of excitatory and inhibitory postsynaptic currents. This tonic drive represents chemosensory and mechanosensory feedback. Hierarchical levels are randomly connected with a fixed connection probability or density. We analyzed the spike histogram of the hypoglossal motoneuron population which represents the whole-nerve activity recorded from cranial nerve XII in experiments. Two nonlinear variability measures were used: mutual information and sample entropy.

We studied the relationship between properties of the tonic drive to preBötC cells and the resulting variability in the motor output pattern. We varied the quantity of tonic inputs and connection densities. We found that increases in the quantity of inputs and connection densities to preBötC cells both produced an increase in overall variability.

This study proposes a computational model that describes how variability in respiratory patterns may be affected by physiological properties of the respiratory neural control system, including chemosensory and mechanosensory feedback. A nonlinear effect is determined by multiple properties of the control network. Knowledge of this relationship at the kernel level is important in understanding how variability is produced and controlled within the larger closed-loop system that both controls and reacts to changes in respiratory patterns.

**ABSTRACT 20**

# MODELING COAGULATION ACTIVATION IN TRAUMA PATIENTS

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**Objectives:** Acute traumatic coagulopathy occurs when trauma injury is combined with shock, and is associated with considerable morbidity and mortality. While studies link the clinical presentation of coagulopathy to interventions and outcomes, they provide little mechanistic insight into the molecular drivers of coagulopathy and coagulation that influence outcome. The purpose of this work is to examine coagulation in individual trauma patients by inferring a mechanistic model for coagulopathy, parameterizing the model for each patient, and investigating the correspondence between model outputs and patient outcomes.

**Methods:** Two modeling methods are discussed in this work. The first method involves a mechanistic investigation of an existing coagulation model to validate its suitability for traumatic coagulopathy and to determine any correspondence between model outputs and trauma patient outcomes. The existing model is the 2002 Hockin-Mann model, with 34 states and 43 chemical kinetic equations, which was developed to model coagulation for hemorrhagic diseases and venous or coronary thrombosis. A popular indicator of coagulation activity was employed to validate this model. The model's output of thrombin concentration with time, after activation by tissue factor, was compared to Calibrated Automated Thrombogram (CAT) data for severely injured patients admitted to San Francisco General Hospital (SFGH). The model's utility was determined by clustering and comparing its output of the concentrations of blood factors VIIIa and Va 60 seconds after model initialization to patient outcomes. The clustering methods chosen were k-means clustering and support vector machines.

The second method discussed is the black-box modeling of CAT data using techniques from the field of system identification. A simplified single-input, single-output linear time-invariant dynamical system model of thrombin generation was identified and then parameterized for each patient with Simulink Design Optimization. The effects of initial concentrations of a patient's blood factors on the model's parameters were determined through forward regression. This determination facilitated a generic prediction of the concentration of thrombin over time after activation by tissue factor given any trauma patient's initial blood condition.

**Results:** Our results indicate that the thrombin output of the Hockin-Mann model does not match trauma patient CAT data for nearly all SFGH patients. In addition, the Hockin-Mann model clustered outputs are no more useful than the clustered initial data when indicating mortality outcomes and clinical intervention effects. The results also show that the black-box thrombin model output more closely predicts actual CAT data than the Hockin-Mann model, yet is much simpler at only three states and five parameters. Despite its simplicity, the black-box model parameters account for known coagulation cascade effects such as factor inhibition and the extrinsic and intrinsic pathways, providing insight into drivers of traumatic coagulopathy.

**Conclusions:** Our work demonstrates that it is possible to model and identify important trauma patient-specific coagulopathy variables, and to track these variables accurately over time. The results of this work provide insight into the dynamic mechanisms behind coagulation after trauma, reduce the diagnostic space, and provide a step towards identifying molecular drivers of outcome. Future work will investigate the utilization of these mechanisms to accurately predict trauma patient outcomes.

**ABSTRACT 21**

# LATE ONSET NEONATAL SEPSIS DETECTION IN NEWBORN INFANTS VIA MULTIPLE PHYSIOLOGICAL STREAMS

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Objectives: Early diagnosis of neonatal sepsis is challenging because the clinical features are non-specific in the early stages of infection. Recent work suggests that late onset neonatal sepsis (LONS) patients are characterized by low heart rate variability (HRV) and normal respiratory rate variability (RRV); whereas patients receiving narcotics have reduced HRV and RRV[1].

Using 60 second spot readings from the Women and Infant's Hospital, Rhode Island (WIHRI), where data was collected remotely using Artemis Cloud[2]; we employ temporal abstraction to create hourly HRV and RRV summaries. We examine the relationship between low HRV and LONS, testing the hypothesis that low HRV is present prior to LONS diagnosis. We further investigate whether RRV improves model discrimination.

## Methods

We analyzed data from 128 patients admitted to the WIHRI NICU for more than four days between March 2010 and April 2011. Variability was calculated by taking the absolute value of the difference between consecutive time points and creating hourly abstractions based on number of minutes where the absolute value of the difference is less than a given threshold.

The population was classified by LONS status; t tests examined relationships between continuous variables. Logistic regression assessed the association between the portion of the NICU admission classified as low HRV (defined as 37 minutes low HRV per hour), and LONS; and with the proportion of the NICU admission classified as low RRV (defined as 20 minutes low RRV per hour), and LONS. The research was approved by the Hospital's Research Ethics Board.

## Results

LONS occurred in 10.3% of patients. The mean length of data collection for LONS patients was 77.1 days as compared to 40.7 days for non-LONS patients ($p<.0001$). The mean % low HRV for LONS patients was 27.6% as compared to 9.8% for non-LONS patients ($p<.0001$). Regression models showed that over the patient stay, each one unit increase in % low HRV was associated with a 6.2% increase in the odds of LONS ($c=0.823$). After relatively aligning to the point of diagnosis, the mean % low HRV for LONS patients was 50.0% as compared to 9.8% for non-LONS patients ($p<.0001$). The average length of stay before LONS was 18.5 days. The mean gestational age for LONS patients was 29.2 weeks as compared to 32.9 weeks for non-LONS patients ($p<.0001$). Each one unit increase in % low HRV was associated with a 10.3% increase in the odds of LONS ($c=0.944$), showing that low HRV is associated with LONS before clinical diagnosis. The results support the hypothesis that low RRV alone is not associated with LONS: the mean % low RRV for

LONS patients was 3.4% as compared to 2.5% for non-LONS patients (p=0.3514). Each one unit increase in % low RRV was associated with a 14.5% decrease in the odds of LONS; however, the results were not statistically significant.

**Conclusions**

Low HRV was positively associated with LONS prior to clinical diagnosis. Future work will analyze shorter time windows and include infusion pump data to report on the results of drug existence and dosage on HRV and RRV.

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**ABSTRACT 22**

# TISSUE-SPECIFIC PATTERNS OF CASPASE-1 AND CYTOKINES IN EXCISIONAL WOUNDS ARE ALTERED BY SHOCK IN RAT SKIN AND MUSCLE

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**Objectives:** Skin and muscle wounds often lead to significant inflammation in the affected tissue. The primary mechanism by which inflammation is initiated, sustained, and terminated is cytokine-mediated immune signaling, but this can be altered by cardiogenic shock. The complexity and context sensitivity of immune signaling in general stymied a clear understanding of these signaling dynamics. We hypothesized that advanced numerical and biological function analysis methods would help elucidate the inflammatory response to skin and muscle wounds in rats, both with and without concomitant shock.

**Methods:** We studied two experimental groups: Wound only ("wound group"), and wound with cardiogenic shock ("shock group"). In the "wound group", 4 Lewis rats were anesthetized and an excision biopsy was taken from the lateral aspect of the thigh on one of the hind limbs in each of the rats. In the "shock group", 4 Lewis rats were sacrificed and excision biopsy (wound) was carried out 15-30 seconds after cessation of heartbeat. Skin and muscle tissue was then separated and assayed for total protein content by BCA assay, and the inflammation biomarkers interferon (IFN)-γ, interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-18, monocyte chemotactic protein (MCP-1), growth-related oncogene (GRO)/KC, tumor necrosis factor (TNF)-α, and granulocyte-macrophage colony stimulating factor (GM-CSF) were assayed by Luminex™. Caspase-1, which drives activation of the NLRP-3 inflammasome, was assessed by western blot assay. Statistical and computational analyses of cytokine network profiles (one-way balanced ANOVA, unpaired one-tailed heteroscedastic t-test, principal components analysis [PCA], and confirmatory factor analysis [FAN]) were performed in Matlab™. **Results:** GM-CSF was elevated in the wound group ($p<0.05$), while IL-4, IL-12p70, IFN-γ, and IL-18 were elevated in the shock group ($p<0.05$). IL-1α and IL-18 were more elevated in skin vs. muscle for ($p<0.05$), which was suggestive of inflammasome activation in the skin. MCP-1, IL-1β, IL-2, IL-6, IL-10, IL-4, IL-12p70, and TNF-α ($p<0.05$) were also differentially higher in skin vs. muscle. Immunoblotting revealed caspase-1 activation in skin but not muscle. Notably, IL-1α and IL-18, along with caspase-1, were greatly elevated in the skin following cardiogenic shock ($p<0.05$). PCA suggested that >95% of observed variance could be explained by two principal components in skin and muscle, and suggested distinct groups of inflammatory mediators induced in the "wound group" vs. the "shock group". IL-18 and IL-1α were primary contributors to the first principal component, while IL-6, MCP-1, GRO/KC, and IL-1β were primary contributors to the second principal component. PCA results were reinforced by FAN.

**Conclusions:** Caspase-1 and the NLRP-3 inflammasome appear to be key factors in determining the type and severity of the inflammatory response to excisional wounding, especially in the presence of shock. Activated caspase-1 is associated with defined, compartmentalized patterns of cytokine production that may be discerned via data-driven modeling.

