Computational Physiology and Clinical Inference

Academic and Research Staff
Prof. George Verghese
Dr. Thomas Heldt

Graduate Students
Varun Chirravuri
Bryan Haslam
Faisal Kashif
Ekavali Mishra
Shamim Nemati
Priya Ramaswamy
William Richoux

Undergraduate Students
Jerry Wang

Research Support Staff
Ankit Gordhandas

The overarching objectives of the research in RLE's Computational Physiology and Clinical Inference (CPCI) Group are to enhance patient monitoring, improve clinical decision-making, and better understand physiological and pathophysiological processes. We develop and use mathematical models derived from physiology, along with signal processing and estimation methods, to extract relevant information from clinical data. The models provide the constraints that allow readily observable data streams (such as waveforms of ECG, arterial blood pressure and oxygen saturation, respiration and end-tidal gas concentrations, cerebral blood flow velocity, near-infrared transmission through cerebral tissue, and/or EEG) to be related to physiological variables and parameters that are unmeasured but more directly reflective of changes in pathological state (quantities such as cardiac output, cardiac contractility and ejection fraction, peripheral resistance, respiratory chemoreflex loop gain, intracranial pressure, cerebral metabolism and/or seizure activity). The models thereby form the basis for estimation of unmeasured quantities from measured ones, thus enabling a fuller assessment and tracking of patient state, and a more comprehensive description of the underlying physiology. Our research currently involves the following projects.

1. Integrating Data, Models, and Reasoning in Critical Care

Sponsors
National Institute of Biomedical Imaging and Bioengineering 5R01EB001659-07 &
3R01EB001659-07S1

Project Staff
Prof. George Verghese
Dr. Thomas Heldt
Varun Chirravuri
Faisal Kashif
Ekavali Mishra

Scientific Collaborators
Prof. Roger Mark (MIT, HST)
Prof. Peter Szolovits (MIT, CSAIL)
Dr. Balachundar Subramaniam (Beth Israel Deaconess Medical Center, Boston)

Modern intensive care units (ICUs) employ an impressive array of technologically sophisticated instrumentation to provide detailed measurements of various important variables and parameters for each patient. Providing care in the ICU is becoming an increasingly complex task, however, because of the growing volume of relevant data that must be screened, integrated, and interpreted in order to extract clinically relevant and actionable information. This project combines the resources of an interdisciplinary team of investigators from academia (research groups from HST, CSAIL and RLE at MIT), industry (Philips Healthcare), and clinical medicine (Beth Israel Deaconess Medical Center, Boston) to develop and evaluate advanced ICU patient monitoring systems that will support improved efficiency, efficacy, and timeliness of clinical decision-making in critical care. A substantial part of the effort on this project goes towards assembling a rich and extensive database of de-identified ICU data – the MIMIC II database – comprising high-resolution waveforms from bedside monitors, along with clinical notes and laboratory results, for several thousand patients. This database also constitutes the platform for much of the research on the project, and is being made available to researchers worldwide (http://mimic.mit.edu).

In her MEng project, Ekavali Mishra is developing signal processing algorithms that analyze blood pressure signals and other data from patients undergoing cardiothoracic surgery. She is exploring the use of these signals, and estimates derived from them, to improve peri-operative monitoring and to predict adverse outcomes following an operation. In related work, and through funding from the MIT-Italy Progetto Rocca Fund, we have begun a collaboration with Profs. Sergio Cerutti and Giuseppe Baselli, as well as Drs. Manuela Ferrario and Federico Aletti, of the Politecnico di Milano to investigate improved physiological monitoring modalities for peri-operative care.

In his MEng thesis, Varun Chirravuri explored means for quantitative assessment of the arterial baroreflex. This is a fast-acting control mechanism that the body relies on to regulate arterial blood pressure dynamically. Previous efforts to model the baroreflex have focused primarily on non-parametric descriptions of the transfer characteristics from blood pressure to heart rate. Of the parametric models proposed, most focus on matching empirical transfer functions with continuous-time models. The use of these models is often restricted to simulation, and consequently not focused on prediction. We use a beat-to-beat, one-pole model for the baroreflex that can parsimoniously capture both the empirical frequency-domain and time-domain characteristics of the baroreflex. We have developed a robust identification method for on-line estimation of the parameters of this model from clinical data, and are exploring the use of these estimates in classification of autonomic state.

