Control of the Human Cardiovascular-Respiratory System under an Time-Varying Ergometric Workload

Dissertation

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List of Symbols and Abbreviations

Symbols

\( Q_l \) left cardiac output
\( Q_r \) right cardiac output
\( R_p \) resistance in the peripheral region of the pulmonary circuit
\( R_s \) peripheral resistance in the systemic circuit
\( F_s \) blood flow perfusing the tissue compartment
\( F_p \) blood flow perfusing the lung compartment
\( H \) heart rate
\( V_A \) alveolar gas volume
\( \dot{V}_A \) alveolar ventilation
\( u_1 \) control function, \( u_1 = \dot{H} \)
\( u_2 \) control function, \( u_2 = \dot{V}_A \)
\( w_1 \) weight factor of \( u_1 \) in the cost functional
\( w_2 \) weight factor of \( u_2 \) in the cost functional
\( V_o \) total blood volume
\( W \) imposed work load

Abbreviations

\( HJB \) Hamilton-Jacobi-Bellman
\( EL \) Euler-Lagrange
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Dedicated To

To late Mother and Father
Abstract

In this work a combined model developed by Grodins, Kappel, Peer and Khoo representing the human cardiovascular and respiratory system is considered. The cardiovascular part is based on the four compartments representing the blood vessels of the pulmonary and systemic circuits. The respiratory part is based on the two compartments representing the lungs and tissues. Mechanisms included are Frank-Starling’s law and the Bowditch effect. Heart rate and alveolar ventilation are assumed to be the quantities through which the central nervous system controls the arterial partial pressure of carbon dioxide $P_{a,CO_2}$ close to 40mmHg. The transition from the rest phase to an exercise phase under a time varying ergometric workload is simulated. Here the action of cardiovascular and respiratory control is represented by an optimal control which minimizes a quadratic cost functional.
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Chapter 1

Physiology

In this chapter, the basic notations and concepts related to cardiovascular and respiratory physiology are summarized. The main focus is put on the physiology of cardiovascular and respiratory control. More detailed and extensive elaborations can be found in Batzel [1], Guyton [7], Keener and Sneyd [8] and Timischl [5]. Most material covers Guyton [7].

1.1 Cardiovascular system

The cardiovascular system consisting of organs like heart, blood vessels performs many important functions, which includes supply of oxygen from the lungs to various cells of the body and removal of carbon dioxide which is produced as a result of metabolism. Another important mechanism is the regulation of concentration of hydrogen ions in the body. To perform these functions the blood is pumped by the heart through two vascular circuits: the pulmonary circuit which transfers blood through the lungs region and the systemic circuit which transport blood through the tissue region.

The human heart is situated at the center of the chest and is approximately the size of a clenched fist. It performs the function of a muscular pump, wherein it expands and contracts to pump blood into the blood vessels and the rest of the body. It consists of four chambers, the upper two are known as the left and the right atria and the lower two are known as the left and right ventricles. The deoxygenated blood is carried to the right side of the heart which pumps it into the lungs where blood absorbs more oxygen and releases carbon dioxide. This oxygenated blood moves to the left side of the heart which pumps it to the various body parts.

There are three different types of blood vessels in the human body, the arteries, the capillaries and the veins. The arteries are of three types, the pulmonary arteries, the systemic arteries and the coronary arteries. The systemic arteries perform the function of carrying oxygenated blood from the left heart to the other parts of the body, whereas the pulmonary arteries carried deoxygenated blood from the right heart to the lungs. The coronary arteries supply the heart muscle with oxygenated blood. In the capillary region the gas exchange takes place, oxygen is delivered to the cells and carbon dioxide is removed. The veins carry deoxygenated blood from the various organs of the body to the right heart, respectively oxygenated blood from the lungs to the left heart.

1.2 Blood circulation

The left atrium and ventricle receive blood coming from the lungs full of oxygen and pumps it into aorta for the distribution to all regions of the body. The vasculature bifurcates.
into progressively smaller vessels, from larger to smaller systemic arteries, further on to systemic arterioles down to the systemic capillaries. In the capillary region the substrates for metabolism of cells as well as oxygen are delivered and metabolic end products, in particular carbon dioxide, are removed.

Leaving the systemic capillaries, the blood, now enriched with carbon dioxide and depleted of oxygen, enters the systemic venous system and reaches the right atrium through veins of progressively larger diameter (venules, small veins, superior and inferior vena cava). The right ventricle pumps the blood into the pulmonary artery and the pulmonary arterial tree, which distributes the blood flow to the alveolar region of the lungs. In the pulmonary capillaries carbon dioxide is removed and oxygen enters the blood. Leaving this region the blood flows through the pulmonary veins to the left atrium. Under resting conditions one passage through the systemic and the pulmonary circuits takes around one minute.

1.3 Ventricular functioning

One usually considers two phases of heart cycle, ventricular systole and ventricular diastole. Ventricular systole is the contraction of the muscles of the left and right ventricles. Ventricular systole induces increased pressure in the left and right ventricles. Pressure in the ventricles rises to a level above that of the atria, thus closing the tricuspid and mitral valves. Ventricular pressure continues to rise in isovolumetric contraction with maximal pressure generation occurring during this phase, until the pulmonary and aortic valves open in the ejection phase. In the ejection phase, blood flows down its pressure gradient through the aorta and pulmonary artery from left and right ventricles respectively. At rest ventricle ejects 65% of volume which was in the ventricle at the beginning of the systole.

Ventricular diastole is the period during which the ventricles are relaxing and are filled with blood after systole. During ventricular diastole, the pressure in the (left and right) ventricles drops from the peak that it reaches in systole. When the pressure in the left ventricle drops to below the pressure in the left atrium, the mitral valve opens, causing accumulated blood from the atrium to flow into the ventricle. The diastole comes to an end when the heart muscle starts to contract.

1.4 Frank-Starling mechanism

The heart pumps 4 to 6 liters of blood each minute in a rest situation. However, during severe exercise it may be required to pump as much as five times this amount. The heart has intrinsic autoregulation ability to adapt itself to such extreme situation. This intrinsic ability of the heart to adapt itself to changing loads of inflowing blood is called the Frank-Starling Law of the heart.

Basically, the Frank-Starling law of the heart states that the more the heart is filled during diastole, the larger will be the quantity of blood pumped into the aorta. In other words, the heart can pump either a small amount of blood or large amount, depending on the amount that flows into it from the veins; and it automatically adapts to whatever this load might be as long as the total quantity does not rise above the physiologic limit the heart can pump. The primary mechanism by which the heart adapts to changing inflow of blood is the following. When the cardiac muscle becomes stretched an extra amount, as it does when extra amount of blood enter the heart chambers, the usually stretched muscle contracts with a greatly increased force, thereby automatically pumping the extra blood into the arteries. This ability of stretched muscle to contract with increased force is characteristic of all striated muscles and not only of the cardiac muscle. The increased force of contraction is probably caused by the fact that the actin and myosin filaments
are brought to a more nearly optimal degree of interdigitation for achieving contraction. This ability of the heart to contract with increased force as its chambers are stretched is sometimes called heterometric autoregulation of the heart.

### 1.5 Autonomic nervous system

The nervous system is divided into the central nervous system consisting of the brain and the spinal cord and the peripheral nervous system consisting of nerve branches originating from the brain and spinal cord. The peripheral nervous system is further divided into the somatic and the autonomic nervous system. It is the autonomic nervous system that controls the visceral function of the body. The autonomic nervous system is activated mainly by centers located in the spinal cord, brain stem and hypothalamus. The autonomic impulses are transmitted to the body through two major subdivisions called sympathetic and parasympathetic systems.

The sympathetic nerves originate in the vertebrate column beginning in the first thoracic segment of the spinal cord, extending up until the second or the third lumbar segments. While parasympathetic nerve fibers are in the vagus nerves, passing to the entire thoracic and abdominal regions of the body.

The main function of the sympathetic nervous system is to mobilize the body’s response under stressful circumstances. Thus, the sympathetic nervous system initializes the ‘fight or flight’ response of the body. While, parasympathetic nervous system is responsible for the ‘rest and digest’ phase of the body. In general, sympathetic stimulation increases the overall activity of the heart. This is accomplished by increasing both the rate and force of the heart beat. Parasympathetic stimulation causes mainly the opposite effects, decreasing the overall activity of the heart. Sympathetic stimulation unfortunately increases the metabolism of the heart while parasympathetic stimulation decreases its metabolism and allows the heart a certain degree of rest. Blood vessels of abdominal viscera and the skin of the limbs, are constricted by the sympathetic stimulation. Parasympathetic stimulation generally has almost no effects on blood vessels but does dilate vessels in certain restricted areas such as in the blush area of the face.

The arterial pressure in the circulatory system is caused by the propulsion of blood by the heart and by resistance to the flow of this blood through the vascular system. In general, sympathetic stimulation increases both propulsion by the heart and resistance to flow, which can cause the pressure to increase greatly. On the other hand, parasympathetic stimulation decreases the pumping effectiveness of the heart, which lowers the pressure a moderate amount. The structure in the lungs do not have sympathetic or parasympathetic innervation. Therefore, all effects of stimulation are mild. Sympathetic stimulation can mildly dilate the bronchi and mildly constrict the blood vessels. On the contrary, parasympathetic stimulation can cause mild constriction of the bronchi and can perhaps mildly dilate the vessels.

### 1.6 Baroreceptor loop

The baroreceptor loop is a global feedback control mechanism using the nervous system to adjust the heart rate, the venous resistance, and thereby the venous pressure in order to maintain the arterial pressure at a given level, with the ultimate goal of regulating the cardiac output.

The need to regulate cardiac output is apparent. During exercise, when the demand for oxygen goes up, cardiac output normally rises at a linear rate, with slope about 5 (since 5 liters of blood are required to supply 1 liter of oxygen). In normal situations, the cardiac output and heart rate are roughly proportional, indicating that the stroke volume remains
essentially constant. However, if heart rate is artificially driven up with a pacemaker, with no increase in oxygen consumption, then the cardiac output remains virtually the same, indicating a decrease in stroke volume. Similarly, in exercise with a fixed heart rate (set by a pacemaker), total cardiac output increases to meet the demand.

The primary nervous mechanism for the control of cardiac output is the baroreceptor reflex. This reflex is initiated by stretch receptors, called baroreceptors or pressoreceptors, located in the walls of the carotid sinus and aortic arch, large arteries of the systemic circulation. A rise in arterial pressure is detected and causes a signal to be sent to the central nervous system from which feedback signals are sent through the autonomic nervous system to the circulatory system, thereby enabling the regulation of arterial pressure. For example, the baroreceptor reflex occurs when a person stands up after having been lying down. Immediately upon standing, the arterial pressure in the head and upper body falls, with dizziness or loss of consciousness a distinct possibility. The falling pressure at the baroreceptors elicits an immediate reflex, resulting in a strong sympathetic discharge throughout the entire body, thereby minimizing the decrease in blood pressure in the head.

1.7 Autoregulation

Autoregulation is a manifestation of local blood flow regulation. It is defined as the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. For example, if perfusion pressure is decreased to an organ (e.g., by partially occluding the arterial supply to the organ), blood flow initially falls, then returns toward normal levels over the next few minutes. This autoregulatory response occurs in the absence of neural and hormonal influences and therefore is intrinsic to the organ. When perfusion pressure (arterial minus venous pressure, $P_a - P_v$) initially decreases, blood flow ($F$) falls because of the following relationship between pressure, flow and resistance:

$$F = \frac{P_a - P_v}{R}$$  \hspace{1cm} (1.7.1)

When blood flow falls, arterial resistance ($R$) falls as the resistance vessels (small arteries and arterioles) dilate. The metabolic and myogenic mechanisms are responsible for this vasodilation. As resistance decreases, blood flow increases despite the presence of reduced perfusion pressure.

1.8 Cerebral circulation

The normal blood flow through brain tissue average 50 to 55 ml per 100 grams of brain per minute. For the entire brain of the average adult, this is approximately 750 ml per minute, or 15 per cent of the total resting cardiac output. This blood flow, even under extreme conditions, usually does not vary greatly from the normal value because the control system are especially geared to maintain constant cerebral blood flow. Some exception to this occurs when the brain is subjected to excess carbon dioxide, hydrogen ions, or lack of oxygen.

An increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increase cerebral blood flow. Carbon dioxide increase cerebral blood flow by combining with water in the body fluids to form carbonic acid, with subsequent dissociation to form hydrogen ions. The hydrogen ions then cause vasodilation of the cerebral vessels—the dilatations being almost directly proportional to the increase in hydrogen ion concentration. Increased hydrogen ion concentration greatly depresses neuronal activity. Conversely, diminished hydrogen ion concentration greatly increases neuronal activity. Therefore, an increase in hydrogen ion concentration causes an increase in the blood flow, which in turn
carries both carbon dioxide and dissolved acids away from the brain tissue at an increased rate. Loss of carbon dioxide removes carbonic acid from the tissue, and this, along with the removal of other acids, reduces the hydrogen ion concentration back toward normal.

Except during short periods of intense brain activity, the utilization of oxygen by the brain tissue remains within very narrow limits—within a few percent of 3.5 ml of oxygen per 100 grams of brain tissue per minute. If the blood flow to the brain ever becomes insufficient to supply this needed amount of oxygen, the oxygen deficiency mechanism for vasodilation starts in essentially all tissues of the body, immediately causing vasodilation, and bringing the blood flow and transport of oxygen to the cerebral tissues back to the normal.

1.9 Respiratory system

The respiratory system is responsible for gas transfer between the tissues and the outside air. Carbon dioxide that is produced by metabolism in the tissues must be moved by the blood to the lungs and oxygen that is supplied to the tissues must be extracted from the outside air by the lungs. The nose, mouth, pharynx, larynx, trachea, bronchial trees, lung air sacs and respiratory muscles are the structures that make up the respiratory system.

The nasal cavities are specialized for warming and moistening inspired air and for filtering the air to remove large particles. The larynx, or “voice box,” contains the vocal folds that vibrate as air passes between them to produce sounds. Below the larynx the respiratory system divides into airways and alveoli. The airways consist of a series of branching tubes that become smaller in diameter and shorter in length as they extend deeper into the lung tissue. They terminate after about 23 levels of branches in blind sacs, the alveoli. The terminal bronchioles represent the deepest point of the bronchial tree to which inspired air can penetrate by flowing along a pressure gradient. Beyond the terminal bronchioles, simple diffusion along concentration gradients is primarily responsible for the movement of gases.

Alveoli are thin-walled air sacs that provide the surface across which gases are exchanged. Each lung contains about 300 million alveoli with a combined surface area of about 7085 square meters. The alveoli are surrounded by respiratory membrane that serve to bring air and blood into close contact with a large surface area. In the lung capillaries, from 70 to 140 ml of blood is spread over the surface area of the lungs.

1.10 Alveolar ventilation

The rate at which the alveolar air is renewed each minute by the atmospheric air. The alveolar ventilation per minute is not equal to the minute respiratory volume because a large portion of the inspired air fills the respiratory passage ways, the membranes of which are not capable of significant gaseous exchange with the blood. The air that fills the respiratory passages with each breath is called dead space air. On inspiration, much of the new air must first fill the different dead space areas—the nasal passageways, the pharynx, the trachea, and the bronchi—before it reaches the alveoli. Then, on expiration, all the air in the dead space is expired first before any of the air from the alveoli reaches the atmosphere. The volume of air that enters the alveoli with each breath, therefore, is equal to the minute volume minus the dead space volume,

\[
\dot{V}_A = \dot{V}_E - \dot{V}_D
\]

where \( \dot{V}_E \) represents minute ventilation (liters inhaled per minute), \( \dot{V}_A \) represents the alveolar or effective ventilation and \( \dot{V}_D \) represents the total dead space ventilation. Thus it is \( \dot{V}_A \) that really counts for the respiratory function.
Besides dead space, there are alveoli themselves are not functional and must be considered also to be dead space because there are not blood flow to the adjacent pulmonary vessels. Also, at other times the ratio of pulmonary blood flow to ventilation in certain alveoli is so low that these alveoli are only partially functional, so that they too, can be considered to be partially dead space. When the alveolar dead space is included in the total measurement of dead space this is then called the physiological dead space.

1.11 Gas exchange

The respiratory unit is comprised of a respiratory bronchiole, alveolar ducts, atria and alveolar sacs or alveoli. The alveolar walls are extremely thin, and within them is an almost solid network of interconnecting capillaries. The flow of blood in the alveolar wall has been described as a “sheet” of flowing blood. Thus, it is obvious that the alveolar gases are in close proximity to the blood of the capillaries.

Consequently, gaseous exchange between the alveolar air and the pulmonary blood occurs through the membranes of all the terminal portions of the lungs. These membranes are known as respiratory membrane. At the respiratory membrane, each gas diffuses in the direction where the partial pressure of that gas is less. In other words, oxygen diffuses towards the blood and is taken up by hemoglobin, and carbon dioxide diffuses towards the alveolus and mixes with the air. No active process is involved. Oxygen simply diffuses through the membrane and plasma, and is taken up by the red blood cells. Although the diffusion occurs very rapidly, the gases do not have time to totally equilibrate.

The total surface area of the respiratory membrane is approximately 70 square meters in the normal adult. This is equivalent to the floor area of a room approximately 30 feet long by 25 feet wide. The total quantity of blood in the capillaries of the lung at any given instant is 60 to 140 ml. This structure is a facilitating factor for respiratory exchange of gases accruing as rapidly as it does.

1.12 Transport of oxygen and carbon dioxide

Once oxygen has diffused from the alveoli into the pulmonary blood, it is transported principally in combination with hemoglobin to the tissue capillaries where it is released for the use by the cells. The presence of hemoglobin in the red cells of the blood allows the blood to transport 30 to 100 times as much oxygen as could be transported simply in the form of dissolved oxygen in the water of the blood. In the tissue cells oxygen reacts with various foodstuffs to form large quantities of carbon dioxide. This in turn enters the tissue capillaries and is transported by the blood back to the lungs. Carbon dioxide, like oxygen, also combines with chemical substances in the blood that increases carbon dioxide transport 15-to-20 fold.

1.12.1 Oxygen transport

Normally, about 97 percent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells, and the remaining 3 per cent is carried in dissolved state in the water of the plasma and cells. Thus, under normal conditions the transport of oxygen in the dissolved state is negligible. However, when a person breathes oxygen at very high pressure, as much oxygen can sometimes be transported in the dissolved state as in chemical combination with hemoglobin.
1.12.2 Diffusion of oxygen

Gases can move from one point to another by diffusion. The cause of this movement is always a pressure difference from the first point to the other. Thus, oxygen diffuses from the alveoli into the pulmonary capillary blood because of a pressure difference—that is, the oxygen pressure \( P_{O_2} \) in the alveoli is greater than the \( P_{O_2} \) in the pulmonary blood. The \( P_{O_2} \) of the venous blood entering the pulmonary capillary is only 40 mmHg because a large amount of oxygen has been removed from this blood as it has passed through the tissue capillaries. The \( P_{O_2} \) in the alveolus is 104 mmHg, giving an initial pressure difference for diffusion of oxygen into the pulmonary capillary of 64 mmHg.

