The 9th International Conference on Complexity in Acute Illness

September 10-12, 2010

Atlanta Airport Gateway Marriot Hotel
Atlanta, Georgia

SCAI
The Society for Complexity in Acute Illness
www.scai-med.org

9-th International Conference on Complexity in Acute Illness

Scientific Program

Date/Time	Event	Presenter(s)
Friday, Sept. 10 8:00–8:45 AM	**Breakfast**	
8:45–9:00 AM	**Welcome and Introductory Remarks**	**Cohen/Batchinsky**
9:00 AM—12:00 PM	**Unraveling fundamental laws in Biology: Dynamic models and biological interactions during acute illness**	**Moderator: Tim Buchman Panelists: Benjamin Mann, Ary Goldberger, Chris Macedonia, Michael Deem, Patrick Norris**
9:00–9:25 AM	On Dirac limits and a new point of view on mathematical biology	Benjamin Mann
9:25–9:50 AM	Biochronicity	Chris Macedonia
9:50–10:15 AM	Breakdown of spatio-temporal complexity in acute illness: Toward dynamical biomarkers in the ICU	Ary Goldberger
10:15–10:40 AM	Spontaneous emergence of modularity as a law in biology	Michael W. Deem
10:40—11:05 AM	From data capture to decision support: The past, present, and future of SIMON	Patrick Norris
11:05—12:00 PM	Questions and free discussion	Moderator and experts
12:00—1:00 PM	**Lunch**	**Hotel**

Date/Time	Event	Presenter(s)
Friday, Sept. 10 1:00—3:30 PM	**Monitoring biological control and regulation**	**Moderator: John Karemaker** **Panelists: Bruce West, Dwain Eckberg, Tom Kuusela, Ted Dick, John Doyle**
1:00—1:20 PM	Overview of the cardiovascular regulatory system. Blood pressure variability	John Karemaker
1:20—1:40 PM	Measuring cardiovascular regulation using heart rate variability analysis: what it is and what it is not	Dwain Eckberg
1:40—2:00 PM	Semantics of complexity: Implications for understanding control in physiology	Bruce West
2:00—2:20 PM	Measuring cardiovascular control using tools from nonlinear dynamics: from physics to physiology and back	Tom Kuusela
2:20–2:40 PM	Breathing pattern variability: Neural mechanisms & modeling	Ted Dick, Rishi Dhingra, Frank Jacono, Christopher G. Wilson, Kenneth A. Loparo, Mikkel Fishman and Ilya Rybak
2:40—3:00 PM	Cardiovascular control and regulation: from mathematics to physiology and back	John Doyle
3:00—3:30 PM	Questions and free discussion	Moderator and experts
3:30—6:00 PM	**Invited Overview Talk: Modeling methods and tools**	**Moderator: Gary An. Panelists: Ioannis Androulakis, Scott Diamond, Eberhard Voit, Yoram Vodovotz**
3:30—3:50 PM	Characterization of fundamental aspects of biology with abstract mathematics: Category theory as a pathway for dynamic computational modeling of biological systems	Gary An
3:50—4:10 PM	Towards a mechanistic understanding of Inflammation and physiologic variability	Ioannis Androulakis
4:10—4:30 PM	Novel methods and approaches to modeling coagulation	Scott Diamond
4:30—4:50 PM	Systems analysis of the role of bone Morphogenic Pro-	Eberhard Voit, Weiwei Yin
4:50—5:10 PM	Computational models of inflammation: translational applications to acute Illness	Yoram Vodovotz
5:10—6:00 PM	Questions and free discussion	Moderator and experts Refreshments
6:00—7:00 PM	Poster session	Chairs: Gilles Clermont, Sven Zenker

Date/Time	Event	Presenter(s)
Saturday, Sept. 11 7:00–8:00 AM	**Breakfast**	**Hotel**
8:00–11:00 AM	**Multidisciplinary translational research: From fundamental science to practice. Life-saving interventions and other clinical outcome measures**	**Moderators: Charles Wade, Mitchell Cohen Panelists: John Holcomb, Lepoldo Cancio, José Salinas, Andriy Batchinsky, Wassim Haddad, David Baer, Edmund Neugebauer, Gari Clifford**
8:00 AM—8:20 AM	Clinical Outcome Measures	John Holcomb
8:20–8:40 AM	Detecting the need for LSIs using bio-sensor-derived data	Leopoldo C. Cancio
8:40–9:00 AM	Development of a decision support framework to improve time to administration of LSIs	José Salinas
9:00–9:10 AM	Tapering off mechanical ventilation: Objective criteria for weaning	Andriy Batchinsky
9:10—9:20 AM	A model of pressure- and work-limited neuroadaptive control for mechanical ventilation of critical care patients	Wassim Haddad
9:20—9:40 AM	Rehabilitation of combat warriors and return to duty	David Baer
9:40—10:00 PM	Quality of life as an outcome measure in Trauma	Edmund Neugebauer
10:00—10:20 PM	Dealing with contradictory, noisy and missing ICU data; why we should recycle information	Gari Clifford
10:20—11:00 AM	Discussion	
11:00—12:00 PM	Presentations by industry	TBD
12:00—1:00 PM	**Lunch**	**Hotel**

Notes:

Date/Time	Event	Presenter(s)
Saturday, Sept. 11 1:00—5:00 PM	**Summit. Managing Information Flow at the Bedside: Toward Standardizing Clinical Use of Biological Signals**	**Moderator: John Karemaker** **Panelists: Bruce West, Dwain Eckberg, Tom Kuusela, Ted Dick, John Doyle**
1:00—1:45 PM	Keynote: Integration of biomedical informatics to clinical medicine. Perspective of the end-user of the future	Marek Malik
1:45—2:00 PM	Managing Information Flow at the Bedside: Current Monitoring Systems e variability analysis: what it is and what it is not	Moderator: Brahm Goldstein. Panelists: Marek Malik, Randall Moorman, Jan Zebrowski, Soojin Park, Andrew Seely, Ivaylo Hristov, George Moody
2:00—2:20 PM	Multivariate assessment of patient status at the bedside	Brahm Goldstein
2:20—2:40 PM	Continuous risk prediction at the bedside: early diagnosis of sepsis in premature infants	Randall Moorman
2:40–3:00 PM	Stochastic analysis of heart rate variability: asymmetry, respiration and echocardiography parameters in hypertrophic cardiomyopathy	Jan Zebrowski
3:00—3:20 PM	Data visualization: Design and evaluation of user interfaces within the ICU workflow	Soojin Park
3:20—3:40 PM	Development and application of multiorgan variability monitoring	Andrew Seely
3:40—4:00 PM	Assessment of signal quality: implications for continuous monitoring at the bedside	Ivaylo Hristov
4:00—4:20 PM	Progress in forecasting, shared data use and open engineering challenges in critical care	George Moody
4:20—5:00 PM	Discussion/refreshments	Moderator and experts
5:00—6:30 PM	Breakout Session 1: Regulatory issues with biosensor-derived data. Data capture, storage, integration and assessment. Web survey results and discussion	Moderators: José Salinas and Patrick Norris Panel: Mark Darrah, George Moody, George Kramer
5:30—6:30 PM	Breakout Session 2: Development of methodological standards for use of physiologic waveform data in the clinical setting	Leaders: Brahm Goldstein and Andriy Batchinsky Panel: Randall Moorman, Ivaylo Hristov, Anton Burykin, Tom Kuusela, Dwain Eckberg, Madalena Costa, Andrew Seely
7:00 PM	**Gala dinner**	**Hotel**

Date/Time	Event	Presenter(s)
Sunday, Sept. 12 7:00—8:00 AM	**Breakfast**	**Hotel**
8:00—9:00 AM	**Session 1: Requirements to the next generation monitoring systems**	**Session Leaders: Marek Malik and Brahm Goldstein**
9:00—9:30 AM	Discussion/refreshments	Hotel
9:30—10:30 AM	**Session 2: Discussion of conference proceedings and position manuscript**	**Session Leaders: Tim Buchman and Yoram Vodovotz**
10:30—11:00 AM	**Boxed lunch/adjournment**	Hotel

Submitted Abstracts/Poster Presentations

Quantification of Fuzzy Modularity in Biologic Networks

Nathan Menke[1]

[1]Lincoln Medical and Mental Health Center

Objectives: 1) Utilize fuzzy set theory to analyze biological networks to provide an added layer of analysis consistent with real world systems/data. 2) Utilize fuzzy modularity analysis to help predict possible side effects of therapeutic modalities. 3) Utilize fuzzy modularity analysis to provide insight into the abnormal physiology of complex diseases.

Methods: Network Definitions: Four networks were taken from the literature as commonly used examples used in modularity analysis. The example networks were analyzed using basic network statistics. The statistics were generated using in house software as well as Pajek v1.257. Modularity Definition: The modules were generated by the Newman 2006 algorithm2. This algorithm is a variation of spectral partitioning with a Kernighan-Lin refinement. The modules are created by dividing the network partitions in such a way that maximizes the Q score. Modularity Fuzzification: The results of the modularity analysis are fuzzified by creating a membership function that is defined as the proportion of edges from a given node to a given module. A membership function for a node i and a module M is defined as the fraction of edges of i that connect to members of M. Fuzzy Modularity Quantification: The Q score is redefined to take into account partial memberships that are generated when applying to the modules generated by the Newman algorithm.

Results: The basic network statistics are summarized in Table 1. Table 2 provides an example of the modularity scores for an example vertex generated by the modularity analysis of the karate network. Table 3 summarizes the results of the modularity analysis. The difference between the Q and Qf score provides a metric that quantifies the amount of interconnectedness among the network modules. Not surprisingly, the biggest difference occurs in the metabolic network as metabolism is a process in which there is a large amount of overlap among different pathways.

