A Global Model
for the
Cardiovascular and Respiratory System

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Susanne Timischl

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Abstract. In this thesis a global model for the cardiovascular and respiratory system is developed. The cardiovascular part of the model is based on the four compartment model by Grodins and includes modifications by Kappel and Peer. The respiratory part is based on the two compartment model by Khoo et al.. The underlying models are reviewed, extended and combined. The combined model contains as subsystems the systemic and pulmonary circulation, the left and right ventricles, and the tissue and the lung compartment. Mechanisms included are Frank-Starling’s law, the Bowditch effect, and variable cerebral blood flow.

In particular, the model is adapted to the situation of dynamic exercise. The initial anaerobic energy supply, the mechanism of metabolic autoregulation in the peripheral regions, and the dilatation of pulmonary vessels are taken into account. Heart rate and alveolar ventilation are assumed to be the quantities through which the central nervous system controls the mean arterial blood pressure and the blood gas concentrations. The transition from rest to exercise under a constant ergometric workload is simulated. Here the action of cardiovascular and respiratory control is represented by a linear feedback control which minimizes a quadratic cost functional. As an alternative, also a nonlinear feedback is implemented.

Keywords and phrases. Optimal control, Cardiovascular system, Respiratory system, Baroreceptor Loop, Autoregulation.
To Gerald
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Introduction

The human body has literally thousands of control systems in it. Many control systems operate within the organs to control functions of individual parts. Others operate throughout the entire body to control the interrelations between the organs. To mention only a few, there are the genetic control systems that operate within all cells to control intracellular function and all life processes, the insulin control system for regulating the glucose concentration in the extracellular fluid, the control of body temperature, the control of blood volume, the regulation of oxygen and carbon dioxide in the extracellular fluid, or the regulation of arterial blood pressure. Most of these control systems are negative feedback systems. For example, a high concentration of carbon dioxide in the extracellular fluid causes increased pulmonary ventilation, which in turn decreases the carbon dioxide concentration. In short, a high concentration causes a negative time derivative for this concentration, which is negative to the initiating stimulus.

It is intriguing to think of a biological system, such as the human body, as operating in an optimal way. One may assume that during the millions of years of evolution a biological system would have eliminated those mechanisms that involved the use of too much energy. If the energy expenditure is too large, too many basic nutrients are needed to fuel the system. Therefore, it seems reasonable to postulate that the human organism has evolved to make use of minimum energy requirements.

In many cases it is a simple matter to set up the mathematical description of a performance criterion involving the minimization of energy in a biological system. But the assumption of optimization can be applied to other quantities besides energy. One may, for instance, assume that the human body, or organs, work in such a way that the stress upon certain organs is minimized or at least must stay within certain bounds.

One of the purposes of optimal control theory in medicine is to gather information on the nature of the controller. It is also useful to analyze predictions which are suggested by the controller. This way optimal control theory improves our understanding of aspects of control of normal and diseased organisms. An interesting application of optimal control theory in medicine is, for instance, the use of an optimal feedback control for the automatic delivery of drugs such as insulin or hypotensive drugs via microprocessors (cf., e.g., Swan [66]). For a survey of applications of optimal control theory in biomedicine see, e.g., Swan [66] or Noordergraaf and Melbin [51]. General aspects on mathematical modeling in medicine can be found in the books by Bellman [2], Hoppensteadt [19], Hoppensteadt and Peskin [20], or Mosekilde and Mouritsen [47].

There are many investigations concerned with modeling of various parts of the circulatory system. Almost all global models for the cardiovascular system and its short-term reactions are extensions or modifications of Grodins’ compartment model (see Grodins [15], [16]). We only mention Kappel and Peer [23], Möller [46], and Ranft [59] as examples. Studies on the optimal matching between heart and arterial system were made for instance by Kenner and
Pfeiffer [29], Noldus [49], Ono et al. [53], or Pfeiffer and Kenner [57]. For a survey of models of this type see, e.g., Noordergraaf [50] or Swan [66]. A comprehensive discussion of the control mechanisms in the human cardiovascular system is given in Guyton [17] or Rowell [60].