In his doctoral work, Faisal Kashif has been investigating noninvasive monitoring of intracranial pressure. We describe this work separately in the following subsection.

2. Noninvasive Continuous Estimation of Intracranial Pressure (ICP) and Cerebral Autoregulation

Sponsors
National Institute of Biomedical Imaging and Bioengineering 5R01EB001659-07 &
3R01EB001659-07S1
Center for the Integration of Medicine and Innovative Technologies

Project Staff
Prof. George Verghese
Dr. Thomas Heldt
Faisal Kashif

Scientific Collaborators
Dr. Marek Czosnyka (University of Cambridge, UK)
Dr. Vera Novak (Beth Israel Deaconess Medical Center, Boston)
Dr. Ajith Thomas (Beth Israel Deaconess Medical Center, Boston)

Brain tissue is highly vulnerable to unbalanced oxygen demand and supply. A few seconds of oxygen deficit may trigger neurological symptoms, and sustained oxygen deprivation over a few minutes may result in severe and often irreversible brain damage. The rapid dynamics coupled with the potential for severe injury necessitate continuous cerebrovascular monitoring in the populations at greatest risk for developing or exacerbating brain injury. One of the key variables to monitor in patients with brain injury is intracranial pressure (ICP), which determines the pressure on brain tissue and also affects cerebral perfusion. Current measurement modalities for ICP require the penetration of the skull and the placement of a pressure-sensitive probe in the brain parenchyma or cerebral fluid spaces. This risks causing tissue damage and increasing vulnerability to infection. With colleagues from neurosurgery, vascular neurology, internal and critical care medicine (Beth Israel Deaconess Medical Center, Boston, as well as the University of Cambridge, UK), we are developing noninvasive methods to assess ICP continuously (beat-by-beat) and robustly, in a patient-specific and calibration-free manner. The availability of noninvasive ICP estimation will also enable monitoring of a much bigger at-risk patient pool.

Our model-based approach to estimation of the desired quantities from the available non-invasive clinical measurements uses a reduced-order mathematical model of cerebrovascular dynamics to relate cerebral blood flow (in the middle cerebral artery) to arterial blood pressure (ABP). The only parameters in the model are ICP, cerebrovascular resistance, and compliance. We have developed a suite of estimation algorithms to identify ICP and the other model parameters from minimally invasive or noninvasive measurements of ABP and cerebral blood flow velocity waveforms. Estimated ICP is also used to estimate cerebral perfusion pressure (CPP= ABP – ICP). We anticipate that variations in estimated cerebrovascular resistance and compliance in response to variations in CPP will reflect the state of cerebral autoregulation.

For validation, our noninvasive beat-by-beat estimates of ICP were compared against invasive measurements (recorded at Addenbrooke's Hospital, Cambridge, UK) from 45 comatose brain-injury patients. Our noninvasive estimates (red) do track measured ICP (blue) closely over a range of variations, as shown in the two examples in Fig. 1. The largest root mean square normalized error (46%) was obtained for the second subject, but even here the estimate closely tracks the sharp transitions. The mean difference (bias) over all patients is 1.8 mm Hg, and the standard deviation of differences is 6.8 mm Hg; the absolute error is < 6 mm Hg in 33 subjects.