There is progressive rise in the blood \( P_{O_2} \) as the blood passes through the capillary. The \( P_{O_2} \) rises essentially to the level in the alveolar air before reaching the midpoint of the capillary, becoming approximately 104 mmHg. The average pressure difference for oxygen diffusion through the pulmonary capillary during normal respiration is about 11 mmHg. This is a time-integrated average and not simply an average of the 64 mmHg pressure difference at the beginning of the capillary and the final zero pressure difference at the end of the capillary, because the initial pressure difference lasts for only a fraction of the transit time in the pulmonary capillary, while the low pressure difference lasts for a long time.

Then the pulmonary blood is transported by the way of the circulation to the peripheral tissue. There the \( P_{O_2} \) is lower in the cells than in the arterial blood entering the capillaries. Here again, the much higher \( P_{O_2} \) in the capillary blood causes oxygen to diffuse out of the capillaries and through the interstitial spaces to the cells. At the tissue capillaries, oxygen diffuses into the tissues by a process essentially the reverse of that which takes place in the lungs. The \( P_{O_2} \) in the interstitial fluid immediately outside a capillary is low, and, though very variable, averages about 40 mmHg, while that in the arterial blood is high, about 95 mmHg. Therefore, at the arterial end of the capillary, a pressure difference of 55 mmHg causes diffusion of oxygen. By the time blood has passed through the capillary a large portion of the oxygen has diffused into the tissues, and the capillary \( P_{O_2} \) has approached the 40 mmHg oxygen pressure in the tissue fluid. Consequently, the venous blood leaving the tissue capillaries contains oxygen at essentially the same pressure as that immediately outside the tissue capillaries, 40 mmHg. Since oxygen is always being used by the cells, the intracellular \( P_{O_2} \) remains lower than the interstitial fluid \( P_{O_2} \). When the interstitial fluid \( P_{O_2} \) falls, the intracellular \( P_{O_2} \) falls and vice versa. Oxygen diffuses through cell membranes extremely rapidly. Therefore, the intracellular \( P_{O_2} \) is almost equal to that of the interstitial fluids.

1.12.3 Transport of oxygen in combination with hemoglobin

Oxygen molecules combine loosely and reversibly with the heme portion of the hemoglobin. When \( P_{O_2} \) is high, as in the pulmonary capillary, oxygen binds with the hemoglobin, but, when the \( P_{O_2} \) is low, as in the tissue capillaries, oxygen is released from the hemoglobin. This is the basis for oxygen transport from the lungs to the tissues. Thus already a small decrease of tissue \( P_{O_2} \) causes extreme amounts of \( P_{O_2} \) to be released. Therefore, during exercise, the tissue \( P_{O_2} \) needs to change only a little further to get the extra amount of oxygen delivered from the hemoglobin. The blood of a normal person contains approximately 15 grams of hemoglobin in each 100 ml of blood, and each gram of hemoglobin can bind with a maximum of about 1.34 ml of oxygen. Therefore, on the average, the hemoglobin in 100 ml of blood can combine with a total of almost exactly 20 ml of oxygen.
1.12.4 Transport of oxygen in the dissolved state

At the normal arterial $P_O_2$ of 95 mmHg, approximately 0.29 ml of oxygen is dissolved in every 100 ml of water in the blood. When the $P_O_2$ of the blood falls to 40 mmHg in the tissue capillaries, 0.12 ml of oxygen remains dissolved. In other words, 0.17 ml of oxygen is transported into the dissolved state to the tissues by each 100 ml of blood water. This compares with about 5 ml transported by the hemoglobin. Therefore, the amount of oxygen transported to the tissues in the dissolved state is normally slight, only about 3 per cent of the total as compared with the 97 per cent transported by the hemoglobin. During heavy exercise, when the utilization coefficients rise, the quantity transported in the dissolved state falls to as little as 1.5 per cent.

1.12.5 Carbon dioxide transport

Transport of carbon dioxide is not nearly such a great problem as transport of oxygen, because even in the most abnormal conditions carbon dioxide can usually be transported by the blood in far greater quantities than oxygen. However, the amount of carbon dioxide in the blood does have much to do with acid-base balance of body fluids. Under normal resting conditions an average of 4 ml of carbon dioxide is transported from the tissues to the lungs in each 100 ml of blood.

1.12.6 Diffusion of carbon dioxide

Because of the large quantities of carbon dioxide continuously formed in the cells, the intercellular $P_{CO_2}$ tends to rise. However, carbon dioxide diffuses about 20 times easier than oxygen and therefore from the cells extremely rapidly into the interstitial fluids and then into the capillary blood.

The intracellular $P_{CO_2}$ is shown to be 46 mmHg, while that in the interstitial fluid immediately adjacent to the capillaries is about 45 mmHg, a pressure difference of only 1 mmHg. Arterial blood entering the tissue capillaries contains carbon dioxide at a pressure of approximately 40 mmHg. As the blood passes through the capillaries, the blood $P_{CO_2}$ rises and approaches the 45 mmHg of $P_{CO_2}$ of the interstitial fluid.

When arriving in the lungs, the $P_{CO_2}$ of the venous blood is about 45 mmHg while that in the alveoli is 40 mmHg. The initial pressure difference for diffusion is only 5 mmHg, which is far less than that for diffusion of oxygen across the membranes. Yet, even so, because of the 20 times larger diffusion coefficient for carbon dioxide compared to that for oxygen, the excess carbon dioxide in the blood is rapidly transferred into the alveoli.

1.12.7 Transport of carbon dioxide in the dissolved state

A small portion of carbon dioxide is transported in the dissolved state to the lungs, which is about 7 percent of all the carbon dioxide transported. The dissolved carbon dioxide in the blood reacts with water to form carbonic acid. The reaction occurs so rapidly in the red blood cells that it reaches almost equilibrium within a fraction of a second.

To a small fraction of a second the carbonic acid formed in the red blood cells dissociates into hydrogen and bicarbonate ions. This dissociation is about 99.9 per cent complete, so that only an infinitesimal fraction of the carbonic acid remains in the undisassociated form. Most of the hydrogen ions formed inside the red blood cells react rapidly with hemoglobin, which is a powerful acid-base buffer. In reacting with hemoglobin the hydrogen ions are removed from the fluid and leave, dissolved in the fluid, a large quantity of bicarbonate ions. Many of these ions then diffuse into plasma while chloride ions diffuse
into the red blood cells to take their place. Thus, the chloride content of venous red blood cells is greater than that of arterial cells, a phenomenon called the chloride shift.

The reverse combination of carbon dioxide with water in the red blood cells under the influence of carbonic anhydrase accounts for an average 70 per cent of all carbon dioxide transported from the tissues to the lungs. Thus, this means of transporting carbon dioxide is by far the most important of all the methods for transport.

1.12.8 Transport of carbon dioxide in combination with hemoglobin

Carbon dioxide reacts directly with hemoglobin. The combination of carbon dioxide with hemoglobin is a reversible reaction that occurs with very loose bond. The compound formed by this reaction is known as “carbaminohemoglobin”.

A small amount of carbon dioxide also reacts in this same way with plasma proteins, but this is much less significant because of the one-fourth as great quantity of these proteins in the blood.

The theoretical quantity of carbon dioxide that can be carried from the tissues to the lungs in combination with hemoglobin and plasma proteins is approximately 30 per cent of the total quantity transported. This reaction is much slower than the reaction of carbon dioxide with water inside the red blood cells. Therefore, it is doubtful that this mechanism provides transport of more than 15 to 25 per cent of the total quantity of carbon dioxide.

1.12.9 Change in pH value

The carbonic acid formed when carbon dioxide enters the blood in the tissues decreases the blood pH. Thus, the reaction of this acid with the buffers of the blood prevents the hydrogen ion concentration from rising greatly.

Arterial blood has a pH of approximately 7.40, and as the blood acquires carbon dioxide in the tissues, the pH falls to approximately 7.36. In other words, a pH change of 0.04 units take place. The reverse occurs when carbon dioxide is released from the blood in the lungs, the pH rising to the arterial value once again. In exercise, in other conditions of high metabolic activity, or when the blood flow through the tissues is sluggish, the decrease in pH in the tissue blood can be as much as 0.5, or on occasion even more than this, thus causing tissue acidosis.

1.12.10 Bohr and Haldane effects

The presence of carbon dioxide in the blood influences the binding of oxygen to hemoglobin. An important feature of this effect is that the reduction in carbon dioxide concentration that develops as blood passes through the lungs promotes oxygen binding, while the increase in carbon dioxide that occurs in the tissues has the opposite effect, promoting oxygen unloading. This phenomenon is referred to as the Bohr effect.

The level of oxygen bound to hemoglobin in turns affects the level of carbon dioxide concentration in the blood. As hemoglobin become deoxygenated there is room for carbon dioxide related compounds to attach to hemoglobin. Hydrogen ions also has room to bind with hemoglobin thus allowing for increased formation of carbonic acid. The net result is that a reduction in oxygen raises the carrying capacity of blood for carbon dioxide. An increase in oxygen binding has the opposite effect and this oxygen influence on blood carbon dioxide carrying capacity is referred to as the Haldane effect.
1.13 Regulation of respiration

The nervous system adjusts the rate of alveolar ventilation almost exactly to the demands of body so that the blood oxygen pressure \( P_{a,O_2} \) and carbon dioxide pressure \( P_{CO_2} \) are hardly altered even during strenous exercise or other types of respiratory stress.

1.13.1 The respiratory centre

The so called “respiratory centre” is a widely spread group of neurons located biltaterally in the reticular substance of the medulla oblongata and pons. It is divided into three major areas: (1) the medullary rhythmicity area, (2) the apneustic area, and (3) the pneumotaxic area.

The medullary rhythmicity area, which is also frequently referred to simply as the medullary respiratory centre, is located diffusely in the reticular substance of the medulla. Microelectrodes inserted into this centre detect some neurons throughout the centre that discharge during inspiration and others that discharge during expiration. Thus, in general, inspiratory neurons and expiratory neurons intermingle in the medullary rhythmicity centre. When respiration increases, both inspiratory and expiratory neurons become excited far above normal, transmitting greatly increased numbers of inspiration signals to the respiratory muscles during inspiration and greatly increased numbers of expiratory signals during expiration.

The apneustic and pneumotaxic areas are located in the reticular substance of the pons. They are not necessary for maintenance of the basic rhythm of respiration. However, when the apneustic area is still connected to the medullary rhythmicity area but the pons has been transected between the apneustic and pneumotaxic areas, the breathing is accomplished with the pattern of prolonged inspiration and very short expiration, which is exactly opposite to the pattern that occurs when breathing is done by the medullary rhythmicity area alone. Finally, if the pneumotaxic area is also connected to the rhythmicity centre, the pattern of respiration becomes essentially that normally observed, having a reasonable balance between inspiration and expiration. Also, stimulation of the pneumotaxic area can change the rate of respiration, which is the reason for its name, pneumotaxic area.

1.13.2 Effects on respiratory centre

The changes in respiration result from the nerve impulses arriving in the respiratory centre from other parts of the nervous system. When the spinal cord is cut shortly below the medulla, the respiratory centre becomes only weakly active. Yet stimulation of the cut off fiber tracts leading from the transected cord to the medulla will re-establish normal respiratory rhythm. Therefore, impulses from the spinal cord play a facilitatory role in keeping the respiratory centre active. In the lungs are many receptors that detect stretch. These are located mainly in the bronchi and bronchioles. When the lungs become stretched, the stretch receptors transmit impulses through the vagus nerves to the tractus solitarius of the brain stem and then into the respiratory centre where they inhibit inspiration and thereby prevent further inflation.

Most factors that increase the activity of the vasomotor centre, thereby increasing blood pressure, also increase the pulmonary ventilatory rate. Perhaps the vasomotor centre itself excites the respiratory centre, or it is possible—if not probable—that the same factors excite both the vasomotor centre and respiratory centre at the same time—particularly since these centres are actually intermingled among each other in the reticular substance of the brain stem. For instance, inhibition of the baroreceptors increases the rate of pulmonary ventilation as well as increase vasomotor activity. Therefore, in many, if not most instances, parallel
degrees of activity occur in the vasomotor and respiratory centers at the same time.

1.14  Humoral regulation of respiration

The ultimate goal of respiration is to maintain proper concentration of oxygen, carbon dioxide and hydrogen ions in the body fluid. The respiratory activity is highly responsive to even slight changes in any one of these in the fluids. Carbon dioxide and hydrogen ions control respiration primarily by acting directly on the respiration centre in the brain; both of these excite respiratory activity. On the other hand, a decreased oxygen concentration excites respiratory activity by acting on peripheral chemoreceptors located in the carotid and aortic bodies rather than on the respiratory centre itself. The chemoreceptors in turn transmit signal to the brain to excite the respiratory activity.

1.14.1  Carbon dioxide effects on alveolar ventilation

An increase in carbon dioxide concentration or increase in hydrogen ion concentration increase alveolar ventilation. When there is an increase in alveolar $P_{CO_2}$ from the normal level of 40 mmHg to 63 mmHg, it causes a 10 fold increase in alveolar ventilation; this is about one and a half times as great as that which occurs when both pH and $P_{a, O_2}$ are artificially kept at normal values. The cause of this difference is that an increase in $P_{CO_2}$ causes an almost proportional increase in hydrogen ion concentration in all the body fluids. Therefore, an increase in $P_{CO_2}$ stimulates alveolar ventilation not only directly but also indirectly through its effects on hydrogen ion concentration.

Since carbon dioxide is one of the end products of metabolism, its concentration in the body fluid greatly affects the chemical reaction of the cells and also affects the tissue pH. For this reason, the tissue fluid $P_{CO_2}$ must be regulated exactly. As the blood and the interstitial fluid $P_{CO_2}$ are determined to a great extent by the rate of alveolar ventilation. Stimulation of the respiratory centre by carbon dioxide provides an important feedback mechanism for regulation of the concentration of carbon dioxide throughout the body. That is, (1) an increase in $P_{CO_2}$ stimulates the respiratory centre; (2) this increase in alveolar ventilation and reduces the alveolar carbon dioxide; (3) as a result, the tissue $P_{CO_2}$ returns most of the way back toward normal. In this way, the respiratory centre maintains the $P_{CO_2}$ of the tissue fluid at a relatively constant level and, therefore, might well be called a “carbon dioxide pressostat.”

1.14.2  Oxygen effects on alveolar ventilation

The role oxygen of in normal regulation of respiration is little as compared to carbon dioxide and hydrogen ion concentration. Because, in the usual range of arterial oxygen concentration-between $P_{a, O_2}$’s of 80 mmHg and 140 mmHg—there is little effect of oxygen on alveolar ventilation.

Changes in the alveolar $P_{a, O_2}$ have extremely little effects on alveolar ventilation when $P_{CO_2}$ and pH are not controlled. Because when both $P_{CO_2}$ and pH are controlled, the arterial $P_{a, O_2}$ must fall below 70 mmHg before a marked effect on alveolar ventilation occurs, because arterial blood does not develop any significant degree of desaturation until $P_{a, O_2}$ falls below 70. The second cause of the poor effect of $P_{a, O_2}$ changes on respiratory control is a “baking” effect caused by both the carbon dioxide and the hydrogen ion control mechanism.

Thus, one can see that for the control of the usual normal respiration the $P_{CO_2}$ and pH feedback control mechanisms are extremely powerful in relation to the $P_{a, O_2}$ feedback control of respiration. Indeed, under normal conditions the $P_{a, O_2}$ mechanism is of almost no significance in the control of respiration.
1.15 Chemoreceptors

Chemoreceptors located outside of the central nervous system are responsive to changes in oxygen, carbon dioxide, and hydrogen ion concentrations. These transmit signals to the respiratory centre to help regulate respiratory activity. These chemoreceptors are located primarily in association with the large arteries of the thorax and neck; most of them are in the carotid and aortic bodies, along with their afferent nerve connections to the respiratory centre. The carotid bodies are located bilaterally in the bifurcations of the common carotid arteries, and their afferent nerve fibres pass through Hering’s nerves to the glossopharyngeal nerves and hence to the medulla. The aortic bodies are located along the arch of the aorta; their afferent nerve fibres pass to the medulla through the vagus nerves. Each of these bodies receives a special blood supply through a minute artery directly from the adjacent arterial trunk.

Changes in arterial oxygen concentration have no direct stimulatory effect on the respiratory centre itself, but when the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated, which shows the relationship between arterial $P_{a, O_2}$ and the rate of nerve impulse transmission from a carotid body. The impulse rate is particularly sensitive to changes in arterial $P_{a, O_2}$ in the range between 60 and 30 mmHg, which is the range in which the arterial hemoglobin saturation with oxygen decreases rapidly.

An increase in either carbon dioxide concentration or hydrogen ion concentration also excite the chemoreceptors and in this way indirectly increases respiratory activity. However, the direct effects of both these factors in the respiratory centre itself are so much more powerful than their effects mediated through the chemoreceptors that for most practical purposes one can disregard the indirect effects through the chemoreceptors.