Models dealing with the regulation of breathing date back to the beginning of this century (Haldane and Priestley [18]). First quantitative studies were made by Gray [12] with his multiple factor theory. The first dynamic model of carbon dioxide regulation was developed by Grodins et al. [13]. In particular, there are many studies concerning the optimal regulation of respiration during exercise. We mention here only Poon [58], Yamashiro and Grodins [72] and [73], and Yamashiro et al. [74]. For a survey on models for the respiratory system see Khoo and Yamashiro [34]. Comprehensive reviews on respiratory control can also be found in the books edited by Khoo [33] and Swanson [67].

In this thesis the cardiovascular model as presented by Kappel and Peer [24], is revised and extended. We develop a model which describes the interactions of the cardiovascular and the respiratory system. The respiratory part of the model is based on the model by Khoo et al. [30]. The combined model contains all essential subsystems, such as systemic and pulmonary circulation, left and right ventricles, the tissue and the lung compartment.

In particular, the model is adapted to the situation of dynamic exercise. The initial anaerobic energy supply, the mechanism of metabolic autoregulation in the peripheral regions, and the dilatation of pulmonary vessels are considered. The transition from rest to exercise under a constant ergometric workload is simulated. It is assumed that the heart rate and the ventilation rate are adapted such that the mean arterial pressure is regulated to a new elevated operating point and the arterial carbon dioxide concentration remains constant during exercise. This adaption occurs optimal in the sense that the feedback control is chosen to minimize a quadratic cost criterion.

The organization of this thesis is as follows. In Chapter 1 the physiology of the respiratory and the cardiovascular system is reviewed. In particular, the role of the autonomic nervous system is described as well as the baroreceptor reflex, metabolic autoregulation, cerebral blood flow, the Frank-Starling mechanism, the Bowditch effect, and the role of oxygen and carbon dioxide in respiratory control.

Chapter 2 is dedicated to the respiratory part of the model. The model is composed of two compartments, the lungs and the tissue compartment. The compartments are connected by the circulating blood. For each compartment, a mass balance equation for oxygen and for carbon dioxide is derived. An empirical relationship accounting for a variable brain blood flow depending on the arterial partial pressure of carbon dioxide is included. Furthermore, dissociation relationships are implemented which allow to express the gas concentrations in terms of partial pressures. Finally, an empirical formula for the dependence of ventilation on carbon dioxide and oxygen is given.

Chapter 3 deals with the cardiovascular part of the model. It consists of four compartments which are the arterial and venous parts of the systemic and the pulmonary vascular system. The compartments are connected by systemic and pulmonary resistances and by two
pumps, the left and the right ventricle. For each of the four compartments, a mass balance equation for the contained blood volume is derived. The dependence of cardiac output on blood pressure is taken into account by a simple first-order-model of the viscous filling of the ventricle (diastole) and via Frank-Starling’s law (systole). Based on the Bowditch effect a second-order model for the relationship between the heart rate and the contractilities is implemented.

In Chapter 4 the general combined model is presented. At this stage, no restriction to a particular situation is yet made. All relationships developed so far are summarized.

In Chapter 5 we adapt the model to the situation of dynamic exercise. Under the assumption of aerobic exercise the behavior of the metabolic rates is modeled by an empiric relation which takes into account the initial anaerobic energy supply. Moreover, metabolic autoregulation of the blood vessels is considered by assuming that the systemic vessel resistance depends on the oxygen concentration in venous blood. A dilatation of the pulmonary blood vessels during exercise is also taken into account. Heart rate and alveolar ventilation are assumed to be the quantities through which the central nervous system controls the mean arterial blood pressure and the blood gas concentrations. As a consequence, the variations of heart rate and alveolar ventilation are chosen as control functions.

