Research in Medical Physics:
Physiological Signals and Dynamics

Incidents of apnea or of sepsis create critical situations in a neonatal intensive care unit (NICU). Of the 4.2 million babies born annually in the U.S., more than 12% are at least three weeks preterm, and this percentage has risen by more than 33% since the 1980s (with, happily, a few percent decline in recent years). Approximately 5% of births require NICU hospitalization for some period. The goal of this research is to improve outcomes for this very vulnerable population. In addition to the human reward of saving the lives of tiny babies, there is a financial incentive: noting the daily NICU cost of $1200, we find that reducing the average NICU length of stay by only two days could save over half a billion dollars yearly.

We work together with colleagues at University of Virginia, who have been collecting and analyzing electronic signals such as EKG's, Chest Impedance (CI) and Pulse Oximeter waveforms, together with vital signs such as heart rate, oxygen saturation (SpO2), and respiration rate. The hypothesis underlying our work is that *these formerly-discarded, noninvasive, purely electronic signals contain clinically important, and sometimes predictive, information that can be extracted by using newly available technology for storing data, and using new and innovative computational and mathematical tools for analyzing those data.*

Heart Rate Variability and Sepsis in Infants

For many years physicians have studied electrocardiograms, and used them to evaluate health or illness of the heart. Can these signals give a noninvasive monitor of other aspects of health or illness? Several years ago, Dr. Randall Moorman and his colleagues began collecting data on heart rates of infants in the neonatal intensive care unit at University of Virginia. In general the infants have healthy hearts, but they are vulnerable to a variety of bacterial, viral or fungal infections. The resulting systemic inflammatory response, which can be more damaging than the original infection, is called sepsis. The diagnosis of neonatal sepsis is difficult and time-consuming, so it would be good to have a continuous noninvasive monitor.

Figure 1 shows time between beats vs. beat number for four babies: (a) has a very high variability in its heart rate – the graph looks like that of the stock market – while (b) has a heart

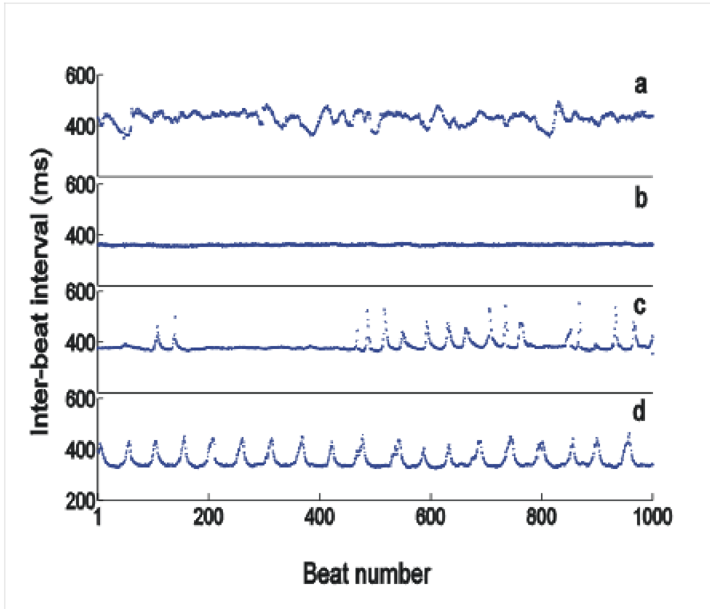


Figure 1 Four samples of heart rate records of infants.
(a) Inter-beat interval series for a healthy NICU patient.
(b) Inter-beat interval series for a NICU patient showing reduced heart rate variability prior to diagnosis of sepsis.
(c) Inter-beat interval series for NICU patient showing sixteen decelerations.
(d) Inter-beat interval series showing periodic decelerations near sepsis.

that is ticking like a clock, with scarcely any variation in its rate. The peaked structures in Figure 1 (c) and (d) are called "decelerations." (d) shows striking periodicity (period ~40 beats), which lasted for almost two days.