The blood flow through the carotid and aortic bodies is extremely high, the highest that has been found for any tissues in the body. Because of this, the arterial -venous oxygen difference is only about one volume percent, which means that the venous blood leaving the carotid bodies still has a $P_{O_2}$ nearly equal to that of the arterial blood. It also means that the $P_{a, O_2}$ of the tissue in the carotid and aortic bodies at all times remains also almost equal to that of the arterial blood. Therefore, it is the arterial $P_{a, O_2}$ that normally determines the degree of stimulation of the chemoreceptors. In hypotension, particularly when the mean arterial pressure falls below 80 mmHg, the blood flow through the carotid and aortic bodies then become sluggish, and the tissue $P_{O_2}$ falls considerably below the arterial $P_{a, O_2}$. Therefore at these low pressures the chemoreceptors are stimulated in response to the hypotension even when the arterial $P_{a, O_2}$ is normal. This give rise to the reflexes that enhance respiration and that cause also peripheral vasoconstriction that increases the arterial pressure back towards normal.
Chapter 2
The Combined Model

2.1 The model for the cardiovascular-respiratory system

We collect the equations for the combined model as given in [1]:

\[
\begin{align*}
\dot{P}_{as} &= \frac{1}{c_{as}} (Q_{\ell} - F_{s}), \\
\dot{P}_{vs} &= \frac{1}{c_{vs}} (F_{s} - Q_{r}), \\
\dot{P}_{ap} &= \frac{1}{c_{ap}} (Q_{r} - F_{p}), \\
\dot{P}_{vp} &= \frac{1}{c_{vp}} (F_{p} - Q_{\ell}), \\
\dot{S}_{\ell} &= \sigma_{\ell}, \\
\dot{\sigma}_{\ell} &= -\gamma_{\ell}\sigma_{\ell} - \alpha_{\ell}S_{\ell} + \beta_{\ell}H, \\
\dot{S}_{r} &= \sigma_{r}, \\
\dot{\sigma}_{r} &= -\gamma_{r}\sigma_{r} - \alpha_{r}S_{r} + \beta_{r}H, \\
\dot{H} &= u_{1}(t),
\end{align*}
\] (2.1.1)

\[
\begin{align*}
V_{A,CO_{2}}\dot{P}_{a,CO_{2}} &= 863F_{p}(C\_{v,CO_{2}} - C\_{a,CO_{2}}) + \dot{V}_{A}(t)(P_{1,CO_{2}} - P_{a,CO_{2}}), \\
V_{A,O_{2}}\dot{P}_{a,O_{2}} &= 863F_{p}(C\_{v,O_{2}} - C\_{a,O_{2}}) + \dot{V}_{A}(t)(P_{1,O_{2}} - P_{a,O_{2}}), \\
V_{T,CO_{2}}\dot{C\_{v,CO_{2}}} &= MR_{CO_{2}} + F_{s}(C\_{a,CO_{2}} - C\_{v,CO_{2}}), \\
V_{T,O_{2}}\dot{C\_{v,O_{2}}} &= -MR_{O_{2}} + F_{s}(C\_{a,O_{2}} - C\_{v,O_{2}}), \\
\dot{V}_{A}(t) &= u_{2}(t).
\end{align*}
\] (2.1.2)
CHAPTER 2. THE COMBINED MODEL

In the cardiovascular part we have, (see [1, Chapter 1])
\[ R_s = A_{pesk} C_v, O_2, \]
\[ F_s = \frac{1}{R_s} (P_{as} - P_{vs}), \]
\[ F_p = \frac{1}{R_p} (P_{ap} - P_{vp}), \]
\[ Q_t = H \frac{c_t a_t(H) P_{vp} S_t}{a_t(H) P_{as} + k_t(H) S_t}, \]
\[ Q_f = H \frac{c_f a_f(H) P_{as} S_f}{a_f(H) P_{vp} + k_f(H) S_f}, \]

where
\[ k_t(H) = e^{-(c_t R_t)^{-1} t_d(H)} \quad \text{and} \quad a_t(H) = 1 - k_t(H), \]
\[ k_d(H) = e^{-(c_d R_d)^{-1} t_d(H)} \quad \text{and} \quad a_d(H) = 1 - k_d(H). \]

For the duration \( t_d(H) \) of the diastole we use Bazett’s formula (duration of the systole \( = \kappa / H^{1/2} \)) which implies
\[ t_d(H) = \frac{1}{H^{1/2}} \left( \frac{1}{H^{1/2}} - \kappa \right). \]

In the respiratory part (2.1.2) we have to use the dissociative laws for \( O_2 \) and \( CO_2 \):
\[ C_v, CO_2 = K CO_2 P_v, CO_2 + k CO_2, \]
\[ C_a, CO_2 = K CO_2 P_a, CO_2 + k CO_2, \]
\[ C_v, O_2 = K_v, 1 \left( 1 - e^{-K_{a,2} P_v, O_2} \right)^2, \]
\[ C_a, O_2 = K_a, 1 \left( 1 - e^{-K_{a,2} P_a, O_2} \right)^2. \]

The metabolic rates \( MR_{O_2} \) and \( MR_{CO_2} \) depend on the imposed workload:
\[ MR_{O_2}(t) = M_{O_2} + \rho_{O_2} W(t), \]
\[ MR_{CO_2}(t) = M_{CO_2} + \rho_{CO_2} W(t). \]

For the respiratory part we take the arterial partial pressures \( P_{a, CO_2}, P_{a, O_2} \) and the venous concentrations \( C_v, CO_2, C_v, O_2 \) as the state variables. Using the dissociative laws (2.1.6) we obtain the following equations for the respiratory part:
\[ V_{a, CO_2} \dot{P}_{a, CO_2} = 863F_p (C_v, CO_2 - K CO_2 P_{a, CO_2} - k CO_2) + \dot{V}_A(t)(P_t, CO_2 - P_{a, CO_2}), \]
\[ V_{a, O_2} \dot{P}_{a, O_2} = 863F_p (C_v, O_2 - K_{a, 1} \left( 1 - e^{-K_{a,2} P_{a, O_2}} \right)^2) + \dot{V}_A(t)(P_t, O_2 - P_{a, O_2}), \]
\[ V_{t, CO_2} \dot{C}_v, CO_2 = MR_{CO_2} + F_s (K CO_2 P_{a, CO_2} + k CO_2 - C_v, CO_2), \]
\[ V_{t, O_2} \dot{C}_v, O_2 = -MR_{O_2} + F_s \left( K_{a, 1} \left( 1 - e^{-K_{a,2} P_{a, O_2}} \right)^2 - C_v, O_2 \right), \]
\[ \dot{V}_A(t) = u_2(t). \]

The cardiovascular-respiratory model, i.e., equations (2.1.1) and (2.1.8) – (2.1.12) can be written as
\[ \dot{x}(t) = f(t, x(t)) + Bu(t), \quad t \geq 0, \]
where
\[ x = (P_{as}, P_{vs}, P_{ap}, P_{vp}, S_\ell, \sigma_\ell, S_t, \sigma_t, H, P_{a,CO_2}, P_{a,O_2}, C_v, CO_2, C_v, O_2, \dot{V}_\Lambda)^T \in \mathbb{R}^{14} \] (2.1.14)
is the state vector and \( u(t) = (u_1(t), u_2(t))^T \) is the control vector. The matrix \( B = (b_{i,j}) \in \mathbb{R}^{14 \times 2} \) is given by
\[ b_{10,1} = b_{14,2} = 1, \quad b_{i,j} = 0 \text{ otherwise.} \]

### 2.2 Equilibria

In case of an equilibrium solution we have \( u_1(t) = u_2(t) \equiv 0, \) \( \dot{W} = 0 \) for rest, \( \dot{W} = 75 \) for exercise. System (2.2.1) has a two-parameter family of equilibria. As parameters we can choose \( \bar{H} \) and \( \bar{P}_{a,CO_2} \) as we shall see in the computations below.

In an equilibrium situation all blood flows in the system have to be constant and equal, which gives the following equations:
\[ F_s = F_p = Q_\ell = Q_t \equiv F. \] (2.2.2)

Starting with the respiratory system we get the following equations:
\[ F = \frac{\dot{V}_\Lambda}{863} \frac{P_{a,CO_2} - P_L,CO_2}{C_v,CO_2 - K_{CO_2} P_{a,CO_2} - k_{CO_2}}, \] (2.2.3)
\[ F = \frac{\dot{V}_\Lambda}{863} \frac{P_{a,O_2} - P_L,O_2}{C_v,O_2 - K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2}, \] (2.2.4)
\[ F = \frac{MR_{CO_2}}{C_v,CO_2 - K_{CO_2} P_{a,CO_2} - k_{CO_2}}, \] (2.2.5)
\[ F = \frac{MR_{O_2}}{K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2 - C_v,O_2}. \] (2.2.6)

Equations (2.2.3) and (2.2.5) imply
\[ MR_{CO_2} = \frac{\dot{V}_\Lambda}{863} (P_{a,CO_2} - P_L,CO_2) \]
or equivalently
\[ \dot{V}_\Lambda = 863 \frac{MR_{CO_2}}{P_{a,CO_2} - P_L,CO_2}. \] (2.2.7)

Analogously we get from equations (2.2.4) and (2.2.6)
\[ P_{a,O_2} = P_{L,O_2} - \frac{MR_{O_2}}{MR_{CO_2}} (P_{a,CO_2} - P_L,CO_2). \] (2.2.8)
Using (2.2.7) in equation (2.2.3) we obtain
\[ C_{v,CO_2} = K_{CO_2} P_{a,CO_2} + k_{CO_2} + \frac{MR_{CO_2}}{F}, \] (2.2.9)

Equation (2.2.6) implies
\[ C_{v,O_2} = K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2 - \frac{MR_{O_2}}{F}. \] (2.2.10)

For the cardiovascular system we get immediately
\[ \bar{\sigma}_\ell = \bar{\sigma}_r = 0, \]
\[ \bar{S}_\ell = \frac{\beta_\ell}{\alpha_\ell} \bar{H}, \]
\[ \bar{S}_r = \frac{\beta_r}{\alpha_r} \bar{H}. \] (2.2.11)

We consider the equations (2.2.2) as equations for the equilibrium values of the pressures \( \bar{P}_{as}, \bar{P}_{vs}, \bar{P}_{ap} \) and \( \bar{P}_{vp} \). With these equations we get together with
\[ c_{as} \bar{P}_{as} + c_{vs} \bar{P}_{vs} + c_{ap} \bar{P}_{ap} + c_{vp} \bar{P}_{vp} = V_{tot} \]
the following linear system:
\[
\begin{pmatrix}
0 & 0 & 1 & -1 & R_v F \\
1 & -1 & 0 & 0 & R_a F \\
0 & \mu_r(\bar{H}) & - a_r(\bar{H}) F & 0 & \lambda_r(\bar{H}) F \\
\alpha_r(\bar{H}) F & 0 & 0 & - \mu_\ell(\bar{H}) & - \lambda_\ell(\bar{H}) F \\
c_{as} & c_{vs} & c_{ap} & c_{vp} & V_{tot}
\end{pmatrix},
\] (2.2.12)

where
\[ \mu_r(\bar{H}) = \bar{H} \bar{S}_r c_r a_r(\bar{H}) = \frac{\beta_r}{\alpha_r} c_r a_r(\bar{H}) \bar{H}^2, \]
\[ \mu_\ell(\bar{H}) = \frac{\beta_\ell}{\alpha_\ell} c_\ell a_\ell(\bar{H}) \bar{H}^2, \]
\[ \lambda_r(\bar{H}) = \bar{S}_r k_r(\bar{H}) = \frac{\beta_r}{\alpha_r} k_r(\bar{H}) \bar{H}, \]
\[ \lambda_\ell(\bar{H}) = \frac{\beta_\ell}{\alpha_\ell} k_\ell(\bar{H}) \bar{H}. \]

Of course, we have to observe that
\[ R_a = A_{pesk} C_{v,O_2} = A_{pesk} \left( K_{a,1} \left( 1 - e^{-K_{a,2} \bar{P}_{a,O_2}} \right)^2 - \frac{MR_{O_2}}{F} \right), \] (2.2.13)

where \( \bar{P}_{a,O_2} \) is given by (2.2.8).
The determinant of the matrix for the first four equations in system (2.2.12) is given by

\[
D := \det \begin{pmatrix}
0 & 0 & 1 & -1 \\
1 & -1 & 0 & 0 \\
0 & \mu_t(\bar{H}) & -a_t(\bar{H})F & 0 \\
a_t(\bar{H})F & 0 & 0 & \mu_t(\bar{H})
\end{pmatrix}
\]

(2.2.14)

\[
= a_t(\bar{H})a_t(\bar{H})F^2 - \mu_t(\bar{H})\mu_t(\bar{H}).
\]

Let

\[
F_0 = \left( \frac{\mu_t(\bar{H})\mu_t(\bar{H})}{a_t(\bar{H})a_t(\bar{H})} \right)^{1/2} = \left( \frac{c_\ell c_\ell \beta_\ell \beta_\ell}{\alpha_\ell \alpha_\ell} \right)^{1/2} H^2.
\]

Then the first four equations of system (2.2.12) have a unique solution for any \( F \neq F_0 \). In order that also system (2.2.12) is uniquely solvable a solvability condition has to be satisfied, which in this case can be written as:

\[
g(F, \bar{H}) = \det \begin{pmatrix}
0 & 0 & 1 & -1 & R_p F \\
1 & -1 & 0 & 0 & R_s F \\
0 & \mu_t(\bar{H}) & -a_t(\bar{H})F & 0 & \lambda_t(\bar{H})F \\
a_t(\bar{H})F & 0 & 0 & -\mu_t(\bar{H}) & -\lambda_t(\bar{H})F \\
c_{as} & c_{vs} & c_{ap} & c_{vp} & V_{tot}
\end{pmatrix} = 0.
\]

Simple computations yield

\[
g(F, \bar{H}) = V_{tot} \left( a_t(\bar{H})a_t(\bar{H})F^2 - \mu_t(\bar{H})\mu_t(\bar{H}) \right) + c_{as} \left( \mu_t(\bar{H})(\lambda_t(\bar{H}) + \mu_t(\bar{H})R_s) + a_t(\bar{H})(\lambda_t(\bar{H}) + \mu_t(\bar{H})R_p) \right) F \\
+ c_{vs} \left( \mu_t(\bar{H})(\lambda_t(\bar{H}) + a_t(\bar{H})R_p F) + a_t(\bar{H})(\lambda_t(\bar{H}) + a_t(\bar{H})R_s F) \right) F \\
+ c_{ap} \left( \mu_t(\bar{H})(\lambda_t(\bar{H}) + \mu_t(\bar{H})R_p) + a_t(\bar{H})(\lambda_t(\bar{H}) + \mu_t(\bar{H})R_s) \right) F \\
+ c_{vp} \left( \mu_t(\bar{H})(\lambda_t(\bar{H}) + a_t(\bar{H})R_s F) + a_t(\bar{H})(\lambda_t(\bar{H}) + a_t(\bar{H})R_p F) \right) F.
\]

(2.2.15)

The solvability condition can be considered as an equation for \( F \) provided \( \bar{H} \) is given. Note that \( R_s \) is a function of \( \bar{P}_a,CO_2 \) and \( F \) (see (2.2.13)).

Once \( F \) is computed from \( g(F, \bar{H}) = 0 \), we get \( \bar{C}_{v,CO_2} \) and \( \bar{C}_{v,O_2} \) from (2.2.9) and (2.2.10). Since \( \bar{P}_a,CO_2 \) is given (\( \bar{P}_a,CO_2 = 0 \) mmHg), we get \( \bar{V}_A \) and \( \bar{P}_a,O_2 \) from (2.2.7) and (2.2.8). Since also \( \bar{H} \) is given (\( \bar{H} = 78.5 \) beats/min), we obtain \( \bar{\sigma}_r, \bar{\sigma}_\ell, \bar{S}_r \) and \( \bar{S}_\ell \) from (2.2.11). Equation (2.2.13) provides \( \bar{R}_s \) and the compartmental pressures in the
cardiovascular system are obtained as the unique solution of system (2.2.12):

\[
\begin{align*}
\bar{P}_{as} &= -\frac{1}{D}\left(\mu_T(\bar{H})(\lambda_T(\bar{H}) + \mu_T(\bar{H})R_s) + a_T(\bar{H})(\lambda_T(\bar{H}) + \mu_T(\bar{H})R_p)F\right)F \\
&= R_sF + \bar{P}_{vs}, \\
\bar{P}_{vs} &= -\frac{1}{D}\left(\mu_T(\bar{H})(\lambda_T(\bar{H}) + a_T(\bar{H})R_pF) + a_T(\bar{H})(\lambda_T(\bar{H}) + a_T(\bar{H})R_sF)F\right)F, \\
\bar{P}_{ap} &= -\frac{1}{D}\left(\mu_T(\bar{H})(\lambda_T(\bar{H}) + \mu_T(\bar{H})R_p) + a_T(\bar{H})(\lambda_T(\bar{H}) + \mu_T(\bar{H})R_s)F\right)F \\
&= R_pF + \bar{P}_{vp}, \\
\bar{P}_{vp} &= -\frac{1}{D}\left(\mu_T(\bar{H})(\lambda_T(\bar{H}) + a_T(\bar{H})R_pF) + a_T(\bar{H})(\lambda_T(\bar{H}) + a_T(\bar{H})R_sF)F\right)F.
\end{align*}
\]

In Table 2.1 we present the equilibrium values of the state variables of system (2.1.1), (2.1.2) in case of the rest situation with the system parameters given by (2.2.17).

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\bar{P}_{as}$</th>
<th>$\bar{P}_{vs}$</th>
<th>$\bar{P}_{ap}$</th>
<th>$\bar{P}_{vp}$</th>
<th>$\bar{S}_T$</th>
<th>$\sigma_T$</th>
<th>$\bar{S}_r$</th>
<th>$\sigma_r$</th>
<th>$\bar{H}$</th>
<th>$\bar{P}_{a,CO_2}$</th>
<th>$\bar{P}_{a,O_2}$</th>
<th>$\bar{C}_v,CO_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>107.0696</td>
<td>4.5399</td>
<td>12.82</td>
<td>5.5311</td>
<td>64.3882</td>
<td>0</td>
<td>3.8683</td>
<td>0</td>
<td>40</td>
<td>100</td>
<td>78.5</td>
<td>5116</td>
</tr>
</tbody>
</table>

In case of the equilibrium in a constant exercise situation (which was considered in [5]) the preassigned values are $\bar{H} = 107$ beats/min, $\bar{P}_{a,CO_2} = 40$ mmHg and $\bar{W} = 75$ Watt. In addition we have to change the parameter values for $R_p$ and $A_{pesk}$ to the following values: $R_p = 0.3$, $A_{pesk} = 270$. The equilibrium values for the states are given in Table 2.2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\bar{P}_{as}$</th>
<th>$\bar{P}_{vs}$</th>
<th>$\bar{P}_{ap}$</th>
<th>$\bar{P}_{vp}$</th>
<th>$\bar{S}_T$</th>
<th>$\sigma_T$</th>
<th>$\bar{S}_r$</th>
<th>$\sigma_r$</th>
<th>$\bar{H}$</th>
<th>$\bar{P}_{a,CO_2}$</th>
<th>$\bar{P}_{a,O_2}$</th>
<th>$\bar{C}_v,CO_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>124.79</td>
<td>3.6314</td>
<td>10.4529</td>
<td>7.9854</td>
<td>87.7647</td>
<td>0</td>
<td>5.2727</td>
<td>0</td>
<td>107</td>
<td>40</td>
<td>100.7853</td>
<td>0.5681</td>
</tr>
</tbody>
</table>

In Table 2.1: Equilibrium ‘rest’ for system (2.1.1), (2.1.2). Preassigned values are in boldface.

