SFB OPTIMIERUNG UND KONTROLLE IN MEDIZIN UND TECHNIK: CURRENT AND PROPOSED RESEARCH PROJECTS

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1. Introduction

A number of physiological systems in the human body act to stabilize critical quantities or state variables such as systemic blood pressure P_{as} and arterial carbon dioxide CO_2. In general, the mechanism involves a negative feedback loop which depends on a sensory system to measure the critical quantity and provide information to a control system which can act to alter the level of the critical quantity. Significant delay in the feedback loop can result in the system reacting to information which no longer accurately describes the state of the system. This can result in the so called "hunting phenomenon" where the system control incorrectly adjusts the control response to stabilize a state which no longer obtains. Excessive or diminished controller gain also affects feedback effectiveness. Considered as a dynamical system with delay, well known mathematical results such as given in [5] show that long delay times in the feedback control loop will destabilize a system and produce oscillations. These effects in the respiratory control system have been studied analytically in Batzel and Tran 2000 [3] and [4].

Because of these considerations, it is useful to apply the mathematical techniques available from Control Theory to study complex physiological systems. Furthermore, many physiologists believe that physiological control systems often act to optimize efficiency and minimize variations in the system in an effort to conserve energy or to minimize deviations from steady state values of critical quantities. For this reason Optimal Control theory can be used to study physiological systems and to test this supposition. Our efforts in the cardiovascular-respiratory group 310 of SFB Optimierung und Kontrolle focus on modeling and studying the complex cardiovascular-respiratory control system. We consider applications of this modeling to special topics such as newborn human infant respiratory stability, parameter identification, medical conditions in which extensive delays (such as congestive heart failure) can have serious consequences, and to mathematical issues involved in the analysis and numerical solution of mathematical systems with delay. We turn first to a brief consideration of the cardiovascular system.

2. General area of interest and current topics

The purpose of the respiratory system is to exchange the unwanted gas byproducts of metabolism, such as carbon dioxide CO_2, for oxygen O_2, which is necessary for metabolism. The site of this exchange is the alveoli, small bubble-like sacs which are found in the lungs. As the result of a branching process of 23 generations starting in the trachea, the boundary between alveolus and surrounding micro-blood vessels (capillaries) is so thin that the gas exchange is accomplished by passive diffusion. Since this exchange is by passive diffusion, the only way to compensate for increased load demands is to increase the rate of air flow exchange between the lungs and the ambient air. The control mechanism which responds to the changing needs of the body to exchange O_2 for CO_2 depends on a sensory system which detects the blood levels of these gases.

The sensory system consists of two main components: the central sensors located in the brain respond to brain CO_2 levels and the peripheral sensors located in the carotid artery respond to both O_2 and CO_2 (via partial pressures $P_{a_{CO_2}}$ and $P_{a_{O_2}}$). The control processor response of the central and peripheral signals is additive. Delay is introduced into the control system due to the physical distance which CO_2 and O_2 levels must be transported to the sensory sites before the ventilatory response can be adjusted. The delay in transfer of partial pressure information from lung to chemosensors depends on cardiac output in general and blood flow rate to the brain in particular. Thus, it is important to know how cardiac output and blood flow rates to various tissue centers are controlled and in particular how they vary with $P_{a_{CO_2}}$, $P_{a_{O_2}}$ and pH (which are the quantities controlled by the respiratory system). The dependence of the transport delay on the levels of $P_{a_{CO_2}}$ and $P_{a_{O_2}}$introduces state dependent delay into the control system as well as delay induced instability. This instability can result in forms of involuntary breathing referred to collectively as periodic breathing as well as apnea (cessation of breathing).