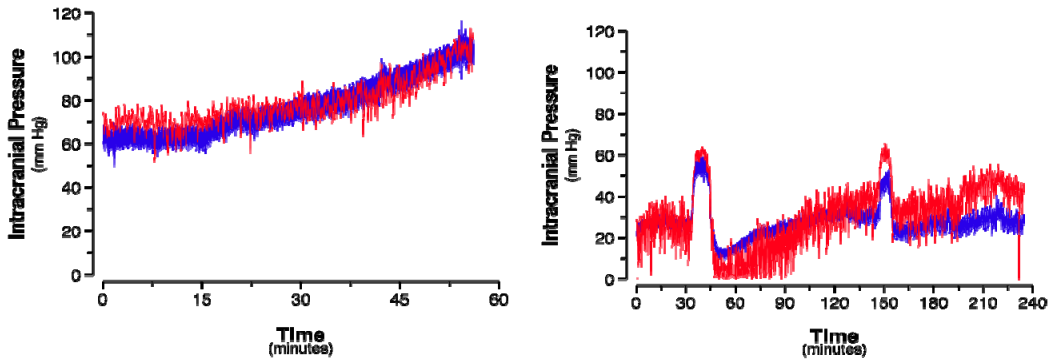

Figure 1: Measured mean intracranial pressure (blue) and estimated mean intracranial pressure (red). Left: progressive intracranial hypertension; right: 'plateau-waves' in intracranial pressure.

3. Wearable Micropower Medical Platform

Sponsors
Texas Instruments
National Defense Science and Engineering Graduate Fellowship

Project Staff
Dr. Thomas Heldt
Prof. George Verghese
Ankit Gordhandas
Bryan Haslam

Scientific Collaborators
Prof. Anantha Chandrakasan (MIT, MTL)
Prof. Charles Sodini (MIT, MTL)
Dr. Dennis Buss (TI)
Eric Winokur (MIT, MTL)
Margaret Delano (MIT, MTL)

Improvements in integrated circuit technology enable the development of miniaturized, low-power, wearable physiological sensors and associated data-storage and processing platforms. This provides the opportunity for continuous, wireless, nonintrusive medical monitoring of at-risk patient populations. With colleagues from Texas Instruments and MIT's MTL, RLE and CSAIL laboratories, we are developing a next-generation wearable, wireless, micropower medical monitoring platform to allow for continuous monitoring of certain vital signs for periods of days to weeks. Such data are potentially valuable in risk stratification, but will also provide important insights into the ranges of normal physiology. We are particularly interested in developing novel algorithms, implemented on the micropower processor and run in real-time, that analyze and aggregate the acquired data on-chip, in order to intermittently communicate important changes in patient status to health-care providers.

We have built a setup for collecting ECG and accelerometer data from the MTL prototype device simultaneously with standard clinical ECG, noninvasive arterial blood pressure, pulse plethysmograph, and respiration recordings; see Fig. 2. This allows us to directly evaluate the performance of the prototype device and to collect additional data of physiological interest in the context of ambulatory monitoring, as in Fig. 3.

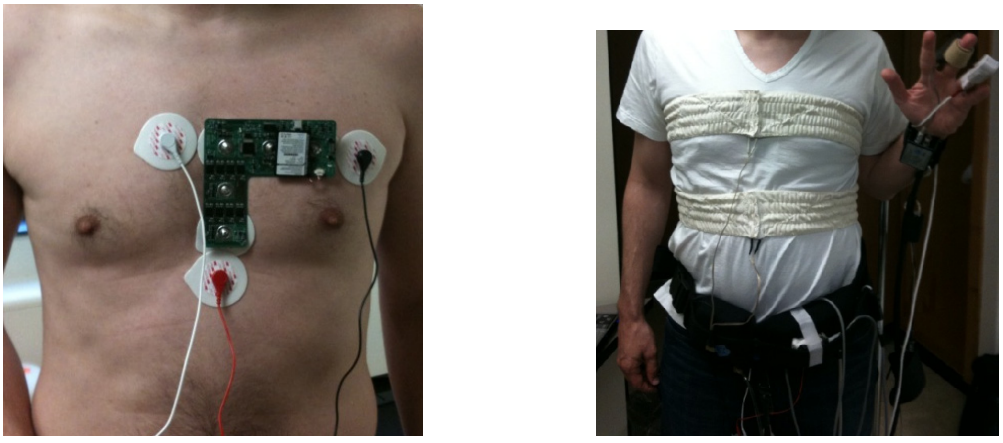

Figure 2: Left: prototype wearable ECG monitor along with standard ECG electrodes. Right: instrumentation for continuous monitoring of respiration, arterial blood pressure, and blood oxygen saturation.