In Table 2.2: Equilibrium ‘exercise’ for system (2.1.1), (2.1.2). Preassigned values are in boldface.
For our computations we used the following parameter values:

\[
\begin{align*}
    c_{as} &= 0.01016, & \quad c_{vs} &= 0.6500, & \quad c_{ap} &= 0.03608, \\
    c_{vp} &= 0.1408, & \quad c_{r} &= 0.02305, & \quad c_{t} &= 0.04413, \\
    R_{l} &= 0.2671, & \quad R_{f} &= 0.04150, & \quad \kappa &= 0.05164, \\
    \alpha_{l} &= 30.5587, & \quad \alpha_{r} &= 28.6785, & \quad \beta_{l} &= 25.0652, \\
    \beta_{r} &= 1.4132, & \quad \gamma_{l} &= -1.6744, & \quad \gamma_{r} &= -1.8607, \\
    M_{O_{2}} &= 0.35, & \quad M_{CO_{2}} &= 0.35, & \quad \rho_{CO_{2}} &= 0.011, \\
    R_{p} &= 1.5446, & \quad A_{pesk} &= 177.682, & \quad P_{T,CO_{2}} &= 150, \\
    R_{V_{T,CO_{2}}} &= 0, & \quad V_{A,O_{2}} &= 2.5, & \quad V_{A,CO_{2}} &= 3.2, \\
    V_{T,CO_{2}} &= 6.0, & \quad V_{T,CO_{2}} &= 15.0, & \quad K_{CO_{2}} &= 0.0057, \\
    k_{CO_{2}} &= 0.224, & \quad K_{a,1} &= 0.2, & \quad K_{a,2} &= 0.05.
\end{align*}
\]
Table 2.4: State variables of the combined model.

<table>
<thead>
<tr>
<th>State variable</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{as}$</td>
<td>mmHg</td>
<td>blood pressure in the arterial systemic compartment</td>
</tr>
<tr>
<td>$P_{vs}$</td>
<td>mmHg</td>
<td>blood pressure in the venous systemic compartment</td>
</tr>
<tr>
<td>$P_{ap}$</td>
<td>mmHg</td>
<td>blood pressure in the arterial pulmonary compartment</td>
</tr>
<tr>
<td>$P_{vp}$</td>
<td>mmHg</td>
<td>blood pressure in the venous pulmonary compartment</td>
</tr>
<tr>
<td>$S_l$</td>
<td>mmHg</td>
<td>contractility of the left ventricle</td>
</tr>
<tr>
<td>$\sigma_l$</td>
<td>mmHg/min</td>
<td>time derivative of $S_l$</td>
</tr>
<tr>
<td>$S_r$</td>
<td>mmHg</td>
<td>contractility of the right ventricle</td>
</tr>
<tr>
<td>$\sigma_r$</td>
<td>mmHg/min</td>
<td>time derivative of $S_r$</td>
</tr>
<tr>
<td>$H$</td>
<td>1/min</td>
<td>heart frequency</td>
</tr>
<tr>
<td>$P_{a,CO_2}$</td>
<td>mmHg</td>
<td>partial CO$_2$-pressure in arterial blood</td>
</tr>
<tr>
<td>$P_{a,O_2}$</td>
<td>mmHg</td>
<td>partial O$_2$-pressure in arterial blood</td>
</tr>
<tr>
<td>$C_v,CO_2$</td>
<td>mmHg</td>
<td>CO$_2$-concentration in venous blood</td>
</tr>
<tr>
<td>$C_v,O_2$</td>
<td>mmHg</td>
<td>O$_2$-concentration in venous blood</td>
</tr>
<tr>
<td>$V_A$</td>
<td>liters/min</td>
<td>alveolar ventilation</td>
</tr>
</tbody>
</table>
Chapter 3

Results from Optimal Control

3.1 Introduction

Optimal control theory of nonlinear systems can be based on two optimization techniques: Dynamic Programming and the Pontryagin Maximum Principle. In this chapter, we present these two basic approaches to the problem of nonlinear optimal control. The dynamic programming approach to the problem of optimal control leads to the Hamilton-Jacobi-Bellman equation. It provides a global control law in the form of a state feedback controller. While the maximum principle, which represents a far-reaching generalization of the Euler-Lagrange equations from the classical calculus of variations, requires the solution of a two-point boundary value problem for ordinary differential equations. The solution of the Euler-Lagrange equation is computationally tractable as compared to solving the Hamilton-Jacobi-Bellman equation, which is computationally intractable. More details about this can be seen in James A. Primbs [2, Chapter 2], Donald E. Kirk [9, Chapter 1], Arthur E. Bryson, Jr. and Yu-Chi Ho [10] and Michael Athans and Peter L. Falb [3].

The nonlinear system under consideration will be of the form

\[
\begin{align*}
\dot{x}(t) &= f(t, x(t)) + Bu(t), \\
x(0) &= x_0.
\end{align*}
\]

where \( f(t, x(t)) \) is a nonlinear function of the state \( x \in \Omega \subset \mathbb{R}^m \), \( u : [0, T] \rightarrow \mathbb{R}^k \) is the control, and \( B \) is a constant \( m \times k \) matrix. The cost functional will be of the form

\[
J(x_0, u) = \int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T))
\]

with a given constant-valued, symmetric positive semi-definite \( m \times m \) matrix \( Q \) and a symmetric positive definite \( k \times k \) matrix \( R \). The desired solution is a state feedback control law which minimizes the cost for all possible initial conditions \( x_0 \). \( \phi(x(T)) \) is the terminal cost applied at the end of the time horizon.

3.2 Dynamic Programming

In this section, we shall consider the method of dynamic programming discussed in James A. Primbs [2, Chapter 2] for the solution of nonlinear optimal control problem, which leads to the Hamilton-Jacobi-Bellman partial differential equation. In the method of dynamic programming, an optimal policy is found by employing the intuitively appealing concept called the principle of optimality, which is formally stated as follows.
Theorem 3.1. If $u^*(\cdot)$ is optimal over the interval $[t, t_f]$, starting at state $x(t)$, then $u^*(\cdot)$ is necessarily optimal over any subinterval $[t + \Delta t, t_f]$, where $\Delta t$ satisfies $t_f - t \geq \Delta t > 0$.

3.2.1 The Hamilton-Jacobi-Bellman Equation (HJB Equation)

Consider the system of non-linear differential equations
\[
\dot{x}(t) = f(t, x(t)) + Bu(t),
\]
\[
x(0) = x_0.
\]
(3.2.1)

is to be controlled to minimize the cost functional
\[
J = \int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T)).
\]
(3.2.2)

Define $V(x_0)$ to be the minimum of the cost functional taken over all admissible trajectories $(x(t), u(t))$ where $x$ starts at $x_0$: \[
V(x_0) = \min_{u(\cdot)} \int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T))
\]
(3.2.3)

s.t
\[
\dot{x}(t) = f(t, x(t)) + Bu(t), \quad x(0) = x_0.
\]
(3.2.4)

The function $V$ which assigns an optimal value with each initial point, is called the value function of the optimal control problem. Rather than just searching for the $V(x(t))$ for various $x_0$, the problem can be approached by considering the evaluation of $V(x(t))$ for all $x(t)$.

Let us apply the principle of optimality. Consider $V(x)$ given by (3.2.3), and let $u[0, T]$ be defined as the control signal over the interval $[0, T]$. Using the additive properties of integrals and the principle of optimality yields
\[
V(x(t)) = \min_{u[0, t+\Delta t]} \left\{ \int_t^{t+\Delta t} (x(t)^TQx(t) + u(t)^TRu(t))d\tau + \int_t^{t+\Delta t} (x(t)^TQx(t) + u(t)^TRu(t))dt + V(x(t + \Delta t)) \right\}
\]
(3.2.5)

Assuming further, that the second order partial derivatives of $V$ exist and are bounded, then applying a multivariable Taylor-series expansion of $V(x(t + \Delta t))$ about the point $x(t)$ to obtain
\[
V(x(t)) = \min_{u[0, t+\Delta t]} \left\{ \int_t^{t+\Delta t} (x(t)^TQx(t) + u(t)^TRu(t))d\tau + V(x(t)) + \left[ \frac{\partial V}{\partial x} \right]^T [x(t + \Delta t) - x(t)] + \text{terms of higher order} \right\}
\]
(3.2.6)
Continuing further, when $\Delta t$ is very small, the above integral (3.2.6) can be approximated by $[(x(t)^TQx(t) + u(t)^TRu(t))]\Delta t$, and $x(t + \Delta t) - x(t)$ can be approximated by $[f(t, x(t)) + Bu(x(t))]\Delta t$, so the equation (3.2.6) becomes

$$V(x(t)) = \min_{u(t)} \left\{ (x(t)^TQx(t) + u(t)^TRu(t))\Delta t + V(x(t)) + V_x^T[f(t, x(t)) + Bu(x(t))]\Delta t + o(\Delta t) \right\},$$

where $V_x$ denotes the gradient of $V$ with respect to the vector $x$, and $o(\Delta t)$ denotes higher-order terms in $\Delta t$. Cancelling $V(x(t))$ on both sides gives

$$0 = \min_{u(t)} \left\{ (x(t)^TQx(t) + u(t)^TRu(t))\Delta t + \frac{1}{2} V_x^T[f(t, x(t)) + Bu(x(t))]\Delta t + o(\Delta t) \right\}.$$

Dividing by $\Delta t$ and taking the limit as $\Delta t \to 0$ gives

$$0 = \min_{u(t)} \left\{ x(t)^TQx(t) + u(t)^TRu(t) + V_x^T[f(t, x(t)) + Bu(x(t))] \right\}.$$

The boundary condition for this equation is given by

$$V(x(T)) = \phi(x(T)).$$

we define the Hamiltonian $H$ as

$$H(t, x(t), u(t), V_x) = (x(t)^TQx(t) + u(t)^TRu(t)) + V_x^T[f(t, x(t)) + Bu(x(t))]$$

and

$$H(t, x(t), u^*(x(t), V_x), V_x) = \min_{u(t)} H(t, x(t), u(t), V_x).$$

So, the Hamilton-Jacobi equation takes the following form

$$0 = H(x(t), u^*(x(t), V_x), V_x).$$

Two more steps can often be formed to reach a more convenient form

1. First, the minimization of Hamiltonian gives following control law

$$u^* = -\frac{1}{2} R^{-1} B^TV_x$$

2. When we substitute this $u^*$ into (3.2.8), we obtain the following form

$$V_x^Tf(x) - \frac{1}{4} V_x^TRB^{-1}B^TV_x + x(t)^TQx(t) = 0$$

Equation (3.2.14) is what we will call as Hamilton-Jacobi-Bellman equation (HJB Equation). But in order to compute the optimal control, first we have to solve the Hamilton-Jacobi-Bellman equation for $V(x)$, then this is put into control law (3.2.13) where we obtain the optimal control action that minimizes the cost functional.
3.2.2 Solution of the Hamilton-Jacobi-Bellman Equation

The resulting solution is a state feedback law and closed loop control. The solution of the equation provide a sufficient condition for the solution to the corresponding optimal control problem and provides the optimal control trajectory from every initial conditions. Hence, it solves the optimal control problem for every initial condition. The most important feature of the HJB equation is that in general it is computationally intractable.

3.3 The Euler-Lagrange Equations (EL Equations)

In this section the techniques of classical variational calculus to the optimal control problem discussed in James A. Primbs [2, Chapter 2] is considered, which leads to the derivation of the Euler-Lagrange equations. The optimal control problem solved in this section is not equivalent to that solved in the previous section by dynamic programming techniques. Nevertheless, it will creat fundamental differences between the dynamic programming and calculus of variations approaches.

The Euler-Lagrange solution results by considering the optimal control problem in the framework of a constrained optimization:

$$\min_{u(.)} \int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T)).$$

subject to

$$\dot{x}(t) = f(t, x(t)) + Bu(t),$$

$$x(0) = x_0.$$  (3.3.2)

Adjoining system differential equation (3.3.2) with the cost functional by Lagrange multipliers $p(t) \in \mathbb{R}^n$. Thus the augmented cost functional is given by

$$\int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T)) + \int_0^T p(t)^T \{f(t, x(t)) + Bu(t) - \dot{x}(t)\}dt$$

After re-arranging, we obtain

$$\phi(x(T)) + \int_0^T \left\{ (x^T(t)Qx(t) + u^T(t)Ru(t)) + p(t)^T (f(t, x(t)) + Bu(t) - \dot{x}(t)) \right\} dt$$

(3.3.3)

For convenience, define a scaler function $H$, called the Hamiltonian,

$$H(t, x(t), u(t), p(t)) = (x^T(t)Qx(t) + u^T(t)Ru(t)) + p(t)^T (f(t, x(t)) + Bu(t))$$

(3.3.4)

Also, applying integration by parts to the last term of the right hand side of equation (3.3.3) yields

$$\phi(x(T)) - p^T(T)x(T) + p^T(0)x(0) + \int_0^T [H(t, x(t), u(t), p(t)) + p^T(t)x(t)] dt$$

(3.3.5)

Now the problem of determining the control function $u(t)$ that minimizes the original cost functional subject to the constraints (3.3.2) has been converted to the problem of finding stationary points of (3.3.5) without constraints.
Now consider the variations of the equation (3.3.5) with respect to $u(t)$ for the fixed times 0 and $T$

\[
\left[ \left( \frac{\partial \phi}{\partial x} - p^T(t) \right) \delta x \right]_{t-T} + [p^T(t) \delta x]_{t=0} + \int_0^T \left[ \left( \frac{\partial H}{\partial x} + p^T(t) \right) \delta x + \frac{\partial H}{\partial u} \delta u \right].
\] (3.3.6)

It will be difficult to determine the variations of $\delta x$ produced by a given $\delta u$, so we choose the multiplier functions $p(t)$ to cause the coefficients of $\delta x$ in (3.3.6) to vanish:

\[
\dot{p}(t) = - \left( \frac{\partial H}{\partial x} \right)^T, \quad 0 \leq t \leq T,
\] (3.3.7)

with boundary condition

\[
p(T) = \left( \frac{\partial \phi}{\partial x(T)} \right)^T.
\] (3.3.8)

So, the equation (3.3.5) becomes

\[
p^T(0) \delta x(0) + \int_0^T \left[ \frac{\partial H}{\partial u} \delta u \right].
\] (3.3.9)

Now, since in this problem the initial condition is given and fixed, this implies $\delta x(0) = 0$. Finally, since for a stationary point the variation must be zero for arbitrary $\delta u(t)$, the following must be satisfied

\[
\frac{\partial H}{\partial u} = 0, \quad 0 \leq t \leq T,
\] (3.3.10)

The above equations, (3.3.7), (3.3.8), and (3.3.10), plus the state equation and initial condition, represent necessary conditions for optimality known as the Euler-Lagrange equations. In summary, to find a control function $u(t)$ that produce a stationary value of the cost functional, we must solve the following differential equations:

\[
\dot{x}(t) = f(x(t)) + Bu(x(t)),
\]

\[
\dot{p}(t) = - \left( \frac{\partial H}{\partial x} \right)^T,
\] (3.3.11)

where $u(t)$ is determined by

\[
\frac{\partial H}{\partial u} = 0, \quad i.e \quad u(t) = - \frac{1}{2} R^{-1} B^T p(t).
\] (3.3.12)

The boundary conditions for (3.3.11) are split, i.e, some are given at $t = 0$ and some are given at $t = T$,

\[
x(0) = x_0,
\]

\[
p(T) = \left( \frac{\partial \phi}{\partial x(T)} \right)^T,
\] (3.3.13)

where $x(t)$ and $p(t)$ denote the solution corresponding to the optimal trajectory. Note that the Lagrange multiplier $p(t)$ is a dynamical variable that satisfies its own dynamical equation (3.3.7), the so-called costate or adjoint equation. The Euler-Lagrange equations are coupled ordinary differential equations with two-point boundary conditions. That is, they are expressed by the state equation with initial condition and co-state equation with final condition. The optimal control $u(t)$ is then generally determined in terms of $x(t)$ and $p(t)$ by using the stationarity condition given by (3.3.10). This condition guarantees a stationary point with respect to changes in $u(t)$. Finally, expression (3.3.12) does not yield an optimal control feedback law, but an optimal open-loop control (time function)
3.3.1 Solution of the Euler-Lagrange Equation

The resulting optimal trajectory is explicitly solved for as a function of time $u(t)$, not as a feedback law but as open loop control. The resulting solution is only valid for the specified initial condition $x(0)$. When a new initial condition is specified, the problem must be resolved. Since the Euler-Lagrange equations specify the conditions for the existence of a stationary point, they represent necessary conditions for an optimal trajectory.

3.4 Penalization

The penalty function method discussed in [6] involves optimizers to attack a problem such as

\[
\begin{align*}
\text{minimize} & \quad f(x) \\
\text{subject to} & \quad h_i(x) = 0, \quad i = 1, 2, \ldots, p,
\end{align*}
\] (3.4.1)

by solving instead the unconstrained approximating problem

\[
\text{minimize}(f(x) + K \sum_i^p h_i^2(x))
\] (3.4.2)

for some large positive constant $K$. For sufficiently large $K$ it can be reasoned that solution of the problem (3.4.1) and (3.4.2) will be nearly equal. The term $K \sum_i^p h_i^2(x)$ is referred to as a penalty function since in effect it assigns a specific cost to violations of the constraints. In the practical implementation of the penalty function method, we are driven on the one hand to select $K$ as large as possible to enhance the degree of approximation, and on the other hand to keep $K$ somewhat small so that when calculating gradients the penalty terms do not completely swamp out the original objective functional. A common technique is to progressively solve problem (3.4.2), the unconstrained approximation, for a sequence of $K$’s which tend to infinity. The resulting sequence of approximate solutions can then be expected to converge to the solution of the original constrained problem.
Chapter 4

Numerical Techniques for Optimal Control

4.1 Introduction

Variational techniques are used to derive the necessary conditions for optimal control. However, the variational approach to optimal control problem leads to a nonlinear two point boundary value problem, known as Euler-Lagrange equation, that can not be solved analytically to obtain the optimal control law, or even an optimal open loop control. In order to solve this two point boundary value problem, we will consider three numerical techniques, the single shooting method, the implicit Euler method and the trapezoidal method. The single shooting procedure is based on using trial initial conditions to satisfy the second boundary condition, which is the “target”. A mechanism of readjusting the initial conditions is based on the amount by which the target has been missed, is provided by Newton’s method. The implicit Euler and trapezoidal methods are based on finding approximating solution of the two point boundary value problem in terms of some discrete set of parameters. For more details refer to Robert D. Russell and Uri M. Ascher [4].

