Respiratory Physiology & Neurobiology 189 (2013) 223–231

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Review

Forecasting respiratory collapse: Theory and practice for averting life-threatening infant apneas☆

James R. Williamson[a], Daniel W. Bliss[b], David Paydarfar[c,d,*]

[a] MIT Lincoln Laboratory, Lexington, MA, United States
[b] School of Electrical, Computer and Energy Engineering, Arizona State University, Tempe, AZ, United States
[c] Department of Neurology, University of Massachusetts Medical School, Worcester, MA, United States
[d] Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, United States

ARTICLE INFO

Article history:
Accepted 28 May 2013

Keywords:
Infant apnea
Statistical modeling
Respiratory control
Monitoring devices
Signal processing
Machine learning
Stochastic resonance

ABSTRACT

Apnea of prematurity is a common disorder of respiratory control among preterm infants, with potentially serious adverse consequences on infant development. We review the capability for automatically assessing apnea risk and predicting apnea episodes from multimodal physiological measurements, and for using this knowledge to provide timely therapeutic intervention. We also review other, similar clinical domains of respiratory distress assessment and prediction in the hope of gaining useful insights. We propose an algorithmic framework for constructing discriminative feature vectors from physiological measurements, and for building robust and effective statistical models for apnea assessment and prediction.

1. Introduction

One in eight live births in the United States is preterm (<37 weeks post-conception) (Public Data, 1992–2002) and these high risk births require specialized monitoring and treatment in neonatal intensive care units (NICU). Apneic pauses causing transient hypoxia and associated bradycardia – often referred to as "adverse cardio-respiratory events" – are common in preterm infants, with severity ranging from presumably benign periodic apnea with mild oxygen desaturations and cardiac decelerations to severe life-threatening apnea that requires mechanical ventilation. Prospective studies have linked intermittent hypoxia with a number of acute and long-term complications (Poets, 2010a,b; Zhao et al., 2011; Mathew, 2010; Martin et al., 2011), including multi-organ dysfunction, retinopathy (Di Fiore et al., 2010), developmental delays, and neuropsychiatric disorders. There remains uncertainty regarding how immaturity of respiratory control leads to poor outcomes. However, it is clear that apnea of prematurity (AOP) is a major factor in prolonging hospitalization as well as raising concerns for subsequent risk of apparent life-threatening events and sudden infant death syndrome (SIDS) at home (Poets, 2010a,b; Zhao et al., 2011; Mathew, 2010; Martin et al., 2011). Despite the existence of interventions for apnea of prematurity (Zhao et al., 2011; Mathew, 2010; Kattwinkel et al., 1975; Schmidt et al., 2007, 2012), there remains strong endorsement by neonatologists (Poets, 2010a,b; Zhao et al., 2011; Mathew, 2010; Martin and Wilson, 2009; Martin et al., 2011) for developing new approaches to stabilize breathing patterns and to prevent intermittent hypoxia and bradycardia episodes in preterm infants.

There are many fruitful approaches for enhancing respiratory control in vulnerable infants. Traditionally, clinicians and neuroscientists seek to discover specific biological mechanisms underlying the control of breathing, and their role in causing life-threatening central apnea. Knowledge of these mechanisms has led to important therapeutic interventions. On the other hand, the science of forecasting, rooted largely in the field of signal processing and machine learning, does not require a priori knowledge of specific underlying mechanisms. Rather, the key to discovery is the availability of large datasets of physiological signals that capture normal and disordered control.

Timely therapeutic intervention requires the ability to assess ongoing baseline risks for apnea and to predict individual apnea events. Developing algorithms to do this requires sufficient amounts of multimodal physiological measurements collected from each infant in order to build effective, individualized statistical predictive models. This approach promises revolutionary changes in our ability to make real-time assessments and to implement effective therapeutic interventions to avert life-threatening events.

☆ This paper is part of a special issue entitled "Clinical Challenges to Ventilatory Control", guest-edited by Dr. Gordon.

* Corresponding author at: Department of Neurology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, United States. Tel.: +1 508 856 4147; fax: +1 508 856 6778.
E-mail address: david.paydarfar@umassmed.edu (D. Paydarfar).

1569-9048/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.resp.2013.05.034

We believe this new approach is especially applicable to apnea of prematurity.

The goals of anticipatory medical monitoring for improving respiratory control in infants can be divided into three classes. The first of these is a baseline *assessment* of respiratory risks associated with each infant, described in Section 2. Our specific focus is on assessing an infant's susceptibility for experiencing severe apneas and associated bradycardia and hypoxemia. This enables a determination of the type of monitoring and therapeutic treatment that is appropriate over a long time horizon (on the order of days). This capability is analogous to, and can draw guidance from, other algorithmic work that has been done in respiratory risk assessment, such as assessments of risk for asthma attacks, or risks for failure of weaning from a mechanical ventilator. Fig. 1 (top) illustrates the typical methodology used for making these types of respiratory risk assessments.

