

MATHEMATICAL MODELING OF THE RESPIRATORY SYSTEM

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Contents

1. Introduction
 - 1.1. History of Model Development
2. Respiratory physiology: key concepts and important clinical issues
 - 2.1. Primary Elements of Respiration
 - 2.1.1. Ventilation and Gas Exchange
 - 2.2. Connections to the Cardiovascular System
 - 2.3. Control Mechanisms
 - 2.3.1. Chemosensors and the Chemical Control System
 - 2.3.2. Negative Feedback
 - 2.3.3. Quantitative Relations
 - 2.4. Clinical Issues Related to Respiratory System Dysfunction
3. Models
 - 3.1. Types of Models
 - 3.2. A Representative Respiratory Model
 - 3.2.1. State Equations
 - 3.2.2. Auxiliary Equations
 - 3.2.3. Transport Delay
 - 3.2.4. Control Equation
 - 3.2.5. Transcutaneous Blood Gases
 - 3.2.6. Model Advantages and Disadvantages
 - 3.3. Model Simulations
4. Model complexity
 - 4.1. Minimal Model
 - 4.2. Mid-Level Models
 - 4.3. Large-Scale Models
 - 4.4. Models Relating Anatomy and Physiology
5. Clinical applications
 - 5.1. Sleep Apnea
 - 5.2. Influences of High Altitude and Hypoxia
 - 5.3. Congestive Heart Failure
 - 5.4. Cerebral Blood Flow and Orthostatic Stress
6. Parameter estimation problem
 - 6.1. Data Collection and Experimental Design

6.2. Model Identifiability

6.2.1. Definitions

6.2.2. Sensitivity Analysis

6.3. Sensitivity Analysis Examples

6.3.1. Sensitivity Analysis for Control Parameters

6.3.2. Sensitivity Analysis for Compartment Volume Parameters

6.3.3. Sensitivity Analysis for Metabolic Rate Parameters

6.3.4. General Observations

7. Current issue and key questions

Acknowledgments

Glossary

Bibliography

Biographical Sketches

Summary

The respiratory system plays a central role in maintaining physiological processes related to metabolism. Complex feedback loops act to maintain adequate oxygen delivery and carbon dioxide removal, even as the level of metabolism changes. Consequently, dysfunction at any of the various levels of respiratory system function has important consequences for overall normal and stable physiological operation. Modeling is a key tool for studying the intricate interactions of the elements of this system as well as interactions with other physiological systems such as the cardiovascular system. This chapter describes the main elements involved in modeling the human respiratory system, and clinical problems that can be examined via modeling. We note that many parallels can be found in the respiratory physiology of other species. The main steps in model development are examined including model derivation based on physiological principles, decisions on model complexity in the context of data availability for model validation, and parameter estimation which is the bridge to applying models to particular problems and individual subjects in the clinical setting. A detailed survey of recent modeling applications in medicine provides a strong case for the role of modeling in exploring respiratory function.

1. Introduction

In this chapter we examine key elements of the respiratory system (focusing on human respiration) and its control mechanisms and mathematical models that have been proposed to study this system. We begin with a short history of modeling in this area.

1.1. History of Model Development

In the early part of the twentieth century J. S. Haldane and J. G. Priestly discussed the negative feedback character of respiratory control (see Haldane and Priestley work of 1905) and in the late 1940's J. S. Gray initiated the efforts to quantify the respiratory control system responses to levels of blood gases. Beginning in the 1950's, as engineering methodologies were advanced and mathematical control theory developed, initial attempts were made to develop mathematical models of the respiratory control system. The work of F. S. Grodins and colleagues (see for example the Grodins model

of 1954) played a major role in laying the groundwork of future research. Based on such groundwork, a number of important models were put forward to study various aspects of respiratory system function. Important examples of model studies include the work of G. S. Longobardo and collaborators in 1966, Grodins and colleagues in 1967, J. Duffin model of 1972, M. C. K. Khoo and colleagues model studies in 1982 and 1991, and G. S. Longobardo and collaborators work in 1989.. This list does not cover all the important research efforts but provides an accessible starting point for becoming acquainted with the literature. Further discussion on models is given in Sections 3 and 4. Excellent reviews of the history and impact of modeling can be found in the review by Khoo and Yamashiro which appeared in 1989 and the N. S. Cherniack and G. S. Longobardo review in 2006.