**ABSTRACT 23**

# GLOBAL SENSITIVITY ANALYSIS OF ENDOTOXIN-INDUCED ACUTE INFLAMMATORY RESPONSES PREDICTS THE MULTIMODAL DEPENDENCE OF GLOBAL TISSUE DAMAGE BOTH ON HOST IL-6 RESPONSES AND ENDOTOXIN DOSE

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**Introduction**: Acute inflammatory responses to various stimuli involve complex nonlinear interactions among inflammatory cells and their products. We previously developed a nonlinear ordinary differential equation (ODE) model to explain the dynamics of endotoxin (lipopolysaccharide; LPS)-induced acute inflammation and associated whole-animal damage/dysfunction (a proxy for the health of the organism, whose likely molecular correlate is damage-associated molecular pattern molecules) [1]. That model includes the inflammatory mediators TNF-α, IL-6, IL-10, and nitric oxide (NO), and was calibrated in part on LPS doses of 3, 6, and 12 mg/kg in C57Bl/6 mice. In the current work, we analyzed the major determinants of the resulting tissue damage using a global sensitivity approach.

**Methods:** The precise inflammatory role of IL-6 and its utility as a biomarker or therapeutic target have been the source of much debate, presumably due to the complex pro- and anti- inflammatory effects of this cytokine Therefore, we chose to investigate the sensitivity of the area under the IL-6 curve ($AUC_{IL6}$) and the area under the damage curve ($AUC_D$) to the 51 rate parameters of the ODE model for different levels of simulated LPS challenge (1 to 15 mg/kg). Due to the complex nonlinear interactions between the rate parameters, we chose a variance-based global sensitivity approach. Specifically, we chose the Random Sampling High Dimensional Model representation (RS-HDMR) developed by Rabitz et al. in order to reduce the computational cost associated with Monte Carlo Sampling of the parameter space[2]. $10^5$ Monte Carlo samples were generated by 100-fold variation of the rate parameters around their nominal values. Then, the Sobol' global sensitivity indices were estimated for each output: $AUC_{IL6}$ and $AUC_D$.

**Results:** As expected, the overall damage was highly dependent on the parameters affecting the activity of IL-6 during the different stages of acute inflammation. The $AUC_{IL6}$ showed a bimodal distribution, with the higher peak becoming prominent with increasing LPS concentration. On comparing the $AUC_{IL6}$ and $AUC_D$, we found that overall damage was minimal at low and high $AUC_{IL6}$. In contrast, intermediate levels of $AUC_{IL6}$ resulted in high damage, and this appeared to be due to the insufficiency of damage recovery driven by nitric oxide-mediated anti-inflammatory responses of IL-6.

**Conclusion**: These studies suggest that the host's health status during acute inflammatory events depends in a nonlinear fashion both on the magnitude of the inflammatory stimulus, as well as on the host's propensity to produce the key mediator IL-6 and NO-mediated downstream responses.

**References:**

[1] Torres *et al*. Shock 32(2), pp. 172-178, 2009

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## ABSTRACT 24

### INFORMED TARGET DISCOVERY FOR GENE AND STEM CELL THERAPY IN ACUTE LUNG INJURY

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**Introduction:** As the most severe form of acute lung injury, sepsis-induced ARDS accounts for 9% of all patient deaths in the ICU, and 18000 Canadian deaths annually. Despite this urgent need for treatment, the main available strategy is protective lung ventilation which improves patient survival by lowering the ventilating tidal volume, and there are no specific pharmacological treatments that target sepsis-induced acute lung injury. Thus, microarray technology acts as a high-throughput tool that identifies targets for therapeutic regulation.

**Objectives:** 1) To identify genes that show differential expression across sham, cecal ligation perforation (CLP)-operation and mesenchymal stem cell (MSC)-treatment in the murine model, using microarray technology; 2) To identify miRNAs that exhibit significant changes in expression levels in the 3 conditions, using miRNA array; 3) To identify candidate target genes of therapeutic potential which can be regulated by miRNA for ARDS/ALI treatment.

**Methods:** Genes with differential expression patterns that can be targeted to treat and suppress ARDS/ALI were identified through microarray and microRNA array technology. In the murine model of cecal ligation perforation (CLP)-induced ARDS, mRNA microarray was employed to investigate changes in the global gene expression patterns in the lung due to CLP-induced sepsis and mesenchymal stem cell treatment. Separately, microRNA array was also performed to elucidate changes in miRNA expression. SAM analysis identified genes that showed significant transcriptional changes between sham, CLP-operated mice, and CLP followed by MSC treatment in the mRNA profile. While LIMMA analysis revealed the microRNAs that exhibited significant fold change across the three conditions.

**Results:** A total of 4702 genes with differential expression between sham and CLP-operated mice was identified by SAM analysis, with a false discovery rate at 3.0%. On the miRNA side, algorithms provided by targetscan.org and microrna.org generated two lists of putative targets of mmu-miR-762 (LIMMA-selected, adjusted $p=0.049$). Merging the SAM-selected genes with statistical significance, with the putative targets of mmu-miR-762, produced a joined list of 343 genes. Among the 343 genes, the classical sepsis marker, angiotensin converting enzyme (ACE), was identified. ACE is of great clinical relevance and has also been implicated in the pathogenesis of ARDS with its effector peptide angiotensin (Ang) II. From the mRNA profile, ACE was shown to be down regulated after CLP-operation in comparison to the control group, and this was also confirmed by western blots. Similarly, the expression pattern of heme oxygenase-1 (HO-1) from the *in silico* data matched the protein level analysis by western blot.

**Discussion/Conclusion:** The combination of microarray and microRNA array is highly information-intensive in the identification of candidate therapeutic mRNAs and target microRNAs that could be used to regulate gene expression levels, in the treatment of sepsis-induced ARDS. Mesenchymal stem cell administration after CLP-operation in the murine model acts as a tool that offers great insight in the detection of therapeutically relevant genes to treat ARDS/ALI.

**ABSTRACT 25**

# LIÉNARD-CLASS DYNAMICAL MODELS OF THE HUMAN HEART ATRIUM: HOW TO INCLUDE THE AUTONOMIC MODULATION OF HEART RATE?

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**Objectives:** Heart rate variability is one of the major factors in the effective functioning of the cardiovascular system. Usually, existing physiological models of the heart are too complex to allow an investigation of the long time dynamical properties of the heart rate. As a consequence, very rarely do they simulate heart rate variability comparable in length with portable ECG recordings. At the ICCAI 2011 conference in Bonn, we presented a model of the right atrium which made this possible. To verify its properties, in this presentation, we study supraventricular arrhythmias, including AVNRT and atrial parasystole. We will extend the model presented at ICCAI 2011 and discuss several ways to include into the model the autonomic modulation of the heart rate. We describe ways to introduce models of external modulation with different degrees of complexity.

**Methods:** In the model of the right atrium proposed here, different cardiac tissues are described by sets of different ordinary differential equations, all belonging to the class of Liénard nonlinear dynamical systems. We have developed a series of models of the complete right atrium with differing anatomical simplifications, from a simple 1D strip of tissue up to a 2D mapping of the atrium including chosen anatomical details.

**Results:** The simulations allowed to reconstruct the phase response of the atrium to a brief vagal stimulation. We discuss and present examples of the variance of the interspike intervals as a function of the type of the external modulation. We also discuss the shift of the location of the pacemaker within the sinoatrial node in response to vagal nerve stimulation.

**Conclusions:** The introduction of a simple Liénard nonlinear dynamical system model of the nodal tissue enabled the study of ways to introduce the autonomic modulation of the heart rate into the simulations. This allows an investigation of the long time dynamical properties of the simulated heart rate and a comparison with heart rate variability measured in clinical recordings, also during arrhythmia.

**ABSTRACT 26**

# MICROARRAY META-ANALYSIS IDENTIFIES ACUTE LUNG INJURY BIOMARKERS IN DONOR LUNGS THAT PREDICT DEVELOPMENT OF PRIMARY GRAFT FAILURE IN RECIPIENTS

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**Objectives:** To characterize an injury-specific gene expression signature that allows calculated assessments of the development of lung injury in humans, using meta-analysis of gene expression microarray data based on animal models of lung injury.

**Methods:** Our microarray meta-analysis consists of 77 microarray chips across six platforms, in two species and various animal models exposed to lung injury with or without mechanical ventilation. Each of the gene chips were categorized based on how lung injury was elicited. The two main strategies to pool chips were: (1) one-hit and (2) two-hit lung injury models, and effect size (change in gene expression) was calculated between non-injurious and injurious conditions. In order to integrate individual effect sizes calculated from each experiment, a random effects model was used. The gene expression signatures produced by the meta-analysis were used to generate classification models to predict the development of lung injury in human lung transplant recipients.

**Results:** In validating two injury-specific lists of genes with differential expression that were also generated from the meta-analysis of lung injury models, external data sets and prospective data from animal models of ventilator-induced lung injury (VILI) were used. Both new and previously implicated VILI-related pathways were enriched with differentially regulated genes, as revealed in the pathway analysis. From these identified gene expression signatures in animals models of lung injury, classification model predicted the development of primary graft failure (PGF) in lung transplant recipients with accuracy greater than 80% based on injury profiles from transplant donors. With the aid of meta-analysis to identify differentially-expressed genes, superior classifier performance can be achieved in comparison to a single study-based differential analysis.

**Conclusions:** Meta-analysis of microarray chips was able to generate a list of genes with differential expression that have been implicated in VILI-related pathways. Expression patterns of these identified genes were used to produce more reliable classification models that could predict future development of lung injury (PGF) in humans with high accuracy.

**ABSTRACT 27**

# NETWORK ANALYSIS OF TRANSCRIPTIONAL RESPONSES INDUCED BY MESENCHYMAL STEM CELL TREATMENT OF EXPERIMENTAL SEPSIS

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**Objectives:** To identify molecular targets and mechanisms of the protective effects conferred by MSC treatment in sepsis by investigating transcriptional responses of target organs subjected to MSC therapy.

**Methods:** Cecal ligation and perforation (CLP) was performed in C57BI/6J mice to induce a polymicrobial model of sepsis, after which MSCs or saline were administered intravenously 6 hours later. Twenty-eight hours after CLP, total RNA extracted from lungs, hearts, kidneys, livers and spleens was subjected to microarray and hybridized to Illumina Mouse WG-6v2 bead arrays. The transcriptional profiles of all organs were analyzed using a network knowledge-based approach.

**Results:** A list of 4751 genes showed significant differential expression between the placebo-treated group and MSC-treated mice (LIMMA: linear model for microarray analysis, 2,305 up and 2,446 down-regulated, adjusted p-value $\leq 0.05$). In all 5 organs examined, 3 common effects of MSC administration were detected through the analyses on transcriptional responses: 1) mitigation of sepsis-induced mitochondrial-related functional derangement; 2) reduction of sepsis-induced innate immune pro-inflammatory transcriptional responses; and 3) coordinated expression of transcriptional programs implicated in the preservation of endothelial/vascular integrity.