In health the heart rate (or the time between beats, called the RR interval) has high variability; Moorman and colleagues have shown that reduced variability and decelerations are warning signs for possible impending sepsis (a deceleration is a transient slowing of the heart followed by a return to normal rhythm). These signals may appear 24 hours before any other signs of illness are evident. A clinical trial using their early-warning system gave a reduction of sepsis-induced infant death by about 20%.

In that work, they had accurate measures of variability, but only indirect measures of decelerations. I co-directed the PhD thesis of Abigail Flower, who developed a computer algorithm for direct measurement and characterization of decelerations in records of RR intervals. We showed that decelerations are indeed a warning sign for sepsis, and that measuring and counting decelerations provides independent information giving early warning of impending illness. We also showed that decelerations sometimes occur periodically, and that the transition from a regular heart rhythm to periodic decelerations has the character of a Hopf bifurcation. We searched for a physiological explanation of this phenomenon in mathematical models of the natural pacemaker of the heart (the sino-atrial node), and in models of the dynamics of the baroreflex loop. Neither of these fit the observations, and we now know that periodic decelerations are often associated with periodic apneas, discussed below.

In current work, we are applying new measures of variability and we are applying the measures to a larger dataset, testing the hypothesis that additional measures can give better and earlier predictions of sepsis.

Central Apnea in Premature Infants

Apnea (cessation of breathing) is usually less deadly than sepsis, but it is even more common in neonates, and response must occur within seconds. It occurs in more than half of VLBW infants, and in essentially all ELBW infants. It may be a cause, a predictor, or an effect of other clinical illnesses including sepsis, or it may be an indicator of immature or abnormal neurological development. Apneas are divided into three categories: obstructive apnea, wherein there is a blockage of the airway, typically accompanied by struggling or thrashing motions of the infant; central apneas, in which there is cessation of respiratory drive, and the infant makes no effort to breathe; and mixed apneas, which most often begin with obstructive apnea and change to central apnea (the order can also be reversed).

The breathing of all infants is irregular, and they all stop breathing for a few seconds at a time. Apnea is considered to be a clinical event if (A) cessation of breathing lasts for more than 20 seconds, or (B) cessation of breathing lasts for more than 10 seconds, and is accompanied by either bradycardia (slowing of the heart below 100 beats per minute) or oxygen desaturation ($SpO2 < 80\%$). In any case apnea is a serious clinical event that needs medical attention within seconds.

However, the current generation of monitors for apnea is unsatisfactory.

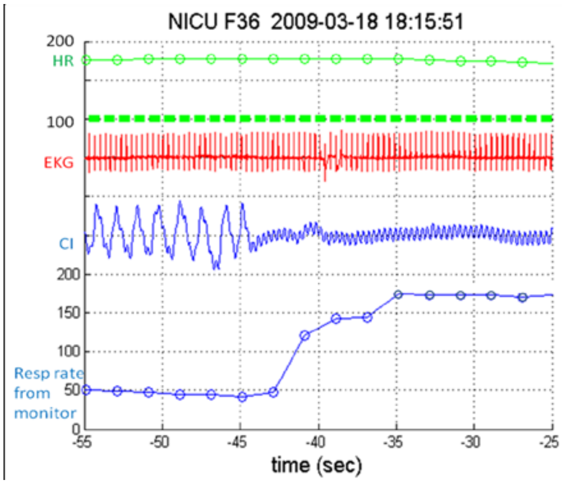


Figure 2 Signals from current monitors. Top to bottom: heart rate (green open circles) and threshold for bradycardia alarm (green dashed line); EKG (red); Chest Impedance (CI) showing breathing then apnea (blue); Respiration rate as interpreted by monitor (blue); Respiration rate as interpreted by monitor (blue open circles), changing from 50 breaths per minute to 175 breaths per minute.