4.2 The Two Point Boundary Value Problem

Applying variational approach to optimal control problem

\[ \min_{u(t)} \int_0^T (x^T(t)Qx(t) + u^T(t)Ru(t))dt + \phi(x(T)) \] (4.2.1)

subject to

\[ \dot{x}(t) = f(t, x(t)) + Bu(t), \]
\[ x(0) = x_0 \in \mathbb{R}^n \] (4.2.2)

results in the following necessary conditions for optimality known as the Euler-Lagrange equations,

\[ \dot{x}(t) = \frac{\partial H(t, x, p)}{\partial p} = f(t, x(t)) + Bu(t), \]
\[ \dot{p}(t) = -\left(\frac{\partial H(t, x, p)}{\partial x}\right)^T = -2Qx(t) - \left(\frac{\partial f(t, x(t))}{\partial x}\right)^T p(t), \] (4.2.3)
\[ x(0) = x_0, \quad p(T) = \left(\frac{\partial \phi}{\partial x(T)}\right)^T. \]
CHAPTER 4. NUMERICAL TECHNIQUES FOR OPTIMAL CONTROL

The optimal control \( u(t) \) is obtained from

\[
0 = \frac{\partial H(t, x, p)}{\partial u} = 2u^T R + p^T (t) B,
\]

which is equal to

\[
u(t) = -\frac{1}{2} R^{-1} B^T p(t).
\]

If we use (4.2.5) in (4.2.3) we see that we have to solve the following two point boundary value problem:

\[
\begin{align*}
\dot{x}(t) &= f(t, x(t)) - \frac{1}{2} BR^{-1} B^T p(t), \\
\dot{p}(t) &= -2Qx(t) - \left( \frac{\partial f(t, x(t))}{\partial x} \right)^T p(t), \\
x(0) &= x_0, \quad p(T) = \left( \frac{\partial \phi}{\partial x(T)} \right)^T.
\end{align*}
\]

4.3 Single Shooting Method

In order to solve a two point boundary value problem (4.2.6), we make the substitution \( y = (x, p) \), so that the above problem becomes

\[
\begin{align*}
\dot{y}(t) &= \tilde{f}(t, y(t)), \\
0 &= r(y(0), y(T)) \quad (\text{boundary conditions}).
\end{align*}
\]

The boundary value problem,

\[
\begin{align*}
\dot{y}(t) &= \tilde{f}(t, y(t)), \\
0 &= r(y(0), y(T)) \quad (\text{boundary conditions}).
\end{align*}
\]

has \( 2n \) differential equations \( \dot{y} = \tilde{f}(t, y(t)) \), and \( 2n \) boundary conditions \( r \). It is therefore a well-defined problem. In this general form, the associated initial value problem is

\[
\begin{align*}
\dot{y}(t) &= \tilde{f}(t, y(t)), \\
y(0) &= y_0.
\end{align*}
\]

where \( y_0 \in \mathbb{R}^{2n} \) is an initial trial vector. We denote by \( y(t, y_0) \) the solution of (4.3.3) and assume that it exits on \([0, T]\). Then we have to find the terminal value \( y(T; y_0) \). We are looking for an initial vector \( y_0 \) such that

\[
F(y_0) := r(y_0, y(T; y_0)) = 0.
\]

Since \( r \) has as many components as \( y_0 \), we apply Newton’s method in order to solve

\[
F(y_0) = 0.
\]

We obtain \( y_0 \) as the limit of the iteration

\[
y_{0}^{k+1} = y_{0}^{k} - \left( \frac{\partial F}{\partial y_0}(y_0^k) \right)^{-1} F(y_0^k).
\]
Thereby, Jacobian matrix of the function $F(y_0)$ has to be computed,

$$\frac{\partial F}{\partial y_0}(y_0^k) = \frac{\partial r}{\partial y}(y_0^k, y(T, y_0^k)) + \frac{\partial r}{\partial y}(y_0^k, y(T, y_0^k)) \frac{\partial y}{\partial y_0}(T, y_0^k). \quad (4.3.5)$$

The Jacobian $\frac{\partial y(t; y_0)}{\partial y_0}$ exists and is continuous provided $f$ has continuous partial derivative with respect to the coordinates of $y$.

We set $M(t) = \frac{\partial y}{\partial y_0}(t, y_0)$. Then $M(t)$ satisfies the matrix differential equation

$$\dot{M}(t) = \frac{\partial f}{\partial y}(t, y(t; y_0)) M(t), \quad 0 \leq t \leq T, \quad M(0) = I. \quad (4.3.6)$$

Then, in order to simultaneously compute $F(y_0)$ and $\left(\frac{\partial F}{\partial y_0}(y_0)\right)$, we can integrate the initial value problem (4.3.3) together with that for its Jacobian,

$$\begin{cases}
\dot{y} = \tilde{f}(t, y(t)), \\
\dot{M}(t) = \frac{\partial f}{\partial y}(t, y(t; y_0)) M(t), \quad 0 \leq t \leq T, \\
y(0) = y_0, \quad M(0) = I,
\end{cases} \quad (4.3.7)$$

and get

$$F(y_0) = r(y_0, y(T); y_0), \quad \frac{\partial F}{\partial y_0}(y_0) = \frac{\partial r(y_0, y(T; y_0))}{\partial y_0} + \frac{\partial r}{\partial y(y_0, y(T; y_0))} M(T). \quad (4.3.8)$$

Although the procedure is formally straightforward, it is difficult to implement. For one thing, we may not be able to integrate (4.3.7) on the whole interval $[0, T]$; some component may blow up before we reach the end point $T$. An other problem has to do with the convergence of Newton’s method. Typically, this requires $y_0$ in (4.3.7) to be very close to the true initial vector for one of the possible solutions of the boundary value problem.

### 4.4 Implicit Euler Method

In order to avoid the difficulties arising with the single shooting method, we approximate the solution of the two point boundary value problem (4.2.6) on a uniform line mesh by Euler’s implicit method.

We set $h = T/N$ and choose the mesh points $t_k = (k-1)h$, $k = 1, \ldots, N+1$. Applying the implicit Euler method to system (4.2.6), starting for $x$ at $t_1 = 0$ and for $p$ at $t_{N+1} = T$, we obtain the following system of nonlinear equations:

$$\begin{align*}
x_{k+1} &= x_k + h(f(t_{k+1}, x_{k+1}) - BR^{-1}B^T p_{k+1}), \quad k = 1, \ldots, N, \\
x_1 &= x_0, \\
p_k &= p_{k+1} - h \left( 2Qx_k + \left( \frac{\partial f(t_k, x_k)}{\partial x} \right)^T p_k \right), \quad k = 1, \ldots, N, \\
p_{N+1} &= \left( \frac{\partial \phi}{\partial x(T)} \right)^T
\end{align*} \quad (4.4.1) \quad (4.4.2)$$

This is a system of equations for the $2Nn$-vector

$$x_k \approx x(t_k), \quad k = 2, \ldots, N+1, \quad p_k \approx p(t_k), \quad k = 1, \ldots, N.$$
Note, that equations (4.4.2) correspond to the Euler scheme for the adjoint variables starting at the end condition $p(T) = \left( \frac{\partial \phi}{\partial x(T)} \right)^T$. We set 

$$z = \text{col}(x_2, \ldots, x_{N+1}, p_1, \ldots, p_N) \in \mathbb{R}^{2N}$$

and define the functions $F_1, \ldots, F_{2N}$ by 

$$F_k(z) = x_k - x_{k+1} + h(f(t_{k+1}, x_{k+1}) - BR^{-1}B^T p_{k+1}), \quad k = 1, \ldots, N,$$

$$F_k(z) = p_{k+1} - p_k - h\left(2Q(x_k) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k\right), \quad k = N + 1, \ldots, 2N.$$ 

We obtain a solution of (4.4.1), (4.4.2) by minimizing the cost functional 

$$J(z) = \sum_{k=1}^{2N} F_k(z)^2. \quad (4.4.3)$$

### 4.5 The trapezoidal scheme

Since the implicit Euler method is only a first order method, we also tried the trapezoidal scheme, which is a 2nd order scheme. However, the trapezoidal scheme is A-stable whereas the implicit Euler scheme is A-stable and L-stable (See [12]). Instead of equations (4.4.1) and (4.4.2) we get the equations

$$x_{k+1} = x_k + \frac{h}{2}(f(t_k, x_k) + f(t_{k+1}, x_{k+1}) - BR^{-1}B^T (p_k + p_{k+1})), \quad k = 1, \ldots, N,$$

$$x_1 = x_0,$$

$$p_k = p_{k+1} - \frac{h}{2}\left(2Q(x_k + x_{k+1}) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k\right. + \left.\left(\frac{\partial f(t_{k+1}, x_{k+1})}{\partial x}\right)^T p_{k+1}\right), \quad k = 1, \ldots, N, \quad (4.5.2)$$

The functions $F_k$ are given by 

$$F_k(z) = x_k - x_{k+1} + \frac{h}{2}\left(f(t_k, x_k) + f(t_{k+1}, x_{k+1}) - BR^{-1}B^T (p_k + p_{k+1})\right)$$

for $k = 1, \ldots, N$ and by

$$F_k(z) = p_{k+1} - p_k - \frac{h}{2}\left(2Q(x_k + x_{k+1}) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k + \left(\frac{\partial f(t_{k+1}, x_{k+1})}{\partial x}\right)^T p_{k+1}\right)$$

for $k = N + 1, \ldots, 2N$. Again, the solutions of (4.5.1) and (4.5.2) are obtained by minimizing the cost functional (4.4.3).
Chapter 5

The Control Problem

5.1 Formulation as a constraint optimization problem

For a given possibly time-varying workload \( W(t) \) and given initial state \( x(0) = x_{\text{rest}} \) of the system we want to construct a control \( u(t) = (u_1(t), u_2(t))^T \) which steers the arterial systemic partial CO\(_2\)-pressure \( P_{a,CO_2} \) to the nominal value \( P_{a,CO_2}^{\text{nominal}} = 40 \) mmHg on the interval \([0, T]\), where \( T \) is given. For instance \( T = 10 \) min.

We define the vector \( x^{\text{nominal}} \) by \( x^{\text{nominal}}_i = 0, i = 1, \ldots, 14, i \neq 10, \) and \( x^{\text{nominal}}_{10} = P_{a,CO_2}^{\text{nominal}} \). The matrix \( Q = \text{diag}(q_1, \ldots, q_{14}) \) is given by \( q_{10} = 1 \) and \( q_i = 0, i \neq 10. \) In order to formulate this problem as an optimization problem we define

\[
J(u) = \frac{1}{2} \int_0^T \left( (x(t) - x^{\text{nominal}})^T Q (x(t) - x^{\text{nominal}}) + u(t)^T R u(t) \right) dt + \frac{1}{2} (x(T) - x^{\text{nominal}})^T Q (x(T) - x^{\text{nominal}}), \quad u(\cdot) \in L^2(0, T; \mathbb{R}^2),
\]

where \( x(t) \) solves (2.1.13). The \( 2 \times 2 \)-matrix \( R \) is positive definite and represents the weights for the controls. We shall take

\[
R = \text{diag}(w_1, w_2), \quad w_1, w_2 > 0.
\]

We shall deal with the control problem in the following formulation as an constraint optimization problem:

Find \( \hat{u} = \arg\min_{u \in L^2(0, T; \mathbb{R}^2)} J(u) \) under the constraint (2.1.13).

The Hamilton function for this problem is defined as

\[
H(t, x, p, u) = \frac{1}{2} (x - x^{\text{nominal}})^T Q (x - x^{\text{nominal}}) + \frac{1}{2} u^T R u + p^T (f(t, x) + Bu), \quad x, p \in \mathbb{R}^{14}, \ u \in \mathbb{R}^2, \ t \in [0, T].
\]

The co-state \( p(t) \) considered as a column vector has to satisfy the following terminal
value problem:
\[
\dot{p}(t) = -\left(\frac{\partial H}{\partial x}\right)^T = -Q(x(t) - x_{nominal}) - \left(\frac{\partial f(t, x(t))}{\partial x}\right)^T p(t),
\]
\[p(T) = p_T := Q(x(T) - P_{nominal})_{a,CO},\]
where \(x(t)\) is a solution of system (2.1.13),
\[
\dot{x}(t) = \frac{\partial H}{\partial p}(t, x(t), p(t), \hat{u}(t)) = f(t, x(t)) + B\hat{u}(t), x(0) = x^{rest}.
\]

The optimal control \(\hat{u}(\cdot)\) is determined by
\[
0 = \frac{\partial H}{\partial u}((t, x(t), p(t), \hat{u}(t)) = \hat{u}(t)^TR + p(t)^TB,
\]
which gives
\[
\hat{u}(t) = -R^{-1}B^T p(t), \quad 0 \leq t \leq T.
\]
If we use (5.1.6) in (5.1.5) we see that we have to solve the following two point boundary value problem:
\[
\dot{x}(t) = f(t, x(t)) - BR^{-1}B^T p(t),
\]
\[
\dot{p}(t) = -Q(x(t) - x_{nominal}) - \left(\frac{\partial f(t, x(t))}{\partial x}\right)^T p(t),
\]
\[x(0) = x^{rest}, \quad p(T) = Q(x(T) - x_{nominal}).\]

Using the definition of the matrices \(B\) and \(R\) we get
\[-BR^{-1}B^T p(t) = \left(0, \ldots, 0, -\frac{1}{w_1}p_9(t), 0, \ldots, 0, -\frac{1}{w_2}p_{14}(t)\right)^T, \quad 0 \leq t \leq T.\]

### 5.2 The single shooting method

In order to solve the two point boundary value problem (5.1.7) we solve the initial value problem
\[
\dot{x}(t) = f(t, x(t)) - BR^{-1}B^T p(t),
\]
\[
\dot{p}(t) = -Q(x(t) - x_{nominal}) - \left(\frac{\partial f(t, x(t))}{\partial x}\right)^T p(t),
\]
\[x(0) = x^{rest}, \quad p(0) = z.
\]

With following initial guess
\[
\begin{pmatrix}
  x(0) \\
  p(0)
\end{pmatrix} = \begin{pmatrix}
  x^{rest} \\
  z
\end{pmatrix}.
\]

The solution is
\[
\begin{pmatrix}
  x(t, x^{rest}, z) \\
  p(t, x^{rest}, z)
\end{pmatrix}.
\]

The requirements is
\[
p(T, x^{rest}, z) = p_T,
\]
i.e., $z \in \mathbb{R}^{14}$ has to be determined such that

$$p(T; x^{\text{rest}}, z) = Q(x(T; x^{\text{rest}}, z) - x^{\text{nominal}}).$$  \hfill (5.2.5)

Because of the special form of $Q$ and $x^{\text{nominal}}$, this condition is equivalent to

$$p_j(T; x^{\text{rest}}, z) = \begin{cases} x_{10}(T; x^{\text{rest}}, z) - P_{a,\text{CO}_2}^{\text{nominal}} & \text{for } j = 10, \\ 0 & \text{otherwise.} \end{cases}$$  \hfill (5.2.6)

If we define the mapping $G : \mathbb{R}^{14} \to \mathbb{R}$ by

$$G(z) = \frac{1}{2}\|p(T; x^{\text{rest}}, z) - p_T)\|^2$$

$$G(z) = \frac{1}{2} \sum_{j=1, j \neq 10}^{14} p_j(T; x^{\text{rest}}, z)^2 + \frac{1}{2} \left(p_{10}(T; x^{\text{rest}}, z) - (x_{10}(T; x^{\text{rest}}, z) - P_{a,\text{CO}_2}^{\text{nominal}})\right)^2,$$  \hfill (5.2.7)

then condition (5.2.6) is equivalent to

$$G(z) = 0.$$  \hfill (5.2.8)

In order to determine $z$, we apply Newton method for root finding, i.e., we have $z = \lim_{m \to \infty} z^m$, where

$$z^{m+1} = z^m - \left(\frac{\partial G(z)}{\partial z}(z^m)\right)^{-1} G(z^m),$$

where $\frac{\partial G(z)}{\partial z}$ is the gradient of $G(z)$,

$$\frac{\partial G(z)}{\partial z} = \sum_{j=1, j \neq 10}^{14} p_j(T; x^{\text{rest}}, z) \frac{\partial p_j(T; x^{\text{rest}}, z)}{\partial z}$$

$$+ \left(p_{10}(T; x^{\text{rest}}, z) - (x_{10}(T; x^{\text{rest}}, z) - P_{a,\text{CO}_2}^{\text{nominal}})\right)$$

$$\times \left(\frac{\partial p_{10}(T; x^{\text{rest}}, z)}{\partial z} - \frac{\partial x_{10}(T; x^{\text{rest}}, z)}{\partial z}\right).$$

With $x(t, x^{\text{rest}}, z)$, $p(t, x^{\text{rest}}, z)$ denoting the solution of (5.2.1), we let $v(t)$ and $w(t)$ be the corresponding gradients (with respect to $z$),

$$v(t) = \frac{\partial x(t, x^{\text{rest}}, z)}{\partial z} \quad 0 \leq t \leq T$$

$$w(t) = \frac{\partial p(t, x^{\text{rest}}, z)}{\partial z}$$  \hfill (5.2.8)

where the dependence on $z$ is suppressed in the notation for $v$ and $w$. Knowing that differentiation with respect to $t$ and $z$ may be interchanged, we can write

$$\frac{\partial G(z)}{\partial z} = \sum_{j=1, j \neq 10}^{14} p_j(T; x^{\text{rest}}, z) w_j(T)$$

$$+ \left(p_{10}(T; x^{\text{rest}}, z) - (x_{10}(T; x^{\text{rest}}, z) - P_{a,\text{CO}_2}^{\text{nominal}})\right)$$

$$\times \left(w_{10}(T) - v_{10}(T)\right)$$
Furthermore, \( x(t, x^{\text{rest}}, z), p(t, x^{\text{rest}}, z) \) satisfy, identically in \( z \)

\[
\dot{x}(t, x^{\text{rest}}, z) = f(t, x^{\text{rest}}, z) - BR^{-1}B^T p(t, x^{\text{rest}}, z),
\]

\[
\dot{p}(t, x^{\text{rest}}, z) = -Q(x(t, x^{\text{rest}}, z) - x^{\text{nominal}}) - \left( \frac{\partial f(t, x^{\text{rest}}, z)}{\partial x} \right)^T p(t, x^{\text{rest}}, z),
\]  

(5.2.9)

from which, by differentiation with respect to \( z \) and interchanging differentiation with
respect to \( t \) and \( z \) where necessary, one gets

\[
\dot{v}(t) = \frac{\partial f(t, x^{\text{rest}}, z)}{\partial z} - BR^{-1}B^T w
\]

\[
= \frac{\partial f(t, x^{\text{rest}}, z)}{\partial x} v(t) - BR^{-1}B^T w
\]

\[
\dot{w}(t) = -\left( \frac{\partial^2 f(t, x^{\text{rest}}, z)}{\partial x^2} v(t) \right)^T p(t, x^{\text{rest}}, z)
\]

\[
- \frac{\partial f(t, x^{\text{rest}}, z)}{\partial x} w,
\]