**Conclusions:** The protective effect of MSC therapy in sepsis is not confined to an individual mediator or pathway as indicated by the transcriptomic analysis, on the contrary, a variety of complementary activities that have an effect on biological networks play crucial roles in the regulation of host cell metabolism and inflammatory response.

**ABSTRACT 28**

# STEPS TO A COUPLING ANALYSIS OF TRANSIENT CARDIOVASCULAR DYNAMICS

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**Objectives:** The analysis of effects from coupling in and between systems is important in data driven investigations as practiced in many scientific fields. It allows deeper insights into the mechanisms of interaction emerging among individual smaller systems when forming complex systems as in the human circulatory system. For systems featuring various regimes usually only the epochs before and after a transition between different regimes are analysed, although relevant information might be hidden within these transitions. Transient behaviour of cardiovascular variables may emerge on the one hand from the recovery of the system after a severe disturbance or on the other hand from adaptive behaviour throughout changes of states. It contains important information about the processes involved and the relations between state variables like heart rate, blood pressure and respiration. Therefore, the analysis of time-dependant couplings during these transient epochs is an important current research problem. Hence it is essential to extend existing coupling measures for a time-variant coupling analysis which is capable of determining coupling direction, strength and time offset $\tau$ from transient dynamics in multivariate cardiovascular data.

**Methods:** We use multiple realizations of time dependant dynamics in order to estimate existing coupling measures not over the time domain of one time series but over a certain time point of several realizations of the same system. This allows us to analyse coupling behaviour even on very short time scales which cannot be done by using e.g. windowed methods. This method can be applied to almost any existing coupling measure, permitting us to use the scope of nonlinear, multivariate measures already developed. We chose the method of Symbolic Coupling Traces (SCT) for a first test of the ensemble method. Besides using model data we applied the methods to stationary stages of a polysomnographic data set consisting of 9 patients suffering from obstructive sleep apnea and 10 controls to assess the performance of the new measure.

**Results:** We analysed the coupling between systolic (S) and diastolic (D) blood pressure and beat-to-beat intervals (B). First we applied the time-domain SCT. We found significant couplings ($p<0.01$) from D on S (symmetric, $\tau = 1$), from B to S (diametric, $\tau = 2$) and feedback connections between D and B (diametric, $\tau = 0$) and B and S (symmetric, $\tau = 0$) in both groups. Applying the ensemble SCT we were able to show the same coupling relationship for each individual time-point. As we regarded only stationary segments of the time series in this first test, no time dependant fluctuations in the results of the ensemble SCT could be seen.

**Conclusions:** The coupling analysis of transient cardiovascular dynamics is important. The first results of our new method show potential in order to get new insights about the short-term nonlinear cardiovascular regulation and to better predict potential health risks using the ensemble approach. The next steps are to compare several methods from the fields of Granger causality, information theory and symbolic pattern analysis to select appropriate measures for transients and non-stationary physiological data. These new methods will then be applied to the data of two larger studies, consisting of sleep data and data recorded during an orthostatic test.

**ABSTRACT 29**

# VALIDATION OF THE AUTOMATED ELECTROCARDIOGRAM SELECTION OF PEAKS (AESOP) ALGORITHM DURING ACUTE CHANGES IN THE ELECTROCARDIOGRAM DUE TO HEMORRHAGIC SHOCK AND SELECTIVE AUTONOMIC BLOCKADE IN CONSCIOUS SEDATED SWINE

NEHEMIAH T LIU, KERFOOT III WALKER, JOSÉ SALINAS

LEOPOLDO C CANCIO AND ANDRIY I BATCHINSKY

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**BACKGROUND:** Previous studies have shown that heart-rate complexity (HRC) is useful for monitoring patients during critical states. However, clinical use of HRC will require continuous, accurate, and automated R-wave detection. The Automated Electrocardiogram Selection of Peaks (AESOP) algorithm was developed to meet this requirement as well as optimize sensitivity (Se) and positive predictive value (+P). Unlike existing algorithms which employ a single detection approach, the AESOP algorithm fuses the outputs of four published R-wave detectors (Hamilton-Tompkins, Afonso-Tompkins-Nguyen-Luo, Christov, and Zong-Moody-Jiang) into a single output based on a K-nearest-neighbor approach. The purpose of this study was to validate AESOP against an electrocardiogram (ECG) waveform dataset consisting of multi-hour records under conditions of hemorrhagic shock (HS) and partial-to-total autonomic blockade yielding a wide range of ECG morphologies.

**MATERIALS AND METHODS:** This study involved 32 ECGs from a conscious sedated porcine model of severe hemorrhagic shock (HS) which involved removal of 60% of estimated blood volume over 60 minutes. ECGs were acquired at sampling frequency of 500 Hz and contained electromechanical noise (motion artifacts) as well as organic noise, i.e., arrhythmic changes consistent with severe exsanguinations and pre-terminal and terminal loss of ECG morphology. Of these 32, 10 swine were given vagal blockade (VB, via 0.05mg/kg intravenous atropine bolus before HS followed by a 0.5mg/kg/hr continuous rate infusion during HS) and 12 were given sympathetic blockade (SB, via 0.5mg/kg propranolol bolus before HS followed by a 0.5mg/kg/hr continuous rate infusion during HS). The remaining 10 swine (control, CTL) underwent hemorrhage alone. Lengths of records varied from approximately 2 to 5 hours depending on survival. The gold standard for validation was manual verification of R waves. A 50-millisecond tolerance window was used for classifying detected beats as true beats.

**RESULTS:** For 32 ECG records, the AESOP algorithm achieved an overall Se of 97.9% and a +P of 97.5%, thereby outperforming each of its component algorithms in terms of mean Se/+P, i.e., tradeoff between Se and +P. Similarly, AESOP performed better than the rest against records from each experimental group.

**DISCUSSION/CONCLUSION:** AESOP's optimizations and overall high Se and +P under varying conditions from unperturbed through near-total selective autonomic blockade to HS, organic and electromechanical noise demonstrates its potential application for real-time R-wave detection and HRC monitoring of trauma patients.

**FROM/TO TIME PERIOD OF STUDY:** January 1, 2011 – May 15, 2012.

**ABSTRACT 30**

# ROBUST REAL-TIME CALCULATION OF HEART-RATE COMPLEXITY USING MULTIPLE NOISY WAVEFORM SOURCES

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**PURPOSE/AIMS:** Heart-rate complexity (HRC) has been proposed as a new vital sign for combat casualty care. The purpose of this research was to develop a robust method for determining HRC continuously in real time in critically ill patients that employs multiple waveform channels and compensates for noise and the untrustworthiness of data.

**DESIGN:** Retrospective study.

**POPULATION/SAMPLE STUDIED:** 250 critical care patients, as described by records in the Massachusetts General Hospital/Marquette Foundation Waveform Database, were selected for this study. Of these patients, 155 were males, 77 were females, and 18 were not specified. In addition, 20 patients had atrial fibrillation (AF), 65 had sinus tachycardia (ST), 111 had sinus rhythm (NSR), and the remaining patients had other various underlying rhythms, such as sinus bradycardia and ventricular pacing.

**METHOD(S):** Using simultaneously acquired ECG (Leads I, II, V) and ABP waveforms sampled at 360 Hz from 250 patients (over 375 hours of patient data), we evaluated a new data fusion framework for computing HRC in real time. The framework employs two algorithms--one for detecting the R waves of an ECG lead waveform, and the other for detecting the peaks of the ABP waveform--as well as signal quality indices. All R waves were also manually verified. HRC was then calculated (via the method of sample entropy).

**DATA ANALYSIS:** Continuous data were analyzed by Wilcoxon test. Two separate analyses were conducted in order to obtain Bland-Altman plots for HRC values derived from manually verified sequences, and for those derived from automatically detected peaks. Box plots of differences between mean HRC values were also obtained.

**FINDINGS:** HRC values varied by rhythm: AF ($1.0 \pm 0.9$); NSR ($0.9 \pm 0.5$); and ST ($0.7 \pm 0.5$) ($p=0.0002$). For both analyses (Bland-Altman and box plot), the "fusion" of waveform sources produced better error density distributions than those derived from individual waveforms.

**CONCLUSIONS/RECOMMENDATIONS:** Lower HRC for ST patients is consistent with the fact that this group often has concomitant illnesses. The data fusion framework was shown to provide in real-time a reliable continuously streamed HRC value, derived from multiple waveforms in the presence of noise and artifacts. This approach will be validated and tested for assessment of HRC in trauma patients.

**FROM/TO TIME PERIOD OF STUDY:** August 3, 2011 – January 20, 2012.

**ABSTRACT 31**

# TOWARDS THE IDENTIFICATION OF INDEPENDENT MEASURES OF HEART RATE VARIABILITY

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**Objectives:** There is a plethora of measures applied to the study of heart rate variability (HRV). The physiological explanation of those measures remains unclear; most measures track similar phenomena, and high correlation exists among them. Eliminating redundancy for patient classification is a principal objective (e.g. distinguishing patient who will develop infection from those who will not). Indeed, redundant features may impair a classifier derived from HRV, reducing its ability to produce reliable decision boundaries. This work addresses this issue, proposing a robust procedure to identify a set of uncorrelated measures of arbitrary size (i.e. tuned for a specific application).

**Methods:** This study uses a dataset tracking the diurnal variations in HRV in 42 ambulatory healthy subjects with heterogeneous age and fitness levels (i.e. Body Mass Index and clinical history). For each subject, 93 measures of HRV were tracked over time through a windowed analysis (5 min window size, no overlap over 24 hours) of the relative R-R interval time series. For each pair of measures the amount of shared information was estimated by extracting their Spearman correlations. Then, through bootstrapping (i.e. iterative recalculation) the population statistics were estimated, obtaining the mean and standard error (and median and interquartile range error) of the values of non-linear correlation between each pair of measures. A greedy optimization algorithm was then used to create a decision surface showing the trade-off between the number of measures to select and their correlation; this enables the determination of an optimal set of uncorrelated variability measures.