In Chapter 6 the steady state relationships for the combined model are examined by stepwise increasing the imposed workload. In order to be able to compute the steady state, two additional relations are set up: the proportional increase of heart rate with oxygen uptake and the constancy of the arterial partial pressure of carbon dioxide. Interconnections between the variables are investigated qualitatively. Finally, the steady state relationships are studied for different situations, such as constant pulmonary resistance or constant heart rate during exercise.

Chapter 7 summarizes some important results from control theory as will be needed in succeeding chapters. Key words are: Stability, controllability, stabilizability, reconstructibility, observability, detectability, linear state feedback control, quadratic cost criterion, and stabilization of a nonlinear system via linear feedback.

Chapter 8 motivates the formulation of the control problem for exercise. The hypothesis of the existence of a predefined ”operating-value” for the mean arterial pressure is analyzed. Furthermore, the assumption of optimal behavior is discussed.

In Chapter 9 a linear feedback is constructed which minimizes a quadratic cost criterion. The control which steers the system from the steady state ”rest” to the steady state ”exercise” is determined. Furthermore the numerical simulations with Mathematica are documented and the results are presented. In particular, the role of the weights in the cost criterion is discussed. Simulations are presented for the assumption of an unchanged operating value for the blood pressure and for the assumption that also the arterial partial pressure of oxygen is controlled.

Chapter 10 implements a nonlinear feedback law as an alternative. The corresponding simulation results are presented and discussed.
Finally, Chapter 11 contains a review of the results obtained so far, of shortcomings, and of feasible modifications of the model.

Appendix A explains physical principles used in this thesis. Among them are the ideal gas law, partial pressures and Dalton’s law, different measuring conditions for gas volumes (standard temperature and pressure, dry (STPD); body temperature and pressure, saturated (BTPS)), Henry’s law.

Appendix B provides numerical values from literature.

Finally, Appendix C contains a glossary of notation.

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Chapter 1

Physiology of respiratory and cardiovascular control

1.1 The autonomic system

The nervous system consists of three major parts: the sensory portion, the central nervous system, and the motor portion. The sensory receptors detect the state of the body or surroundings (e.g., baroreceptors). The central nervous system consists of the brain and the spinal cord. The brain stores information, generates thoughts, creates ambition, and determines the reactions which the body performs in response to the sensations. Appropriate signals are transmitted through the motor portion of the nervous system to carry out the "commands" of the brain.

A large segment of the nervous system is made up by the vegetative or autonomic nervous system. It operates at a subconscious level and controls many functions of the internal organs such as the heart or the gastrointestinal tract. The autonomic system is activated mainly by centers in the brain stem, the spinal cord, and the hypothalamus. There are also portions of the cerebral cortex and especially of the limbic system which influence autonomic control by transmitting impulses to the lower centers. Moreover, sensory signals can enter the centers of the autonomic ganglia, cord, brain stem, or hypothalamus and these in turn transmit appropriate reflex responses back to the visceral organs to control their activities. Autonomic signals are transmitted to the body through two major subdivisions: the sympathetic and the parasympathetic systems.

When sympathetic stimulation excites a particular organ, often parasympathetic stimulation inhibits it. That is, the two systems occasionally act reciprocally to each other. However, most organs are mainly controlled by one or the other of the two systems. For the control of circulation, the effects of the two systems on the heart, on the blood vessels, and on the arterial pressure are most significant.
The heart is controlled by both systems. Sympathetic stimulation increases the heat rate and enhances the strength of its pumping. Parasympathetic stimulation causes mainly the opposite effects, it decreases the heart rate and also slightly decreases contractility. In short, sympathetic activity increases the effectiveness of the heart as a pump whereas parasympathetic stimulation decreases the pumping capability of the heart.

Most blood vessels are constricted by sympathetic stimulation. Sympathetic constriction of the small arteries and the large arterioles increases the resistance and therefore reduces the blood flow through the vessels. Sympathetic stimulation of the veins decreases the volume of these vessels and therefore translocates the blood into the heart. Parasympathetic stimulation has little or no effect on blood vessels. It merely dilates vessels in certain restricted areas, such as in the blush area of the face.