Table 1: Network Statistics

	# of nodes	# of edges	Average vertex degree	Network connectedness	Network diameter
Karate	34	78	4.59	0.139	5
Jazz	198	2742	27.70	0.141	6
Metabolic	453	2040	8.97	0.0199	7
Email	1,133	5451	9.62	0.00850	8

Table 2: Modularity Scores

	Module 0	Module 1	Module 2	Module 3
Newman	0	1	0	0
Fuzzified Newman	0.0625	0.625	0.25	0.0625

Table 3: Modularity Summary

	Number of Modules	Newman Q score	Q_f	Q_f-Q
Karate	4	0.419	0.432	0.013
Jazz	4	0.442	0.434	-0.008
Metabolic	10	0.435	0.562	0.127
Email	11	0.572	0.607	0.035

Conclusions: Crisp set theory has provided useful tools for the analysis of networks; however, crisp set algorithms are limited in their ability to translate qualitative biologic data into quantitative concepts. This abstract represents a proof of concept of how fuzzification of modularity algorithms provides biological plausibility to the analysis of complex interconnected networks. This fuzzification better represents the real-world networks that contain elements that serve more than one function or allow communication between different pathways. Fuzzy modularity is a dynamic modeling tool that allows the study of dynamic non-linear networked systems. The complexity of biologic organisms has stymied experimental efforts to gain a system level understanding. Utilizing fuzzy set theory to analyze biological networks provides an added dimension consistent with real world data. Crosstalk among different functional pathways leads to unanticipated adverse effects of therapeutic interventions (an anti-inflammatory medicine causing myocardial infarctions). The use of fuzzy networks may allow the prediction of such adverse events and provide insight into the abnormal physiology of complex diseases.

Data-Driven Segregation of Trauma Patients Using Principal Component Analysis (PCA) Yields Novel, Patient-Specific Insights into Acute Inflammation

Ali Ghuma, Cordelia Giraldo, Rajaie Namas, Juan Ochoa, Timothy Billiar, Qi Mi, Ruben Zamora, Yoram Vodovotz

[1]University of Pittsburgh, PA

Objectives: The human inflammatory response to trauma is a multi-dimensional, complex process that manifests in patient-to-patient variability. We have attempted to elucidate aspects of this response using mathematical approaches, with the goal of improved diagnosis and treatment

Methods: Thirty-three trauma patients (20 males, 13 females; age 44±3; Injury Severity Score [ISS] 24±3) were recruited following IRB approval. Serial blood samples were obtained from all 33 patients; with 3 samples within the first 24 h. Twenty-five inflammatory cytokines in plasma were quantified using Luminex™. NO2-/NO3- was measured using the nitrate reductase/Griess assay. Principal Component Analysis (PCA) followed by hierarchical clustering was used to suggest patient-specific principal inflammatory drivers.

Results: PCA suggested that trauma-induced inflammation was dominated by GM-CSF, TNF-α, IL-10, IL-15, and IL-β in this patient cohort. Individualized PCA was carried out using cytokine and NO2-/NO3- data obtained in the first 24 h, in order to discern individual features of inflammation. We found that IL-1Ra (n=16 patients), RANTES (n=16 patients), MIP-1β (n=14 patients), TNF-α (n=12 patients), and IL-6 (n=11 patients) dominate in the first component in these patients. This analysis delineated groups that differed significantly in their Marshall Score (Group A: 1.6 ± 0.25 vs. Group B: 4.33 ±0.37) within the first 24 h post-injury. Patients in Groups A and B, who were segregated based on patient-specific PCA based on inflammation biomarker data obtained within the first 24 h, remained segregated (significantly lower Marshall Score in Group A vs. Group B) for up to 4 days.

Conclusions: While additional work is needed, these findings raise the potential for multiplexed cytokine analysis coupled with patient-specific PCA as a potential biomarker framework for outcome prediction in trauma.

Pathway Crosstalk Ratios Change During Early Shock Trauma

Mary F. McGuire[1], M. Sriram Iyengar[1], David W. Mercer[2]

[1]University of Texas Health Science Center, Houston

[2]University of Nebraska Medical Center, Omaha

Objectives: Crosstalk relates to how the molecular interactions in biological pathways determine functional specificity, how ubiquitous messengers transmit specific information, and how redundant messages crosslink within the system while undesired signals are minimized. Objective, quantitative measures of crosstalk can yield useful insights into underlying mechanisms of disease progression. Here we propose such a metric called XTALK that calculates the changing proportions of molecular interaction types, such as expression and inhibition, over time. XTALK is then applied to the biological pathways evoked by cytokine signalling in the first 24 hours from insult.

Methods: Biological pathways can be represented as directed graphs that can be made computable when converted to matrices. In matrix terms, the minimum number of molecular interactions (edges) required for a molecular function is the same as the rank, the number of linearly independent rows in the incidence matrix constructed from the edges. A metric of crosstalk is then defined as XTALK = 1- (rank/number of edge rows). XTALK was calculated and compared across time, outcome and interaction type in biological pathways evoked by cytokine signalling in trauma. Incidence matrices were constructed over time periods within the first 24 hours from trauma; over two outcomes: multiple organ failure (MOF) and non-multiple organ failure (NMOF); and over types of molecular interactions including activation, expression, inhibition, and transcription.

Results: XTALK ranged from 0% to more than 70% over all stratifications; the crosstalk ratio was highest in activation and expression interactions in all time periods and outcomes. Other interaction types also showed differences over time and outcome.

Conclusions: The XTALK measure provides a quantitative comparison of crosstalk in biological pathways across time, outcome, and molecular interaction type, and can supply insights into disease progression that may have implications for the timing of therapeutic interventions that target specific molecular interactions. If there is low crosstalk in inhibition interactions, as there is in initial shock trauma, one can expect to get specific inhibitory effects by therapeutically targeting just one inhibitory molecular interaction. If there is high crosstalk as there is in activation in the first 24 hours of trauma, an intervention on one activation interaction will likely trigger activation on many others, which may not be desirable. This means one might consider performing the intervention at a later time when activation crosstalk is lower.

A Physiological Model for Autonomic Heart Rate Regulation in Human Endotoxemia

Panagiota Foteinou[1], Steven Calvano[2], Stephen Lowry[2], Ioannis Androulakis[1]

[1]Rutgers University
[2]UMDNJ-RWJMS

Objectives: The systemic inflammatory response syndrome (SIRS) often accompanies critical illnesses. Marked abnormalities in cardiovascular function accompany acute illnesses manifested as sustained tachyarrhythmias which are but one manifestation of systemic dysregulation. Because cardiac pacemaker activity is under control of the autonomic nervous system (ANS), the analysis of heart rate variation for assessing autonomic activities is being increasingly evaluated as a possible tool that may have clinical and/or diagnostic relevance. In acute illnesses, autonomic imbalance manifesting in part as parasympathetic attenuation is associated with increased morbidity in patients who manifest the SIRS phenotype. Decreases in cardiac vagal tone and increases in heart rate are also elicited during the acute inflammatory condition mediated by endotoxin administration in healthy volunteers. Predicated upon the fact that overall vari! ations in heart rate are largely dependent on autonomic modulation, a multiscale model of human endotoxemia, as a prototype model of systemic inflammation in humans, is developed that quantifies critical aspects of the complex relationship between inflammation and autonomic heart rate regulation.

Methods: Using the human endotoxin challenge model, vital signs including heart rate and parameters of heart rate variability, namely pNN50, were recorded. The time domain statistic measure, pNN50, was used to assess parasympathetic influences on the heart. The present study expanded our prior work in an attempt to include systemic level interactions associated with the effect on heart rate of the dynamic interplay between sympathetic and parasympathetic branches of ANS. Physicochemical interactions related to the release and binding of cardiac neurotransmitters in the synapses between neural fibres and the sinoatrial nodal cells were explicitly incorporated. Further, the two major autonomic control systems were considered to act antagonistically giving rise to changes in heart rate. Finally, quantifiable relationships among these complex physiologic signals were established using the principles of indirect response modelling. Thus, this study links inflammation and clinical outcomes via a multiscale host response model.

Results: This modeling effort describes cardiovascular responses to acute endotoxin injury, phenotypically expressed as tachycardia, as a result of autonomic imbalance that reflects sympathetic activity excess and parasympathetic attenuation. Such dysregulation is mediated by an acute neuroendocrine stress response evoked by inflammation making it a critical enabler for assessing the cardiovascular effects of antecedent stresses upon the systemic inflammatory manifestations of human endotoxemia. For instance, the proposed model captures the vagolytic influence of exogenously-induced catecholamine excess as

observed in relevant human experimental studies. Further, a series of non-linear but relevant inflammatory scenarios are simulated that explore the impact of anti-inflammation on compromising outcome during the course of unremitting inflammation. Such scenarios associate adverse stress outcomes with severe cardiovascular complications simulated as persistent tachycardia.

Conclusions: The major conclusion of this work was to demonstrate the feasibility of a multiscale, physiology-based human inflammation model that links inflammation and autonomic control of cardiovascular function. Such a relationship is disturbed in actual acute illnesses and therefore the proposed model lays the foundation for a translational computational model that could potentially clarify the clinical contexts in which autonomic dysregulation contributes to morbidity in acutely stressed patients.

Decreased communication leads to diminished physiologic variability in a multiscale model of inflammation

Jeremy D. Scheff[1], Steven E. Calvano[2], Stephen F. Lowry[2], Ioannis P. Androulakis[1, 3]

[1]Biomedical Engineering, Rutgers University, Piscataway, NJ 08854
[2]Department of Surgery, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ 08901
[3]Chemical and Biochemical Engineering Department, Rutgers University, Piscataway, NJ 08544

Objectives: Decomplexification in physiological signals, such as heart rate, is often observed in critically ill patients and has been linked to adverse clinical outcomes. Similar decreases in physiologic variability have also been observed in human endotoxemia. These changes may be due to decreased communication between physiological systems. Although the relationship between coupling of systems and variability has been established in simple mathematical models, the underlying hypothesis has yet to be explored in the context of a physiologically-based model. By adding stochasticity to a multiscale model of inflammation, the extent of physiologic variability and how perturbations to the model affect variability were assessed. By perturbing the model such that spatially distinct compartments have diminished communication or that certain systemic signalling molecules are secreted more regularly, diminished physiologic variability is attained in a number of variables.