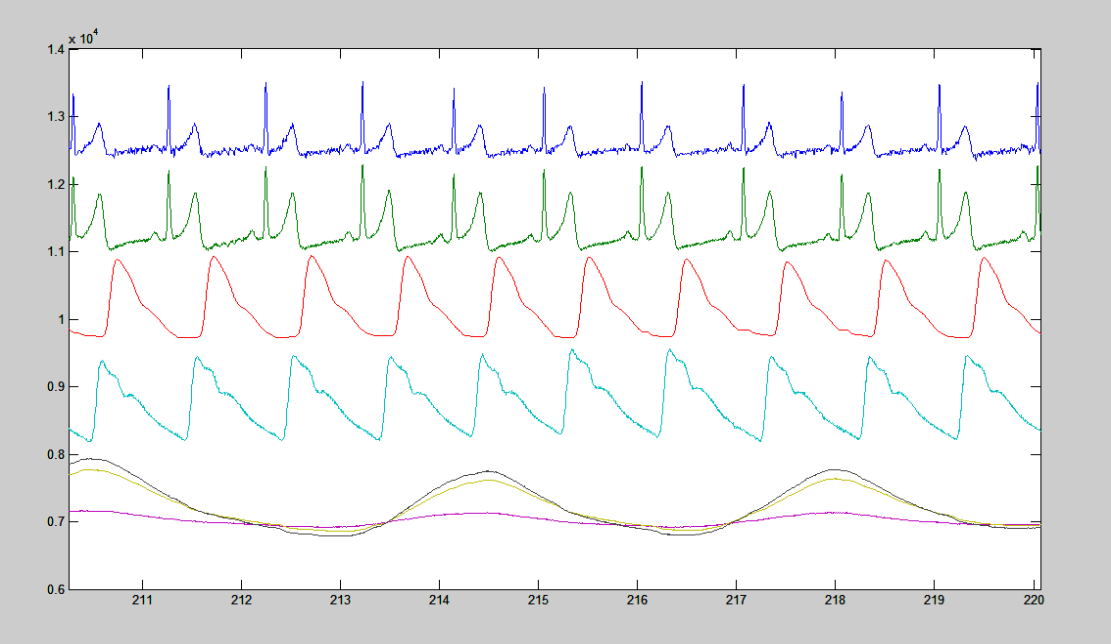

Figure 3: Data taken from a subject resting in a supine position. The y-axis is in arbitrary units and the x-axis in seconds. The blue trace on the top is the prototype ECG, the green is the clinical ECG, the red is the arterial blood pressure signal, the cyan is the pulse plethysmograph signal, and the bottom three are respiration signals (chest, abdomen, and the sum of chest and abdomen signals).

4. Brain Injury in the Preterm Neonate

Project Staff
Dr. Thomas Heldt
Prof. George Verghese
Faisal Kashif
Priya Ramaswamy

Scientific Collaborators
Dr. Adré du Plessis (Children's National Medical Center, Washington, DC)
Dr. Carmen Fons (Children's Hospital Boston & Sant Joan de Déu Hospital, Barcelona)
Dr. Mustafa Suleymanci (Children's Hospital Boston)
Heather O'Leary (Children's Hospital Boston)
Manon Ranger (McGill University, Montreal)

Advances in neonatal critical care over the past several decades have contributed to a dramatic decline in mortality of prematurely born infants. However, survivors of prematurity are at great risk of developing brain injury, which often results in lifelong disability. The greatest advances in survival have been achieved in the smallest and sickest of babies, who also form the group at greatest risk for devastating brain injury. Working with colleagues from Children's Hospital Boston and Children's National Medical Center in Washington, DC, our group is interested in a wide range of fundamental physiological and biomedical questions relating to the care of prematurely born infants. We are particularly interested in identifying physiological antecedents of neonatal brain injury.

In her MEng project, Priya Ramaswamy is investigating seizure activity in newborns with documented brain injury. Recent studies associating heart rate variability with seizures in neonates suggest an autonomic deregulation associated with seizure activity. However, the

clinical and scientific understanding of the connection between the immature autonomic control of newborn infants and seizure activity is little understood. This is the focus of our research in this area.