(5.2.10)

\[
v(0) = 0, \quad w(0) = I, \quad (14 \times 14 \text{ identity matrix}).
\]

Then, in order to simultaneously compute \( G(z) \) and \( \frac{\partial G(z)}{\partial z} \), we can integrate the initial
value problem (5.2.1) adjointed with that for its gradient,

\[
\dot{x}(t) = f(t, x) - BR^{-1}B^T p(t),
\]

\[
\dot{p}(t) = -Q(x(t) - \bar{x}) - \left( \frac{\partial f(t, x(t))}{\partial x} \right)^T p(t),
\]

\[
\dot{v}(t) = \frac{\partial f(t, x^{\text{rest}}, z)}{\partial z} - BR^{-1}B^T w
\]

\[
= \frac{\partial f(t, x^{\text{rest}}, z)}{\partial x} v_k(t) - BR^{-1}B^T w,
\]

(5.2.11)

\[
\dot{w}(t) = -\left( \frac{\partial^2 f(t, x^{\text{rest}}, z)}{\partial x^2} v(t) \right)^T p(t, x^{\text{rest}}, z)
\]

\[
- \frac{\partial f(t, x^{\text{rest}}, z)}{\partial x} w,
\]

\[
v(0) = 0, \quad w(0) = I, \quad x(0) = x^{\text{rest}}, \quad p(T) = p_T = Q(x(T) - \bar{x}).
\]

### 5.3 Implicit Euler method and trapezoidal method

As we can see from the results of Section 5.5.1 the single shooting method fails to provide
a solution to the two-point boundary value problem (5.1.7). The obvious reason for this
is the stiffness of the equations for the adjoint variables. Therefore we tried to obtain the
solution of (5.1.7) by using the implicit Euler scheme and the trapezoidal scheme, both
schemes being A-stable (see [12]). As we shall see, the attempt with the implicit Euler
scheme is successful whereas the trapezoidal scheme tended to show oscillatory behavior
of the approximations.
CHAPTER 5. THE CONTROL PROBLEM

5.3.1 The implicit Euler scheme

We set \( h = T/N \) and choose the mesh points \( t_k = (k-1)h, \ k = 1, \ldots, N + 1 \). Applying the implicit Euler method to system (5.1.7) we obtain the following system of nonlinear equations

\[
\begin{align*}
    x_{k+1} &= x_k + h(f(t_{k+1}, x_{k+1}) - BR^{-1}B^Tp_{k+1}), \quad k = 1, \ldots, N, \\
    x_1 &= x^{\text{rest}}, \\
    p_k &= p_{k+1} + h\left(Q(x_k - x^{\text{nominal}}) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k\right), \quad k = 1, \ldots, N, \\
    p_{N+1} &= Q(x_{N+1} - x^{\text{nominal}})
\end{align*}
\]

for the \( 2N \times 14 \) variables \( x_k \approx x(t_k), \ k = 2, \ldots, N + 1, \ p_k \approx p(t_k), \ k = 1, \ldots, N \).

Note, that equations (5.3.2) correspond to the Euler scheme for the adjoint variables starting at the end condition \( p(T) = -Q(x(T) - x^{\text{nominal}}) \). We set

\[
    z = \text{col}(x_2, \ldots, x_{N+1}, p_1, \ldots, p_N) \in \mathbb{R}^{14 \cdot 2N}
\]

and define the functions \( F_1, \ldots, F_{2N} \) by

\[
\begin{align*}
    F_k(z) &= x_k - x_{k+1} + h\left(f(t_{k+1}, x_{k+1}) - BR^{-1}B^Tp_{k+1}\right), \quad k = 1, \ldots, N, \\
    F_k(z) &= p_{k+1} - p_k + h\left(Q(x_k - x^{\text{nominal}}) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k\right), \quad k = N + 1, \ldots, 2N.
\end{align*}
\]

We obtain a solution of (5.3.1), (5.3.2) by minimizing the cost functional

\[
    J(z) = \sum_{k=1}^{2N} F_k(z)^2.
\]

5.3.2 The trapezoidal scheme

In this case we get instead of equations (5.3.1) and (5.3.2) the equations

\[
\begin{align*}
    x_{k+1} &= x_k + \frac{h}{2}\left(f(t_k, x_k) + f(t_{k+1}, x_{k+1}) - BR^{-1}B^T(p_k + p_{k+1})\right), \quad k = 1, \ldots, N, \\
    x_1 &= x^{\text{rest}}, \\
    p_k &= p_{k+1} + \frac{h}{2}\left(Q(x_k + x_{k+1} - 2x^{\text{nominal}}) + \left(\frac{\partial f(t_k, x_k)}{\partial x}\right)^T p_k \\
    &\quad + \left(\frac{\partial f(t_{k+1}, x_{k+1})}{\partial x}\right)^T p_{k+1}\right), \quad k = 1, \ldots, N, \\
    p_{N+1} &= -Q(x_{N+1} - x^{\text{nominal}}).
\end{align*}
\]

The functions \( F_k \) are given by

\[
    F_k(z) = x_k - x_{k+1} + \frac{h}{2}\left(f(t_k, x_k) + f(t_{k+1}, x_{k+1}) - BR^{-1}B^T(p_k + p_{k+1})\right)
\]
CHAPTER 5. THE CONTROL PROBLEM

for \( k = 1, \ldots, N \) and by

\[
F_k(z) = p_{k+1} - p_k + \frac{h}{2} \left( Q(x_k + x_{k+1} - 2x_{\text{nominal}}) + \left( \frac{\partial f(t_k, x_k)}{\partial x} \right) p_k + \left( \frac{\partial f(t_{k+1}, x_{k+1})}{\partial x} \right) p_{k+1} \right)
\]

for \( k = N + 1, \ldots, 2N \). Again, the solutions of \((5.3.1)\) and \((5.3.2)\) are obtained by minimizing the cost functional \((5.3.3)\).

5.4 Penalization

The simulations with the implicit Euler scheme (see Section 5.3.1) as presented in Section 5.8.3, Figures 5.23 – 5.26, show that the values for some state variables after about 3 minutes are to small in comparison to the equilibrium values for exercise as given in Table 2.2. For instance, we have \( H \sim 94 \) instead of \( H = 107 \) or \( \dot{V}_A \sim 17 \) instead of \( \dot{V}_A = 20 \).

This led to a modification of our control approach which we are going to describe in this section. The main task of the cardiovascular-respiratory system in case of an imposed ergometric workload is to satisfy the metabolic needs of tissues, i.e., to provide the necessary flow of oxygen to the tissues and also to remove carbon dioxide at the rate it is produced. Completely matching the rates at which \( \text{O}_2 \) is needed and \( \text{CO}_2 \) is produced, according to \((2.1.10)\) and \((2.1.11)\),

\[
MR_{\text{CO}_2} + F_s(K_{\text{CO}_2} P_{\text{a,CO}_2} + k_{\text{CO}_2} - C_{\text{v,CO}_2}) = 0,
- MR_{\text{O}_2} + F_s(K_{\text{a,1}} \left( 1 - e^{-K_{\text{a,2}} P_{\text{a,O}_2}} \right)^2 - C_{\text{v,O}_2}) = 0.
\]

\((5.4.1)\)

Since a complete matching as expressed by \((5.4.1)\) seems to be unrealistic, we did not consider \((5.4.1)\) as a constraint for minimizing the cost functional \((5.3.3)\). Instead we use a penalization approach and minimize the cost functional

\[
J_{\text{pen}}(z) = J(z) + \alpha G_{\text{O}_2}(z) + \beta G_{\text{CO}_2}(z), \quad \alpha > 0, \beta > 0,
\]

\((5.4.2)\)

where the functions \( G_{\text{O}_2}(z) \) and \( G_{\text{CO}_2}(z) \) are defined as follows:

\[
G_{\text{O}_2}(z) = \sum_{j=1}^{N+1} \left( -MR_{\text{O}_2}(t_j) + F_s(t_j) \left( K_{\text{a,1}} \left( 1 - e^{-K_{\text{a,2}} x_j(11)} \right)^2 - x_j(13) \right) \right)^2,
\]

\[
G_{\text{CO}_2}(z) = \sum_{j=1}^{N+1} \left( MR_{\text{CO}_2}(t_j) + F_s(t_j) \left( K_{\text{CO}_2} x_j(10) + k_{\text{CO}_2} - x_j(12) \right) \right)^2,
\]

Here we use the MatLab notation \( x_j(k) = (x_j)_k \). This penalization approach also means that, dependent on the values for the coefficients \( \alpha \) and \( \beta \), the two-point boundary value problem \((5.1.7)\) is not precisely solved but only approximately. In view of the fact that our model like any other model is only an approximation to the real system this should not create a serious problem. For \( \alpha = 20 \) and \( \beta = 5 \) we now have \( \dot{V}_A \sim 20.6 \), but still \( H \sim 94 \). Introducing the penalty terms in general improves the behavior of the respiratory part and not so much that of the cardiovascular part. However, we should have in mind that we are not doing any parameter identification in this thesis.
5.5 Numerical Computation with Matlab

The numerical computations for solving the control problem are made with Matlab 2009b. In equation (2.2.17), parameters used for the simulation are given. Parameters values can be taken either from Kappel and Peer [11] or from literature. The following steps are taken to compute the state variables, adjoint variables and controls. First, the equilibrium rest for $W = 0$, as initial value for the state system are computed. That is

$$0 = f(x_{\text{rest}}; 0),$$

(5.5.1)

The computed equilibrium values for the equilibrium rest are given in Table 2.1. To solve the two point boundary value problem (5.1.6), first the single shooting approach was applied, but we were not able to integrate the system on the whole interval $[0, T]$, because some components blow up before reaching the end point $T$. Secondly, the implicit Euler method and the trapezoidal method were applied to the two point boundary value problem (5.1.6), which involves the minimization of the cost functional (5.4.2) involving the penalization terms.

In order to solve the two point boundary value problem, we need to choose values for the weights of controls in the cost functional plus the values for penalty coefficients $\alpha$ and $\beta$ involving in the equation (5.4.2). However, these weights do not have a physiological meaning and for this reason they can not be determined by measurements. Their values need to be obtained by parameter identification, which will be a concern of future research. For the time being, we will choose the weights for the controls equal to .01 and penalty coefficients $\alpha$ and $\beta$ equal to 20 and 5 respectively. The next sections provides simulation results.

5.6 Simulation results for the Single Shooting method

The time courses of state and adjoint variables for constant work load $W=75$ Watt are depicted in Figures 5.1 - 5.2.
In Figures 5.1 – 5.2 we show typical results obtained with the single shooting method for a constant workload (= 75 Watt). Each time we did choose some initial value \( z = p(0) \) we could not obtain a solution of (5.2.1) on the given time interval \([0, T]\), because some of the adjoint variables had a vertical asymptote as \( t \uparrow t_0 \) for some \( t_0 < T \). The reason seems to be the extreme stiffness of the adjoint equation near \( t = 0 \) (compare also section 5.8.3).

5.7 Simulation results for the trapezoidal scheme
Figure 5.4: Dynamics of heart rate $H$ and alveolar ventilation $V_A$.

Figure 5.5: Dynamics of the arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$.

Figure 5.6: Dynamics of blood pressures in the four cardiovascular compartments.
In Figures 5.3 – 5.6 we show the results we obtained with the trapezoidal scheme for a constant workload (= 75 Watt) with $N = 80$, $\alpha = 20$ and $\beta = 5$, which were also the standard parameters for the implicit Euler scheme. We can see that some of the states show an oscillatory behavior near $t = 0$. This is due to the fact that the equations of system (5.1.7) are very stiff in a neighborhood of $t = 0$, because at $t = 0$ we have a jump in the workload from 0 Watt to 75 Watt. The implicit Euler scheme does not show these oscillations, a reason being that the implicit Euler scheme is not only A-stable but also L-stable in contrast to the trapezoidal rule which is only A-stable.

5.7.1 Simulation results for the trapezoidal schemes with time varying workload

The time courses of some variables for time varying work load $W = 37.5 \sin(\pi t) + 37.5$ Watt and $\alpha = 20$, $\beta = 5$, $N = 80$ are depicted in Figures 5.7 - 5.10.
Figure 5.9: Dynamics of the arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$.

Figure 5.10: Dynamics of blood pressures in the four cardiovascular compartments.
5.8 Simulation results for the implicit Euler scheme

The time courses of some variables for constant work load $W=75$ Watt and $\alpha = 20, \beta = 5, N = 80$ are depicted in Figures 5.11 – 5.14. Except for $P_{as}$ and $H$ we see a very good coincidence of the values for the state variables for $t = 3$ with equilibrium values given in Table 2.2. The values for $P_{as}$ and $H$ which we can see in the figures are too low. However, we have in mind that no parameter identification for this model has been undertaken. we just took the parameter values available in [11] respectively in [5].
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Figure 5.13: Dynamics of arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$.

Figure 5.14: Dynamics of blood pressures in the four cardiovascular compartments.
5.8.1 Simulation results for the implicit Euler scheme with $N=20$

The time courses of some variables for constant work load $W = 75$ Watt and $\alpha = 20, \beta = 5, N = 20$ are depicted in Figures 5.15 - 5.18.

![Approximation for the controls](image1)

Figure 5.15: Dynamics of the controls.

![Approximation for $H$ and $\dot{V}_A$](image2)

Figure 5.16: Dynamics of heart rate $H$ and alveolar ventilation $\dot{V}_A$. 
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Figure 5.17: Dynamics of arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$.

Figure 5.18: Dynamics of blood pressures in the four cardiovascular compartments.
5.8.2 Simulation results for the implicit Euler scheme with N=40

The time courses of some variables for constant work load $W = 75$ Watt and $\alpha = 20, \beta = 5, N = 40$ are depicted in Figures 5.19 - 5.22.

Figure 5.19: Dynamics of the controls.

Figure 5.20: Dynamics of heart rate $H$ and alveolar ventilation $\dot{V}_A$. 
Approximation for $P_{a,CO_2}$

Approximation for $P_{a,O_2}$

Approximation for $P_{as}$

Approximation for $P_{va}$

Approximation for $P_{ap}$

Approximation for $P_{vp}$

Figure 5.21: Dynamics of arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$.

Figure 5.22: Dynamics of blood pressures in the four cardiovascular compartments.

In Figures 5.11 – 5.22 we show the approximations for some state variable with $\alpha = 20$, $\beta = 5$ and $N = 20, 40, 80$ in order to demonstrate convergence of the implicit
Euler scheme.

5.8.3 Simulation results for the implicit Euler scheme with $\alpha = 0$, $\beta = 0$

The time courses of some variables for constant work load $W = 75$ Watt and $\alpha = 0$, $\beta = 0$, $N = 80$ are depicted in Figures 5.23 - 5.27.

Figure 5.23: Dynamics of the controls.

Figure 5.24: Dynamics of heart rate $H$ and alveolar ventilation $\dot{V}_A$. 
Figure 5.25: Dynamics of arterial gas concentrations $P_{a, CO_2}$ and $P_{a, O_2}$.

Figure 5.26: Dynamics of blood pressures in the four cardiovascular compartments.
Figure 5.27: Dynamics of some of the adjoint variables

The simulation results for the adjoint variables (see Figure 5.27) show a considerable amount of stiffness of the corresponding differential equations near $t = 0$, which explains why we should expect difficulties when solving the adjoint equations starting at $t = 0$. This also explains the oscillatory behavior of the approximations obtained by the trapezoidal rule.

5.8.4 Simulation results for the implicit Euler scheme with time varying workload

The time courses of some variables for time varying work load $W = 37.5 \sin(\pi t) + 37.5$ Watt and $\alpha = 20, \beta = 5, N = 80$ are depicted in Figures 5.28 - 5.31.
Figure 5.28: Dynamics of the controls.

Figure 5.29: Dynamics of heart rate $H$ and alveolar ventilation $V_A$.

Figure 5.30: Dynamics of arterial gas concentrations $P_{a,CO_2}$ and $P_{a,O_2}$. 
Figure 5.31: Dynamics of blood pressures in the four cardiovascular compartments.
Chapter 6

Conclusion And Future Work

In this chapter, we summarize the work presented in this thesis and list some possible future research direction that are relevant to this work.

6.1 Conclusion

In this work, an optimal control for the cardiovascular and the respiratory system under a time varying ergometric work load as a model for the so called baroreceptor loop was developed. The important point in this work is the fact that it is not assumed that the system tends to an equilibrium, which usually was assumed in this context. The calculus of variation techniques were used to derive the necessary conditions for optimal control. However, the variational approach to optimal control problem leads to a nonlinear two point boundary value problem, known as Euler-Lagrange equation, that can not be solved analytically to obtain the optimal control law, or even an optimal open loop control. In order to solve this two point boundary value problem, we considered three numerical techniques, the single shooting method, the implicit Euler method and the trapezoidal method. The single shooting failed to provide a solution to the two-point boundary value problem. The obvious reason for this was the stiffness of the equations for the adjoint variables. Therefore, we tried to obtain the solution of (5.1.7) by using the implicit Euler scheme and the trapezoidal scheme, both schemes being A-stable (see [12]). As we saw, the attempt with the implicit Euler scheme was successful whereas the trapezoidal scheme tended to show oscillatory behavior of the approximations. Also the results presented in this thesis show that the underlying model describes the interactions between the cardiovascular and the respiratory state variables in a rather satisfactory way. There are various details which need improvement and further investigations.

6.2 Future Work

In this work we have laid down the ground work for the optimal control of the cardiovascular and the respiratory system under a time varying ergometric work load. Below we list three areas in which further improvement and investigations can be made.

6.2.1 Modelling: Improvement in the Combined Model

- Parameter identification can be made with the help of experimental data.
The brain compartment can be included in the combined model (cf., e.g., Fincham and Tehrani [14] or Grodins[13]).

There can be improved model for the process of metabolic autoregulation, which takes into account a more complex relationship between oxygen and vessel resistance.

The role of decrease of vessel resistance in response to an increased blood flow can be considered in detail.

The role of the sympathetic and para-sympathetic nervous system on the compliances of the venous compartments can be considered.

### 6.2.2 Control Aspects:

Optimal control problem leads to a nonlinear two point boundary value problem (5.1.7), known as Euler-Lagrange equation, that can be solved analytically to obtain the optimal control law. Which means

- Designing a feedback control of the cardiovascular and the respiratory system under a time varying ergometric work load.

And also pH driven control of combined model with time varying work load can be considered.

### 6.2.3 Numerical Analysis:

Considering the fact that the single shooting method fails to provide a solution to the two-point boundary value problem (5.1.7), the following alternatives should be investigated:

- Multiple shooting method
- Spline interpolation method
Appendix A

A.1 Derivatives with respect to the state variables

In order to use system (5.1.7) we have to compute the derivatives of the function \( f(t, x(t)) = (f_1(t, x(t)), \ldots, f_{14}(t, x(t)))^T \) with respect to the state variables (2.1.14).