Methods: Our previous multiscale model of inflammation consists of a system of ordinary differential equations (ODEs). These ODEs were translated to stochastic differential equations (SDEs) by adding a Gaussian noise term to each equation, representing biological noise. As the neuroendocrine and immune systems communicate through the release of cytokines, hormones, and neurotransmitters, communication links between physiological systems in our model are represented by variables for pro-inflammatory signalling, anti-inflammatory signalling, cortisol, epinephrine, and melatonin. To quantitatively assess the variability of these components, Sample Entropy (SampEn) was applied to the simulated time series. SampEn estimates the probability that subseries of data that match within a defined tolerance will also match at the next time point; this allows the determination of the predictability or regularity of the data. Then, communication between systems is artificially decreased by lowering the model parameters governing the influence of the communicating variables on other variables. This simulates a tolerance effect in which the host becomes unresponsive to inflammation-linked signalling. Simulations were also run in which variability in individual communicating variables was decreased and SampEn was calculated for the other variables to assess the effect of dysregulation in one signal on the system as a whole.

Results: Variables representing inter-compartmental communication are pro-inflammatory signalling (P), anti-inflammatory signalling (A), cortisol (F), epinephrine (EPI), and melatonin (MEL). Regularity was imposed by setting the physiologic variability in one variable at a time to zero, simulating either the dysregulation of function of a certain tissue or a constant exogenous infusion. Next, regularity was also imposed by decreasing the coupling between each signaling variable and all other model components. Signal regularity was assessed via SampEn for each of these signalling variables and was shown to be generally diminished when decreased communication between compartments is induced as described above.

Conclusions: This work lays the foundation for developing quantitative models of inflammation that link changes in physiologic variability with mechanistic physiology-based network structure. Further, it gives support to the hypothesis that diminished physiologic variability in response to inflammatory instigators is fundamentally a manifestation of decreased communication between biological systems.

Dynamics of Thermoregulatory Responses after Cardiac Surgery

Kristien Van Loon[1], Jasmine Craps[1], Geert Meyfroidt[2], Greet Van den Berghe[2], Daniel Berckmans[1], Jean-Marie Aerts[1]

[1]Division Measure, Model &Manage Bioresponses, Katholieke Universiteit Leuven, Kasteelpark Arenberg 30, B-3001 Leuven, Belgium.
[2]Department of Intensive Care Medicine, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

Objectives: The dynamics of thermoregulatory responses of a patient after cardiac surgery have been shown in literature to be indicative for the health status of the patients. The first objective of the present study was to quantify the dynamic thermoregulatory responses of off-pump coronary artery bypass (OPCAB) patients during the first hours of the ICU stay. Second, the correlation between these dynamic features and intensive care unit (ICU) length of stay (LOS) was examined.

Methods: 11 patients, admitted to the ICU after OPCAB, were followed for the first ten hours after admission. Temperatures of the blood and of the skin surface of the calf and the toe were monitored in these patients and saved with a sample interval of 1 minute in the Patient Data Management System (Metavision ®, iMD-Soft ®). Also time of starting and turning off a forced-air warming blanket (Bair Hugger ®) was accurately recorded. The thermoregulatory response of patients to the removal of the warming blankets was modeled using single-input, single-output (SISO) discrete-time transfer function models. The input was a step input: the transition from active warming using the warming blanket to no active warming. As output the difference between the temperature of the blood (core temperature) and the toe (peripheral temperature) was used. The parameters of the best models were used to calculate the time constant (TC) and the steady state gain (SSG) of the responses. The TC is defined as the time the difference between core and the peripheral temperature needs to reach 63% of its final value. The SSG is the change in the process output divided by the change in the process input (Figure 1). The regression line between TC, SSG and ICU LOS was drawn, and R^2 and p-values were calculated.

Results: For all patients, a first order model seemed to be the best choice based on the used statistical performance criteria (mean $R^2 = 0.959$, standard deviation = 0.079. The mean time constant was 69 minutes and the mean SSG was -0.084. There was no significant correlation between ICU LOS and TC ($R^2 = 0.0017$, p-value = 0.90), nor between ICU LOS and SSG ($r^2 = 0.05$, p-value = 0.52). In the subset of nine patients with ICU LOS of less than 7 days, the LOS and SSG were correlated ($R^2 = 0.66$, p-value = 0.008). The patients with a shorter length of stay had a smaller TC and a smaller SSG in absolute value. This means that they returned faster to a stable thermoregulation and showed a smaller decrease in peripheral temperature after removal of the warming blanket in comparison with patients that had to stay longer in the ICU.

Conclusions: In this preliminary study, no significant relation between dynamic model features of the responses of core and skin temperature of the patient to the turning off of the warming blanket at one side and the LOS on the other side could be found. The observed trends for nine patients with a LOS of less than seven days suggest however that the dynamics of the thermoregulation possibly contains useful information concerning the outcome of patients after cardiac surgery. Further research is necessary using more patient data and additional variables in order to investigate the value of dynamic features as an indicator of the health status of the patient. Caption for Figure 1: Figure 1: Time Constant (TC) and Steady State Gain (SSG) of a first order response (y = process output) to a step input (u = process input).

Agent based model of instant blood-mediated inflammatory reaction (IBMIR) effects on immediate graft loss following intra-portal islet cell transplantation

John Seal[1], Gary An[1]

[1]University of Chicago, Department of Surgery

Objectives: The immediate loss of islet cells transplanted into the portal vein for the treatment of insulin insufficiency remains a significant barrier to the success of the therapy. The instant blood-mediated inflammatory reaction (IBMIR) is a culmination of coagulation, platelet aggregation, complement activation and immune cell infiltration. Understanding the interplay between these potential mechanisms of early graft loss is essential for improving therapeutic and preventative strategies to improve overall graft survival. Agent based modeling is a useful technique to dynamically represent interactions between multiple physiologic processes in a spatially heterogeneous and dynamic context. We developed an ABM of IBMIR incorporating potential mechanisms of graft loss to study the effects of therapeutic interventions.

Methods: An agent based model (ABM) of early islet cell graft loss was created using NetLogo. Agents representing individual cells, including islet grafts, platelets, endothelium and immune affector cells interact in a virtual milieu of the portal vein post-islet cell transplantation. Rules governing agent interactions were extrapolated from well-established components of intrinsic and extrinsic coagulation, complement activation, platelet aggregation and immune cell chemotaxis and infiltration. Islet cell expression of chemokines and retention of extra-cellular debris during pre-transplant preparation were represented as modifiable agent variables. Preventative and therapeutic interventions including intravenous heparin and anti-platelet therapy were included as patch variables.

Results: The key components of IBMIR were integrated into an ABM of intra-portal islet cell transplantation that abstractly reproduces essential behaviors associated with early graft loss. Baseline model behavior was calibrated to reproduce a high portion of graft loss in the absence of preventative therapies. The combination of multiple preventative strategies including heparinization, platelet inhibition and anti-inflammatory agents produced the greatest graft survival in the model, underscoring the significance of multiple contributing mechanisms.

Conclusions: Agent based modeling is well suited to dynamically represent the complex interaction of mechanisms responsible for severe early graft loss which remains the most significant barrier to islet cell transplantation. With this introductory model, additional detail can be incorporated to define critical points of interaction and optimal strategies to attenuate IBMIR. The modular architecture provides opportunity to incorporate pre-existing and more sophisticated models of inflammation, platelet aggregation and complement activation. Ultimately, this dynamic representation of IBMIR will serve as an adjunct to hypothesis formation in collaboration with wet lab research to facilitate and accelerate therapeutic development.

The Feasibility of Continuous Heart and Respiratory Rate Variability Analysis in the ICU: A Pilot Investigation

Beverly Bradley[1], Geoffrey Green[1], Rajeev Yadav[1], Izmail Batkin[1], Andrew J.E. Seely[1,2,3]

[1] Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[2]Division of Thoracic Surgery, University of Ottawa, Ottawa, Ontario, Canada
[3]Department of Critical Care Medicine, University of Ottawa, Ottawa, Ontario, Canada

Objectives: There is increasing evidence that heart rate variability (HRV) is reduced in association with stress, age and disease including critical illness; and degree of alteration correlates with illness severity. Respiratory rate variability (RRV) is also altered in association with critical illness, with reduced RRV during spontaneous breathing trials being evaluated as a predictor of extubation failure. The clinical value of longitudinal or continuous tracking of HRV and/or RRV in critically ill patients remains to be characterized. We hypothesize that continuous HRV and RRV monitoring could provide a means to track severity of illness and patient trajectory in critically ill patients; however feasibility has not been demonstrated. We have developed CIMVA (Continuous Individualized Multiorgan Variability Analysis) as a software tool to enable standardized, comprehensive and transparent continuous multiorgan variabili! ty monitoring. The objective of this study was to explore the feasibility of applying CIMVA to critically ill patients in the ICU, evaluating waveform data quality, disconnection, arrhythmia, beat and breath detection and variability analyses.

Methods: 34 critically ill patients experiencing respiratory and/or cardiac failure were enrolled, undergoing continuous recording of electrocardiogram (ECG) and end tidal capnography (CO2) waveforms using Philips Intellivue monitors. With waived consent approved by institutional REB, ECG monitoring was initiated at time of ICU admission and continued until ICU discharge or a maximum of 14 days; CO2 monitoring was initiated when CO2 modules were applied at time of enrollment, and continued until extubation or a maximum of 14 days. Waveform data was downloaded daily on a per-patient basis using the Philips Intellivue Information Centre. De-identified data was then transferred from the Philips Database Server over the hospital network to a research file server where data processing occurred using the CIMVA software engine. For each patient, variability of their inter-beat and inter-breath intervals were calculated over 5-min! ute windows of waveform data; in total, 25 measures of variability representing time, frequency, time-frequency, entropy, scale-invariant, and non-linear domains of complexity analysis were computed for every interval. The feasibility of continuous monitoring and variability analysis was assessed qualitatively, evaluating setup and ease of use, and quantitatively, evaluating the proportion of missing or rejected data versus usable high quality waveform data remaining. Measures of data quality included quantification of disconnection, and number of inter-beat and inter-breath intervals removed due to artifact and/or arrhythmia, most commonly atrial fibrillation.