Blood pressure is elevated by sympathetic stimulation because sympathetic activity increases propulsion of the blood by the heart and increases vessel resistance. The parasympathicus influences blood pressure the opposite way. Blood pressure is regulated by means of the baroreceptor reflex, which will be studied in more detail in the next section.

### 1.2 The baroreceptor reflex

The baroreceptor reflex is the most powerful tool in the control of systemic arterial pressure. Baroreceptors are spratype nerve endings lying in the walls of the carotid sinus and the aortic arch. The impulse rate of the baroreceptors is a precise image of the transmural pressure.

The firing rate increases during systole and decreases during diastole. Hence, the mean firing rate increases with mean arterial pressure. Moreover, the faster the pressure changes, the greater is the response of the baroreceptors. In the absence of arterial baroreceptors, the mean arterial pressure would be higher and there would be large variations around the mean value.

The baroreceptor afferents have a continuous inhibitory effect on the vasomotor center which is located in the medulla oblongata and the lower third of the pons. As soon as the blood pressure falls and hence the baroreceptors are less stimulated, the vasomotor center increases the sympathetic tone and decreases the parasympathetic tone. As a consequence, heart rate and contractility increase and the small arteries and large arterioles are constricted. This way the arterial blood pressure is regulated towards normal again.

In case of strong sympathetic stimulation, also the systemic veins are constricted. Although this does not significantly change the overall total peripheral resistance, the capacity of the veins is decreased. As a consequence, the veins hold less blood at a given blood pressure, which shifts the blood towards the heart and increases venous return.
1.3 Local blood flow control

Another important mechanism of circulatory control is the ability of each tissue to control its own local blood flow according to its need.

Certain vessels, particularly arteries in the brain and the kidneys, can adapt their resistance such that the blood flow remains nearly constant if the blood pressure changes. This mechanism is called Bayliss effect or myogenic autoregulation. It is based on the fact that the increase in transmural pressure increases the vessel diameter and the smooth muscle length commensurately. This evokes a counteracting activation of muscle tone, which increases the vessel resistance and thus maintains an approximately constant blood flow.

Another important mechanism of blood flow control, the metabolic autoregulation, exists in the small arterioles. If the metabolic rate increases or less oxygen is available, different chemical substances ("metabolic cocktail") are released which cause vasodilatation of the small arterioles. Thus the blood flow is increased and therefore on the one hand more nutrients per time are carried to the tissues and on the other hand excessive waste products are removed from the tissues. Metabolic vasodilatation is superimposed onto the constrictory effect caused by the sympathetic innervation. In some situations, such as exercise, the two mechanisms exert opposite effects.

1.4 Other mechanisms of blood flow control

Other more or less important mechanisms of blood pressure control are: the chemoreceptors, the low pressure receptors and the central nervous system ischemic response.

The chemoreceptors are chemosensitive cells located in the carotid bodies and the aortic bodies. Their afferents pass along with the baroreceptor fibers into the vasomotor center. The carotid and aortic bodies are supplied with an abundant blood flow so that they are always in close contact with arterial blood. If the arterial blood pressure falls below a critical level, the chemoreceptors are stimulated because of diminished availability of oxygen and excess carbon dioxide. The vasomotor center is excited. However, the vasoconstriction is soon dominated by a hypoxic vasodilatation. The chemoreceptors play a more important role in respiratory control.

The low pressure receptors are stretch receptors located in the large veins, the pulmonary artery, and the atria and ventricles. Due to their location they prevent pressure changes in the low pressure range which mainly are caused by changes in blood volume.

If the blood flow to the vasomotor center is decreased such that the neuronal cells are not supplied with enough nutrients and excess carbon dioxide is built up, the neurons of the vasomotor center are directly stimulated. This CNS ischemic response is kind of an emergency arterial pressure control system and does not become very active until the mean arterial blood pressure falls as low as 60 mmHg.
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1.5 Cerebral blood flow

As in most other vascular areas of the body, the blood flow through the brain is highly responsive to the metabolism of the brain tissue. It has been observed that changes in oxygen, carbon dioxide and hydrogen ion concentration have very potent effects on cerebral blood flow.