A.1.1 Derivatives with respect to \( P_{as} \)

With the derivatives
\[
\frac{\partial F_s}{\partial P_{as}} = \frac{1}{R_s},
\]
\[
\frac{\partial Q_\ell}{\partial P_{as}} = -\frac{c_\ell a_\ell(H)^2 P_{vp} S_\ell H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2}
\]
we get
\[
\frac{\partial f_1}{\partial P_{as}} = \frac{1}{c_{as}} \left( \frac{\partial Q_\ell}{\partial P_{as}} - \frac{\partial F_s}{\partial P_{as}} \right) = -\frac{1}{c_{as}} \left( \frac{c_\ell a_\ell(H)^2 P_{vp} S_\ell H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2} + \frac{1}{R_s} \right),
\]
\[
\frac{\partial f_2}{\partial P_{as}} = \frac{1}{c_{vs}} \frac{\partial F_s}{\partial P_{as}} = \frac{1}{c_{vs}} \frac{1}{R_s},
\]
\[
\frac{\partial f_3}{\partial P_{as}} = 0,
\]
\[
\frac{\partial f_4}{\partial P_{as}} = -\frac{1}{c_{vp}} \frac{\partial Q_\ell}{\partial P_{as}} = \frac{1}{c_{vp}} \frac{c_\ell a_\ell(H)^2 P_{vp} S_\ell H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2},
\]
\[
\frac{\partial f_5}{\partial P_{as}} = \frac{\partial f_6}{\partial P_{as}} = \frac{\partial f_7}{\partial P_{as}} = \frac{\partial f_8}{\partial P_{as}} = \frac{\partial f_9}{\partial P_{as}} = \frac{\partial f_{10}}{\partial P_{as}} = \frac{\partial f_{11}}{\partial P_{as}} = 0,
\]
\[
\frac{\partial f_{12}}{\partial P_{as}} = \frac{1}{V_{T,CO_2}} (K_{CO_2} P_{a,CO_2} + k_{CO_2} - C_{v,CO_2}) \frac{\partial F_s}{\partial P_{as}}
\]
\[
= \frac{1}{V_{T,CO_2} R_s} (K_{CO_2} P_{a,CO_2} + k_{CO_2} - C_{v,CO_2}),
\]
\[
\frac{\partial f_{13}}{\partial P_{as}} = \frac{1}{V_{T,O_2} R_s} \left( K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2 - C_{v,O_2} \right) \frac{\partial F_s}{\partial P_{as}}
\]
\[ \frac{\partial f_{14}}{\partial P_{\text{vs}}} = 0. \]

**A.1.2 Derivatives with respect to \( P_{\text{vs}} \)**

Using

\[ \frac{\partial F_s}{\partial P_{\text{vs}}} = \frac{1}{R_s}, \]
\[ \frac{\partial Q_r}{\partial P_{\text{vs}}} = \frac{c_t a_t(H) S_H}{a_t(H) P_{\text{ap}} + k_t(H) S_t}, \]

we obtain

\[ \begin{align*}
\frac{\partial f_1}{\partial P_{\text{vs}}} &= -\frac{1}{c_a} \frac{\partial F_s}{\partial P_{\text{vs}}} = \frac{1}{c_a R_s}, \\
\frac{\partial f_2}{\partial P_{\text{vs}}} &= \frac{1}{c_v} \left( \frac{\partial F_s}{\partial P_{\text{vs}}} - \frac{\partial Q_r}{\partial P_{\text{vs}}} \right) = -\frac{1}{c_v} \left( \frac{1}{R_s} + \frac{c_t a_t(H) S_H}{a_t(H) P_{\text{ap}} + k_t(H) S_t} \right), \\
\frac{\partial f_3}{\partial P_{\text{vs}}} &= \frac{1}{c_{\text{ap}}} \frac{\partial Q_r}{\partial P_{\text{vs}}} = \frac{1}{c_{\text{ap}}} \frac{c_t a_t(H) S_H}{a_t(H) P_{\text{ap}} + k_t(H) S_t}, \\
\frac{\partial f_4}{\partial P_{\text{vs}}} &= \frac{\partial f_5}{\partial P_{\text{vs}}} = \frac{\partial f_6}{\partial P_{\text{vs}}} = \frac{\partial f_7}{\partial P_{\text{vs}}} = \frac{\partial f_8}{\partial P_{\text{vs}}} = \frac{\partial f_9}{\partial P_{\text{vs}}} = \frac{\partial f_{10}}{\partial P_{\text{vs}}} = \frac{\partial f_{11}}{\partial P_{\text{vs}}} = 0, \\
\frac{\partial f_{12}}{\partial P_{\text{vs}}} &= \frac{1}{V_{T,\text{CO}_2}} \left( K_{\text{CO}_2 P_{\text{a,CO}_2}} + k_{\text{CO}_2} - C_{V,\text{CO}_2} \right) \frac{\partial F_s}{\partial P_{\text{vs}}} \\
&= -\frac{1}{V_{T,\text{CO}_2}} \frac{1}{R_s} \left( K_{\text{CO}_2 P_{\text{a,CO}_2}} + k_{\text{CO}_2} - C_{V,\text{CO}_2} \right), \\
\frac{\partial f_{13}}{\partial P_{\text{vs}}} &= \frac{1}{V_{T,\text{O}_2}} \left( K_{a,1} \left( 1 - e^{-K_{a,2} P_{\text{o}_2}} \right)^2 - C_{V,O_2} \right) \frac{\partial F_s}{\partial P_{\text{vs}}} \\
&= -\frac{1}{V_{T,\text{O}_2}} \frac{1}{R_s} \left( K_{a,1} \left( 1 - e^{-K_{a,2} P_{\text{o}_2}} \right)^2 - C_{V,O_2} \right), \\
\frac{\partial f_{14}}{\partial P_{\text{vs}}} &= 0.
\end{align*} \]

**A.1.3 Derivatives with respect to \( P_{\text{ap}} \)**

We have

\[ \frac{\partial F_p}{\partial P_{\text{ap}}} = \frac{1}{R_p}, \]
\[ \frac{\partial Q_r}{\partial P_{\text{ap}}} = -\frac{c_t a_t(H)^2 P_{\text{vs}} S_H}{\left( a_t(H) P_{\text{ap}} + k_t(H) S_t \right)^2}, \]

which implies

\[ \frac{\partial f_1}{\partial P_{\text{ap}}} = 0, \]
\[
\frac{\partial f_2}{\partial P_{ap}} = -\frac{1}{c_{vs}} \frac{\partial Q_{\ell}}{\partial P_{ap}} = \frac{1}{c_{vs}} \frac{c_t a_t(H)^2 P_{as} S_{\ell} H}{(a_t(H) P_{ap} + k_t(H) S_{\ell})^2}, \\
\frac{\partial f_3}{\partial P_{ap}} = \frac{1}{c_{ap}} \left( \frac{\partial Q_{\ell}}{\partial P_{ap}} - \frac{\partial F_p}{\partial P_{ap}} \right) = -\frac{1}{c_{ap}} \left( \frac{c_t a_t(H)^2 P_{as} S_{\ell} H}{(a_t(H) P_{ap} + k_t(H) S_{\ell})^2} + \frac{1}{R_p} \right), \\
\frac{\partial f_4}{\partial P_{ap}} = \frac{1}{c_v p} \frac{\partial F_p}{\partial P_{ap}} = \frac{1}{c_v p R_p}, \\
\frac{\partial f_5}{\partial P_{ap}} = \frac{\partial f_6}{\partial P_{ap}} = \frac{\partial f_7}{\partial P_{ap}} = \frac{\partial f_8}{\partial P_{ap}} = \frac{\partial f_9}{\partial P_{ap}} = 0, \\
\frac{\partial f_{10}}{\partial P_{ap}} = \frac{863}{V_{\alpha,CO_2}} \left( C_{V,CO_2} - K_{CO_2} P_{a,CO_2} - k_{CO_2} \right) \frac{\partial F_p}{\partial P_{ap}} \\
= \frac{863}{V_{\alpha,CO_2} R_p} \left( C_{V,CO_2} - K_{CO_2} P_{a,CO_2} - k_{CO_2} \right), \\
\frac{\partial f_{11}}{\partial P_{ap}} = \frac{863}{V_{\alpha,O_2}} \left( C_{V,O_2} - K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2 \right) \frac{\partial F_p}{\partial P_{ap}} \\
= \frac{863}{V_{\alpha,O_2} R_p} \left( C_{V,O_2} - K_{a,1} \left( 1 - e^{-K_{a,2} P_{a,O_2}} \right)^2 \right), \\
\frac{\partial f_{12}}{\partial P_{ap}} = \frac{\partial f_{13}}{\partial P_{ap}} = \frac{\partial f_{14}}{\partial P_{ap}} = 0.
\]

### A.1.4 Derivatives with respect to \(P_{vp}\)

Using

\[
\frac{\partial F_p}{\partial P_{vp}} = -\frac{1}{R_p}, \\
\frac{\partial Q_{\ell}}{\partial P_{vp}} = \frac{c_t a_t(H) S_\ell H}{a_t(H) P_{as} + k_\ell(H) S_\ell},
\]

we get

\[
\frac{\partial f_1}{\partial P_{vp}} = \frac{1}{c_{as}} \frac{\partial Q_{\ell}}{\partial P_{vp}} = \frac{1}{c_{as}} \frac{c_t a_t(H) S_\ell H}{a_t(H) P_{as} + k_\ell(H) S_\ell}, \\
\frac{\partial f_2}{\partial P_{vp}} = 0, \\
\frac{\partial f_3}{\partial P_{vp}} = -\frac{1}{c_{ap}} \frac{\partial F_p}{\partial P_{vp}} = \frac{1}{c_{ap} R_p}, \\
\frac{\partial f_4}{\partial P_{vp}} = \frac{1}{c_v p} \left( \frac{\partial F_p}{\partial P_{vp}} - \frac{\partial Q_{\ell}}{\partial P_{vp}} \right) = -\frac{1}{c_v p} \left( \frac{1}{R_p} + \frac{c_t a_t(H) S_\ell H}{a_t(H) P_{as} + k_\ell(H) S_\ell} \right), \\
\frac{\partial f_5}{\partial P_{vp}} = \frac{\partial f_6}{\partial P_{vp}} = \frac{\partial f_7}{\partial P_{vp}} = \frac{\partial f_8}{\partial P_{vp}} = \frac{\partial f_9}{\partial P_{vp}} = 0, \\
\frac{\partial f_{10}}{\partial P_{vp}} = \frac{863}{V_{\alpha,CO_2}} \left( C_{V,CO_2} - K_{CO_2} P_{a,CO_2} - k_{CO_2} \right) \frac{\partial F_p}{\partial P_{vp}} \\
= -\frac{863}{V_{\alpha,CO_2} R_p} \left( C_{V,CO_2} - K_{CO_2} P_{a,CO_2} - k_{CO_2} \right),
\]
\[
\frac{\partial f_{11}}{\partial P_{vp}} = 863 \frac{V_{A,O}}{V_{A,O_2}} \left( C_{v,O_2} - K_{a,1} \left( 1 - e^{-K_{a,2} P_{as,O_2}} \right) \right) \frac{\partial F_p}{\partial P_{vp}}
\]
\[
\frac{\partial f_{12}}{\partial P_{vp}} = \frac{\partial f_{13}}{\partial P_{vp}} = \frac{\partial f_{14}}{\partial P_{vp}} = 0.
\]

A.1.5 Derivatives with respect to \( S_\ell \)

We have
\[
\frac{\partial Q_\ell}{\partial S_\ell} = \frac{c_\ell a_\ell(H)^2 P_{ap} P_{vp} H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2}
\]
and get
\[
\frac{\partial f_1}{\partial S_\ell} = \frac{1}{c_{as}} \frac{\partial Q_\ell}{\partial S_\ell} = \frac{1}{c_{as}} \frac{c_\ell a_\ell(H)^2 P_{ap} P_{vp} H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2},
\]
\[
\frac{\partial f_2}{\partial S_\ell} = \frac{\partial f_3}{\partial S_\ell} = 0,
\]
\[
\frac{\partial f_4}{\partial S_\ell} = -\frac{1}{c_{vp}} \frac{\partial Q_\ell}{\partial S_\ell} = -\frac{1}{c_{vp}} \frac{c_\ell a_\ell(H)^2 P_{ap} P_{vp} H}{(a_\ell(H) P_{as} + k_\ell(H) S_\ell)^2},
\]
\[
\frac{\partial f_5}{\partial S_\ell} = 0,
\]
\[
\frac{\partial f_6}{\partial S_\ell} = -\alpha_\ell,
\]
\[
\frac{\partial f_7}{\partial S_\ell} = \frac{\partial f_8}{\partial S_\ell} = \frac{\partial f_9}{\partial S_\ell} = \frac{\partial f_{10}}{\partial S_\ell} = \frac{\partial f_{11}}{\partial S_\ell} = \frac{\partial f_{12}}{\partial S_\ell} = \frac{\partial f_{13}}{\partial S_\ell} = \frac{\partial f_{14}}{\partial S_\ell} = 0.
\]

A.1.6 Derivatives with respect to \( \sigma_\ell \)

These derivatives are given by
\[
\frac{\partial f_1}{\partial \sigma_\ell} = \frac{\partial f_2}{\partial \sigma_\ell} = \frac{\partial f_3}{\partial \sigma_\ell} = \frac{\partial f_4}{\partial \sigma_\ell} = 0,
\]
\[
\frac{\partial f_5}{\partial \sigma_\ell} = 1,
\]
\[
\frac{\partial f_6}{\partial \sigma_\ell} = -\gamma_\ell,
\]
\[
\frac{\partial f_7}{\partial \sigma_\ell} = \frac{\partial f_8}{\partial \sigma_\ell} = \frac{\partial f_9}{\partial \sigma_\ell} = \frac{\partial f_{10}}{\partial \sigma_\ell} = \frac{\partial f_{11}}{\partial \sigma_\ell} = \frac{\partial f_{12}}{\partial \sigma_\ell} = \frac{\partial f_{13}}{\partial \sigma_\ell} = \frac{\partial f_{14}}{\partial \sigma_\ell} = 0.
\]

A.1.7 Derivatives with respect to \( S_r \)

Using
\[
\frac{\partial Q_r}{\partial S_r} = \frac{c_r a_r(H)^2 P_{ap} P_{vs} H}{(a_r(H) P_{ap} + k_r(H) S_r)^2}
\]
we obtain
\[ \frac{\partial f_1}{\partial S_r} = 0, \]
\[ \frac{\partial f_2}{\partial S_r} = -\frac{1}{c_{vs}} \frac{\partial Q}{\partial S_r} = -\frac{1}{c_{vs}} \frac{c_t a_t(H)^2 P_{ap} P_{vs} H}{(a_t(H) P_{ap} + k_t(H) S_t)^2}, \]
\[ \frac{\partial f_3}{\partial S_r} = \frac{1}{c_{ap}} \frac{\partial Q}{\partial S_r} = \frac{1}{c_{ap}} \frac{c_t a_t(H)^2 P_{ap} P_{vs} H}{(a_t(H) P_{ap} + k_t(H) S_t)^2}, \]
\[ \frac{\partial f_4}{\partial S_r} = \frac{\partial f_5}{\partial S_r} = \frac{\partial f_6}{\partial S_r} = \frac{\partial f_7}{\partial S_r} = 0, \]
\[ \frac{\partial f_8}{\partial S_r} = \frac{\partial f_9}{\partial S_r} = \frac{\partial f_{10}}{\partial S_r} = \frac{\partial f_{11}}{\partial S_r} = \frac{\partial f_{12}}{\partial S_r} = \frac{\partial f_{13}}{\partial S_r} = \frac{\partial f_{14}}{\partial S_r} = 0. \]

A.1.8 Derivatives with respect to \( \sigma_r \)

These derivatives are given by
\[ \frac{\partial f_1}{\partial \sigma_r} = \frac{\partial f_2}{\partial \sigma_r} = \frac{\partial f_3}{\partial \sigma_r} = \frac{\partial f_4}{\partial \sigma_r} = \frac{\partial f_5}{\partial \sigma_r} = \frac{\partial f_6}{\partial \sigma_r} = 0, \]
\[ \frac{\partial f_7}{\partial \sigma_r} = 1, \]
\[ \frac{\partial f_8}{\partial \sigma_r} = -\gamma_r, \]
\[ \frac{\partial f_9}{\partial \sigma_r} = \frac{\partial f_{10}}{\partial \sigma_r} = \frac{\partial f_{11}}{\partial \sigma_r} = \frac{\partial f_{12}}{\partial \sigma_r} = \frac{\partial f_{13}}{\partial \sigma_r} = \frac{\partial f_{14}}{\partial \sigma_r} = 0. \]

A.1.9 Derivatives with respect to \( H \)

We first have to compute the derivatives
\[ t'_d(H) = -\frac{1}{H^2} \left( 1 - \frac{\kappa}{2} H^{1/2} \right), \]
\[ k'_t(H) = -\frac{1}{c_t R_t} k_t(H) t'_d(H) = \frac{1}{c_t R_t} k_t(H) \frac{1}{H^2} \left( 1 - \frac{\kappa}{2} H^{1/2} \right), \]
\[ a'_t(H) = -k'_t(H), \]
\[ k'_r(H) = -\frac{1}{c_r R_r} k_r(H) t'_d(H) = \frac{1}{c_r R_r} k_r(H) \frac{1}{H^2} \left( 1 - \frac{\kappa}{2} H^{1/2} \right), \]
\[ a'_r(H) = -k'_r(H). \]

with this we obtain
\[ \frac{\partial Q_t}{\partial H} = c_t P_{vp} S_t \frac{a_t(H) (a_t(H) P_{as} + k_t(H) S_t) - k'_t(H) S_t H}{(a_t(H) P_{as} + k_t(H) S_t)^2}, \]
\[ \frac{\partial Q_r}{\partial H} = c_r P_{vs} S_t \frac{a_t(H) (a_t(H) P_{ap} + k_t(H) S_t) - k'_t(H) S_t H}{(a_t(H) P_{ap} + k_t(H) S_t)^2}. \]
and
\[
\begin{align*}
\frac{\partial f_1}{\partial H} &= \frac{1}{c_{as}} \frac{\partial Q_\ell}{\partial H}, \\
\frac{\partial f_2}{\partial H} &= -\frac{1}{c_{sa}} \frac{\partial Q_r}{\partial H}, \\
\frac{\partial f_3}{\partial H} &= \frac{1}{c_{op}} \frac{\partial Q_r}{\partial H}, \\
\frac{\partial f_4}{\partial H} &= -\frac{1}{c_{vp}} \frac{\partial Q_\ell}{\partial H}, \\
\frac{\partial f_5}{\partial H} &= 0, \\
\frac{\partial f_6}{\partial H} &= \beta_\ell, \\
\frac{\partial f_7}{\partial H} &= 0, \\
\frac{\partial f_8}{\partial H} &= \beta_r, \\
\frac{\partial f_9}{\partial H} &= \frac{\partial f_{10}}{\partial H} = \frac{\partial f_{11}}{\partial H} = \frac{\partial f_{12}}{\partial H} = \frac{\partial f_{13}}{\partial H} = \frac{\partial f_{14}}{\partial H} = 0.
\end{align*}
\]