Results: Mean age of patients was 56.5 (±15.9) years. On the day of admission, mean APACHE II score was 22.8 (±6.7) and mean daily MODS score was 6.8 (±2.9). Mean number of days enrolled in the study was 11.0 (±3.6) and on average, 10.3 (±4.3) days of ECG data and 8.2 (±4.9) days of CO2 data were collected per patient. The mean proportion of missing data was 6.1% (±9.25%) and 10.37% (±18.34%) for ECG and CO2 waveforms, respectively. 94% of enrolled patients had over 75% of their ECG waveform data available for data processing, whereas this proportion was 88% for CO2 data. HRV and RRV variability data were computed successfully from inter-beat interval and inter-breath interval time series derived from the waveform data available. The average proportion of variability windows remaining after data quality filtering was 81.2% and 87.5% for HRV and RRV data respectively. Of the 7 patients who had >25% of their HRV windows rej! ected by data quality filters, all 7 experienced atrial fibrillation or another form of non-sinus rhythm. An average of 1.6% (±1.0%) of 5 minute HRV windows were rejected due to disconnection artifact. Disconnection artifact was higher for CO2 data (9.1% ±8.7%), possibly due to short periods of apnea being detected as disconnections.

Conclusions: We evaluated the feasibility of continuous heart and respiratory rate variability analysis in two principal ways, namely by (1) quantifying the degree of missing waveform data (evaluating quality of continuous waveform data harvest), and (2) quantifying removed or rejected variability data after CIMVA processing (evaluating feasibility of continuous variability computations). Maintenance activity (software update) on the patient monitoring network and minor issues with tubing for the CO2 module were the major contributing causes of missing waveform data. While it is still unclear how much data can be missing without fundamentally compromising analysis of variability, the trajectories plotted for individual patients subjectively demonstrate the potential to observe both short term and long term trends in variability despite missing data. Variability analysis remains indeterminate for patients with non-sinus rhy! thm, and this study highlights their prevalence and its implications for continuous HRV analysis in this population. Although applied with a Philips Intellivue monitoring system and network, the general setup presented is applicable to other waveform monitoring systems, and work is ongoing to interface CIMVA with these systems. By evaluating both the quality of the waveforms as well as the subsequent variability data, we conclude that continuously recorded ECG and CO2 waveform data in critically ill patients is of adequate quality for subsequent continuous multiorgan variability analysis, and that long-term continuous monitoring of variability in the ICU is feasible without excessive data loss.

Early Prediction of Length of ICU Stay from Inflammatory Mediators in Trauma Patients

Cordelia Ziraldo[3], Ali Ghuma[1], Rajaie Namas[1], Juan Ochoa[1], Timothy R. Billiar[1], Ruben Zamora[1], Qi Mi[2], Yoram Vodovotz[1]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA
[2]Department of Sports Medicine, University of Pittsburgh, Pittsburgh, PA
[3]Department of Computational Biology, University of Pittsburgh, Pittsburgh, PA

Objectives: The prognosis for any two trauma patients that suffer the exact same injury can be vastly different. The body's inflammatory response to trauma has a major contribution to the course of a patient's progress. We hypothesized that assessment of circulating inflammatory mediators combined with a small amount of demographic data is sufficient to define subgroups of patients that will recover vs. those that will require a longer stay and more care. Our goal was to build a classifier that will predict the length of a patient's stay in the ICU.

Methods: We measured 25 cytokines (via Luminex™ xMAP® technology) and NO2-/NO3- (nitrate reductase) from blood serum of 68 patients (49 males, 19 females; median age 42; median Injury Severity Score 24.5). The total number of instances in our dataset was 139 since some patients had multiple blood samples taken throughout the first 24 h of hospitalization. For these, we treated each set of measurements as independent, but noted when they were from the same patient. We also noted age, sex, ISS, and type of injury for each patient. Three different classification methods (Naïve Bayes, Support Vector Machines [SVM], and Artificial Neural Networks [ANN]) were implemented to predict length of ICU stay with respect to a threshold (7, 14, 21 or 28 d). We estimated our accuracy using leave-one-patient-out cross-validation.

Results: We considered a classifier to be successful when it outperformed a "dummy classifier" that always guessed a patient would stay less than the threshold. We were able to outperform the dummy classifier with all three classification methods, with the most success at earlier thresholds. When predicting whether a patient would stay less than 7 d in the ICU, ANN achieved a 5-fold improvement over the dummy classifier, SVM was nearly 3-fold better, and Naïve Bayes achieved approximately 1.5-fold improvement.

Conclusions: Using these data-driven methods, we were able to utilize cytokine measurements to help predict ICU LOS. More validation studies with larger patient cohorts are necessary to estimate the generalized error of these classifiers.

Dynamic Knowledge Representation of Cellular Redox Homeostasis and Oxidative Stress Response in a Systems Dynamics Model

Daniel Katz[1], Gary An[2]

[1]Northwestern University Feinberg School of Medicine
[2]University of Chicago, Department of Surgery

Objectives: Cells are thermodynamically dissipative structures that maintain their informational integrity by existing in dynamic equilibrium. The redox state of the cell represents a critical metric fro characterizing both the baseline metabolic homeostasis of the cell, as well as the cell's response to stress and danger. The cellular oxidative stress response (COSR) exhibits Janus-faced properties in human disease states: effective response to insults and infection require an intact and appropriately vigorous COSR, however, excessive or inappropriate manifestation of the COSR can produce unintended and paradoxically detrimental effects. The biochemistry of the COSR is well characterized; however, since it represents a dynamic process, dynamic computational representation is required for the effective understanding and evaluation of the behaviour of the system. We utilized a Systems Dynamics (SD) approach to produce a mathematical model of the primary components of the COSR.

Methods: Information concerning the components and processes of cellular energy metabolism in both baseline homeostasis and the COSR was obtained by a review of the published literature. This information was converted into a series of process flow diagrams, and then these diagrams were used to produce a SD model using NetLogo (1). Model development proceeded through progressive addition of pathways, compartments and detail, leading to the production of a series of increasingly complex SD models.

Results: Five progressively detailed SD models of the COSR were produced using the SD capacity in NetLogo. These models increasingly incorporate the basic components of redox homeostasis, cytosol and mitochondrial compartments, specific subtypes of reactive oxygen species and antioxidants, metabolic pathways and cycles, abstracted damage interventions and effects, and stochastics related to the manifestation of the COSR. The SD models qualitatively reproduce baseline redox metabolic homeostasis, the initiation of the COSR and consequences of cellular damage and repair.

Conclusions: The redox states of cells are a critical component in the pathogenesis of human disease, and effective characterization of the dynamic processes involved in the COSR requires dynamic knowledge representation with mathematical/computational models. In particular, recognizing that the development of disease must be identified as a deviation of a baseline healthy state emphasizes the importance of being able to capture the dynamic equilibrium in which cells exist. It is only with this type of system representation that control and intervention strategies can be generated and evaluated. The abstract general model presented herein can be used as a base model for development of more specific cell types and eventually be integrated into hybrid tissue/organism

Agent-based of human endotoxemia accounting for circadian variability

Tung T. Nguyen[1], Steve E. Calvano[2], Stephen F. Lowry[2], Ioannis P. Androulakis[3]

[1]BioMaPS Institute for Quantitative Biology, Rutgers University, Piscataway, NJ 08854
[2]Department of Surgery, Robert Wood Johnson Medical School, UMDNJ, Piscataway, NJ 08854
[3]Biomedical Engineering and Chemical & Biochemical Engineering Department, Rutgers University, Piscataway, NJ 08854

Objectives: Despite increasing knowledge about pathophysiological pathways and processes involved in sepsis as well as promising results on animal studies and preclinical trials, the molecular mechanisms and physiological significance of the systemic inflammatory response are still not fully understood. Due to the complex nature of the problem, researchers have realized that combinations of in vivo and in silico approaches can lead to the development of novel treatment strategies. Thus, in an attempt towards a better understanding of the molecular mechanisms and the complex dynamics of the host inflammatory responses, we previously developed a semi-mechanistic indirect response model using a system of ordinary differential equations (ODEs). In order to overcome the limitations of ODE models, most notably homogeneity in local conditions, continuous time representation and the lack of stochasticity of cellular events, we exp! lore an alternative approach based on agent-based modeling (ABM) which naturally accounts for these biological phenomena (e.g. stochasticity, heterogeneity) with the aim of (1) establishing a homeostatic multi-scale model of human endotoxemia; (2) examining the systemic behaviors under the activity of circadian rhythms; and (3) providing an in silico platform for further examination on inflammation-specific phenomena.

Methods: Genome-wide blood leukocyte transcript abundances were collected and measured with Affymetrix microarrays before and at 2, 4, 6, 9, and 24 hours after an intravenous administration of bacterial endotoxin (LPS–2ng/kg) was given to healthy human subjects (GSE#3284). With the assumption that transcriptional signatures can characterize the cellular dynamics in response to inflammatory agents, the high-dimensional transcriptional data were decomposed into significantly coexpressed clusters which are classified into three main patterns of the systemic inflammatory responses including pro-inflammatory, anti-inflammatory, and bio-energetic transcriptional patterns. Such dynamic responses are assumed to be mainly regulated by the activity of critical transcription factors (e.g. NFêB) which are activated by signalling cascades that translate extra-cellular signals to intra-cellular responses. Furthermore, there is an increasing awareness that circadian rhythms have critical roles in the host inflammatory response, characterizing by the release of melatonin and cortisol. While the cortisol periodicity has the peak in early morning, melatonin is tightly regulated to have a peak of production in the late night and remain at a low level in the rest of the day. Therefore, in the proposed model, cortisol and melatonin are selected to drive the circadian variation of the system by an automatic mechanism of production from the brain following the timeline of days and nights. The regulatory mechanistic relationships between components of the model have been established based on the principles of indirect response modeling and literature evidence.

Results: One of key aspects in our approach is the modeling of dynamic transcriptional signals that drive essential responses which are extracted directly from experimental microarray data. The resulting multi-scale model has been established and implemented using Repast Symphony, an extensive platform for agent-based modeling. Without any external stimulus and circadian activity, parameters including the population sizes and the synthesis rates of components are adjusted to maintain the system in the healthy state with a novel technique based on pharmacokinetic principles. Subsequently, circadian rhythms of cortisol and melatonin are incorporated to fulfill the system. The interplay between components is examined; for instance, pro-inflammatory and anti-inflammatory cytokines are strongly driven under the circadian rhythmicity. Additionally, the model clearly depicts the variability of cell-to-cell and that of inter-communication signals.