2. Respiratory Physiology: Key Concepts and Important Clinical Issues

Respiration is a term that includes in its scope all the elements that are involved in generating energy through metabolism. This includes ventilation, which allows for the exchange of the metabolic byproduct carbon dioxide (CO_2) for the necessary substrate of metabolism, oxygen (O_2). Often the term respiration is used interchangeably with ventilation, but there are other aspects to respiration. These include internal respiration, which describes metabolic production and exchange at the cellular/capillary level, and cellular metabolism that describes metabolic processes at the chemical level (aerobic and anaerobic metabolism). We will consider respiration at the system level, involving the transportation of CO_2 and O_2 between the lungs and tissues, as well as the control processes that act to maintain the levels of these gases at acceptable levels in the system.

2.1. Primary Elements of Respiration

There are many important mechanical and functional features involved in the operation of the respiratory system. Mechanical and structural elements influence gas exchange and matching of air flow to blood flow (ventilation-perfusion matching). For an example of modeling in this area see the work of J.S. Yem and collaborators in 2006. We will focus primarily on functional aspects of the control of respiration and its response to perturbations which challenge the steady operation of the system.

2.1.1. Ventilation and Gas Exchange

Ventilation refers to the inspiration and expiration of air in the lungs. Typical breathing involves moving approximately 7.5 liters of air per minute into and out of the lungs at a breathing frequency of around 15 breaths per minute. Hence, each breath involves a tidal volume of about 500 ml. These nominal values (which vary naturally with body size) increase during exercise and decrease during sleep and can be also influenced by other factors such as high altitude, where the level of O_2 is diminished.

Exchange of CO_2 for O_2 (blood gases) in the lungs occurs in the alveoli which are found at the lowest branches of the lung airway tree. This tree begins at the trachea, which is the starting point for approximately 23 levels of branching bifurcations, ending in alveolar sacs which contain a number of alveoli. Each alveolus is a hollow spherical structure like a bubble. As a result of this extensive branching, the number of alveoli

that can be accommodated is quite large (approximately 500 million) allowing for a surface area of many square meters.

Interfaced and intertwined with the surface area of alveoli are capillaries that lie at the end of a similar branching process originating in the pulmonary arterial vasculature. This extensive branching allow for the creation of an extremely thin alveolar-capillary boundary. This makes possible efficient exchange of gases by diffusion (O_2 into the capillaries and CO_2 into the alveoli). The upper levels of the branching conducting airways do not take part in gas exchange and hence approximately 150 ml. of a 500 ml tidal volume of air (or about 30 %) is not available for gas exchange, which reduces the effective ventilation.

Blood transported from the lungs to the body tissues (such as muscle tissue) is rich in O_2 . The cardiovascular system delivers this blood to the cells by reducing the dimension of the systemic arterial vasculature via a branching process that ends once again in capillaries that are intertwined with body tissue cells. Diffusion of O_2 and nutrients into the cell and CO_2 and other waste products out of the cell takes place via intercellular fluid. Blood, rich in CO_2 and with reduced O_2 returns via the systemic venous system to the lungs where the process of exchange is repeated.

2.2. Connections to the Cardiovascular System

The entire loop connecting tissues to lungs includes the following cardiovascular elements:

- The pulmonary arterial vascular circuit system transports the blood from the right heart (right atrium and ventricle) to the lungs where gas exchange occurs while the pulmonary venous system transports blood back to the left heart (left atrium and ventricle).
- The systemic arterial circuit transports blood from the left heart to the tissues while the systemic venous circuit returns blood to the right heart.
- Characteristics of blood and hemoglobin influence the efficiency and effectiveness of gas transport and uptake.