Figure 4 shows an example EEG recording where a seizure in a neonate propagates globally across the brain and also changes its burst frequency. Utilizing a database of neonates with stroke or hypoxic-ischemic encephalopathy, we hope to gain insight into the autonomic correlates during seizure patterns.

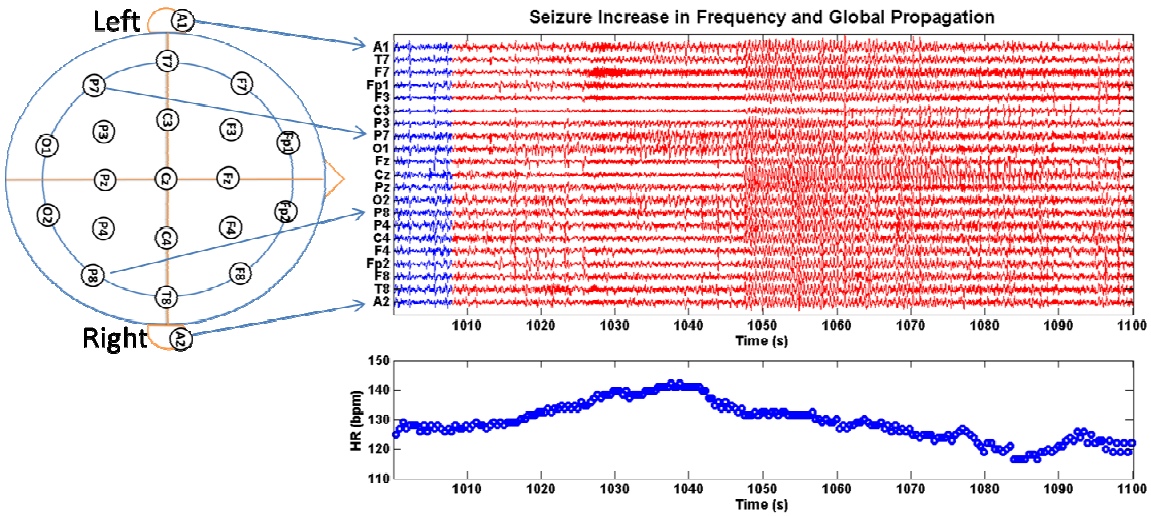

Figure 4: Heart rate (HR) during seizure activity as the EEG burst frequency increases. (The transition from blue to red in the EEG plot indicates the onset of seizure.)

In other work involving sick premature babies, we are developing a signal processing method to derive important estimates of cerebral oxygen metabolism from ventilator-gated analysis of near-infrared spectroscopy data. Oxidative stress during fetal development, delivery, or early postnatal life is a major cause of neuropathology. Despite the obvious need for tight oxygenation monitoring, no technology exists to monitor cerebral oxygen metabolism continuously and noninvasively in infants at high risk for developing brain injury. Consequently, a rational approach to titrating oxygen supply to cerebral oxygen demand – and thus avoiding hyperoxic or hypoxic insults to the developing brain – is currently lacking. Our work aims to close this crucial technology gap by using cerebral near-infrared spectroscopy (NIRS) and signals from conventional ventilators, along with arterial oxygen saturation, to derive continuous (breath-by-breath) estimates of cerebral venous oxygen saturation (SvO_2), cerebral oxygen extraction fraction (OEF), cerebral blood flow (CBF, per 100g of tissue), and cerebral metabolic rate of oxygen ($CMRO_2$, per 100g of tissue).

Our continuous, patient-specific estimates of cerebral oxygen metabolism are shown in Fig. 5 for a preterm infant (27 weeks gestational age). Our estimates compare very favorably to what has been reported in the medical literature using highly invasive and intermittent measurements.