**Results:** The population estimates of correlation showed an error of ± 0.1 (with 95% confidence interval), therefore providing a robust estimate of the relationship between the measures. From the decision surface created by the optimization algorithm for this data set, we selected to keep 4 measures of variability (this number could be appropriate for a study trying to classify two populations of 50 patients each). The maximum correlation among the group of measures was 0.01 (i.e. none of the pairwise correlations was higher than that value). This resulted in the selection of 1) average of the differential of the R-R interval, 2) Kurtosis, 3) forbidden words of the symbolic dynamics and 4) X-intercept of the power law.

**Conclusions:** The proposed method represents a potential means to select a priori a set of uncorrelated measures of variability. Given their lack of redundancy, this set represents an ideal starting set to solve a patient classification task. The validation of the approach on independent datasets is required.

**ABSTRACT 32**

# NEUROMONITORING IN THE PAEDIATRIC INTENSIVE CARE UNIT WITH EEG PHASE SYNCHRONY

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Coma from brain injury is common in the paediatric critical care unit (PCCU). Neurological evaluation of comatose patients is uninformative due to the nature of coma and the therapeutic use of sedatives, opioids and paralytic agents required to maintain life support. Reliable, noninvasive, portable brain monitoring would provide clinicians with information on brain dynamics. Knowledge of changing brain dynamics would assist in guiding treatment and for prognosticating outcome.

Transient coordination between neurons through continual recruitment and dissolution of neuronal networks represents the dynamic nature of a healthy brain. The fluctuation between coordination and dissolution is termed variability. The pathological brain differs from the normal by less variability. Neuronal coordination can be quantified through signal analysis by calculating the phase synchrony of electroencephalographic (EEG) waveforms and the variability of the phase synchrony. Our previous work has shown that patients in coma after head injury who had a good outcome, had a lower phase synchrony and higher variability compared to those with poor outcome.

Our objectives are: 1) to characterize and quantify coma in critically ill children through measures of EEG phase synchrony, spatial complexity and temporal variability, 2) To evaluate whether EEG phase synchrony measures can differentiate patients who had a good outcome from those who had a poor outcome.

A retrospective study (1999 to 2009) evaluated the EEG phase synchrony and spatio-temporal variability of critically ill children in coma from cardiac arrest, traumatic brain injury (TBI) or stroke. Inclusion criteria: children < 18 years of age, admitted to PCCU in coma with one of the three preceding diagnoses and having had a 19 channel EEG.

EEG recordings were processed using the Laplacian transform to eliminate the effect of volume conduction and the common reference electrode. The signals were filtered to 3 Hz and 15 Hz bandwidths as these frequencies are least affected by commonly used medications and muscle artefact. The Hilbert transform was used to extract the instantaneous phase of the signal. Outcome at the time of hospital discharge was assessed through chart review using the 6 point Paediatric Cerebral Performance Category score (PCPC) and dichotomized to good outcome (PCPC 1 to 3) and poor outcome (PCPC 4 to 6). Chi-square was used to evaluate the difference between the two outcome groups.

There were 84 children aged 1 month to 17 years who met inclusion criteria: cardiac arrest, n=30; TBI, n=35 and stroke, n=19. Patients with poor outcome had higher EEG phase synchrony at 15 Hz ($p = 0.03$), lower spatial complexity (0.02) and lower temporal variability ($p = 0.02$) when compared with patients with good outcome. Variability was lowest in the parietal and fronto-central brain regions of patients with poor outcome ($p=0.02$).

Critically ill children in coma who had a poor outcome when discharged from hospital, had higher EEG phase synchrony and lower spatio-temporal variability compared to patients with good outcome. EEG phase synchrony, spatial complexity and temporal variability are measures that can provide information on brain dynamics in comatose paediatric patients when clinical examination is limited or uninformative.

## ABSTRACT 33

# FETAL DEVELOPMENT ASSESSED BY MULTISCALE MULTIFRACTAL ANALYSIS OF HEART RATE VARIABILITY AT THE VERY LOW FREQUENCIES

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**Objectives:** Very low frequencies (VLF) and ultra low frequencies (ULF) components of human heart rate variability (HRV) account for 95% of signal total power but their physiological background is still very uncertain. The main difficulty lies in the lack of appropriate analysis methods for such low frequencies bands better than the basic power spectral analysis. Fractal methods such as DFA or MF-DFA have been used to characterize the frequencies below the LF band also regarding fetal heart rate variability [1].

**Methods:** We applied a new method, the Multiscale Multifractal Analysis (MMA) [2], an extension of MF-DFA in which the Hurst surface is calculated. The method is designed to analyze correlation properties at such low frequencies. We analyzed 158, 30 minute magnetocardiographic HRV recordings from fetuses 21-38 weeks of age. To analyze such short data sets using MMA, we introduced an overlapping sliding window of analysis and limited the range of the scales considered. We distinguish a quiet and an active state of the fetus (related to the developing behavioral states of quiet and active sleep) irrespective of age and also distinguish young (gestational age <29) and old (>34 week) fetuses. For every single series, we calculated the Hurst surface, which represents the properties of the scaling of heart rate fluctuations, depending on their magnitude and frequency range. To show the development stages of HRV in VLF, we calculated the mean Hurst surfaces for every week and also a contour plot showing correlations between the Hurst surface and the gestational age.

**Results:** A large difference between the properties of the HRV of the young fetuses and the older ones is well visible and in agreement with [3]. We chose the most significant areas of the Hurst surface (highly correlated with age) and assessed the changes of their mean values statistically.

**Conclusions:** When introduced the MMA method [2] required at least a 104 RR interval long series. We modified it and obtained a tool allowing to analyze the 4000 RR interval long fetal data (30 min). For adults the means that the requirement for data length is now slightly over 1 h. We observed a difference between the results for small amplitude fluctuations in the signal and for large amplitude fluctuations as well as differences for different scale ranges. In addition, using the results of statistical analysis of Hurst surfaces for the whole group studied, we attempted to prepare criteria to assess the stage of fetal development and gestational age, these results will be discussed at the conference. We hope that our work will help to develop a method of assessing the health status and the exact age of fetuses. Note, that MMA is designed as a tool for the analysis of frequencies below the LF band of HRV.

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**ABSTRACT 34**

# TWO NEW ALGORITHMS FOR MEASUREMENT AND CHARACTERIZATION OF PERIODIC APNEAS

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**Objectives:** Periodic apnea (aka periodic breathing) is common in premature infants, and has long been regarded as benign. Recent evidence leads us to question that sanguine assumption. We developed two new algorithms for measurement and characterization of periodic apneas.

**Methods:** We have collected a large dataset containing all electronic signals, including waveforms (EKG, Chest Impedance, PulseOx) and vital signs (Heart Rate, Respiration Rate, SpO2), continuously from 1438 NICU infants over a 30 month period, and applied a previously developed apnea-recognition algorithm, marking the time, duration, and probability of apnea vs. time. We report here two new algorithms for detection and characterization of periodic breathing: one seeking periodicity in the vital signs, over one-hour periods, the other seeking periodicity in the apnea-probability function, over four minute periods. A quantitative measure of periodic apneas was obtained by computing the power spectrum of respiration rate over one-hour periods, and finding for each infant-hour the maximum power in the periodic apnea frequency band (3-6/min) divided by the mean power in that band.

**Results:** 1. These algorithms provide quantitative information about how much periodic breathing is normal, and therefore can permit clinicians to learn which infants have periodic apneas far outside the norm. 2. We found one case in which an apparently healthy late preterm infant was released from the NICU and later died unexpectedly at home — a case of sudden unexpected infant death (SUID). Applying the new algorithms to this infant's records, we found that periodic apneas had occurred almost continuously through the infant's stay in the NICU. 3. The quantitative measure of ratio of maximum to mean power in the frequency band of interest has a log-normal distribution. By this measure, the SUID infant was two to six standard deviations from the norm.

**Conclusions:** Periodic neonatal apneas and their possible connection to sudden unexplained infant death need more study. Quantitative analyses of large data sets combined with meticulous clinical annotation should provide better clinical assessment and identification of high-risk infants.

# ABSTRACT 35

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**Objectives:**
Cardiorespiratory Synchronization (CRS) has been indicated as a marker for autonomic control and clinical outcome (Bartsch et al., PNAS, May 2012) while its physiological origins are still under discussion. We aim to further the investigation into a causal relationship between outcome and CRS by providing the ability to externally induce this synchronization. Our initial step towards an application in mechanical ventilation was to evaluate the possibility to achieve CRS in healthy conscious subjects by controlled paced breathing.

**Methods:**
We investigated this hypothesis with the help of eight voluntary subjects (all male, age: 20-45) each performing two trials on separate days. A 3-lead electrocardiogram (ECG) as well as a measurement of thoracic extension as proxy for respiratory effort using a piezoelectric respiration belt was recorded in a sitting position. The subjects were asked to breath according to a visual stimulus, which was controlled according to the following protocol: (1) two minutes of spontaneous breathing (inactive circle), after which an individual ratio between respiration and heart-beats was calculated, i.e. the average number of heartbeats per respiratory cycle, (2) 10 minutes of continuous steadily paced breathing (M1 ), or 10 minutes of continuously provided respiratory onsets (M2, compare Almasi et al., IEEE Trans Biomed Eng, 1974, 264-273), where the breathing was paced to comply with the calculated individual pulse-breath ratio, (3) four minutes of spontaneous breathing, (4) 10 minutes of continuous pacing according to the mode (M1 or M2) not performed before, (5) two minutes of spontaneous breathing, terminated with the indication of the end of protocol. The phase of respiration, as calculated from the measured respiratory effort using a Hilbert transformation, and the positions of the QRS-complex as indicator of heartbeats, was used to construct cardiorespiratory n:1 synchrograms (Schäfer et al., Nature, 1998, 238-240). A cardiorespiratory synchronization manifests as an increased likelihood of heartbeats at specific respiratory phases, and can be quantified using the Shannon-entropy of the distribution of heartbeats at (binned) respiratory phase. The null-hypothesis used for the analysis, postulates that there is no synchronization if the Shannon entropy found in the experiment is larger or equal the Shannon entropy calculated for surrogates without systematic cardiorespiratory interaction. The significance level was set at 0.01.

**Results:**
When evaluating the mode M1 the calculated entropy was less than that of each of 100 surrogates, generated using the amplitude adjusted Fourier transformation, for all subjects and trials, thus allowing us to exclude the null-hypothesis with $p < 0.01$ for 100% of all trials. The pacing according to M2 resulted in CRS in a statistically significant manner in 68.8% of the trials.