The standard monitors in NICUs measure the impedance across the chest. A small high-frequency (40-50 KHz) potential difference is applied across two of the electrodes that are already used for EKG measurement. Respiration changes the amount of air in the chest, and thereby changes the impedance. However the pumping of blood by the heart also changes the impedance, leading to what is called "cardiac artifact". **Figure 2** shows some of the signals collected during an apnea event in one infant. In the graph, for t < -44 seconds, we can see in the Chest Impedance (CI) the respiration signal and the cardiac artifact. The monitor interprets this CI signal to give a respiration rate of about 50 breaths per minute (BrPM). At t ~ -44 s, for no visible reason, the baby stops breathing. Now the cardiac artifact dominates the CI signal; close examination indicates that the fluctuations in CI are precisely aligned with the EKG signal. Unfortunately, the monitor concludes that the baby is breathing at 175 BrPM. These monitors set off an alarm if the respiration rate goes below 10 BrPM, but in this case, the monitor mistakes the cardiac artifact for respiration. Further examination of this event shows that the baby stopped breathing for 80 seconds, but the monitor never set off an alarm. Using methods discussed below, we have found that in 14% of apnea events accompanied by bradycardia and desaturation the monitor never recognized the apnea, and did not set off the apnea alarm. Furthermore, we have found that when a monitor does set off an apnea alarm, in about 2/3 of cases it is a false alarm, usually caused by a weak signal. Plainly, a more accurate monitoring system is needed.

We have developed a better system for detecting central apnea. At present the system is being used retrospectively in our database of electronic signals from about 1500 infants in the UVa NICU.

Very Long Apneas

In recent work, *we extracted and studied examples of disturbingly long (>60 second) apneas, which are called Apparent Life-Threatening Events.* **Figure 3** shows a long apnea event that was not detected by the monitor. We studied a selection of unambiguous events that lasted at least 60 seconds and were accompanied by bradycardia and desaturation). We found that they are not rare. They tend to occur in infants under 30 weeks gestational age, within the first few weeks after birth. About 2/3 of the infants having such events had some recognized clinical condition at the time of the long events, but 1/3 did not. We observed that heart rate and blood oxygen drop very slowly in these events, and we developed a theory describing the rate of fall of blood oxygen.

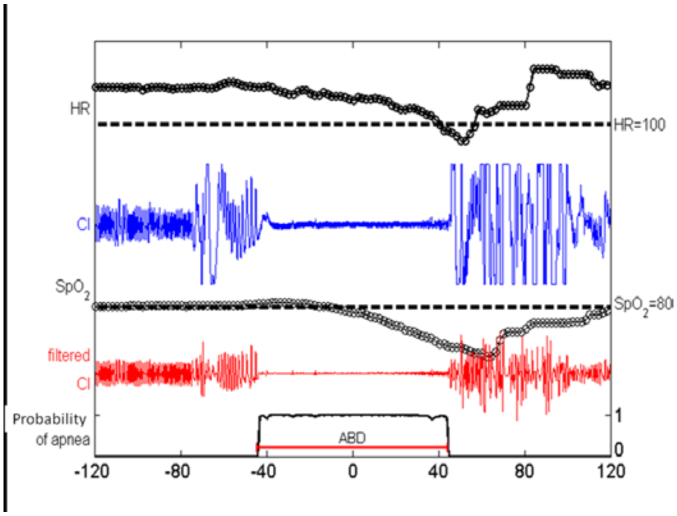
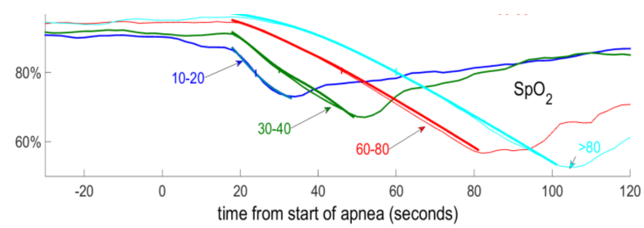


Figure 3 A very long apnea event. Top to bottom: Heart Rate (HR) and threshold for bradycardia alarm (both black); Chest Impedance (CI, blue), Oxygen Saturation and threshold for alarm (SpO2, both black), filtered CI (red), and Probability of Apnea (black) during a 90 second Apparent Life-Threatening Event.

Figure 4 Theory and observation of rate of fall of hemoglobin saturation in short and long apneas.