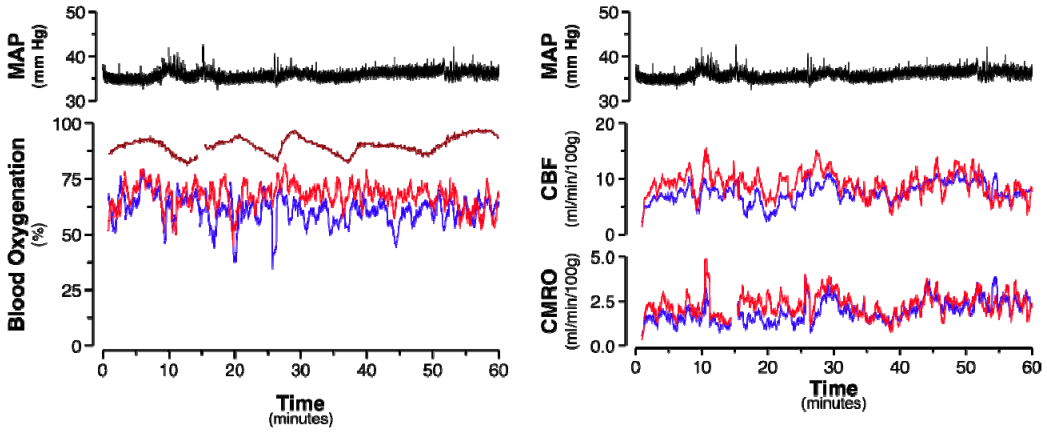

Figure 5: Left: mean arterial blood pressure (MAP; black); systemic arterial blood oxygen saturation (maroon); and estimated right (red) and left (blue) cerebral venous blood oxygen saturation. Right: mean arterial blood pressure (MAP; black); estimated right (red) and left (blue) hemispheric tissue cerebral blood flow (CBF); estimated right (red) and left (blue) hemispheric tissue cerebral metabolic rate of oxygen (CMRO).

5. Model-Based Assessment of Respiratory Chemoreflex Control

Sponsors
American Heart Association
National Institutes of Health

Project Staff
Prof. George Verghese
Shamim Nemati

Scientific Collaborators
Dr. Atul Malhotra (Division of Sleep Medicine, Brigham and Women's Hospital)
Dr. Bradley Edwards (Division of Sleep Medicine, Brigham and Women's Hospital & Monash University, Australia)
Dr. James Butler (Harvard School of Public Health)

Breathing instabilities in the form of cyclic apnea and periodic breathing occur throughout life. Periodic breathing is commonly observed in both preterm and term infants as well as in adult subjects at altitude, and in patients with congestive heart failure. Respiratory control instability is believed to play an important role in the pathogenesis of obstructive sleep apnea, and is generally attributed to a hypersensitive chemoreflex control of breathing (i.e., an increased loop gain).

Our current work is aimed at identifying the relative contributions of the respiratory chemoreflexes and the gas-exchange compartment to the overall closed-loop behavior of the respiratory control system. Our results on data from anesthetized lambs suggest that relatively short segments of spontaneous breathing data can be utilized to assess the frequency dependent gains of the various components of the respiratory chemoreflex feedback loop, as well as to predict the cycle duration that will be evidenced if periodic breathing emerges. Such analysis may be useful in elucidating the primary causes of elevated loop gain as well as in predicting the response to therapies in individuals with breathing instabilities.

