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Model-based estimation of loop gain using spontaneous breathing: A validation study

Elnaz Gederi[a,*], Shamim Nemati[b], Bradley A. Edwards[c], Gari D. Clifford[a,c,e,f], Atul Malhotra[c,d], Andrew Wellman[c]

[a] Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford OX1 3PJ, UK
[b] Harvard School of Engineering and Applied Sciences, 33 Oxford Street, Cambridge, MA 02138, USA
[c] Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA
[d] Pulmonary and Critical Care Division, University of California, San Diego, CA 92037, USA
[e] Department of Biomedical Informatics, School of Medicine, Emory University, Atlanta, GA 30322, USA
[f] Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA

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ABSTRACT

Non-invasive assessment of ventilatory control stability or loop gain (which is a key contributor in a number of sleep-related breathing disorders) has proven to be cumbersome. We present a novel multivariate autoregressive model that we hypothesize will enable us to make time-varying measurements of loop gain using nothing more than spontaneous fluctuations in ventilation and CO_2. The model is adaptive to changes in the feedback control loop and therefore can account for system non-stationarities (e.g. changes in sleep state) and it is resistant to artifacts by using a signal quality measure. We tested this method by assessing its ability to detect a known increase in loop gain induced by proportional assist ventilation (PAV). Subjects were studied during sleep while breathing on continuous positive airway pressure (CPAP) alone (to stabilize the airway) or on CPAP + PAV. We show that the method tracked the PAV-induced increase in loop gain, demonstrating its time-varying capabilities, and it remained accurate in the face of measurement related artifacts. The model was able to detect a statistically significant increase in loop gain from 0.14 ± 10 on CPAP alone to 0.21 ± 0.13 on CPAP + PAV ($p < 0.05$). Furthermore, our method correctly detected that the PAV-induced increase in loop gain was predominantly driven by an increase in controller gain. Taken together, these data provide compelling evidence for the validity of this technique.

1. Introduction

Ventilatory control instability or high loop gain (LG) is a key factor in the pathogenesis of a variety of sleep-related breathing disorders, including Cheyne–Stokes respiration (Bradley and Floras, 2003; Javaheri, 1999; Xie et al., 2002), sleep at altitude in adults (Berssenbrugge et al., 1983; Burgess et al., 2004, 2008; Salvaggio et al., 1998), periodic breathing in neonates (Rigatto and Brady, 1972a,b; von Czettritz et al., 1996; Wilkinson et al., 2007), and obstructive sleep apnea (OSA) (Wellman et al., 2004; Younes et al., 2001). In general, LG is a measure of the stability of a system (e.g. an electrical or a physiological system) controlled by negative feedback loops. In the case of respiration, LG represents the sensitivity of the negative feedback loop that controls ventilation. LG is defined as the ratio of a corrective response (e.g., hyperpnea) to a disturbance (e.g., apnea). A high LG (large ventilatory response to a disturbance) may develop into self-sustaining oscillations i.e. instability. On the other hand, a low LG (small ventilatory response to a disturbance) is more likely to exhibit stable breathing. The two key components of LG are controller gain and plant gain (see Fig. 1). Controller gain reflects chemoresponsiveness, or the hypoxic and hypercapnic ventilatory responses. Plant gain reflects the effectiveness of ventilation at eliminating CO_2. LG is a frequency dependent variable and therefore increases as a function of the circulatory delay and other time dependent variables. A non-invasive method for measuring LG could allow diagnose the contribution of LG to disordered breathing and then potentially treat the condition by using for example, oxygen or acetazolamide (Edwards et al., 2012; Wellman et al., 2008) to lower LG. However, such clinical utility of LG has been limited thus far by the fact that measurements

* Corresponding author at: Institute of Biomedical Engineering, University of Oxford, Old Road Research Campus Building, Headington, Oxford OX3 7DQ, UK. Tel.: +44 01865 617723; fax: +44 01865 617701 (Institution where the work was performed).
E-mail address: elnaz.gederi@eng.ox.ac.uk (E. Gederi).

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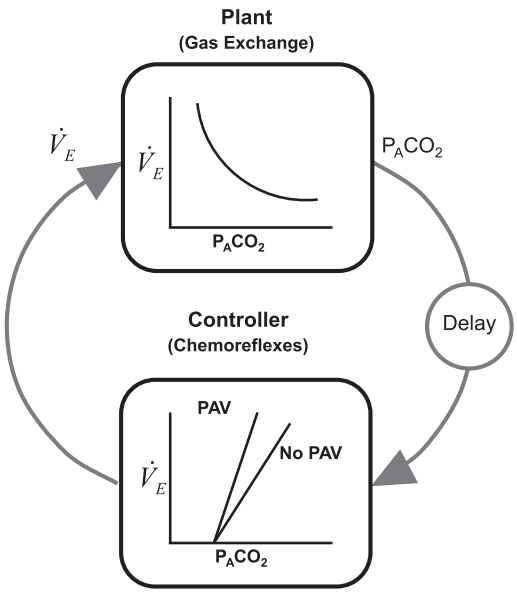

Fig. 1. Schematic diagram of the respiratory control system. The plant represents the gas-exchange system. The input to the plant is ventilation ($\dot{V}_E$), and the output is the alveolar gas tension (P_ACO_2). The delay term represents the time it takes for the pulmonary capillary blood to reach the chemoreceptors. During sleep, the controller primarily represents the ventilatory response to CO_2, i.e. chemorelfexes. PAV works by generating pressure at the airway in proportion to a person's inspiratory effort, thereby resulting in an increase in controller gain. The product of the plant and controller gains equals the loop gain.

from spontaneous breathing have proven inaccurate, and invasive measurements are impractical clinically (Francis et al., 2000).