The respiratory and cardiovascular systems are linked via the blood flows through the lungs and tissues. The amount of oxygen transported to the tissues depends on cardiac output Q and blood flow F to the pulmonary and systemic circuits. Q and F depend upon heart rate H and stroke volume V_{str}. Arterial blood pressure P_{as} is controlled via the baroreceptor negative feedback loop. There is a short (and usually unimportant delay) in this loop. This control mechanism along with the global sympathetic and local metabolic control mechanisms acting on the resistance of the blood vessels have important effects on H, V_{str}, and hence Q. The cardiovascular system in turn is affected by the respiratory quantities CO_2 and O_2 in a number of ways. The concentration of O_2 in tissues effects the local resistance of the systemic blood vessels. Furthermore, $P_{a_{CO_2}}$ and $P_{a_{O_2}}$ can affect cardiac output and contractility as well (see, e.g., Richardson [16]). Hence, the cardiovascular-respiratory system is an intricately connected control system

which acts to stabilize the blood gas levels, cardiac output and systemic arterial blood pressure. This system can be studied in a mathematical setting by applying the methods of Control Theory. The existence of delay in the respiratory control loop adds special features to the behavior dynamics and the mathematical analysis of this system.

In our research we are working with a complex model of the cardiovascular-respiratory control system whose basic structure is derived from the work of Grodins et al. [6] and Khoo et al. [10]. The model consists of 13 differential equations as well as several auxiliary equations which describe important respiratory and cardiovascular states. The control mechanism can be modeled as an optimal control acting to drive the system from one steady state to another in a well defined optimal way. We have extended this model in a number of ways and applied it to a several areas of current research in physiology which we will discuss in Section 3. There are two broad areas of research interest for our group which we now introduce.

2.1. **Current infant respiration modeling areas of interest.** The model of the cardiovascular-respiratory control system can be adapted to study the special conditions which occur in newborn and young infants. The respiratory model has been previously adapted by Batzel and Tran [2] to study respiratory instability and apnea produced by transition to non-rem sleep in infants .

The problem of explaining the causes of and termination of apnea in infants is still poorly understood and there is much interest in studying the mechanism producing and terminating apnea. Univ.Prof. Reinhold Kerbl, who is a practicing pediatrician in the Dept. of Pediatrics at Univ. Hosp. Graz, member of the Sudden Infant Death Syndrome (SIDS) working group at Univ. Hosp. Graz, and professor at Karl Franzens Univ., thinks that obstructive apnea may well be a factor in some forms of SIDS. Mathematical models which study the control of respiration may contribute to the understanding of the mechanisms which precipitate and terminate both obstructive and central apneas in infants, phenomena which certainly contribute to life threatening events. Eventually, we should be able to adapt the full cardiovascular-respiratory model to investigate neonatal and infant physiology. Possible applications would include better monitoring schemes and perhaps screening tests for vulnerability to respiratory malfunction. Examples of the kind of modeling results which we can produce are given in Figures 1 and 2. Figure 1 depicts the changes in arterial carbon dioxide partial pressure $P_{a_{CO_2}}$ and arterial oxygen partial pressure $P_{a_{O_2}}$. Venous levels $P_{v_{CO_2}}$ and $P_{v_{O_2}}$ and brain carbon dioxide $P_{B_{CO_2}}$ are also simulated. Figure 2 depicts tidal volume or breath by breath airflow. The simulation depicts the reduction in control efficiency due to the transition to sleep. The first effects of transition to sleep introduce reductions in controller gain and shift in the operating set point. Coupled with the inefficiency introduced

by the delay in the control loop the system becomes destabilized producing cycles of apnea and arousal.