A.1.10 Derivatives with respect to $P_{a,CO_2}$

These derivatives are given by
\[
\begin{align*}
\frac{\partial f_1}{\partial P_{a,CO_2}} &= \frac{\partial f_2}{\partial P_{a,CO_2}} = \frac{\partial f_3}{\partial P_{a,CO_2}} = \frac{\partial f_4}{\partial P_{a,CO_2}} = \frac{\partial f_5}{\partial P_{a,CO_2}} = \frac{\partial f_6}{\partial P_{a,CO_2}} \\
&= \frac{\partial f_7}{\partial P_{a,CO_2}} = \frac{\partial f_8}{\partial P_{a,CO_2}} = \frac{\partial f_9}{\partial P_{a,CO_2}} = 0, \\
\frac{\partial f_{10}}{\partial P_{a,CO_2}} &= -\frac{863K_{CO_2}}{V_{A,CO_2}} F_p - \frac{1}{V_{A,CO_2}} \dot{V}_A, \\
\frac{\partial f_{11}}{\partial P_{a,CO_2}} &= 0, \\
\frac{\partial f_{12}}{\partial P_{a,CO_2}} &= \frac{K_{CO_2}}{V_{T,CO_2}} F_s, \\
\frac{\partial f_{13}}{\partial P_{a,CO_2}} &= \frac{\partial f_{14}}{\partial P_{a,CO_2}} = 0.
\end{align*}
\]

A.1.11 Derivatives with respect to $P_{a,O_2}$

We get
\[
\begin{align*}
\frac{\partial f_1}{\partial P_{a,O_2}} &= \frac{\partial f_2}{\partial P_{a,O_2}} = \frac{\partial f_3}{\partial P_{a,O_2}} = \frac{\partial f_4}{\partial P_{a,O_2}} = \frac{\partial f_5}{\partial P_{a,O_2}} = \frac{\partial f_6}{\partial P_{a,O_2}} \\
&= \frac{\partial f_7}{\partial P_{a,O_2}} = \frac{\partial f_8}{\partial P_{a,O_2}} = \frac{\partial f_9}{\partial P_{a,O_2}} = \frac{\partial f_{10}}{\partial P_{a,O_2}} = 0, \\
\frac{\partial f_{11}}{\partial P_{a,O_2}} &= -\frac{1726K_{a,1}K_{a,2}F_p}{V_{A,O_2}} \left(1 - e^{-K_{a,2}P_{a,O_2}}\right) e^{-K_{a,2}P_{a,O_2}} - \dot{V}_A,
\end{align*}
\]
\[
\frac{\partial f_{13}}{\partial P_{a,O_2}} = \frac{2K_{a,1}K_{a,2}F_s}{V_{T,O_2}} \left( 1 - e^{-K_{a,2}P_{a,O_2}} \right) e^{-K_{a,2}P_{a,O_2}},
\]
\[
\frac{\partial f_{14}}{\partial P_{a,O_2}} = 0.
\]

### A.1.12 Derivatives with respect to \( C_{v,CO_2} \)

These derivatives are given by

\[
\begin{align*}
\frac{\partial f_1}{\partial C_{v,CO_2}} &= \frac{\partial f_2}{\partial C_{v,CO_2}} = \frac{\partial f_3}{\partial C_{v,CO_2}} = \frac{\partial f_4}{\partial C_{v,CO_2}} = \frac{\partial f_5}{\partial C_{v,CO_2}} = \frac{\partial f_6}{\partial C_{v,CO_2}} = \\
&= \frac{\partial f_7}{\partial C_{v,CO_2}} = \frac{\partial f_8}{\partial C_{v,CO_2}} = \frac{\partial f_9}{\partial C_{v,CO_2}} = 0, \\
\frac{\partial f_{10}}{\partial C_{v,CO_2}} &= \frac{863}{V_{A,CO_2}} F_p, \\
\frac{\partial f_{11}}{\partial C_{v,CO_2}} &= 0, \\
\frac{\partial f_{12}}{\partial C_{v,CO_2}} &= -\frac{1}{V_{T,CO_2}} F_s, \\
\frac{\partial f_{13}}{\partial C_{v,CO_2}} &= \frac{\partial f_{14}}{\partial C_{v,CO_2}} = 0.
\end{align*}
\]

### A.1.13 Derivatives with respect to \( C_{v,O_2} \)

Using

\[
\begin{align*}
\frac{\partial R_s}{\partial C_{v,O_2}} &= A_{pesk}, \\
\frac{\partial F_s}{\partial C_{v,O_2}} &= -\frac{A_{pesk}}{R^2_s} (P_{as} - P_{vs}),
\end{align*}
\]

we obtain

\[
\begin{align*}
\frac{\partial f_1}{\partial C_{v,O_2}} &= \frac{A_{pesk}}{c_{as}R^2_s} (P_{as} - P_{vs}), \\
\frac{\partial f_2}{\partial C_{v,O_2}} &= -\frac{A_{pesk}}{c_{vs}R^2_s} (P_{as} - P_{vs}), \\
\frac{\partial f_3}{\partial C_{v,O_2}} &= \frac{\partial f_4}{\partial C_{v,O_2}} = \frac{\partial f_5}{\partial C_{v,O_2}} = \frac{\partial f_6}{\partial C_{v,O_2}} = \\
&= \frac{\partial f_7}{\partial C_{v,O_2}} = \frac{\partial f_8}{\partial C_{v,O_2}} = \frac{\partial f_9}{\partial C_{v,O_2}} = \frac{\partial f_{10}}{\partial C_{v,O_2}} = 0, \\
\frac{\partial f_{11}}{\partial C_{v,O_2}} &= \frac{863}{V_{A,O_2}} F_p, \\
\frac{\partial f_{12}}{\partial C_{v,O_2}} &= 0, \\
\frac{\partial f_{13}}{\partial C_{v,O_2}} &= -\frac{1}{V_{T,O_2}} F_s.
\end{align*}
\]
\[
\frac{\partial f_{14}}{\partial C_{v,O_2}} = 0.
\]

**A.1.14 Derivatives with respect to \( \dot{V}_A \)**

These derivatives are given by

\[
\frac{\partial f_1}{\partial V_A} = \frac{\partial f_2}{\partial V_A} = \frac{\partial f_3}{\partial V_A} = \frac{\partial f_4}{\partial V_A} = \frac{\partial f_5}{\partial V_A} = \frac{\partial f_6}{\partial V_A} = \frac{\partial f_7}{\partial V_A} = \frac{\partial f_8}{\partial V_A} = \frac{\partial f_9}{\partial V_A} = 0,
\]

\[
\frac{\partial f_{10}}{\partial V_A} = \frac{1}{V_{A,CO_2}}(P_{l,CO_2} - P_{a,CO_2}),
\]

\[
\frac{\partial f_{11}}{\partial V_A} = \frac{1}{V_{A,O_2}}(P_{l,O_2} - P_{a,O_2}),
\]

\[
\frac{\partial f_{12}}{\partial V_A} = \frac{\partial f_{13}}{\partial V_A} = \frac{\partial f_{14}}{\partial V_A} = 0.
\]
Appendix B

Physical Background

B.1 The Ideal gas law

We collect the following material from [5]. A gas consists of molecules in a state of random
motion. The molecules fill any container in which they are enclosed. By colliding with
one another and with the walls of the container a pressure is exerted.

The respiratory gases, which include oxygen \((O_2)\) and carbon dioxide \((CO_2)\) follow the
ideal gas law,

\[
P V = n R T \tag{B.1.1}
\]

where \(P\) is pressure, \(V\) is volume, \(n\) is the number of moles of the gas, and \(T\) is temper-
ature. One mole is per definition the amount of substance which consists of \(6.023 \times 10^{23}\)
gas particles. In respiratory physiology, \(P\) is usually measured in millimeters of mercury
(mmHg), \(V\) in liters (l), and \(T\) in Kelvin (K). The constant \(R = 62.36 \text{ l} \cdot \text{mmHg} \cdot \text{mole}^{-1}
\cdot \text{K}^{-1}\) is called the general gas constant.

The ideal gas law says that if temperature is kept constant, volume and pressure of the
gas are inversely related (Boyle-Mariotte’s law). Also, at a constant volume, the pressure
exerted by a gas is proportional to the absolute temperature (Gay-Lussac’s law). Finally,
under constant external conditions with regard to pressure and temperature, equal volu-
mina of different ideal gases contain equal amounts of molecules (Avogadro’s law). Hence
the three empiric gas laws, Boyle-Mariotte’s law, Gay-Lussac’s law and Avogadro’s law
are combined in the ideal gas law.

Gases behaving according to the ideal gas law are called ideal gases. However, the concept
of an ideal gas is only a model. Actual gases behave according to the ideal gas law only
in certain pressure and temperature ranges depending on the gas species. This is the case
whenever the gas molecules can be considered as isolated points in space with negligible
molecular volumes and exerting no intermolecular forces other than those resulting from
perfectly elastic collisions between molecules. These assumptions are reasonable at the
low pressures encountered in respiratory physiology since in this case the average inter-
molecular distance is about ten times the average molecular size. For instance, consider
the volume (mole volume) occupied by one mole of an ideal gas at physical standard
conditions \((P_0 = 760 \text{ mmHg}, T_0 = 273 \text{ K})\)

\[
\frac{V}{n} = R \frac{T_0}{P_0} = 22.4 \text{ l} \cdot \text{mole}^{-1} \tag{B.1.2}
\]

The \(CO_2\) mole volume under standard conditions is 22.6 l \cdot mole\(^{-1}\) which shows that the
deviation from the ”ideal” mole volume is quantitatively insignificant.
B.2 Gas mixtures and Dalton’s law

If the (B.1.1) holds for any ideal gas, then it is also valid for mixtures of ideal gases. Let us enclose a mixture of \( N \) different gas species characterized by the index \( i, i = 1, \ldots, N \), in a container with volume \( V \) at temperature \( T \). Then the ideal gas law reads

\[
P V = (n_1 + \ldots + n_N)RT,
\]

(B.2.1)

where \( P \) is the pressure exerted by the gas mixture. The pressure \( P_i \) defined by

\[
P_i = \frac{n_i RT}{V}.
\]

(B.2.2)

is called the partial pressure of the gas \( i \) of the gas mixture. According to this definition it is the pressure that would the gas species \( i \) exert alone, that is, if all other gas components were removed and it were occupying the entire volume of the container by itself. Relations (B.2.1) and (B.2.2) imply that the total pressure \( P \) of a gas mixture is equal to the sum of the partial pressures \( P_i \) of all the gases in the mixture,

\[
P = P_1 + P_2 + \ldots + P_N \quad \text{(Dalton’s law)}.
\]

(B.2.3)

This means that the pressure exerted by each individual gas is independent of the pressures of the other gases in the mixture. Each gas behaves as though it were the only gas present in the space.

Moreover, we infer from (B.2.1) and (B.2.2) that the partial pressure \( P_i \) exerted by gas \( i \) is related to the total pressure \( P \) of the gas mixture by

\[
P_i = \frac{n_i}{n} P.
\]

(B.2.4)

This relationship shows that each gas in the mixture exerts a partial pressure proportional to its concentration. The quotient \( \frac{n_i}{n} \) is called the (fractional) concentration of the gas \( i \) in the gas mixture. It is denoted by

\[
F_i = \frac{n_i}{n}.
\]

(B.2.5)

In this definition, \( n \) usually refers to the number of moles of dry gas as will be explained in the next section.

B.3 Dry gas

Inspired air is warmed and humidified as it passes through the upper airways. On reaching the trachea, it has been heated to body temperature and fully saturated with water vapor.

Usually, one is only interested in the behavior of the so called dry gas, that is, all particles except the water particles. Let \( n \) be the number of moles of dry particles. Then the partial pressure of the dry gas is given by

\[
(P - P_{H_2O})V = nRT.
\]

(B.3.1)

where \( P_{H_2O} \) denotes the partial pressure of water vapor. If \( F_i \) is the concentration of the gas species \( i \) in the dry gas then the partial pressure \( P_i \) and the partial pressure \( P - P_{H_2O} \) of the dry gas are related by

\[
P_i = F_i (P - P_{H_2O}).
\]

(B.3.2)
The partial pressure of water vapor depends solely on temperature. At body temperature (37°C), regardless of barometric pressure, water vapor pressure is 47 mmHg. Consequently, the partial pressure of the dry particles in tracheal air is equal to the barometric pressure (760 mmHg) minus the water vapor pressure (47 mmHg), or 713 mmHg. The approximate partial pressure of the gases in inspired tracheal air are proportional to their concentrations,

\[ P_i = F_i \cdot 713. \]  

(B.3.3)

Explicitly, the partial pressure of oxygen \((P_{O_2})\) in inspired tracheal air is 150 mmHg, the partial pressure of carbon dioxide \((P_{CO_2})\) is less than 1 mmHg, and the partial pressure of nitrogen \((P_{N_2})\) is about 563 mmHg. In contrast, the corresponding partial pressures in the atmospheric air are higher (provided that no water vapor is present), since their sum must now equal 760 mmHg,

\[ P_i = F_i \cdot 760. \]  

(B.3.4)

We have then: \(P_{O_2} = 159\) mmHg, \(P_{CO_2}\) is again less than 1 mmHg, and \(P_{N_2} = 601\) mmHg. In the following, \(n\) will always refer to the number of moles of the dry particle.

### B.4 Measuring conditions

Gas volumes may be measured under different conditions of temperature, pressure, and degrees of saturation with water vapor. Conversion between the various conditions can be made using the following relationship based upon the ideal gas law.

Consider \(n\) moles of dry gas under two different conditions characterized by the indices \(I\) and \(II\). Hence, the corresponding temperatures are \(T_I\) and \(T_{II}\), the volumes are \(V_I\) and \(V_{II}\), and the partial pressures of the dry particles are \(P_I - P_{H_2O,I}\) and \(P_{II} - P_{H_2O,II}\). According to the ideal gas law the volumes under the two conditions are given by

\[ V_I = \frac{nRT_I}{(P_I - P_{H_2O,I})}, \]

\[ V_{II} = \frac{nRT_{II}}{(P_{II} - P_{H_2O,II})}. \]  

(B.4.1)

Thus, the two volumes of the dry gas particles are related by

\[ \frac{V_I}{V_{II}} = \frac{(P_{II} - P_{II}H_2O)T_I}{(P_I - P_{H_2O,I})T_{II}T_{II}}. \]  

(B.4.2)

The following conditions are often used in respiratory physiology.

- **BTPS** (body temperature and pressure, saturated): \(T = 37°C = 310K, P_a=\)ambient pressure, \(P_{H_2O} = 47\) mmHg. These are the conditions inside the body.
- **STPD** (standard temperature and pressure, dry): \(T_0 = 0°C = 273K, P_0=\) barometric pressure at sea level = 760 mmHg, \(P_{H_2O} = 0\) mmHg. These are the so called standard conditions.

Using (B.4.2) we obtain

\[ \frac{V_{BTPS}}{V_{STPD}} = \frac{863}{P_a - 47} = 1.21, \]  

(B.4.3)

if we assume \(P_a = 760\) mmHg for ambient pressure. We see that \(V_{BTPS}\) is approximately 20% higher than the volume under STPD conditions. This is a consequence of the higher temperature and hence the greater kinetic energy of the gas molecules. There are two ways...
to understand the volume $V_{BTPS}$, which will be illustrated in the following. Consider $n$ moles of dry air at standard temperature and pressure. According to the ideal gas law, this air occupies the volume

$$V_{STPD} = \frac{nRT_o}{P_o}$$  \hspace{1cm} (B.4.4)

As soon as this dry air enters the respiratory pass ways, it is warmed up to body temperature and totally humidified. Since the total pressure inside the body is the same as outside the body, the ideal gas law reads now

$$P_oV_{BTPS} = (n + n_{H_2O})R(T_o + 37),$$ \hspace{1cm} (B.4.5)

or, if we mentally remove the water particles,

$$(P_o - 47)V_{BTPS} = nR(T_o + 37),$$ \hspace{1cm} (B.4.6)

Hence, $V_{BTPS}$ can be on the one hand regarded as the volume occupied by the dry particles and the water particles at pressure $P_o$. On the other hand, it can be interpreted as the volume occupied by the dry particles alone at pressure $P_o - 47$.

### B.5 Henry’s law

The solubility of gases in liquids is important to the understanding of blood-gas transport mechanisms. When a gas and a liquid are at an equilibrium, statistically the same number of dissolved gas molecules escape from the liquid surface as enter the surface to dissolve. Henry’s law states that the amount of gas that can dissolve in a liquid is directly proportional to the partial pressure of the gas above the liquid when gas and liquid are at an equilibrium,

$$C_i = \alpha_i P_i$$  \hspace{1cm} (Henry’s law) (B.5.1)

Here $i$ denotes a single gas specie. The factor $\alpha_i$ is called the solubility coefficient of the gas $i$. It depends on temperature, on the kind of fluid, and on the gas species. $P_i$ is the partial pressure of the gas $i$ above the liquid when an equilibrium is reached. $C_i$ represents the concentration of the gas $i$. It is defined as volume of gas $i$ (usually specified under STPD conditions) dissolved per volume of liquid.

For instance, the oxygen solubility coefficient in plasma at body temperature is $\alpha_{O_2} = 0.211 \text{ ml} \cdot \text{l}^{-1} \cdot \text{kPa}^{-1}$. This means that at a barometric pressure of 101 kPa, about 21.3 ml_{STPD} of $O_2$ are dissolved in 1l of plasma: $C_{O_2} = 21.3 \text{ ml}_{STPD} \text{l}^{-1}$. Under the same conditions, the solubility coefficient of carbon dioxide is $\alpha_{CO_2} = 5.06 \text{ ml} \cdot \text{l}^{-1} \cdot \text{kPa}^{-1}$. This shows that $CO_2$ is twenty times more soluble than $O_2$.

Note that Henry’s law refers only to the dissolved number of gas particles. It does not take into account chemically bound molecules.
Bibliography