The vascular circuits are depicted in Figure 1. This figure also includes information on features of the control system which adjusts the ventilation rate depending on O_2 demand and levels of CO_2 . This control mechanism is described below while other features of this control system, and the respiratory system in general, will be introduced as we discuss an example model presented in Section 3.2.

It is clear from Figure1 that the respiratory and cardiovascular systems are closely connected and they influence each other in many ways. We mention here heart rate variability (HRV) which denotes small changes in heart rate over time. The ventilation rate modulates heart rate and is one source of HRV. Furthermore, it is clear that cardiac output influences the transport time of oxygen from the lungs to the tissues and hence any changes in blood gases at the lungs due to changes in ventilation will only appear after some time in the tissues. Conversely, the level of blood gases influences cardiovascular parameters, in particular vascular resistance and cardiac output (see, e.g., D. W. Richardson and colleagues' work of 1961).

2.3. Control Mechanisms

The transport time (transport delay) described in the previous section plays an important role in the control of ventilation to meet the metabolic demands of the body. This is because the respiratory control system monitors levels of CO_2 and O_2 at fixed points in the body with the sensing being performed by special cells referred to as chemosensors.

2.3.1. Chemosensors and the Chemical Control System

In the absence of voluntary or specialized responses to stresses such as exercise, the respiratory control system varies ventilation based on levels of the blood gases CO_2 and O_2 . This system is referred to as the chemical control system.

Some chemosensors are located in the carotid bodies of the carotid arteries. These sensors respond to levels of both CO_2 and O_2 and are referred to as the peripheral sensors. Additional chemosensors are located in the brain (referred to as central sensors) but these sensors respond only to CO_2 . These locations are depicted in Figure 1. Typically, levels of the blood gases are measured in partial pressures rather than concentrations so that we reference partial pressures of carbon dioxide and oxygen in the arteries with the symbols P_{a,CO_2} and P_{a,O_2} respectively. Similarly, levels of brain carbon dioxide will be referenced by the symbol P_{B,CO_2} (see Table 1 for full set of symbols).

2.3.2. Negative Feedback

Both sensory sites send information to the central control center in the medulla which integrates this information and adjusts the ventilation rate in response to the state of the system. The control acts as a negative feedback control: as CO_2 increases in the blood, ventilation is stimulated to bring the CO_2 level back to steady state levels while a decrease in CO_2 has the opposite effect.

Similarly, a decrease in O_2 causes ventilation to increase in order to raise the O_2 level (while an increase has the opposite effect). Hence the control always acts to combat any deviation from normal operating levels and this represents a negative feedback control loop. Hence, it is not hard to see why transport delays (which depend on blood flows which transport blood gases) are an important element of the system. Since changes in the blood gases at the tissue level takes time to reach the sensory sites, the information on the state of the system is always a bit delayed. Hence changes in the system induced by ventilation will always be in response to old information. This may result in the ventilatory response being not synchronized with current needs which can lead to unstable system behavior.

2.3.3. Quantitative Relations

The ventilatory response to levels of the blood gases at the sensory sites has been extensively studied both in animals and in humans. Deductions have been drawn that indicate how the information from the sensory sites is combined. A number of models

have been developed to quantify these relations, beginning with the key initial work of J. S. Gray in 1946. Details of the experiments which led to the current general view are summarized in the D. J. C. Cunningham and collaborators article in the Handbook of Physiology appearing in 1986 and an equation that reflects the current view is discussed in Section 3.2.4.

The level of CO₂ plays the primary role in controlling ventilation. Because this blood gas has an important influence on pH levels in the system, which greatly influence metabolic function, it is very important to tightly control the level of CO₂. Oxygen is also critical for metabolism but because of the effectiveness of hemoglobin in storing O₂ a substantial reserve of O₂ is usually maintained in the blood. Only when O₂ levels fall significantly does significant stimulation of ventilation occur. Typically, during normoxic periods, ventilatory response is primarily (70-85 %) generated by levels of CO₂.