**Conclusions:**
We were able induce CRS in healthy subjects using controlled paced breathing. We also showed that using a continuous and steady indicator as stimulus for respiration proved more successful in achieving a CRS state than using a binary indication of respiratory onsets. We will now concentrate on applying our results to mechanical and assisted ventilation enabling a new means of, potentially, protective ventilation.

**ABSTRACT 36**

# CARDIO-PULMONARY INTERACTION DURING LUNG VOLUME RECRUITMENT MANEUVERS IN PRETERM NEWBORNS RECEIVING HIGH FREQUENCY OSCILLATORY VENTILATION: A MATHEMATICAL MODEL

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**Objectives:** High Frequency Oscillatory Ventilation (HFOV) is potentially a lung protective ventilation modality as it consists in applying high frequency oscillations with reduced tidal volume superimposed to a high mean airway pressure (Paw). Recruitment maneuvers (RMs) during HFOV of preterm newborns result in improved oxygenation and lung compliance and reduce the risk of ventilation induced lung injury, but may be critical for hemodynamic stability. The aim of this study was to evaluate which hemodynamic variables are mostly influenced by RMs during HFOV in premature newborns. Moreover, we aimed at simulating the time course of variables, which are not commonly measured in clinical practice (such as right and left ventricular outputs and flow through the ductus arteriosus, when present), and of other variables, which cannot be monitored for invasiveness reasons (such as pressures in pulmonary artery and cardiac volumes).

**Methods:** A model of the mechanical interactions between the circulation and ventilation of the lungs was developed in J-sim software, and its parameters scaled to be set specifically for a preterm newborn of 27 weeks of gestational age (GA), 7 days of post-natal age (PNA) and of 1000 g of body weight (BW). By means of a scaling approach, the parameters could be tuned to become patient-specific and to describe a newborn with different characteristics. A cycle of RMs was simulated by applying a Paw that varied from 8 to 18 cmH2O in steps of 2 cmH2O. Special attention was paid to the influence of the RMs on the intrathoracic pressure and, in turn, on the heart function and on hemodynamics in the intrathoracic arteries. Simulated data at each Paw step were compared with clinical data obtained from 9 newborns with mean characteristics as described above.

**Results:** The trend of right ventricular output Doppler measurements was well reproduced by the model, even though the absolute values of simulated RVO were consistently lower. At Paw = 18 cmH2O cardiac output and stroke volume decreased by 10% of the initial values. Neither peak pressures in the pulmonary artery nor systemic arterial pressures experienced a significant change throughout the maneuver, indicating the absence of pulmonary or systemic hypertension consequent to pressure rise during HFOV. In case of patent ductus arteriosus, the simulations showed left-to-right shunt through the ductus with an increase in systolic pressures in the right ventricle and pulmonary artery, increased left heart volumes and a reduction of systolic and diastolic pressures in the left heart and aorta. RVO and LVO were reduced by the end of the recruitment maneuver of respectively 12% and 6% of their values at 8 cmH2O of CDP.

**Conclusions:** Simulations with a physiological circulation showed that systemic and pulmonary pressures were not significantly affected by the RMs, while cardiac function was more affected by a positive intra-thoracic pressure. The proposed model addressed for the first time the problem of interpreting the relationship between hemodynamics and HFOV ventilation in critically ill neonates, but further clinical data are needed to improve the validation. Also, the possibility to make this model patient specific would enhance its usefulness in supporting the clinicians in assessing the optimal RMs in function of the characteristics of the single patients, in order to take into account the tradeoff between improvement of the ventilation and the impairment of hemodynamics.

**ABSTRACT 37**

# PROFILING TRAUMA INDUCED COAGULOPATHIC STATES

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**Objectives:** Current clinical parameters used to assess coagulopathic status in patients include immediate (e.g. INR, Base Deficit (BD)) and summary measures (Injury Severity Score (ISS)). Additional approaches that would help anticipate coagulopathic complications in trauma patients would be useful. In this study, we test the potential of outputs from computational models of tissue factor-initiated coagulation to correlate with clinical measures used to assess the coagulopathic status of trauma patients.

**Methods:** Coagulation factor data (fII, fV, fVII, fVIII, fIX, fX, antithrombin, tissue factor pathway inhibitor, protein C) representing the plasma composition of 28 trauma patients at the time of emergency room admission were computationally translated into thrombin generation profiles using a model of tissue factor initiated coagulation with or without a set of equations describing the protein C pathway. Thrombin generation profiles representing all of the individuals were produced with both models, thrombin parameters (total thrombin (AUC), maximum level (MaxL), maximum rate (MaxR), clot time (CT)) extracted from these profiles and then analyzed with respect to clinical measures (ISS, BD, INR, and APC concentration) established for each patient.

**Results:** Trauma patients segregated into an acute traumatic coagulopathic (ATC) group (ISS>15, BD<-6, INR>1.3 and APC>5, for 2 or more of these measures (n=14)) and non-ATC group (n=14) showed significant differences in coagulation factor composition: the non-ATC group displayed higher concentrations of fII, fV and PC ($p<0.05$). An assessment of the level of correlation between the concentration of each individual factor and each measure was performed and showed little correlation with BD or APC. The most significant correlations were: for the ATC group, fV versus INR (R2=0.53) and fX versus the ISS (R2=0.44); and for the non-ATC group INR and fVII (R2=0.62). When each individual's coagulation proteome was modeled in the absence of the PC pathway, the non-ATC group averaged significantly higher AUC and MaxL and faster CT ($p<0.05$); no difference in thrombin parameters was observed between the two groups in the presence of the PC pathway. When each clinical measure was assessed individually against each thrombin parameter for all individuals in the ATC and non-ATC cohort, the most significant correlation was observed the in ATC group between the INR and the MaxL parameter when modeled either with (R2=0.34) or without (R2=0.48) the PC pathway. Trauma patients were resegregated after eliminating the ISS criterion into a redefined acute traumatic coagulopathic group (ATC: BD<-6, INR>1.3 and APC>5, for 2 or more of these measures (n=6)) and non-ATC group (n=22). Using these criteria, only the fV concentrations differed significantly between the two groups. When modeled in the absence of the PC pathway, the non-ATC group averaged significantly higher MaxR and MaxL ($p<0.02$-0.04); in the presence of the PC pathway, the non ATC group displayed higher MaxR, MaxL, and AUC ($p\leq0.015$).

**Conclusions:** Outputs from computational models of tissue factor initiated coagulation correlate with immediate clinical measures used to assess the coagulopathic state of trauma patients.

**ABSTRACT 38**

# GLUCOSE VARIABILITY AND MORTALITY AFTER ADJUSTMENT FOR INJURY SEVERITY, GLASGOW COMA SCALE, AND AGE IN CRITICALLY ILL TRAUMA PATIENTS

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**Introduction:** Normoglycemia maintained by tight glucose control protocols are reported to reduce morbidity and mortality in critically ill surgical patients. Glucose variability has been used to characterize glycemic control and efficacy of tight glucose control protocols; however, the definition and methods for determining glucose variability have not been standardized. We hypothesized that the risk of death would increase with glucose variability as measured by wavelet energy in subjects admitted to a trauma intensive care unit.

**Methods:** This was a single-center retrospective review of adult trauma patients admitted to the Surgical Trauma Intensive Care Unit at a Level I Trauma Center between January 2005 and December 2007. Patients were managed with a tight glucose control protocol with target range 80-110mg/dl. Subjects were identified by trauma registry query and glucose values were obtained through the hospital database. Patients with an Injury Severity Score (ISS)≥9 and ICU length of stay≥3 days were included. Data collected included demographics, diagnoses, mechanism of injury, medical history, clinical course and disposition. We measured glucose variability with the signal energy based on a Haar wavelet model.

The primary endpoint was in-hospital mortality after the third day and on or before the 30$^{th}$ day from admission. We hypothesized that the risk of death would increase and time to death would decrease with wavelet energy. We used logistic regression and proportional hazards models to model mortality in terms of signal energy with adjustment for age, ISS, and admission GCS score. We log transformed wavelet energy as appropriate and adjusted for age, ISS and GCS in all statistical models.

**Results:** A total of 546 subjects were included with 97,567 glucose measurements obtained of which 22,695 occurred during the first 3 days. Most subjects were male (69%) with mean±SD ISS of 25.3±10.8, TRISS 0.7 ± 0.3, and admission GCS 10±5.4. The median ICU length of stay was 8 days (range 3 to 139) and the median number of ventilator days was 4 (range 0 to 93). Sixty-three subjects (11.5%) died between the 4$^{th}$ and 30$^{th}$ day. Wavelet energy in log units did not vary significantly with mortality status mean (95% CI) (Dead 0.68 (0.56, 0.81), Alive 0.57 (0.53, 0.62), p=0.11) or ISS (slope=0.02±0.02, p=0.10) and the risk of death did not vary significantly with wavelet energy in a logistic model (OR=1.02, 95% CI 0.99 to 1.05, p=0.064). Time to death was, however, significantly decreased with increased energy (hazard ratio=1.02, 95% CI 1.00 to 1.04, p=0.018).

**Conclusion :** Increased wavelet energy, a measure of variability, in the glucose curve was associated with decreased survival time in critically ill trauma patients. Thus, assessment of signal energy based on a Haar wavelet model may provide an additional method of assessing glucose variability in the trauma intensive care unit.

**ABSTRACT 39**

# EFFECT OF ANALYSIS INTERVAL ON HEART RATE VARIABILITY IN A MURINE MODEL OF SEPSIS

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**Objectives:** Nonlinear analysis of hemodynamic parameters may provide insights into disease pathophysiology undetected by standard linear measures such as heart rate. We have previously shown decreased heart rate variability (HRV) in a murine model of sepsis using a 5-minute time-series technique for assessing HRV that resembles Standard Deviation of the Averages of Normal Sinus to Normal Sinus (SDANN). Different analysis intervals could allow for more detailed time course analyses but may be less precise. We examined the effects of the time segment analysis interval on HRV measurement.

**Methods:** Radio-transmitters were implanted into the ascending aorta of C57/BL6 mice (n=16) for continuous hemodynamic monitoring. Following a minimum of three days of recovery, baseline recordings were taken for 24 hours. The mice were then made septic by cecal ligation and puncture (CLP) and resuscitated with fluids and antibiotics every six hours. Heart rate data for the first 24 hours was divided into 1-, 2-, 5-, and 10-minute intervals and the SD of integer heart rate for each interval was computed. The SD cutoff that represented the lowest 5% of baseline was determined. HRV was calculated as the % of low SDs (low volatility) intervals in the experimental period defined by this cutoff and compared among groups.