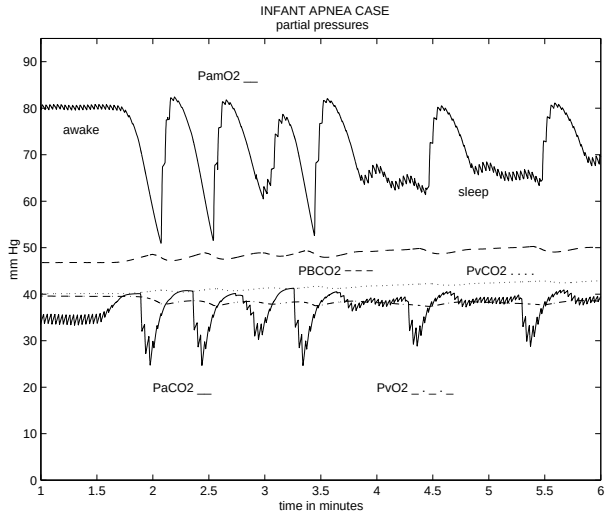

FIGURE 1. blood gases: infant apnea case

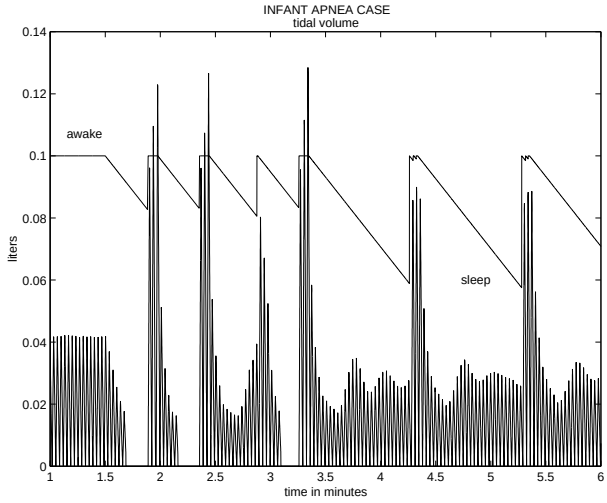

FIGURE 2. tidal volume: infant apnea case

2.2. **Current cardiovascular-respiratory system areas of interest.** As can be seen in the discussion in Section 1, the cardiovascular-respiratory control system is quite complicated and many issues remain unresolved. For example, a well known researcher in sleep physiology and cardiovascular physiology has recently stated in a communication to us [19]:

"There is little information in humans on cardiac output in non-rem (NREM) or non-dreaming quiet sleep, but the consensus would be that it goes down, given the fall in heart rate. I am not aware that this has been accurately measured. SVR quite likely decreases in NREM sleep given the fall in blood pressure and in sympathetic activity. I do not know what happens to lung vascular resistance. Such questions are interesting and important. The uncertainty is in the difficulty in acquiring accurate data on cardiac output etc. in sleeping humans. Some equivalent animal data may be available from the work of Mancia et al. [13]."

We have been developing a model of the cardiovascular-respiratory system which allows predictions of various interactions of states and effects of varying physical parameters in various conditions such as aerobic exercise and NREM sleep. This model allows for predictions of steady state and dynamical behavior of quantities which are either difficult to measure continuously even by invasive methods or not practically measurable at all. This work is further described below.

Another area of current concern is the medical condition referred to as congestive heart failure. Heart failure is a generic term covering a number of physiopathologies in heart performance which result in a decrease in general blood flow. This is to be distinguished from "heart attack" which results in blockage in coronary blood flow or blockage in ventricular or atrial flow. An important delay is introduced into the feedback control loop of the respiratory control system by this decreased blood flow. This delay can produce unstable breathing patterns referred to as Cheyne-Stokes respiration in congestive hear patients (see e.g. [3, 4]). We have modeled congestive heart failure as reduction in heart muscle contractility with some predictive success. Congestive heart failure is becoming of greater concern not only because it is nearly always fatal in a matter of years without heart transplant but also because the incidence is rising as life expectancy rises.

3. Current research in SFB Optimierung und Kontrolle in Medizin und Technik

3.1. **Modeling infant respiration.** Currently, our group is collaborating with Prof. Hien Tran of North Carolina state University and Univ. Prof. Reinhold Kerbl of Univ. Hosp. Graz. Professsor Kerbl has the capability at the Infant Monitoring Clinic to continuously measure a number of physiological parameters for sleeping infants including transcutaneous $P_{a_{CO_2}}$ and $P_{a_{O_2}}$. With such a rich data base we expect to be able to utilize the respiratory submodel to identify certain physiological parameters which are of interest to physicians and physiologists working with infants such as respiratory control gains and transport delays. We have set up a numerical scheme which uses a Nelder-Mead algorithm to optimally choose parameter sets which minimize the deviation of model generated data sets from the observed data sets. The goal is to identify parameters numerically, using the model, which accurately reflect the physiological parameters. We also

are interested in developing a numerical relation between end tidal CO_2 measurements and transcutaneous CO_2 measurements.