Conclusions: We have presented a comprehensive model that mimics physicochemical behaviours at the cellular level and physiological phenomena at the systemic level for assessing the inherent dynamics of the host inflammatory response. This quantifiable system provides an effective tool to easily create a number of 'what if' scenarios to understand the interplay among various components, the connectivity of critical components of the immune system, and the control mechanisms of the onset and resolution of systemic inflammation. Moreover, the model also allows for examining systemic behaviours under different initial component population sizes, which may be associated with specific physiological cases. Also, the use of the agent-based approach has naturally incorporated the stochastic and spatial effects into the model, providing a good platform to study individual cellular dynamics and patterns that lead to distinct outcomes under the administration of different LPS doses.

Trauma / Hemorrhage-Induced Inflammation in Mice: Insights from Data-Driven Models

Qi Mi[3,5], Gregory Constantine[2,5], Cordelia Ziraldo[1], Alexey Solovyev[2], Andres Torres[1], Rajaie Namas[1], Timothy Bentley[4], Ruben Zamora[1], Juan Carlos Puyana[1,5], Yoram Vodovotz[1,5]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213
[2]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260
[3]Department of Sports Medicine and Nutrition, University of Pittsburgh, Pittsburgh, PA 15260
[4]Walter Reed Army Institute of Research, Washington, DC 20307
[5]Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219

Objectives: Trauma/hemorrhagic shock (T/HS) elicits a global acute inflammatory response. We have previously created computational simulations of inflammation and tissue damage/dysfunction to gain insight into this complex response in mice. In the present study, we utilized multiplexing cytokine analysis (Luminex™ xMAP® technology) coupled with data-driven modeling to gain further insights into the inflammatory response to T/HS.

Methods: Using a computerized, closed-loop system, we subjected 54 Male C57/Black mice to surgical cannulation trauma (ST) ± hemorrhagic shock (HS). Eight experimental groups were obtained, in addition to completely non-manipulated animals: a) 1, 2, 3, or 4 h ST alone and b) 1, 2, 3, or 4 h of ST + HS (25 mmHg). Plasma was assayed for 20 cytokines and NO_2^-/NO_3^-. Three data-driven methods (a statistical prediction model, Principal Component Analysis [PCA] to discern main drivers of inflammation, and Dynamic Network Analysis [DNA]) were used to gain insights into the global, dynamic inflammatory response that characterizes ST ± HS.

Results: Based on a multivariate prediction model, IL-12, MIG, and IP10 were the best discriminators between ST and ST/HS. A smaller statistical model constructed using only IL-12 and MIG as predictors could correctly distinguish ST + HS from ST in 46 of 48 (96%) of cases. PCA suggested that the principal cytokines driving the response to ST were IL-6, IL-10, IL-13, GM-CSF and IL-1α, while ST + HS was influenced predominantly by IL-13, IL-10, IL-6, INF-γ and IL-17. DNA suggested that the central nodes were shifting rapidly post-ST, from IP-10 (0-1 h), to IP-10/IL-1β (1 - 2 h), then IL-12/NO2-/NO3- (2-3 h), and lastly TNF-α/ IL-4/IL-2/GM-CSF (3-4 h). The ST response was characterized by a high network density at all time points. In contrast, the central nodes over the same time ranges in ST + HS were MIG (0-1h), MIG/IL-6 (1-2h), MIG (2-3 h), and lastly KC (3-4 h); network density was zero over the first! 2 h and remained lower than that of ST.

Conclusions: Our results suggest that the response to low-level ST is driven by particular cytokines in a complex and well-ordered manner, while the addition of HS leads to the elaboration of distinct inflammatory mediators as part of a much less complex (and perhaps disorganized) response. The data-driven methods described in this study have the potential to facilitate mechanistic understanding of the dynamics of acute inflammation.

Parameter Estimation and Synthesis for Systems Biology: New Algorithms for Nonlinear and Stochastic Models

Sumit Jha[1], Alexandre Donze[2], Rupinder Khandpur[1], Joyeeta Dutta-Moscato[3], Qi Mi[3], Yoram Vodovotz[3], Gilles Clermont[3], Christopher Langmead[1]

[1]Carnegie Mellon University
[2]Verimag Laboratory, France
[3]University of Pittsburgh, Pittsburgh, PA

Objectives: To develop efficient, scalable algorithms for identifying parameters in nonlinear and stochastic models, such as those encountered in Systems Biology.

Methods: We have developed two algorithms for performing synthesis using reachability analysis. Our first algorithm can be applied to systems of nonlinear ordinary differential equations. The second algorithm can be applied to stochastic models, including Agent-Based Models, and Rule-Based Models. Parameter synthesis is the task of identifying ensembles of models, differing only in their choice of parameters, that exhibit qualitatively similar behaviours. In particular, our algorithms partition the space of parameters into disjoint domains of dynamic behaviour corresponding to user-defined constraints (e.g., 'a mild infection triggers an inflammatory response that resolves within 24 to 48 hours'.) These algorithms can also solve the parameter estimation problem (i.e., fitting to data) as a special case. Our methods provide more flexibility than related methods, such as bifurcation analysis, in terms of the kinds of dynamical behaviours that can be considered.

Results: Temporal changes, similar to those observed for endotoxemic mice (Chow et al, Shock 2005) and rats (Daun et al, J. Theretical. Biol. 2008) were observed in all inflammatory analytes. Though TNF was produced to a high degree in all animals, PCA suggested that IL-1β rather than TNF may be a main driver of systemic inflammation in this experimental preparation. The mathematical model was capable of describing the dynamics of inflammatory analytes in swine and predicted qualitative dynamics of MMP-2 and MMP-9.

Conclusions: A mathematical model of inflammation in swine has been defined that will aid us in elucidating the pathogenesis of acute inflammation in this clinically relevant pre-clinical model.

Spatial Effects of Pro- and Anti-inflammatory Cytokines on Chronic Inflammation: A Mathematical Model

Ian Price [1], David Swigon [1], G Bard Ermentrout [1], Gilles Clermont [1,2]

[1]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA
[2]Medical Center, University of Pittsburgh, Pittsburgh, PA

Objectives: Dysregulated pro-inflammatory and anti-inflammatory cytokine production can lead to incomplete healing in tissue with acute trauma, or to regions of inflammation in healthy tissue. We propose a mathematical model including Pro-inflammatory Cytokines, Anti-inflammatory Cytokines, Chemokines, Macrophages, Neutrophils, NOS, and Tissue that we first use to replicate dysregulated states, and then to simulate treatment.

Methods: A nonlinear mathematical model was constructed in a setting of ordinary differential equations. Parameters were fitted to viral response data and mathematical and heuristic biological criteria. Bifurcation analyses were performed. The model was then altered into a spatial setting using partial differential equations. Conditions for pattern formation were established. Different regimes of endogenous anti-inflammatory cytokine production were compared. Various treatment regimes using anti-inflammatory cytokines were implemented on acutely and chronically damaged systems.

Results: In the ODE version of the model, conditions for bifurcations leading to a stable chronic state and loss of stability of the baseline state were found, and in the PDE version, conditions on flux and diffusion for pattern forming instabilities. Self-perpetuating regions of chronic inflammation were reproduced by the model. For various scenarios, a minimal treatment regime was established that would re-establish baseline health of the tissue, if a minimum existed. For scenarios where baseline health did not re-establish, we compare the difference between tissue given long term care and untreated chronic cases.

Conclusions: Spatially oriented models permit some insight into the spread of inflammation throughout the tissue. The mathematical model can explain observations such as rheumatoid arthritis becoming localized in an otherwise homogeneous system. Therefore, any proposed treatment regime must account for the localized rather than systemic nature of a self-perpetuating region of chronic inflammation. The model provides insight into treatment options that may disrupt the localization and speed up healing.

Characterization of fundamental aspects of biology with abstract mathematics: Category Theory as a pathway for dynamic computational modeling of biological systems

Gary An[1]

[1]University of Chicago, Department of Surgery

Objectives: The complexity of biological systems is well recognized, as well as the need and utility of mathematical modeling and computer simulation as means of addressing that complexity. While multiple methods of mathematical and computational modeling have been applied in a tailored fashion to various aspects of biological systems, there is potential significant benefit to identifying and mathematically representing a fundamental description of biology. Category Theory (1) is a branch of abstract mathematics that has been used to bridge and bind various other branches of mathematics, providing a means of allowing tools and methods from one arena to be applied to others. Category Theory may be well suited as a means of describing the fundamental properties of biology from a computational perspective.

Methods: Category Theory is centered on the concept of a "category:" defined as a collection of objects, functions between the objects and the effects of those behaviours on the overall structure of object relationships. Furthermore, Category Theory deals with the transformations of one category into another that preserve the properties that define the category; these transformations are termed "morphisms" and are described by "functors." “Fundamental properties” of biology were identified, specifically targeted at distinguishing biology from physics and chemistry. These classes of properties were then mapped onto a category theoretic framework.

Results: A Category Theory-based description of biological systems was developed as described above. It was determined that biological systems cannot be represented without accounting for their components, and the interactions between those components within an organizational structure that exists in dynamic equilibrium. Furthermore, the organization of biological systems is identified as necessarily hierarchical and recursive, stressing the importance of addressing both context and concurrency in any description. The resulting category-theoretic description is general enough to abstractly describe any biological system: the general category of biology can be expressed as an abstracted biological computational unit (ABCU) [1]. Mathematical descriptions of biological systems can be constructed from instances of ABCUs and the processes that link them. Inversely, incomplete descriptions of aspects of biological systems (such as biochemical pathways) do not fulfill the associative requirement of a category, and are therefore not considered as members of the ABCU set. This \"completeness\" requirement places a constraint on the internal structure of a category theoretic description of a biological system, and can be seen as analogous to the fact that biological systems must follow basic physical and chemical laws.