**Results:** Threshold values of the 5% SD cutoff did not differ for the 1-, 2-, 5-, and 10-minute analysis intervals (10.6 ± 6.4, 11.5 ± 6.6, 12.6 ± 6.6, and 15.0 ± 7.1, respectively, p=NS). Segmented linear regression methodology was used to compare HRV between analysis interval groups. The smallest squared sum of errors observed on a sequence of regression results using a range of breakpoints (3-10 hrs) provides the criterion for selecting optimal breakpoints for each set of timed measurements. A single breakpoint was determined by continuous piecewise linear regression for each set of timed measurement variabilities. The optimal breakpoint and R-squared values for the 1-, 2-, 5-, and 10- minute analysis intervals were 8.6 hrs (adjusted R2=0.91), 8.8 hrs (adjusted R2=0.92), 9.2 hrs (adjusted R2=0.91), and 7.4 hrs (adjusted R2=0.88) respectively.

**Conclusions:** Time-series techniques are less demanding and more intuitive as a means of measuring variability than spectral analysis, but artifact in longer analysis intervals tends to increase SD and biases towards the null hypothesis. In our study, shorter intervals of analysis (i.e. 1- or 2-minutes) did not decrease sensitivity to HRV changes during sepsis. Use of a 10-minute interval decreased sensitivity in HRV measurement early in the experimental period, demonstrating that better filtering techniques may be necessary to minimize the influence of measurement artifact on HRV analysis with longer analysis intervals.

**ABSTRACT 40**

# RISK-ADJUSTMENT OF PATIENT SUBPOPULATIONS IN THE INTENSIVE CARE UNIT USING OASIS, A NOVEL SEVERITY SCORE

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**Objectives:** Risk-adjustment of patient populations is a useful technique for identifying hospitals with outlying performance, allowing for variability in patient disease severity in clinical trials, and for benchmarking. Due to varying demographics, admission health status, and care facilities available, comparison of outcomes between hospitals with distinct patient populations requires adjustment for the severity of illness of the cohort. For patients admitted to the Intensive Care Unit (ICU), there exist several models which provide probabilistic estimates of patient mortality. Such models include the Acute Physiology and Chronic Health Evaluation (APACHE™) system, the Simplified Acute Physiology Score (SAPS), and the Mortality Probability Model (MPM), which all provide estimates of patient in-hospital mortality risk. However, these models often require substantial data collection and quality control, and this has been a barrier to their clinical acceptance. Here we present an application of a recently developed score, the Oxford Acute Severity of Illness Score (OASIS), to risk-adjust ICU patient sub-populations separated according to admitting diagnosis.

**Methods:** OASIS requires 10 distinct physiologic measurements (features), a substantial reduction when compared to SAPS III (39 features), MPM III (23 features), or APACHE IV (140 features), yet has a similar discrimination to APACHE IV (area under the receiver operator curve of 0.87 vs 0.89). A patient's OASIS is calculated by assigning a point value for each feature dependent upon the range in which it falls. This is identical to the method of implementing the well known Acute Physiology Score (APS). We selected 10 diagnostic groups which had sufficient development data (>1000 first day non-readmission entries) and sufficient validation data (>500 first day non-readmission entries). We then re-calibrated OASIS to each diagnostic group using 20%, 40%, 60%, 80%, and 100% of the development data. This was compared to re-calibrations using both APS III and APACHE IV. The models were evaluated using a regression of the expected mortality rate in each diagnostic group to the observed mortality rate in each diagnostic group.

**Results:** Results show that using only 20% of the data, OASIS attained an R2 of 0.986, while APACHE IV did not display sufficient correlation to fit a regression.

**Conclusions:** OASIS provides a simple alternative to more complex models when adjusting for patient severity across distinct patient groups. Here we have shown that it is easily re-calibrated to subpopulations of patients and requires less data than current models. This is advantageous when the economic cost and data collection burden of implementing such a more complicated model is a limiting factor.

**ABSTRACT 41**

# DESATURATION EVENTS ARE FREQUENT WHILE OFTEN UNDOCUMENTED IN ELECTRONIC MEDICAL RECORDS

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**Objectives:** The invention of electronic flowsheets guided the holographic recording of physiologic data into spreadsheet format. Further automation changed the role of the nurse from data gatherer-recorder to data validator. There is evidence that automated polling of data from the monitors has more or less eliminated transcription errors. Yet the electronic flowsheets typically are set to poll those monitors at frequencies far lower than collected by the monitors. The purpose of this study was to estimate the prevalence of adverse excursions in the monitor data unrecorded (unvalidated) in the flowsheets. We used pulse oximetry (SpO2) as a common data type where adverse excursions ("desaturations") are readily recognized.

**Methods:** The source data were obtained from a General Electric monitoring system feeding both a bedside electronic flowsheet (Cerner iView) and a data archiving system (BedMaster Ex) spanning nine intensive care units. SpO2 is polled at one minute intervals by the archiving system whereas nurse validated value intervals varied from 15 minutes to 1 hour. Patients with fewer than 4 nurse validations or fewer than 11 automatic recordings are removed. Data points with SpO2 less than 70% are removed. To reduce confounding minor variation, automatically recorded values are replaced with the median value of 4 prior points and the current point. A desaturation event between two nurse validations is defined as first SpO2 value being greater than 90%, minimum SpO2 value in the interval is less than 90%, the difference between the first and minimum value is at least 5%, and there are at least 3 points below 90%. We tagged those desaturation events and referenced them to the nurse validated data.

**Results:** 1628 patients are included in this study. In point to point comparison of Bedmaster data and nurse validated data, only 0.38% of the 170375 validated points differed by SpO2 value more than 10. Based on Bedmaster data 780/1628 (47.9%) patients had at least one desaturation event. (A total of 4236 destaturation events were identified among these 780 patients.) Only 492/780 (63.08%) patients ever have nurse recorded SpO2 values less than 90.

**Conclusions:** While automated polling has effectively eliminated transcription error, desaturation events are often undocumented. Whether these are unrecognized or merely ignored remains to be determined. Regardless, the discrepancy between what is documented and what actually occurs is concerning that synchronous and subsequent clinical decision-making is compromised. The need to post-process physiologic data to recognize deterioration and prompt early intervention appears important and unmet.

**ABSTRACT 42**

# ORGAN DYSFUNCTION IN CRITICAL ILLNESS: GLASGOW COMA SCORE DOMINATES THE ASSOCIATION BETWEEN ADMISSION SOFA SCORE AND 30-DAY MORTALITY

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**Objectives:** The multiple organ dysfunction syndrome contributes dramatically to mortality in critical illness. The SOFA score attempts to describe patterns in organ dysfunction but weights various organ systems equally. We sought to determine which organ systems measured by the SOFA score are most relevant to predicting mortality and ICU length of stay among survivors.

**Methods:** We calculated SOFA scores retrospectively on all patients admitted during the 2008 calendar year to the 24-bed, mixed-profile Shock Trauma ICU at Intermountain Medical Center. We attempted to define the importance of various organ systems via three techniques, classifying with regard to 30-day mortality. We employed conditional inference trees, random forests and a bootstrap regression method that maximizes area under the curve to define the relative importance of the components of the SOFA score.

**Results:** On bootstrap regression which optimizes AUC using logistic regression, Glasgow Coma Score (GCS) was the single most predictive variable with univariate AUC of 0.80. The addition of age, PF ratio, bilirubin, and hypotension yielded a final AUC of 0.90. Imputation of random forest analysis also found that GCS was far more predictive than the other components with age being an important addition to the score. Conditional inference trees yielded identical results with a division point of GCS of 9. Discriminate analysis yielded an optimized reweighting of the SOFA score, with the addition of age and the omission of creatinine and platelet scores, which achieved an AUC of 0.90 compared to the traditional SOFA which achieved an AUC of 0.84.

**Conclusions:** In a general ICU population, a patient's GCS was most predictive of mortality using all 3 modeling techniques. Creatinine and platelet count were less predictive of mortality than other components. Optimized reweighting of the SOFA score improved the prediction of mortality in our general ICU population. Whether the significance of MODS changes with age or scoring can be improved within specific populations merits further investigation.

## ABSTRACT 43

# DEVELOPMENT OF SIRS DEPRESSES HEART RATE VARIABILITY

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**Objectives:** Heart rate variability (HRV) has been investigated as a noninvasive diagnostic for the onset of sepsis. Since the development of a systemic inflammatory response syndrome (SIRS) has been considered to be a sign of sepsis, we compared HRV values of the ICU patients depending on the SIRS state.

**Methods:** From the bedside monitoring system, vital data of patients admitted in ICU were downloaded. Sampling rate of ECG data is 500 Hz, and HRV is calculated from that. Abnormal heartbeats and trend were eliminated using a stochastic model as described in [IFMBE Proceedings Volume 35, 2011 552-555], and the power spectrum is derived using autoregressive model. As an estimate of HRV, we used the integral value within 0.04 Hz and 0.4 Hz. Vital signs regarding SIRS criteria, i.e., heart rate, respiration rate, and core temperature, are recorded every ten seconds, 0.1Hz. We arranged the data frequency of HRV value and vital data to be 0.017 Hz (one data per minute). For every minute, the state of the patients either SIRS positive or negative can be determined, excluding the count of white blood cells. Thus, HRV values can be categorized depending on either SIRS positive or negative. In order to calculate HRV values for each patient in the state of SIRS positive and negative, we took the median of those categorized, respectively, for the whole term of ICU stay. Statistical test is performed using IBM SPSS ver. 19.

**Results:** The number of patients registered was 49, and the average length of ICU stay was 31.4 days, ranging from 3 to 113 days. The average age of those patients was 64.3 years old. There was no specific disease as registration criteria, but thirty four patients out of 49 suffered from sepsis. According to Wilcoxon's signed-rank test with the sample size of 49, difference between the HRV values for SIRS positive and negative is significant ($p<0.05$). The HRV value for SIRS positive is approximately 2.2% lower than that for SIRS negative on average. In 61.2% of patients, the difference is less than 10%. The percentage of patients to show higher HRV for SIRS positive than that for negative was only 20.4%.