3.2. **Cardiovascular-respiratory system.** Current work involves improving and extending a model which combines a respiratory model developed by Khoo et al. 1982 [10] and a cardiovascular model based on the work of Grodins et al. [6] 1967. To test the notion of an optimally operating control system, The cardiovascular submodel was originally adapted to an optimal control setting by Kappel and Peer 1993 [7] and Kappel-Lafer-Peer 1997 [9]. Timischl 1998 [20] extended this optimal control setting to a combined cardiovascular-respiratory model without delay. Timischl tested the model on the problem of designing an optimal control to move the system from the awake rest steady state to an aerobic exercise steady state. Timischl, Batzel, and Kappel [21] have in late 1999 submitted a paper examining the transition from the awake steady state to stage four steady state non-rem sleep. We have recently extended this optimal control setting to a model with two fixed delays in the state equations [1]. For the two delay case we utilized an empirical formula for the respiratory control while retaining the optimal control for the cardiovascular subsystem. Numerical solutions were found using a numerical scheme developed by Kappel and Propst 1984 [8]. Steady state values for awake and non-rem sleep are consistent with observation. See, e.g., Koo [11], Phillipson [14], Shepard [17], Mancia [13], Podszus [15], Somers [18] and Mateika [12]). With the introduction of state delay we found it appropriate to look at the steady state and dynamic behavior of transition to sleep in patients with various degrees of congestive heart failure. The steady state predictions are consistent with a number of reported state variables involved with the congestive heart condition and the model generated Cheyne-Stokes respiration under certain conditions. Figures 3 and 4 give examples of the simulations produced by the combined cardiovascular-respiratory control model. In these figures we model the transition to sleep of a congestive heart patient. Figure 3 simulates the dynamic changes in arterial blood pressure and systemic venous blood pressure. Figure 4 give the control variables of heart rate H and minute ventilation V_A. Note that in this case the ventilation rate V_A drops nearly to 0 liters/min during the transition simulating an episode of apnea and damped Cheyne-Stokes respiration. We have recently completed a paper describing this work and plan to submit it for publication soon. Ultimately it is our goal to develop a cardiovascular model with a physiologically descriptive control equation. This model must take into account the effects of blood gases on cardiac output.

4. Proposed Research

We have described several areas of ongoing research including parameter estimation for infant respiratory physiology, continuing adaptation and validation of the cardiovascular-respiratory model and its application to the study of the congestive heart condition and developing a relation between

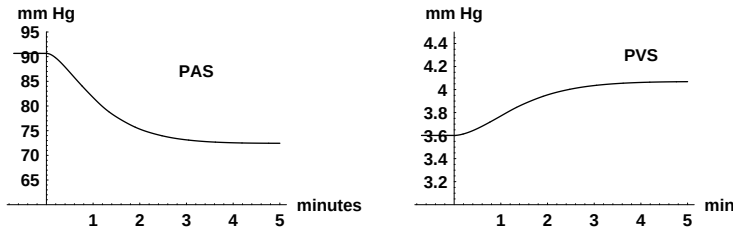

FIGURE 3. $\dot{V}_A$ empirical control: severe congestive heart sleep case

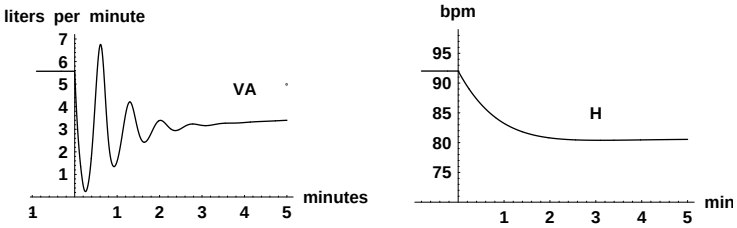

FIGURE 4. $\dot{V}_A$ empirical control: severe congestive heart sleep case

transcutaneous and end tidal carbon dioxide measurements. We have also described the most recent results. There are a number of projects which we hope to pursue in the near future.