2.4. Clinical Issues Related to Respiratory System Dysfunction

There are many clinical problems that arise from mechanical and functional problems in the respiratory system. At the level of control, key problems include:

- Central apnea which is the cessation of breathing due to loss of ventilatory drive;
- Obstructive apnea, which is the cessation of air flow due to blockage of airways. This can in part be caused by changes occurring during sleep which impact respiratory system muscles that dilate the airways;
- Cheyne-Stokes respiration, which involves highly regular patterns of hyperventilation followed by periods of apnea.

Sleep state impacts the respiratory control system's effectiveness. Obstructive apnea often occurs during sleep and obstructive sleep apnea (OSA) has been associated with hypertension, obesity, coronary artery disease, and type 2 diabetes as well as having an impact on daytime alertness and quality of life. Central apnea during sleep also has medical implications and such apneas are observed in patients with congestive heart failure. Both forms of apnea may hasten the deterioration in heart function in patients with heart failure. An important series of studies have been carried out by V.K. Somers and colleagues examining these links. Further discussion is given in Section 4.

3. Models

As can be seen from the above discussion, there are many interacting features of the respiratory control system and important clinical issues are associated with problems in respiratory control. Modeling can be used to test hypotheses about the control system structure, test the implications for system function of non-normal parameter values, and study the system response to perturbations such as sleep apnea, disturbed sleep, reduced cardiac output as seen in congestive heart failure, and other factors that may disrupt control system function.

Parameter	Unit	Symbol
Concentration arterial systemic blood CO ₂	liter/liter	C _{a,CO₂}

Concentration arterial systemic blood O ₂	liter/liter	C_{a,O_2}
Concentration venous blood CO ₂	liter/liter	C_{v,CO_2}
Concentration venous blood O ₂	liter/liter	C_{v,O_2}
Concentration brain tissue CO ₂	liter/liter	C_{B,CO_2}
Partial pressure arterial blood CO ₂	mmHg	P_{a,CO_2}
Partial pressure arterial blood O ₂	mmHg	P_{a,O_2}
Partial pressure venous blood CO ₂	mmHg	P_{v,CO_2}
Partial pressure venous blood O ₂	mmHg	P_{v,O_2}
Partial pressure brain tissue CO ₂	mmHg	P_{B,CO_2}
Minute ventilation (total ventilatory drive)	liter/min	\dot{V}_E
Peripheral ventilatory drive	liter/min	\dot{V}_P
Central ventilatory drive	liter/min	\dot{V}_C
Dead space ventilation	liter/min	\dot{V}_D
Alveolar ventilation	liter/min	\dot{V}_A

Table 1. States and state-defined variables for System Model (equations 1-16)

3.1. Types of Models

Models can be designed for various purposes and with various degree of physiological detail. For example, to assess or capture system performance, input-output models can be employed. To study in detail the interaction of physiological mechanisms, distributed or compartmental models can be designed which incorporate current information about the physiology of specific mechanisms and their interactions. Models should be of sufficient complexity to represent the important details of the system or phenomena under investigation but not more complex as additional assumptions and parameters can needlessly complicate the analysis. Different levels of modeling are described in Section 4.

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Biographical Sketches

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Mostafa Bachar received his PhD from University of Pau et Pays de l'Adour in December, 1999 with areas of research applied mathematics, recently he is working as Assistant Professor in Department of Mathematics, in King Saud University, Saudi Arabia, and his current research are mathematical modeling in mathematical biology and mathematical analysis.

Franz Kappel received his PhD from University of Graz in 1963, was Associate Professor at the University of Würzburg (Germany) from 1971 – 1975 and was Full Professor at the University of Graz from 1975 – 2008.