**Conclusions:** Our analysis shows that the HRV value will decrease when a systemic inflammatory response syndrome (SIRS) is developed for patients in ICU, and it does not contradict previous results [Nihon Rinsho. 2004 Dec;62 (12):2285-90, PLoS ONE. 2009;4:e6642, IFMBE Proceedings Volume 35, 2011 552-555], reporting a decrease of HRV before sepsis. Such observations require HRV to reduce in association with SIRS development, as shown in this study, because SIRS development has been employed as an indication of sepsis occurrence. For the purpose of sepsis diagnostics, however, further investigation is necessary. Our result implies that HRV always decreases as developing SIRS, not specific to sepsis. We suggest taking temporal characteristics of decreasing HRV into consideration. Adjusting frequency range targeting particularly sepsis is another idea.

## ABSTRACT 44

# VARIABILITY ANALYSIS AND THE DIAGNOSIS, MANAGEMENT AND TREATMENT OF SEPSIS

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**Objectives:** Severe sepsis leading to organ failure is the most common cause of mortality amongst critically ill patients. Variability analysis is an emerging science that characterizes patterns of variation of physiologic parameters (e.g. vital signs), and is believed to offer a means to evaluate the underlying complex system producing those dynamics. Recent studies have demonstrated that variability of a variety of physiological parameters offer novel means to help diagnose, manage and treat sepsis. The purpose of this literature review is to examine existing data regarding the use of variability analysis in patients suffering from sepsis, and to highlight potential uses for variability to improve care for patients with sepsis.

**Methods:** 53 articles were identified through a MEDLINE search using search terms: heart rate, respiratory rate, temperature, glucose, variability, sepsis. These articles were reviewed in order to address our hypothesis that variability can provide a novel means for identifying sepsis.

**Results:** Variability, including heart rate, respiratory rate, temperature and glucose variability, has been shown to be a valuable tool in monitoring and prognosticating of the critically ill, specifically those with sepsis. Continuous HRV monitoring may assist in early detection and prognostication of infection. With the greatest foundation of evidence to date, HRV monitoring in neonates appears to save lives simply by alerting physicians that something may be wrong. Along with TV, monitoring HRV and RRV to track severity of illness of infection over time could assist in patient management. In addition to providing a review of the existing literature, this paper also identifies several needs for future research. First, given the assumption that the body is a complex system, there is a lack of evidence investigating how the different elements of variability relate to each other. The heterogeneous information brought by HRV, RRV, TV and GV would likely be enhanced by assessing the information shared between their underlying signals. Second, in contrast to amalgamating multiple organ system variability, further research is needed to determine if trends in individual organ variability may provide specific clinical information on the organ system affected. Third, whereas we have discussed the clinical relevance of variability as found in various studies, there is a lack of literature on whether or not the theories hold true in large, multi-centre trials, and what their applicability in real-life ICU settings is. For variability measures to be integrated into clinical decision making, large multicenter derivation and validation studies followed by randomized controlled trials will be needed to determine the thresholds of variability that predict clinical outcomes, apply them, and determine their impact.

**Conclusions:** Variability has been shown to decrease prior to the onset of severe infection and sepsis, thus providing a method by which clinicians may detect infection in a more timely manner than current practice allows for today. Ultimately, the end goal would be to develop a monitoring system to measure real-time fluctuation in variability that would serve as a tool for physicians to facilitate a diagnosis of sepsis in order to implement early goal-directed and variability-directed therapy. Despite these promising findings in the literature, further research is still needed for this to be used as a standard technique in clinical practice. If this can be accomplished, variability monitoring offers promise to enhance future patient care.

## ABSTRACT 45

# COMPLEX CONCEPTS REQUIRE COMPLEX ALGORITHMS: PERFORMANCE OF SEPSIS IDENTIFICATION CRITERIA IN AN INTENSIVE CARE DATABASE

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**Objectives:** Sepsis is an important medical condition in patients in the intensive care unit (ICU) but its clinical diagnosis is challenging. Identification of patients with sepsis is a key validation step for research in electronic ICU records that are mainly kept for clinical care. Sepsis patients can be expected to have entries of sepsis in free text format, sepsis specific antibacterials, and blood cultures in their clinical records, which therefore represent potential criteria for their automatic identification. Here, we evaluate these criteria for sepsis identification in non-standardized electronic medical records.

**Methods:** We analyzed the electronic medical records of the 26-bed surgical ICU of a tertiary care hospital in Mannheim, Germany, from 2006-2011. We employed three different criteria for identification of sepsis patients in our database and compared their performance using standard diagnostic test evaluation measures. As first criterion we searched ICD 10-GM code labels and free text entries for the text string 'sepsis' and 'septic shock'. Only patients having both (free text criterion) were considered sepsis cases and presumed gold standard for comparison. Second, we searched prescription records for relevant antibacterial exposure based on the broad list of drugs recommended for sepsis therapy by the Paul Ehrlich Society of Chemotherapy (PEG) and a shorter list of drugs primarily used for sepsis therapy in our local ICU. We further restricted this criterion by only including patients meeting three of the criteria for a systemic inflammatory response syndrome (SIRS) in addition to antibacterials. Third, we identified admissions with a laboratory record of blood cultures, irrespective of result, as potential sepsis cases.

**Results:** We assessed 11938 patients with 13553 ICU admissions. 902 admissions (6.7%) had both ICD code labels and free text entries indicating sepsis. During 4210 admissions (31.1%) antibacterials recommended by the PEG were administered. In 1649 admissions (12.2%) administration of drugs from the same list was associated with SIRS. 2061 admissions (15.2%) had antibacterial prescriptions from our local drug list and 901 (6.6%) admissions had both prescriptions from the same list and SIRS. Blood cultures were taken in 1543 (11.4%) admissions. Compared to the free text criterion, the antibacterial criteria all either had high sensitivity and low specificity, or vice versa. Only 579 sepsis patients based on the free text criterion had blood cultures drawn (sensitivity 64.2%), comprising 37.5% of all patients with blood cultures. 17.3% of patients with sepsis based on free text neither received any sepsis-specific antibacterials and had SIRS nor had a blood culture recorded. Kappa-values indicated only moderate agreement for all two-way comparisons and all three criteria applied together.

**Conclusions:** Neither any individual criterion nor combination thereof appeared to clearly delineate sepsis patients. As exemplified by sepsis, reliable automatic detection of complex conditions in non-standardized clinical databases requires more intricate algorithms. Development of suitable algorithms may have to be based on detailed inspection of a sample of records or inclusion of extraneous data sources, such as claims data.

**ABSTRACT 46 (Podium 1)**

# A Computational, Tissue-Realistic Model of Pressure Ulcer Formation in Individuals with Spinal Cord Injury

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Objective

Pressure Ulcers affect 2.5 million US acute care patients per year, costing near $11 billion per year. 80% of patients with Spinal Cord Injury (SCI) experience a pressure ulcer during their lifetime. Mechanistic studies of post-SCI ulcers are challenging due to the difficulty of sampling – and thereby perturbing – such chronic wounds. We hypothesized that serial, non-invasive wound imaging combined with agent-Based Models (ABMs) would allow us to investigate both space- and time-dependent dynamics via visually realistic, mechanistic simulations.

Methods

We created an ABM of the early stages of ulcer formation and development. In this ABM, repeated cycles of ischemia- reperfusion over a bony prominence cause tissue damage and induce inflammation, which leads to cycles of additional damage caused by pro-inflammatory positive-feedback mechanisms. The ABM was calibrated to serial images of post-SCI pressure ulcers obtained following Institutional Review Board approval and informed consent. The ABM was then used to investigate potential treatments *in silico*.

Results

Behaviors encoded in the ABM at the cellular level led to tissue-level phenotypes described in the literature. The ABM recapitulated visual patterns of ulcer formation in SCI patients on which it was not calibrated. Sensitivity Analysis of model parameters revealed that either increasing oxygen availability or the rate at which pressure is applied and released (simulating a patient being turned) led to predictions of improved outcomes. Simulations of the acute inflammatory response to an initial tissue injury revealed two phenotypes that arise stochastically from the same set of parameter values. An initial tissue injury could lead in a stochastic fashion to either resolving inflammation (which prevented ulcer formation) or maladaptive inflammation (which led to a severe ulcer). This commitment to a defined outcome was predicted to occur by 250 h post-injury, well before an ulcer forms. While corticosteroids are generally considered to be a risk factor for chronic, non-healing wounds[1,2], they are also known to suppress acute inflammation[3]. We hypothesized that steroids might have a beneficial effect on the early stages of pressure ulcer formation and development. In an *in silico* clinical trial of steroid treatment, steroids applied early enough and at a high enough dose were effective in attenuating the local inflammatory response, leading to predictions of improved outcomes.

Conclusions

Analysis of *in silico* models combined with clinical/ literature data holds the potential to glean mechanistic insights about the development of post-SCI ulcers while suggesting novel therapies for these ulcers. Furthermore, these models provide a medium through which hypothesized therapies can be vetted before moving into more expensive *in vitro* and *in vivo* testing.

1. Keller et al. Intensive Care Medicine 2002
2. Storder et al. J Cardiovasc Surg (Torino) 1998
3. PJ Barnes. British J Pharmacology 2006

**ABSTRACT 47 (Podium 2)**

# INTRACRANIAL HYPERTENSION FOLLOWING HEAD INJURY IS ASSOCIATED WITH A LOSS OF ICP-COMPLEXITY

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**Objectives:** Physiologic parameters, such as intracranial pressure (ICP), are regulated by interconnected feedback loops, resulting in a variable and complex time course. According to the decomplexification theory of illness [1], disease is generally characterised by a loss of feedback loops and hence a decomplexification of the waveform of physiologic parameters. We hypothesized that the decomplexification theory applies to head injury too, and analysed whether ICP-complexity decreases during intracranial hypertension (IH).

**Methods:** The ICP-time course was monitored using the ICM+-software in head injured patients treated at Addenbrooke's Hospital in Cambridge/UK. Retrospectively, periods of IH (ICP > 25 mmHg for at least 20 minutes) were identified and compared with preceding episodes of intracranial normotension (ICP < 20 mmHg): First, the ICP data were normalised, so that all ICP data sets had an equal mean and standard deviation, irrespective of their true absolute ICP value. Second, the complexity of the ICP time course was estimated by calculating the sample entropy (SampEn [2]) and the scaling exponent alpha by detrended fluctuation analysis (DFA [3]). Finally, SampEn and alpha-values obtained before and during IH were mean averaged within patients and compared by applying a paired t-test. All data are shown are expressed as mean +/- std dev.