Conclusions: Biology is more than an aggregate of chemistry and physics. While it incorporates and utilizes the laws of those domains, the richness of biology cannot be effectively characterized using merely the descriptive capacity of physics or chemistry. In order to develop the mathematics of biology it is necessary to present a mathematical description of the fundamental properties that set biology apart from these other domains. Given the organizational complexity of biological systems, this goal requires the use of more abstract and powerful mathematical tools that those used to delineate the laws of physics or chemistry. Category Theory is particularly well suited to this goal, and it is further suggested that being able to produce a category theoretic description maybe both necessary and sufficient to define a complete biological system, as distinguished from either a biophysical or biochemical one. Furthermore,! since Category Theory is also being applied to various aspects of computer science, programming languages and logic, it may provide a means of formalizing the transition from a biological description to a computable one. References: 1) Walters, RFC: Categories and Computer Science. New York, NY, Cambridge University Press, 1991. 2) Colasanti, R. and An, G. The Abstracted Biological Computational Unit (ABCU): Introduction of a recursive descriptor for multi-scale computational modeling of biological systems. Journal of Critical Care. 2009, 24:e35-36 (abstr), doi:10.1016/j.jcrc.2009.06.043.

Construction of Functions With Prescribed Multiscale Asymmetry. Asymmetric Weierstrass Function

Anton Burykin [1], Madalena Costa [2 3], Chung-Kang Peng [2], Ary Goldberger [2 3], Timothy Buchman [1]

[1]Emory Center for Critical Care (ECCC) and Department of Surgery, School of Medicine, Emory University
[2]Margret and H.A. Rey Institute of Nonlinear Dynamics in Physiology and Medicine, Harvard Medical School
[3]Wyss Institute for Biologically Inspired Engineering at Harvard University

Objectives: Time irreversibility (asymmetry with respect to time reversal) is an important property of many time series derived from processes in nature. Some time series (e.g., healthy heart rate) demonstrate even more complex, multiscale irreversibility, such that not only the original, but also coarse-grained time series are asymmetric over a wide range of scales. Several indices to quantify multiscale asymmetry have been introduced. However, there has been no simple generator of model time series with "tunable" multiscale asymmetry to test such indices.

Methods: We constructed an asymmetric Weierstrass function (using asymmetric sawtooth functions instead of cosine waves) and numerically calculated its multiscale complexity measures: MsAi (multiscale asymmetry index), MsEn (multiscale entropy) and DFA (detrended fluctuation analysis).

Results: Asymmetric Weierstrass function can be used to construct time series with any given value of the multiscale asymmetry. We show that multiscale asymmetry appears to be independent of other multiscale complexity indices, such as fractal dimension and multiscale entropy. We further generalize the concept of multiscale asymmetry by introducing time-dependent (local) multiscale asymmetry and provide examples of such time series. The WA function combines two essential features of complex fluctuations, namely fractality (self-similarity) and irreversibility (multiscale time asymmetry); moreover, each of these features can be tuned independently.

Conclusions: The proposed family of functions can be used to compare and refine multiscale measures of time series asymmetry.

Multi Wave Animator – Open Source MATLAB Tool For Dynamic Visualization of Physiologic Signals Recorded From Bedside Monitors

Anton Burykin [1], Tyler Peck [2], Vladimir Krejci [3], Andrea Vannucci [2], Ivan Kangrga [2], Timothy Buchman [1]

[1]Emory Center for Critical Care (ECCC) and Department of Surgery, School of Medicine, Emory University
[2] Department Anesthesiology, School of Medicine, Washington University in St. Louis
[3]Department of Anesthesiology, University Hospital of Bern

Objectives: Bedside presentation of physiologic data is central to modern critical care. Waveform displays (such as ECG) and simple time-averaged data (such as heart rate) have been the basis for decision-making for at least four decades. Whether these displays provide the optimal data synthesis is unknown. As computer storage has become less expensive, waveform data have started to become archived. However, the technology of recording and archiving physiologic signals has advanced faster than the technology of playing them back, which has attracted only a limited attention.

Methods: We present Multi Wave Animator (MWA) – a set of open source MATLAB scripts aimed to create dynamic visualizations (e.g., video files in AVI format) of patient physiologic signals recorded from bedside (ICU or OR) monitors. The source code of MWA is freely available online (www.burykin.com/mwa/) together with a detailed tutorial and sample datasets.

Results: MWA creates animations in which physiologic signals are displayed to mimic their appearance on current bedside monitors. Thus, clinically relevant information is presented in a format familiar to clinicians. Moreover, MWA can be used to create animations that include many advanced features, such as dynamic visualization of HRV indices or vital sign sonification.

Conclusions: The MWA framework remains a working prototype (proof of principle), however, it can readily be used to construct and experiment with different types of physiologic signal display. Possible applications of MWA include clinical research, education, and patient safety and quality control.

Using "Off-the-Shelf" Tools for Terabyte-Scale Waveform Recording in ICU: Computer System Design, Database Description and Lessons Learned

Anton Burykin [1], Tyler Peck [1], Timothy Buchman [1]

[1]Emory Center for Critical Care (ECCC) and Department of Surgery, School of Medicine, Emory University

Objectives: Until now, the creation of massive (long-term and multichannel) waveform databases in intensive care required an interdisciplinary team of clinicians, engineers and informaticians and, in most cases, also design-specific software and hardware development. Recently, several commercial software tools for waveform acquisition became available. Although commercial products and even turnkey systems are now being marketed as simple and effective, the performance of those solutions is not known. The additional expense upfront may be worthwhile if commercial software can eliminate the need for custom software and hardware systems and the associated investment in teams and development.

Methods: We report the development of a computer system for long-term large-scale recording and storage of multichannel physiologic signals that was built using commercial solutions (software and hardware) and existing hospital IT infrastructure.

Results: Both numeric (1Hz) and waveform (62.5Hz - 500Hz) data were captured from 24 SICU bedside monitors simultaneously and stored in a file-based Vital Sign Data Bank (VSDB) during one-year period (total DB size is 4.21 TB). In total, physiologic signals were recorded from 1175 critically ill patients. Up to six ECG leads, all other monitored waveforms, and all monitored numeric data were recorded in most of the cases. Several datasets from our VSDB are available online (www.burykin.com/sbt/) and more will be uploaded on “PhysioNet Works” (http://physionet.org/data-sharing/).

Conclusions: We describe the details of building blocks of our system, provide description of three datasets exported from our VSDB and compare the contents of our VSDB with other available waveform databases. Finally, we summarize lessons learned during recording, storage, and pre-processing of physiologic signals.

Stochastic analysis of heart rate variability:respiration asymmetry and echocardiographic parameters

Jan J. Zebrowski[1], Monika Petelczyc, Teodor Buchner, Rafa Baranowski

[1]Cardiovascular Physics Group, Physics of Complex Systems Division, Faculty of Physics, Warsaw University of Technology, Warszawa Poland
[2]Institute of Cardiology at Warszawa, Poland

Objectives: Human heart rate is moderated by the autonomous nervous system. One of the dominant factors that determine the heart rate in physiological conditions is its coupling with the respiratory rhythm. Using the language of stochastic processes, we analyzed both rhythms simultaneously taking the data from polysomnographic recordings of two healthy individuals.

Methods: Each rhythm was treated as a sum of a deterministic drift term and a diffusion term (the first two terms of the Kramers-Moyal expansion). We found that normal heart rate variability may be considered the result of a bidirectional coupling of two nonlinear oscillators: the heart itself and the respiratory system. On average, the diffusion (or noise) component measured is comparable in magnitude to the oscillatory (deterministic) term for both signals investigated. In a separate study, the Kramers-Moyal expansion was applied to the heart rate variability of 10 healthy males (age 26 -4/+3 y) and 49 patients with hypertrophic cardiomyopathy (HCM) (25 males, 24 females, age 29.5 -11.5/+10.5 y). The drift and diffusion terms may be used for a stochastic reconstruction of time series and for a description of the properties of the heart rate variability of nighttimes recordings.

Results: New parameters characterizing the diffusion term were introduced: the coefficients of the linear fit to the left (LCF) and right (RCF) branch of the dependence of the diffusion term on a rescaled heart rate. Relations of the new parameters to classical echocardiography parameters were studied. Using the relation between the difference LCF-RCF and the Left Ventricular Systolic Diameter, the HCM patients studied were divided into three groups. In addition, the comparison of the properties of the heart rate variability in the HCM group with that obtained for the healthy young men showed that the parameter LCF-RCF may be treated as a measure of the effect of HCM on heart rate variability and may have diagnostic value.

Conclusions: An asymmetry of heart rate variability was obtained which is related to the acceleration and deceleration ability of heart rhythm. The Kramers-Moyal expansion may be useful for medical diagnostics providing information on the relation between respiration and heart rate variability. This interaction is mediated by the autonomous nervous system, including the baroreflex, and results in a commonly observed phenomenon - respiratory sinus arrhythmia which is typical for normal subjects and often impaired by pathology.

Lyapunov Exponent Calculations As Independent Indices of Complexity of Cardiovascular Regulation During Hemorrhage with Autonomic Blockade

J Ward [1], W Baker [2], AI Batchinsky[2], K Walker III [2], J Salinas [2], LC Cancio [2]

[1]Brooke Army Medical Center
[2]U.S. Army Institute of Surgical Research

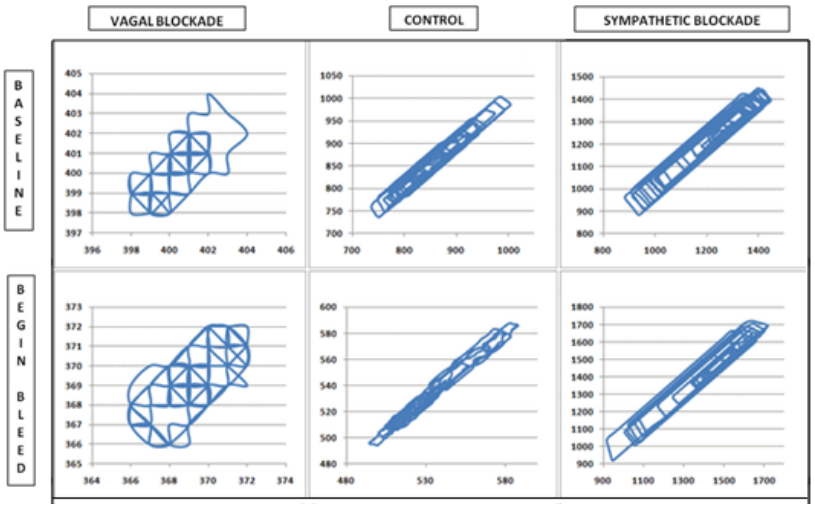
Objectives: The largest Lyapunov exponent (LLE) is a standard method used to characterize the level of chaos in complex physiological systems such as the cardiovascular. Previously we showed that LLE calculated in beat domain remains positive during lethal hemorrhagic shock (HS). We sought to evaluate the utility of LLE and the asymptote of the divergence curve (AS) for monitoring of subjects in time domain using data from a swine model of severe pump-controlled hemorrhagic shock (HS). AS denotes the average Euclidean divergence distance between adjacent orbits of the attractor.