Existing invasive measures for LG include proportional assist ventilation (PAV) (Meza and Younes, 1996), pressure support ventilation (for controller gain) (Dempsey et al., 2004), and pseudo-random binary CO_2 stimulation (Ghazanshahi and Khoo, 1997). All of these techniques are labor intensive and could only be performed by an experienced investigator in a research laboratory. In contrast, the technique proposed in this paper could be used by anyone with access to ventilation and CO_2 time series collected during spontaneous breathing, albeit with continuous positive airway pressure (CPAP) to stabilize the upper airway.

Previous autoregressive models for estimating LG have been proposed (Asyali et al., 2002; Ghazanshahi and Khoo, 1997; Khoo et al., 1995; Modarreszadeh et al., 1995; Nemati et al., 2011). However, they are confounded by artifacts in the signal and only provide a single value of LG for the entire block of data analyzed. Therefore, the presence of changing physiological states that occur naturally during sleep (e.g. sleep-wake transitions, arousals from sleep, changes in controller sensitivities with changes in sleep-state) cannot be evaluated. The first iteration of the multivariate autoregressive model proposed in this paper was validated in an anesthetized, upper-airway bypassed animal preparation (Nemati et al., 2011). The primary goal of this study was to expand on our previous model to provide a *continuous* method for the measurement of LG and its components (controller and plant gain) during sleep in humans as well as to make the method more resistant to artifact noise. In the current study, we aimed to validate this technique in human subjects by testing its ability to detect a directional change in LG produced by PAV.

2. Methods

2.1. Subjects

Thirteen CPAP treated OSA subjects (age: 45 ± 10 yrs) were recruited from the sleep laboratory at Brigham and Women's Hospital. All OSA subjects had an apnea/hypopnea index >10 events/h during supine non-rapid eye movement (NREM) sleep and a documented CPAP use of >5 h per night for at least two months prior to the study. Eight healthy controls (age: 35 ± 10 yrs) were also recruited from the community. Subjects were excluded if they were taking any medication known to influence breathing, sleep/arousal or muscle physiology. Additionally, subjects were excluded if they had a history of renal failure, neuromuscular disease or other major neurological disorders, uncontrolled diabetes, heart failure, central sleep apnea/Cheyne–Stokes respiration, uncontrolled hypertension, thyroid disease, or any other unstable medical condition. Female subjects were screened to ensure that they were not pregnant. All subjects gave written, informed consent before participation in this study, which was approved by the Partners Healthcare Human Research Committee.

2.2. Experimental setup and protocol

Subjects underwent a clinical polysomnogram (PSG) to confirm the presence or absence of OSA and a research PSG to validate the proposed LG estimation algorithm.

2.2.1. Clinical PSG

Subjects were asked to sleep supine for the majority of the night with the standard clinical montage of electroencephalography (EEG; C3/A2, O2/A1), electrooculography, and submental and anterior tibialis electromyography. Oxygen saturation was monitored by using a pulse oximeter attached to the index finger. Airflow was measured using nasal pressure and a thermistor. Piezo-electric bands around chest and abdomen monitored respiratory movements. Data were collected and stored using the Alice digital PSG system (Philips Respironics, Murrysville, PA). Sleep state, arousals, and respiratory events were scored according to standard AASM Criteria (Iber, 2007).

2.2.2. Research PSG

Sleep electrodes were attached similar to the clinical PSG. In addition, subjects were also fitted with a nasal mask (Gel Mask; Respironics, Murrysville, PA) attached to a pneumotachometer (model 3700A; Hans-Rudolph, Kansas City, MO) and pressure transducer for measuring airflow (Validyne, Northridge, CA). CO_2 was continuously recorded from a catheter placed inside the nostril with (Vacumed capnograph, Ventura, CA). The mask was connected to a BiPAP Vision mechanical ventilator (Philips Respironics) which is capable of delivering CPAP alone or in combination with PAV. After the monitoring equipment was placed on the subjects, they lay down in the supine position and breathed on their prescribed level of CPAP (for OSA subjects) or 4 cmH_2O for controls. Once asleep, PAV was slowly increased as high as possible until the patient awoke. Several PAV increases were performed during the night. We estimated LG from 5 to 10 min segments of spontaneous breathing during NREM sleep while subjects breathed on CPAP alone or on CPAP + PAV. A paired *t*-test was used to compare the LG on CPAP alone to the LG on CPAP + PAV. LG is known to be elevated on PAV (Meza and Younes, 1996) and thus if our algorithm detected a significantly higher LG on PAV, this would be interpreted as confirmation that our technique is capable of detecting a directional change in LG, thereby lending validity to the technique.

2.3. Preprocessing and signal quality index

Working with physiological measurements usually involves dealing with common problems such as movement artifact or measurement error. For example, PET_{CO_2} can sometimes be inaccurate due to low expiratory volume or mask leak, which would