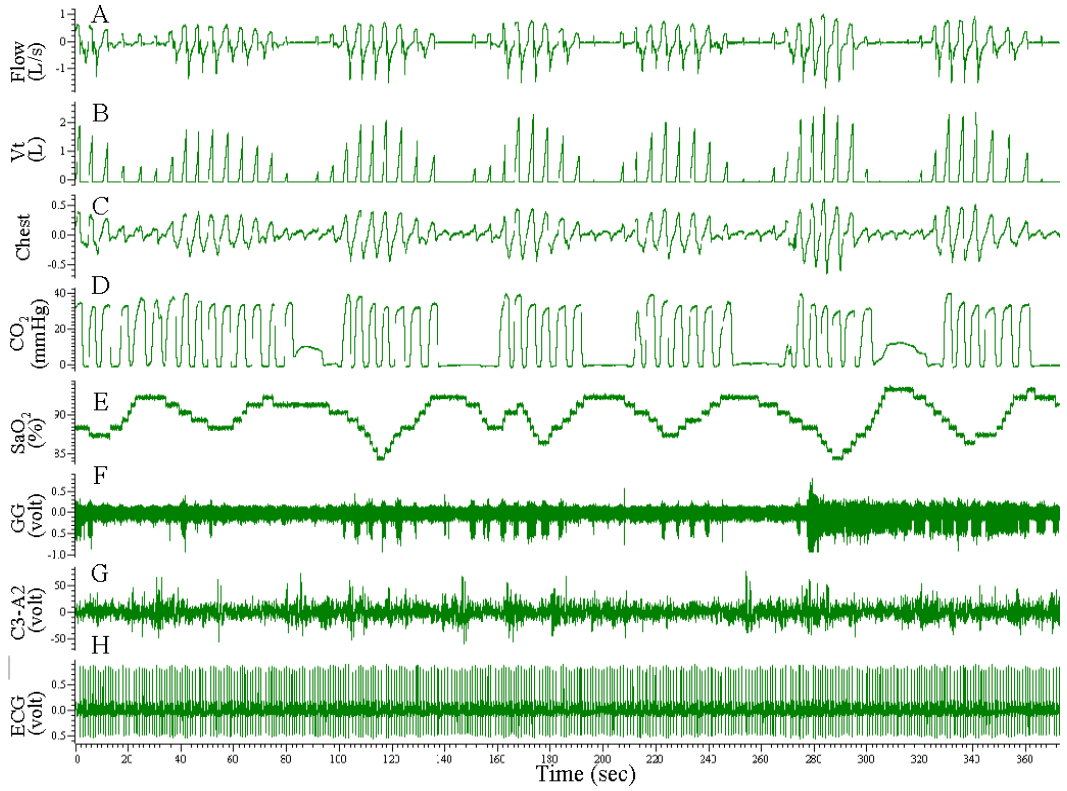

Figure 6: Sleep-induced periodic breathing in a human subject. Measurements of respiratory flow (A), tidal volume (B), chest movements (C), arterial CO_2 (D), oxygen saturation (E), genioglossus motoneuron activity (F), electroencephalogram (G), and electrocardiogram (H). The waxing and waning pattern of breathing followed by apnea, apparent in the tidal-volume signal, is accompanied by a drop in blood oxygen, rise in end-tidal CO_2 concentration, and often an arousal at the end of each bout of apnea. These arousals are generally marked by an increase in sympathetic activity and in blood pressure that often carries over to the daytime.

6. Physiological Markers of Patient Deterioration in the Inpatient Setting

Sponsor
Children's Hospital Boston

Project Staff
Dr. Thomas Heldt
Prof. George Verghese

Scientific Collaborators
Dr. Paul Hickey (Children's Hospital Boston)
Dr. Monica Kleinman (Children's Hospital Boston)
Rita Johnson, RN (Children's Hospital Boston)

Pediatric cardiac arrest typically occurs after a period of respiratory or circulatory insufficiency. Patient safety initiatives to promote early recognition of and intervention for patient deterioration, including rapid response teams and early warning scores, have successfully reduced the rate of cardiac arrest in pediatric inpatient units. These interventions, while important, still involve human factors that might delay escalation of concern or transfer to a higher level of care. The identification of physiologic markers that could predict patient deterioration would permit even earlier identification of patients at risk for a resuscitation event, and would further enhance patient safety. The purpose of this recently initiated study is to determine whether model-based signal

processing algorithms, acting in real-time on the waveform and trend data derived from the bedside monitors, can be developed and used for early detection of cardiorespiratory decompensation.

The following research project in our group relates to questions of inference, but in more abstract models than those dealt with in the projects outlined above.

7. Propagating Partial Information in Networks of Stochastic Automata

Project Staff
Prof. George Verghese
William Richoux

The joint dynamics of a collection or network of interacting discrete-time automata can often be described by a single Markov chain. In general, however, analyzing such a chain is computationally intractable for even moderately sized networks because of the explosion in the size of the state space. In earlier work we introduced the influence model (IM) as a framework for overcoming such limitations. The IM imposes constraints on the update behavior of a network of automata, allowing efficient analysis while still permitting interesting global behavior. The most attractive property of the influence model is the ability to propagate partial information in the form of marginal distributions, in the same way that the full probability distribution can be propagated under the assumption of Markovianity. Some of the
constraints of the IM, however, are unnecessarily restrictive.