Methods: Ten midazolam-sedated, spontaneously breathing sexually mature swine underwent a controlled HS protocol with removal of 60% of blood volume in 1 hour. Controls (n=4) received HS alone. Vagal blockade group (n=3) received atropine 0.005 mg/kg then 0.5 mg/min continuous rate infusion and HS. Sympathetic blockade (n=3) group received propranolol 0.5 mg/kg then 1 mg/min and HS. EKG was recorded at 500Hz, and the R-to-R intervals (RRI) were calculated. The LLE and AS were calculated using Rosenstein's method with an embedding factor of two and a delay of four over a set of 1024 consecutive RRI samples taken at Baseline and HS. The RRI time series was then resampled at 20 Hz to move the LLE calculations from the beat domain to the time domain. Data are medians. Statistics by one-way ANOVA and post hoc analysis.

Results: See Table. Individually scaled representative attractors for each condition are shown in figure. Table Time point Group RRI LLE AS Post Hoc Baseline Control 883 1.70 3.67 Vagal Block 384 1.79 0.28 $p < 0.05$ Symp Block 1057 1.65 4.69 During HS Control 839 1.68 3.65 Vagal Block 336 2.12 0.23 $p < 0.05$ Symp Block 1137 1.45 4.37 ANOVA $p < 0.001$ ns $p < 0.001$

Table

Time point/Variables	Group	RRI	LLE	AS	Post Hoc
Baseline	Control	883	1.70	3.67	
	Vagal Block	384	1.79	0.28	$p < 0.05$
	Symp Block	1057	1.65	4.69	
During HS	Control	839	1.68	3.65	
	Vagal Block	336	2.12	0.23	$p < 0.05$
	Symp Block	1137	1.45	4.37	
	ANOVA	$p < 0.001$	ns	$p < 0.001$	



Conclusions: LLE remained positive in every condition signifying presence of deterministic chaotic trends during HS and HS with branch-specific autonomic blockade. AS was the lowest after vagal blockade distinguishing it from sympathetic blockade and baseline. The simplest attractors are associated with vagal blockade and HS and feature low AS which denotes the degree of constraint of the system in phase space. AS provides useful additional information to LLE in assessment of complexity of cardiovascular regulation during HS.

Locating consensus QRS peaks confounded by multiple noisy ECG leads

Andrew Banooni[1], Joseph Gran[2], Timothy Buchman[3]

[1]Emory University School of Medicine
[2]Department of Physics, University of California Davis
[3]Emory Center for Critical Care and Department of Surgery, Emory University School of Medicine

Objectives: Precise measures of RR intervals (and therefore QRS peaks) are essential for accurate heart rate complexity analysis. Noise and artifact confound peak identification algorithms. Several clinical settings (stress tests, ICU care) facilitate multiple lead data. We therefore sought a strategy to leverage multiple leads to reduce the uncertainty of peak location in noisy data sets.

Methods: Using a set of 12-lead ECGs from 149 exercise stress tests and 81 dobutamine stress tests, three strategies were used to identify consensus fiducial points. The filter bank QRS detection method was used in each case. The strategies were: 1) Averaged - all 12 leads were averaged and the resulting data was run through a QRS detector; 2) Denoised and averaged – the 12 leads were individually denoised using the Hilbert-Huang transform (HHT), then averaged; 3) Maximum Agreement – the 12 leads were initially processed through the QRS detector individually and QRS peaks were recorded. We then classified a QRS peak if and only if 7 of the leads agreed a peak occurred within 10 msec. All analyses were performed using MATLAB.

Results: The Maximum Agreement method correctly detected the QRS peaks using aggregate data, while the first two methods commonly recorded peaks that did not occur or else skipped a beat.

Conclusions: Consensus strategies may be important to identifying QRS locations where multiple-lead data are available. Iterative optimization (consensus reciprocal to a palette of peak detection methods) may have additional value in locating and identifying R waves in clinical data contaminated by noise.

Structured Physiologic and Ethnographic Data Identifies Rules Governing Red Blood Cell Transfusion Practices in Critical Care

David Black[1], Amy Franklin, Zach Milner, Timothy Buchman[1], Jason Stein

[1]Emory Center for Critical Care and Department of Surgery, Emory University School of Medicine
[2]Department of Medicine, Emory University School of Medicine
[3]School of Biomedical Informatics, University of Texas Health Sciences Center at Houston

Objectives: Although red blood cells (RBC) transfusions can augment oxygen delivery, they also increase risk of infectious and ischemic post-operative morbidity and mortality, lengthen intensive care unit stays, and inflate overall costs.1 Multi-specialty consensus guidelines attempt to balance those benefits, risks and costs for perioperative and postoperative RBC transfusion of cardiac surgery patients.2 In order to assess and subsequently optimize RBC utilization, we combined directed ethnography (DE) with physiologic data towards analysis of decisions leading to "unique transfusion events" in two surgical ICUs.

Methods: A unique transfusion event was defined as a decision to transfuse RBCs, insensitive to the reason or RBC volume. The DE involved systematic observation of all activities in the ICU including contextual information, verbal and non-verbal behaviours, use of artifacts, and observer impressions. From these observations, we captured the discussion about each patient, current lab values including the hemoglobin, the recap of patient status based on system, and the decision to transfuse or not to transfuse. Field notes were collected over 45 clinical days by a single individual who had received 20 hours of training from experienced ethnographers and cognitive linguists. Categories for coding the observations were developed using grounded theory. In addition, the investigator and an experienced ethnographer coded the same notes to assess and ensure inter-rater reliability.

Results: Analysis of the field notes yielded 25 categories of behaviours, gestures, and patterns of communication for 140 unique transfusion events. Each category was given an operational definition, such as: urgency of condition as determined by non-standard presentation of systems status, lab values as verbally reported, members of the provider team contributing to the decision, as well as the stated reason given for transfusion decisions. Physiologic parameters for each unique transfusion event included: date, time, and volume of each RBC transfusion; pre- and post-transfusion hemoglobin & lactate levels, mixed venous O2 content, cardiac output/cardiac index; and the volumes of urine and chest tube output 4 hours before and after transfusion (when available).

Conclusions: Collectively, the ethnography and physiology describe a set of rules that leads to a complex phenomenon, namely transfusions. We assert that such a structured approach leading to discernment of the rules that govern clinical behaviours is an essential component towards understanding complexity in (the management of) acute illnesses.

Using Nonlinear Model Predictive Control to Find Optimal Therapeutic Strategies to Modulate Inflammation

Judy Day[1], Jonathan Rubin[2], Gilles Clermont[2]

[1]University of Tennessee
[2]University of Pittsburgh, Pittsburgh, PA

Objectives: Controlling inflammation has become a key focal point in the treatment of critically ill patients. Much of the computational work in this emerging field has been carried out with the goal of unravelling the primary drivers, interconnections, and dynamics of systemic inflammation. In order to implement these computational simulations in a translational fashion, the proper biological targets and their specific manipulations must be identified. One means of achieving this end involves determining a strategy for delivering therapies, in the correct amount, at the right time. One of the tools that can help determine this complex dose regimen is Nonlinear Model Predictive Control (NMPC). We explore the usefulness of this tool in the context of the acute inflammatory response to severe infection.

Methods: A NMPC algorithm was used in conjunction with a four-dimensional ordinary differential equation model of the acute inflammatory response to pathogen (Reynolds, 2006, JTB(242)) to identify therapeutic strategies to combat both septic and aseptic conditions. Model components include phagocytic cells (the pro-inflammatory component), an anti-inflammatory mediator, pathogens and tissue damage. The primary goal of the NMPC strategy was to reduce damage. We have explored a similar NMPC approach previously; herein, the approach was attempted in the setting of patient-model mismatch (i.e. many diverse virtual patients rather than one virtual patient that has parameter values that agree precisely with those of the underlying predictive model). Several model parameters were chosen to vary randomly among the patients and from those of the underlying predictive model. The administration of both anti- and pro-inflammatory ! therapy was considered.

Results: A patient population of 1000 randomly generated patients was considered. Of these virtual patients, 620 were recognized as being ill enough to receive treatment, as defined by levels of phagocytic cells exceeding a predetermined threshold. The algorithm identified individualized therapeutic strategies that enabled up to 20% more patients to be successfully restored to homeostasis (damage reduced to baseline) as compared to other treatment strategies (e.g. placebo or non-individualized therapies). Some individualized therapeutic strategies enabled over 60% improvement; however, they also had deleterious effects in some patients who could have survived without any treatment. The control strategy first targets pathogen destruction by enhancing pro-inflammation, then modulates anti-inflammation to mitigate excessive inflammation and restore health. Differences in dynamic dosing are subtle indeed, while outcomes themselves are strikingly influenced by treatment. This finding argues strongly for individually titrated

therapy, especially given the modest effects observed in this study from constant, untitrated anti-inflammatory therapy and the diverse outcomes obtained from even a standardized dynamic dosing profile.

Conclusions: The application of NMPC to tackle the complexity of controlling the acute inflammatory response is feasible, yet tedious. The iterative process of customizing the algorithm in order to keep the simulations relevant involves a number of considerations not typically present in engineering applications, namely: (1) creation of realistic patient models, (2) determination of intervention windows (timing and intensity), (3) adjustment of the underlying predictive model during run-time based on incompletely observed patient states and (4) scalability to larger models. Nonetheless, our initial theoretical forays into this approach suggest that it might become feasible with certain technological and theoretical improvements.