**Results:** Two hundred-two episodes of intracranial hypertension were analysed in 17 adult patients. During intracranial hypertension (ICP = 32,1 +/- 8,9, normalised ICP = 0 +/- 1 mmHg), both the scaling exponent (alpha = 1,06 +/- 0,24) as well as SampEn (1,37 +/- 0,49) were significantly ($p < 0,05$) different as compared to before IH (ICP = 15,6 +/- 3,3 mmHg, normalised ICP = 0 +/- 1 mmHg, alpha = 0,84 +/- 0,14, SampEn = 1,77 +/- 0,25).

**Conclusions:** The pure numerical increase in ICP during IH would not have influenced the complexity measures. Hence, both the increase in alpha as well as the decrease of sample entropy during IH indicate a true loss of ICP complexity. Therefore, the decomplexification theory applies to head injury too. References [1] Goldberger AL. Fractal variability versus pathologic periodicity: complexity loss and stereotypy in disease. Perspect Biol Med. 1997; 40(4):543-61. [2] Richman JS and Moorman FR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000; 278: H2039-49. [3] Peng CK, Buldyrev SV, Havlin S, Simons M, Stanley HE, Goldberger AL. Mosaic organization of DNA nucleotides. Phys Rev E 1994; 49: 1685-89.

**ABSTRACT 48 (Podium 3)**

# Examination of differential fitness domains and a paradoxical effect of antibiotic culling with an agent-based model of the evolutionary dynamics in host-microbe interactions

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**Objectives:** Host-microbe interactions are increasingly recognized as playing a critical role in the pathogenesis of many human diseases, especially in circumstances where previously innocuous microbes undergo a virulent transformation during critical illness. Given the rapidity of microbial replication, microbial species utilize evolutionary dynamics to respond to heterogeneous environmental conditions. Under optimal growth conditions, such as host health, microbes are selected for their ability to efficiently generate biomass (growth and replication). However, in conditions of environmental stress and scarcity, such as host illness, additional microbial functions such as motility and toxin production facilitating invasiveness, may provide a survival advantage even given a relative decrease in energetic efficiency [1]. Many of these microbial stress responses form the basis of the virulence activation that marks the transition of an innocuous microbe into a pathogen. Herein we present an abstract agent- based model (ABM) of a host-microbe interaction system developed to examine the evolutionary dynamics and functional tradeoffs in the transition between benign and pathologic conditions. We also investigate the effect of a standard medical intervention, antibiotic administration, on those dynamics.

**Methods:** An ABM was constructed of an abstract host-microbial interaction system, such as might be seen in the gut. Host cells representing epithelial cells populate a two-dimensional grid. Simulated bacteria exist in two types: Type 1 representing the non-pathogenic microbe with optimized growth and replication, and Type 2 representing microbes possessing the additional functions of motility and invasiveness, but at extra energetic cost. The degree of Motility was proportional to extra energy cost, and Invasiveness was manifest as the ability to kill/invade host cells as an access to additional energy resources (akin to a Type-III Secretion System [2]). Type 2 capabilities represent a “high-risk/high-reward” survival strategy corresponding to virulent behavior. Initial conditions consisted of only Type 1 bacteria present. A random mutation between Type 1 and Type 2 occurred every 1000 replications. In the healthy host state an extracellular energy resource was constantly replenished at a variable rate, analogous to the normal oral intake of a healthy individual. The stress state was represented by decreasing the resource replenishment rate progressively to 0. Antibiotics were represented by an 80% culling of all microbes present; no antibiotic resistance was incorporated into the bacterial agents. Measured outputs of the ABM included population sizes of Type 1 and 2, and overall host health reflected by the health state of the epithelial cells.

**Results:** The ABM identified differential fitness domains depending on the replenishment rate, virulence energy cost and invasiveness energy recovery. There was a tipping point in the replenishment rate below which Type 2 populations predominated, with a corresponding decrease in host health. There was a paradoxical effect identified with simulated antibiotic administration, where despite decreased overall bacterial populations, there was an even greater decrease in host health and a predominance of Type 2 populations even though they had no antibiotic resistance capability.

**Conclusions:** Simulation experiments demonstrated stress conditions where evolutionary dynamics favored a high-risk/high-reward bacterial strategy consistent with known virulence behaviors. These findings reinforce

the importance of understanding the potential transformation of resident microbial communities into pathogens as a function of host health state, particularly in the acutely and critically ill. The evolutionary paradigm also has implications in microbe-directed therapies, and suggests environmental interdiction as a viable strategy. Identifying the environmental tipping points that favor one phenotype versus another can provide insight into the development of ecologically sound therapeutic interventions that can potentially harness biology as opposed to fighting against it. References: [1] Rohmer, L., Hocquet, D. and Miller, S.I. Are pathogenic bacteria just looking for food? *Metabolism and microbial pathogenesis. Trends in Microbiology*, 2011. 19(7):341-348. Doi: 10.1016/j.tim.2011.04.003. [2] Coburn, B., Sekirov, I. and Finlay, B.B. Type III Secretion Systems and Disease. *Clinical Microbiology Reviews*, 2007, 20(4):535-549. Doi: 10.1128/CMR.00013-07

**ABSTRACT 49 (Podium 4)**

# REAL-TIME HEART RATE COMPLEXITY ON HOSPITAL ARRIVAL PREDICTS THE NEED FOR LIFE-SAVING INTERVENTIONS IN TRAUMA ACTIVATION PATIENTS

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**Objectives:** Heart rate complexity (HRC), commonly described as a "new vital sign", has shown promise in predicting injury severity but its use in clinical practice has been precluded by the absence of real-time data. This study was conducted to evaluate the utility of real-time, automated, instantaneous entropy analysis in predicting the need for life-saving interventions (LSI).

**Methods:** Prospective enrollment of patients who met criteria for trauma code activation was conducted at a Level I trauma center (Sep 2011-Feb 2012). Electric impedance cardiography was employed to calculate HRC and time-domain heart rate variability (HRV) continuously in real time for two hours with a portable, hand-held device from the moment of arrival in the trauma center. Patients who received an LSI were compared to patients without any intervention (non-LSI). Multivariable analysis was performed to control for differences between the groups.

**Results:** Of 82 patients enrolled, 21 (26%) received 67 LSIs within 24 hours of hospital arrival. Initial systolic blood pressure was similar in both groups, but heart rate was significantly higher in the LSI group. Also, LSI patients had a lower GCS (9.2±5.1 vs. 14.9±0.2; $p<0.0001$). The mean HRC value on presentation was 0.8±0.6 in the LSI group compared to 1.5±0.6 in the non-LSI group ($p<0.0001$). Using logistic regression, initial HRC was the only significant predictor of LSI. A cut-off value for HRC of 1.1 yields sensitivity, specificity, negative predictive value, and positive predictive value of 86%, 74%, 94%, 53%, respectively, with an accuracy of 77% for predicting an LSI.

**Conclusions:** Decreased HRC on hospital arrival is an independent predictor of the need for LSI in trauma activation patients. Real-time HRC may be a useful adjunct to standard vital signs monitoring.

**ABSTRACT 50 (Podium 5)**

# The timing and degree of fetal systemic and cerebral inflammatory responses correlate with a subset of heart rate variability measures: Evidence of cholinergic anti-inflammatory pathway activation in sepsis

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**Objectives**: Studies in adult animals treated with LPS to model sepsis as well as clinico-pathologic studies indicate that loss of the cholinergic anti-inflammatory pathway's (CAP) inhibitory influence unleashes innate immunity, increasing pro-inflammatory mediators that exacerbate tissue damage, and decreasing short-term heart rate variability (HRV). One proven measure of HRV is the root mean square of successive differences in R-R intervals of ECG (RMSSD), which reflects vagal modulation of HRV. We have shown an association between CAP activity, fetal HRV (fHRV), and the levels of fetal inflammatory response in an ovine model of worsening hypoxic-acidemia as it may occur during human labour. Here, we hypothesized that this concept of fetal CAP activation also applies during conditions of a lipopolysaccharide (LPS)-induced fetal inflammatory response. This model is relevant to chorioamnionitis. Subclinical chorioamnionitis is frequent (40-60% of all births) and associated with a ~9 fold increased risk for cerebral palsy spectrum disorders with life-long neurological deficits.

**Methods**: With LPS doses of 200-400 ng IV per fetus (n=3) or NaCl as control (n=3), we induced variable degrees of inflammatory response in chronically instrumented non-anesthetized near-term fetal sheep. The systemic inflammatory response was measured by plasma ELISA for TNF-α, IL-1β and IL-6. Cerebral inflammatory response was quantified by Iba1-positive microglia in convexial grey matter layers 1-3 and 4-6 (CGM13, CGM46), periventricular white matter (PVWM), thalamus and hippocampal subregions CA1, CA2/3 and dentate gyrus (DG). CAP activity was quantified by the following three fHRV measures calculated using the CIMVA (continuous individualized multivariate variability analysis) platform: RMSSD, Skewness (measure of asymmetry of R-R peak intervals distribution around its sample mean), and Sample Entropy (higher values mean higher variability).

**Results**: Plasma pro-inflammatory cytokines peaked at 3-24 hours. This was accompanied by a similar temporal profile of fHRV measures in fetal sheep receiving LPS. While RMSSD increased as expected with inflammatory response induced by LPS, we observed this also for several control animals. However, in line with previous findings in septic human neonates, Sample Entropy and Skewness correctly identified all three LPS-treated animals. Values of RMSSD, Skewness and Sample Entropy through the 12th hour of the experiment also correlated to microglia counts in multiple brain regions as follows: DG/RMSSD: R= -0.83, p=0.06; PVWM/RMSSD: R= -0.87, p=0.06; CGM13/Sample Entropy: R=0.93, p=0.02; CGM46/Skewness: R= -0.85, p=0.07; Thalamus/Sample Entropy: R=0.96, p=0.003.

**Conclusions**: These data confirm our hypothesis: Animals with higher CAP activity (i.e., higher RMSSD or Skewness or lower Sample Entropy values) show lower brain inflammatory response. As in the hypoxic-acidemia model, the relationship between CAP and decreased microglial activation was highly brain region-specific. The contrasting dynamics of RMSSD and SampEn during fetal inflammatory response warrants further investigation.