The second goal is real-time *prediction* of individual severe apnea events, described in Section 3. These predictive assessments provide estimates, based on recent physiological measurements, of the probability that an infant will experience an apnea in a short time horizon (on the order of minutes). Predicting infant apneas is analogous in scope to the tasks of predicting apneas and hypopneas in adults based on physiological signals, or of predicting life-threatening sepsis in infants based on cardiorespiratory signals. Fig. 1 (bottom) illustrates the typical methodology used to make real-time predictions of severe respiratory events.

The third goal is *therapeutic intervention*, described in Section 4. Apnea prediction is of no use unless something can be done about it. Interventions can occur on different time scales. One form of intervention, triggered by respiratory risk assessments, could be applied to improve an infant's baseline condition. Another form of intervention, triggered by real-time apnea predictions, could operate quickly to prevent or attenuate apnea severity, but might not be appropriate for continual use.

We review progress that has been made toward the development of medical monitoring algorithms that enable automated detections, predictions, and interventions. We suggest a common computational framework to guide future work in this area. This framework is motivated by successful technologies that have been developed for automated signal detection in other application areas. We also provide recommendations for specific directions of future algorithm development within this signal detection framework.

2. Assessing respiratory risk

Many respiratory diseases exhibit complex phenomenology, with long term correlations and power law distributions in the respiratory measurement values (Frey et al., 1998, 2005; Frey and Suki, 2008). Differences in the means and the variabilities of respiratory signals have been associated with several disordered conditions. These differences can be used for risk stratification of an individual's respiratory condition. We review progress that has been made in the automatic assessment of risk for apnea of prematurity, based on medical monitoring. For comparative purposes, we also review work that has been done in two analogous risk assessment domains: risk for severe asthma attacks, and risk for weaning failure from mechanical ventilation.

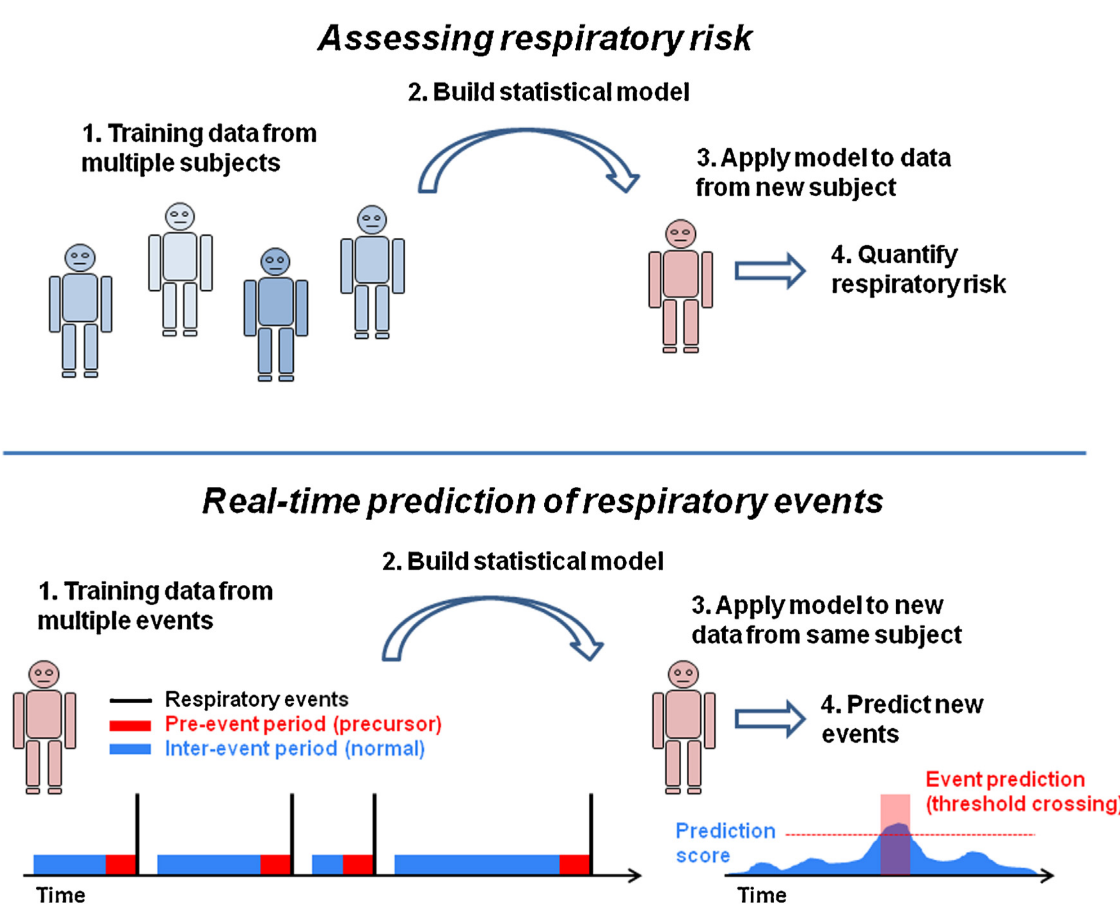

Fig. 1. Typical methodology used for baseline respiratory risk assessments (top), and for real-time prediction of repeating respiratory events (bottom). See text for details.