We have now introduced a generalization of the influence model that relaxes some restrictions of the IM, thereby permitting more complex behavior without losing many of the attractive properties of the IM, and actually enabling simpler proofs of several results. We have also investigated the general properties of probabilistic models for which partial information propagation is possible; we term such models *separable*. Our investigations have emphasized an algebraic and geometric perspective, and have revealed the relative complexity of many canonical examples of separable probabilistic models, including asymptotically as the size of the network grows. We have also developed a computationally efficient learning algorithm for estimating the informative model parameters of separable models. Lastly, we have connected our results to some of the separable models prevalent in the literature, such as mass-action kinetics for chemical reaction networks.

Publications

Journal Articles, Published

Preciado VM, Verghese GC. Low-order spectral analysis of the Kirchhoff matrix of a probabilistic graph with prescribed expected degree sequence. IEEE Trans. on Circuits and Systems 56(6): 1231-1240, 2009.

Zager L, Verghese GC. Epidemic thresholds for infections in uncertain networks. Complexity 14(4): 12-25, 2009.

Journal Articles, Accepted for Publication

Heldt T, Mukkamala R, Moody GB, Mark RG. CVSim: a cardiovascular simulator for teaching and research. The Open Pacing, Electrophysiology and Therapy Journal.

Richoux WJ, Verghese GC. A generalized influence model for networked stochastic automata. IEEE Trans. Systems, Man and Cybernetics, A.

Journal Articles, Submitted for Publication

Saeed M, Villaroel M, Clifford GD, Lehman LW, Moody GB, Heldt T, Kyaw TH, Moody B, Mark RG. MIMIC-II: A public-access ICU database.

Azunre P, Gomez-Uribe C, Verghese GC. Mass fluctuation kinetics: Analysis and computation of equilibria and local dynamics.

Book Chapters

Heldt T, Verghese GC, Mark RG. Mathematical Modeling of Phyisological Systems. Lecture Notes in Mathematics, Springer Verlag. (Under review)

Meeting Papers Presented

Heldt T. Cardiac output estimation: an engineering perspective. Annual meeting of the Pediatric Academic Societies, Vancouver, CA. May 2010.

Heldt T, Verghese GC. Multiparameter data archiving and exploration – implications for outcome analysis. Grand Rounds, Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, April 2010.

Ranger M, Heldt T, O'Leary H, Suleymanci M, Johnston C, du Plessis AJ. Description of global cerebrovascular activation during noxious stimulus in critically ill premature infants. 8th International Symposium on Pediatric Pain, Acapulco, Mexico, March 2010.

Kashif F, Heldt T, Novak V, Czosnyka M, Verghese GC. Noninvasive cerebrovascular monitoring, Annual Stroke Conference, San Antonio, TX, February 2010.

Kashif F, Heldt T, Novak V, Czosnyka M, Verghese GC. Noninvasive model-based cerebrovascular monitoring for neurotrauma. CIMIT Innovation Congress, Boston, MA, October 2009.

Verghese GC. Deconstructing integrative models: the case for model reduction. Workshop on Computational Challenges in Integrative Biological Modeling, Mathematical Biosciences Institute, Ohio State University, Columbus, OH, October 2009.

Heldt T, Model-based estimation in biomedicine. Workshop on Computational Challenges in Integrative Biological Modeling, Mathematical Biosciences Institute, Ohio State University, Columbus, OH, October 2009.

Verghese GC. Getting to the gray box: Some challenges for model reduction. Inaugural plenary lecture, American Control Conference, St. Louis, MO, June 2009.

Patent Application

Kashif FM, Heldt T, Verghese GC. Systems and Methods for Cerebrovascular Modeling and For Noninvasive or Minimally-Invasive Estimation of Intracranial Pressure and Autoregulation. U.S. patent application US 2010/0063405-A1 filed on September 8, 2009; international application number WO 2010/030612-A1.