4.1. **Research topics of interest for physiological modeling.** Univ.Prof. Haidmayer of the Dept. of Physiology at Karl Franzens University, an expert in the Sudden Infant Death Syndrome, has expressed interested in adapting the infant respiratory model to the premature infant case which is harder to model given the fact that the relation between NREM and REM sleep is not well defined. Furthermore, these infants exhibit "paradoxical breathing" in which the breathing rate can actually fall during hypoxia (CO2 held constant). Univ.Prof. Haidmayer is also interested in developing a model for apnea which could take into account temperature on the respiratory control system and other factors which might be related. We have held a number of seminars jointly with the SFB group 312 led by Univ.Prof. Thomas Kenner which focuses on cardiovascular function. It was through these seminars that we were able to meet and interact with Univ.Prof. Haidmayer as well as Univ.Prof. Schneditz of the Department of Physiology at Karl Franzens Univ. As mentioned above, we are working jointly with Univ.Prof. Kerbl of Univ. Hosp. Graz (UHG) , who along with Univ.Prof. Haidmayer and

Univ. Prof. Kenner are members of the UHG Sudden Infant Death Syndrome Working Group. We have established valuable connections with this group and have presented some of our work on modeling infant respiration at their meetings.

Another topic which we hope to pursue is developing the cardiovascular-respiratory model to include more complex pathways of cardiovascular control including sympathetic and parasympathetic influences as well as $P_{a_{CO_2}}$ and $P_{a_{O_2}}$ effects on cardiac output. We hope also to adapt the model to consider variable blood volumes by introducing a new interstitial compartment allowing for fluid to enter or leave the circulation as suggested by Univ.Prof. Kenner. This exchange plays an important role in influencing arterial and venous blood pressure and can be helpful in modeling the dialysis process. A further refinement of the general tissue compartment into subcompartments would allow for a more sophisticated interaction of peripheral blood flows and resistances. All such improvements would make for a more sophisticated model for research, monitoring devices and educational uses.

4.2. **Research topics of mathematical interest.** The delays introduced in the cardiovascular-respiratory model were introduced into the state equations. We hope to consider the problem of introducing delay into the control formulation. This would require an extension of the numerical scheme developed by Kappel and Propst 1984 [8] which was designed for delays occuring only in the state equations and for which solutions of approximating systems were shown to converge to the solution of the exact system in some specified sense. While the extension of the scheme to systems with delay in the control is straight forward, the issue of convergence of solutions of approximating systems to the true solution is of mathematical interest.

At this time all delays are treated as constant point delays. However, the most physiologically correct model would require these delays to be state dependent and distributed since cardiac output varies with the blood gases CO_2 and O_2 and cardiac output is changing through time. These features make the transport delay dependent on the varying past history of blood flow and the delay is calculated by integrating backward the past history of blood flow until the volume linking the lung and sensor site is filled. Very few mathematical results can be found for such state dependent and distributed delays in the literature, though the situation arises quite naturally when information is transported by a varying flow. It would of course be very important to develop some theory in this area.

5. International Cooperation

Prof. Tran has traveled to Graz in the month of January 2000 to meet and work with Univ.Prof. Kerbl and Dr. Batzel. He also presented a talk at the SFB seminar and a gave a presentation to Univ.Prof. Kenner and Univ.Prof. Schneditz on current work involved with non-invasive testing for coronary artery blockage. It is hoped that this collaboration will continue

and lead to new possibilities of joint research between mathematicians and physiologists and physicians. Dr. Batzel has met with and delivered a talk before the Sudden Infant Death Working Group at Univ. Hosp. Graz and has also given an invited talk at the Austrian SIDS Symposium held in Graz, Austria on July 1, 1999. Dr. Batzel will also attend the Pdiatrische Schlafmedizin Conference held in Vienna on February 24-26, 2000. These meetings and interactions are of great help to our research and we look forward to continued collaboration.

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