Periodic apneas or Periodic Breathing

Premature infants, especially those of gestational age around 32 weeks, enter spells of periodic breathing, cycles of breathing and apnea with a typical cycle time around 15 seconds. The apneas may or may not be associated with significant desaturations and bradycardias. These spells are very common, and have long been thought to be harmless, but two recent deaths in the UVa NICU were found to be preceded by excessive periodic breathing. Therefore we collected statistics on these events. We found that necrotizing enterocolitis is often preceded by long spells of periodic breathing, but those spells are so common and so often have no clinical correlates, that they might not be useful as a warning of illness.

Connected with this observational study of periodic apneas, we will develop and apply mathematical physiological models of this phenomenon. There are many such models for both infants and adults. Generally the models involve feedback primarily between high CO2 levels and increased respiration. The time delay between the increase of CO2 in the blood and its detection in the brainstem can put the feedback loop into oscillation. We will compute the predictions of these models to see whether any of them are consistent with our data on infants.

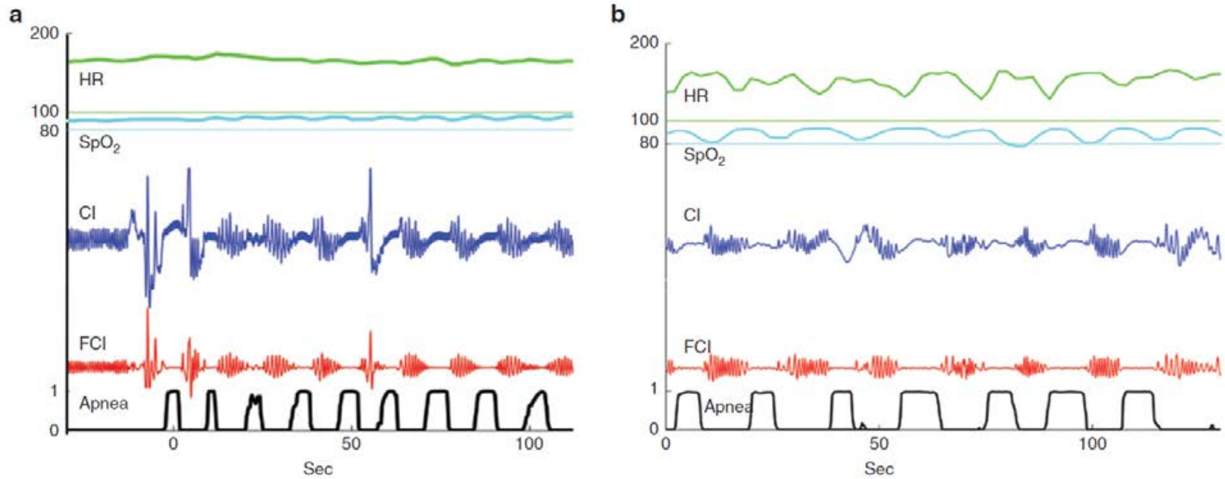


Figure 5 Two examples of periodic breathing or periodic apneas. From top to bottom: heart rate (HR with 100 beats/min indicated by the thin green line), oxygen saturation (SpO2 with 80% indicated by the thin blue line), chest impedance (CI), filtered chest impedance (FCI), and computer algorithm-detected probability of apnea based on low variance in the filtered CI signal as previously reported (27). A wavelet transform analysis of short apneic pauses was previously validated for automated analysis of % time spent in PB (26). (**a**) Example of periodic breathing without significant changes in heart rate or SpO2. (**b**) Example of periodic breathing with decreases in heart rate and SpO2 corresponding to the respiratory pauses.

Future Work

We are beginning new projects applying comparable methods to adult ICUs, again seeking early warning signs of clinical deterioration.

Concluding Remark

Timothy Buchman, who is both a critical care physician and an airplane pilot, uses the phrase “situational awareness” – like a pilot, a physician not only needs information about the present state of the patient, but also needs systems that anticipate what the future state will be. The research in our groups has already led to predictive electronic monitoring, providing early warning of impending sepsis long before any other clinical signs appear. The proposed research will continue in that direction, using noninvasive, purely electronic signals to obtain new and better *predictions of the future states* of infants in NICUs, thereby providing clinicians with timely warnings of impending clinical events.