Software Architecture for Plug & Play Predictive Model Platform (P3MP)

Peter Honching, Li Yong Bai, Paul Vespa, Neil Martin, Xiao Hu

[1]David Geffen School of Medicine, University of California, Los Angeles

Objectives: The translation of advanced signal processing and machine learning algorithms into a form suitable for use in an ICU clinical decision support system remains a challenge. Overcoming this challenge could be best approached by augmenting the role of academic ICUs as a patient care spot to function as a "factory" of deployable decision support modules. The primary objective of P3MP project is to build an enabling software platform for developing and deploying such modules. We envision it to support running predictive models encapsulating complex signal analysis and machine learning algorithms to process continuous signals and other less granular clinical data and to produce early warnings of well-defined acute pathological events and conditions.

Methods: A plug & play capability is an essential feature of the platform and it calls for the adoption of several latest software development techniques. The architecture of the P3MP backend is based on the Service-Oriented Architecture and leverages Windows Communication Foundation (WCF)'s rich support of instance managements and network communication protocols. We use Unity Application Block (Unity) to apply Dependency Injection (DI) pattern to achieve greater flexibility and Separation of Concerns (SoC), and it improves testability of the system. We also make use of Managed Extensibility Framework (MEF) to incorporate dynamic plug-ins of new predictive models described in standard Predictive Model Markup Language. This provides extreme flexibilities of the system. Silverlight is adopted to build the front-end of P3MP as a Rich Internet Application (RIA) and Prism Framework (formerly known as Composite Application Gui! dance) is used to achieve plug-in capability of different graphical user interfaces suitable for different predictive models.

Results: We have built preliminary units of the P3MP based on a design driven and enabled by the above principles and techniques. We have demonstrated that WCF service is capable of delivering real-time waveform data captured from either running monitors or archived data files to the P3MP RIA front-end. In addition, we have used MEF to successfully implement plug & play of predictive models.

Conclusions: Our experience on designing and building P3MP has proven that adopting latest software technologies and design methodologies is effective for building large and complex information systems. The preliminary tests of several P3MP modules have demonstrated efficacy of this approach.

Noninvasive Intracranial Hypertension Detection based on Cerebral Blood Flow Velocity Waveform Alone

Sunghan Kim [1], Fabien Scalzo [1], Marvin Bergsneider [1], Paul Vespa [1], Xiao Hu [1]

[1]University of California, Los Angeles

Objectives: The purpose of our study was to investigate noninvasive detection of intracranial hypertension solely based on the morphological analysis of cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA).

Methods: We obtained intracranial pressure (ICP) and ipsilateral CBFV simultaneously recorded for 71 neurosurgical patients. Sixteen of these patients had at least one instance of intracranial hypertension, which is defined as the ICP elevation above 20 mmHg. We extracted various morphological metrics from the CBFV recording of each patient using an automated pulse morphology analysis algorithm, which is called the Morphological Clustering and Analysis of Continuous Intracranial Pressure (MOCAIP). The MOCAIP can optimally assign three distinct peaks in dominant pulses of CBFV recordings. From those peaks, 128 MOCAIP metrics are derived such as the ratio between peak amplitudes and the curvature at each peak. We adopted a Support Vector Machine (SVM) algorithm both for feature selection and classification, where an SVM can be used to recognize IH once it is trained using MOCAIP features and associated knowledge of the occur! rence of IH. We performed leave-one-patient-out cross-validation to assess the performance of our noninvasive intracranial hypertension detection method.

Results: 13 out of total 128 MOCAIP metrics were identified as important ones based on the weights of individual metrics assigned by SVM during the training process. They include the curvature and amplitude of the peaks and the ratio between the peak amplitudes. With these 13 metrics, the SVM classifier was able to detect intracranial hypertension with a sensitivity of 88%, a specificity of 71%, and an overall accuracy of 75%.

Conclusions: The performance of our intracranial hypertension detection algorithm needs to be enhanced by further research for use in routine clinical practice. However, the results demonstrate the potential of noninvasive IH detection by applying pattern recognition techniques to morphological metrics extracted from conventional CBFV recordings. Our current work suggests a clinically viable way of noninvasively detecting intracranial hypertension.

An Open Source, Grid-based Software Framework for Management and Sharing of Pediatric ICU Data

Randall Wetzel [1], Dan Crichton [2], Chris Mattmann [2], Andrew Hart [2], David Kale [1], Robinder Khemani [1], Patrick Ross [1], Paul Vee [1], Jeffrey Terry [1]

[1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles
[2]NASA Jet Propulsion Laboratory

Objectives: We aim to demonstrate a solution to the problem of sharing large amounts of data, in a way that is open-source, low-cost, and easily adapted to a wide variety of information system environments. Existing health care data standards and software are often proprietary, complex, or designed with billing, not research or sharing, in mind. Our work is focused on enabling seamless sharing of critical care data, for research and decision-support purposes, from disparate data sources and across multiple institutions. The pediatric intensive care unit (PICU) is the perfect setting for this, as PICUs have a higher rate of adoption of electronic health records (EHRs) and information systems and a history of nationwide organization and collaboration. Further, Apache\'s Object Oriented Data Technology (OODT) software is well-suited to this task and has been used with great success for sharing of data in other scientific domains.

Methods: We are developing a reference architecture and accompanying implementation to facilitate the rapid construction and deployment of large-scale, multi-source, multi-institutional, distributed "databases" of critical care data. At the core of our project is the open-source Apache Object Oriented Data Technology (OODT; http://incubator.apache.org/oodt/). OODT was created by engineers at JPL to manage and share scientific data in a variety of domains and consists of loosely-coupled software components, web services, servers, and databases that implement a domain-specific ontology and enable distributed operations over data from heterogeneous sources spread across different geographical locations. We are extending the OODT framework to handle challenges specific to critical care data. Our initial efforts aim to show OODT\'s efficacy in managing the data from one institution, Children’s Hospital Los Angeles, that has tens of thousands of patient episodes across sources ranging from commercial EHRs to bedside monitors to home-grown clinical databases. We are actively recruiting other institutions with whom we plan to demonstrate a prototype distributed data sharing network and building analytical tools that can also be deployed as a part of the OODT framework.

Results: We demonstrate the first version of our reference architecture and pediatric critical care ontology, as well as how to set up and use (and adapt) OODT in a clinical setting. We also share our experiences in extracting data from proprietary systems and using it for research and make recommendations for groups with similar goals.

Conclusions: Large, granular data sets allow for research on an unprecedented scale and enable development of novel data-driven decision support tools that can improve outcomes. However, there are a variety of technological, cultural, procedural, and economic barriers that stand in the way of sharing data and constructing such large data sets. Using a low-cost, open-source framework such as OODT makes overcoming these barriers much easier.

Idea: An Integrated Data Exchange And Archival System

Baker W BS; Clayton NJ BS; Batchinsky AI MD; Cancio LC MD; Salinas J PHD. Brooke Army Medical Center and U. S. Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX, 78234

Abstract: Lack of interoperability between heterogeneous medical devices has consistently been one of the main challenges for implementing the next generation of intelligent medical decision support systems. The inability of medical systems to exchange information and data severely limits the ability of advanced multivariate algorithms to effectively process data streams from different sources needed to make meaningful decisions for many aspects of patient care. The development of a standard communication interface and data exchange protocols is therefore critical to advancing medical decision support systems. In response to the above challenges we propose an Integrated Data Exchange and Archival (IDEA) System. IDEA is a client/server solution developed to provide client applications access to patient devices using a standardized data exchange protocol. IDEA is also a medical device interoperability system that can be used to provide both a hardware and software middleware layer to client applications that require data from multiple medical devices and/or services as part of their function.

Methods: Data capture is provided through device specific drivers, developed to support the equipment used in ongoing studies. HDF5 provides the technological centerpiece of data archival and storage. HDF5 is a data model, library, and file format for storing and managing data developed at the National Center for Supercomputer Applications (NCSA) with ongoing work is sponsored by the National Science Foundation. Real-time data distribution is provided via two protocols. An XML based protocol using TCP/IP provides a client friendly solution to applications where network bandwidth is not a concern. High performance applications use a UDP protocol based on Google's protobuf network protocol. Protobuf is an efficient binary format appropriate for real-time numerics and waveforms.

Results: This software has been successfully used for data collection in on-going protocols at our institute and in theatre.

Conclusions: The IDEA server provides data collection and distribution services, enabling robust medical decision support systems. It provides a uniform interface for access to device data while also enabling analysis and decision support applications. The IDEA server has enabled tools to be developed to provide real-time analysis for the researcher or clinician.

Real-time opimization of cytokine-selective hemoadsorption devices for treatment of acute inflammation.

Justin S. Hogg, Gilles Clermont, and Robert S. Parker.
University of Pittsburgh, Pittsburgh PA.

Objectives:
Hemoadsorption is a blood purification treatment that improves survival in animal models of sepsis. Current hemoadsorption technology removes a broad spectrum of inflammatory mediators from septic blood. We speculate that treatment may be improved by selective removal of specific mediators. Our aim is to predict the potential benefit of selective hemoadsorption using in silico trials of hemoadsorption applied to a model of acute inflammation.

Methods:
We previously presented an framework for real0time optimization of hemoadsorption treatment using model predictive control with particle filter state estimation. Based on an rat endotoxemia model of acute inflammation, our framework predicted that hemoadsorption was most effective when applied with maximum flow rate promptly following endotoxin bolus. After a two hour window of opportunity, hemoadsorption was predicted to have negligible effect and discontinued. To extend these results to selective hemoadsorption, we conceived a hypothetical multi-column hemoadsorption device in which each column is selective for a subset of cytokines. The flow rate through each column is independently controlled, allowing the controller to fine-tune removal of specific cytokines.

Results:
A two-column configuration--one column selective for the pro-inflammatory subset, the other selective for the anti-inflammatory subset--was 50% more effective at reducing inflammatory damage than a single, non-specific hemoadsorption column. A 3-column configuration, selective for TNF, IL-6 or IL-10, did not show improvement over the two-column device. The results were similar for serial and parallel implementations of the multi-column device. As in nonselective hemoadsorption, the two-column configuration was only beneficial in a two hour window following endotoxin bolus.

Conclusions:
Simulations predict that two-column selective hemoadsorption will improve treatment efficacy, but negligible benefits are expected for higher order configurations.