One of the main goals of the regulation of blood flow in the brain is to keep the carbon dioxide concentration in the cerebral fluids within very narrow limits. The reason is that an increase in carbon dioxide concentration induces an increase in hydrogen ion concentration because the carbon dioxide reacts with water to form hydrogen ions and bicarbonate. And an increased hydrogen ion concentration greatly depresses neuronal activity. The effect of increased carbon dioxide is most probably exerted on the arterial side (see Guyton [17] or Lambertsen [42]). It has been observed that an increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increases brain blood flow.

Oxygen plays a minor role as a regulator of cerebral blood flow. Except during periods of intense brain activity the utilization of oxygen by the brain remains relatively constant. If the blood flow to the brain ever becomes insufficient to supply the needed amount of oxygen or if the tissue oxygen partial pressure falls below approximately 30 mmHg (normal value is 35 to 40 mmHg) the cerebral vessels will dilate and thus brain blood flow increases. This is a very important regulatory mechanism since neuronal activity becomes depressed at not much lower levels of oxygen partial pressure. High oxygen tensions produce little or no effect on cerebral vessels (see Lambertsen [42]).

Another important regulatory mechanism is elicited by the Bayliss effect (see Section 1.3). Experiments show that cerebral blood flow is very insensitive to changes in blood pressure between the pressure limits of 80 and 120 mmHg. This autoregulatory mechanism is so powerful that it normally even compensates for effects of the sympathetic stimulation. Only when the autoregulatory mechanism fails to compensate enough then sympathetic regulation of brain blood flow becomes important. For instance, during strenuous exercise when arterial pressure rises to a very high level, sympathetic stimulation constricts the larger arteries and thus prevents the high pressure from reaching the small blood vessels. This way it helps preventing the occurrence of cerebral stroke.

The behavior of brain blood flow during exercise is still a matter of controversy. According to most references (e.g., Despopulous and Silbernagl [5], or Rowell [60]), brain blood flow is unaffected by physical exercise. On the other hand, experiments by Thomas et al. [68], for instance, showed an increase of brain blood flow during submaximal and maximal exercise.
1.6 Frank-Starling mechanism and Bowditch effect

The pumping ability of the heart depends on contractility, preload, afterload and heart rate. The intact heart can increase its contractility with the help of three mechanisms: the Frank-Starling mechanism, the Bowditch effect, and by sympathetic activation.

The Frank-Starling mechanism (cf. Frank [8] and Patterson et al. [54]) means the intrinsic ability of the heart to adapt to changing loads of inflowing blood. The heart pumps all the blood that comes to it into the aorta without allowing excessive damming of blood in the veins. If preload (=enddiastolic volume) is increased, the cardiac muscle is stretched and, in turn, contracts with increased force. This way, an increased stroke volume is pumped against the unchanged aortic pressure. The increased force of contraction is probably caused by the fact that the contractile proteins become more sensitive for calcium when they are stretched ("length-tension-relationship"). One of the most important consequences of the Frank-Starling mechanism is that changes in the arterial pressure against which the heart pumps (= afterload) have almost no effect on stroke volume. If everything else remains constant, stroke volume increases with increased afterload and vice versa. Afterload influences stroke volume by affecting the velocity of contraction ("force-velocity relationship").

The Bowditch effect describes the sensitivity of the cardiac muscle to the interval between contractions. The vigor of contraction is increased if the heart rate is increased. The reason is that the interval between heart beats influences the quantity of calcium available to the cell. This heart rate related increase in contractility is also referred to as the interval-strength relationship. For studies concerning the Bowditch effect see Bowditch [4], Franz et al. [9], Magrini et al. [45], Seed and Walker [62], or Wohlfart [71].

1.7 Oxygen transport in blood

The partial pressure of the gaseous oxygen ($P_{O_2}$) in the alveoli is 104 mmHg, whereas the $P_{O_2}$ of the (mixed) venous blood entering the pulmonary capillaries is only about 40 mmHg. In consequence, there is a large pressure difference which causes oxygen to diffuse from the alveoli into the pulmonary capillaries. By the time the blood has moved a third of the distance through the capillaries, the blood $P_{O_2}$ has risen to approximately the 104 mmHg of the $P_{O_2}$ in alveolar air.

During strenuous exercise, the demand of the body tissues for oxygen can increase tremendously. Furthermore, the increased cardiac output may reduce the time that the blood remains in the capillaries to less than half the normal time. However, since the blood stays in the lung capillaries about three times as long as necessary, even under these conditions the blood is still almost completely saturated with oxygen when it leaves the pulmonary capillaries.

A small percentage of oxygenated blood passes through the bronchial circulation to sup-
ply the lung tissues. It mixes in the pulmonary veins with the oxygenated blood (venous admixture) and causes the $P_O_2$ of the blood pumped into the aorta to fall to approximately 95 mmHg.

When the arterial blood reaches the tissues, its oxygen partial pressure is still 95 mmHg. In the interstitial fluid the $P_O_2$ averages only 40 mmHg, and this tremendous pressure difference causes the oxygen to diffuse rapidly from the arterial blood into the tissues. The $P_O_2$ of the blood entering the veins from the tissue capillaries becomes almost equal the 40 mmHg of the interstitium.

The total content of oxygen in the blood is the sum of physically dissolved and chemically bound components. The physically dissolved component varies linearly with the partial pressure of $O_2$ (Henry’s law, see Appendix A.5) and accounts for only about 3% of the oxygen content in the blood. The remaining 97% of the oxygen is carried in chemical combination with hemoglobin in the red blood cells. The chemically combined component is a complex function of various factors ($P_O_2$, $P_CO_2$, temperature,...).

The $O_2$ dissociation curve describes the dependence of total oxygen upon $P_O_2$. When $P_O_2$ is low (as in the tissues), oxygen is released from the hemoglobin, whereas when $P_O_2$ is high (as in the pulmonary capillaries), oxygen binds with hemoglobin. An important feature of the oxygen dissociation curve is its S-shape. For high $P_O_2$, the slope of the dissociation curve is very small. This has the effect, that even for a large reduction of $P_O_2$ in the inspired air (high altitudes) the blood is still almost saturated with oxygen. For low $P_O_2$, the dissociation curve is very steep. Thus already a small decrease of tissue $P_O_2$ causes extreme amounts of $O_2$ 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.

As mentioned above, the amount of chemically bound $O_2$ depends on various factors. The influence of carbon dioxide is called Bohr effect. If the $CO_2$ concentration is decreased, the $O_2$ dissociation curve is shifted to the left and vice versa. This enhances the oxygenation of the blood in the lungs and the release of oxygen in the tissues. During exercise, the increased $CO_2$ production in the tissues also causes a shift of the dissociation curve to the right so that more $O_2$ is released.

1.8 Carbon dioxide transport in the blood

Carbon dioxide diffuses in exactly the opposite direction as $O_2$, only 20 times as rapidly. Therefore, far smaller pressure differences are required for the diffusion of $CO_2$ than those required for $O_2$.

The partial pressure of carbon dioxide ($P_CO_2$) in the arterial blood entering the tissue capillaries is 40 mmHg. In the interstitial fluid, the $P_CO_2$ is about 45 mmHg, so there is a rapid diffusion of $CO_2$ from the interstitium into the capillary blood which leaves the tissues. The $P_CO_2$ of the venous blood comes to an equilibrium with the interstitial $P_CO_2$. The mixed
venous blood entering the pulmonary capillaries has a $P_{CO_2}$ of about 45 mmHg. Since the $P_{CO_2}$ in the alveoli is only 40 mmHg, $CO_2$ diffuses rapidly from the blood into the alveoli. Even before the blood has passed one third of the distance through the capillaries, its $P_{CO_2}$ has fallen to approximately the 40 mmHg pressure of the alveolar air.

The amount of $CO_2$ in the blood plays an important role for the acid-base balance of the body fluids. Carbon dioxide can exist in the blood in many different forms: as free carbon dioxide, and in chemical combinations with water, hemoglobin, and plasma protein. 7% of all the $CO_2$ transported is physically dissolved. The concentration of dissolved $CO_2$ in the blood is linearly dependent on $P_{CO_2}$ (see Henry’s law, Appendix A.5). The dependence of chemically bound $CO_2$ upon $P_{CO_2}$ is nonlinear. The $CO_2$ dissociation curve describes the dependence of total $CO_2$ concentration in all its forms upon $P_{CO_2}$.

The influence of the oxygen-hemoglobin reaction on carbon dioxide transport is called Haldane effect. An increased $O_2$ concentration shifts the $CO_2$ dissociation curve to the right. Therefore, in the pulmonary capillaries, where the $P_{O_2}$ is high, more $CO_2$ is released. Conversely, in the absence of oxygen, considerably more carbon dioxide can bind. Hence, in the tissues, the Haldane effect causes increased pickup of carbon dioxide.

1.9 The respiratory center

The respiratory center is located in the medulla oblongata and pons and consists of several widely dispersed groups of neurons. The vagal and glossopharyngeal nerves transmit sensory signals into the respiratory center from the peripheral chemoreceptors, the baroreceptors and from different types of receptors in the lungs. Respiratory center activity is also closely related to vasomotor activity. Almost any factor that increases the degree of vasomotor activity does also at least moderately increase respiration. The neurons in the respiratory center generate the rhythm of respiration and transmit nervous signals to the inspiratory muscles.

The overall level of respiratory center activity is controlled according to the ventilatory demands of the body. It is the ultimate goal of respiration to maintain proper concentrations of carbon dioxide, hydrogen ions and oxygen in the body fluids. This is accomplished on the one hand via feedback, since the respiratory center responds to changes in the chemical composition of the blood. On the other hand, respiratory center activity is controlled by excitatory signals from other parts of the nervous system. These signals are especially important during exercise and will be discussed in Section 5.5.

1.10 The role of carbon dioxide in respiratory control

Carbon dioxide is one of the end-products of metabolism. Its concentration in the body fluids greatly influences the chemical reactions of the cells and also the tissue pH. Therefore, the partial pressure of $CO_2$ in the tissue fluid must be kept within very narrow limits. A special
area in the respiratory center, the chemosensitive area, responds very sensitively to changes in either blood CO$_2$ or hydrogen ion concentration and in turn excites the other portions of the respiratory center.

The sensor neurons in the chemosensitive area are particularly stimulated by hydrogen ions. However, hydrogen ions pass both the blood-brain barrier and the blood-cerebrospinal fluid barrier only very poorly. For this reason, changes in hydrogen ion concentration in the blood actually have much less effect in exciting the chemosensitive neurons than do changes in carbon dioxide concentration. Carbon dioxide in the blood, though, stimulates the respiratory neurons indirectly. It easily crosses the blood-brain and the blood-cerebrospinal fluid barrier and reacts with water to form hydrogen ions and bicarbonate. The hydrogen ions then have a potent stimulatory effect.

Most probably, it is the change of the carbon dioxide and hydrogen ion concentration in the interstitial fluid that stimulates respiratory center activity. However, some physiologists believe that also an increased carbon dioxide concentration in the cerebrospinal fluid has a stimulating effect (see Guyton [17], p. 507). A reason for this hypothesis is that within seconds after the blood $P_{CO_2}$ changes, also the $CO_2$ and hydrogen ion concentrations in the cerebrospinal fluid change. On the other hand, several minutes are sometimes required until the $P_{CO_2}$ of the interstitial fluid changes.

### 1.11 The role of oxygen in respiratory control

Changes in arterial oxygen concentration have no direct effect on the respiratory center itself. However, there are chemoreceptors located in the carotid and aortic bodies which respond to changes in CO$_2$, hydrogen ion, and O$_2$ concentrations (compare also Section 1.4). They transmit signals to the respiratory center and help thus regulate respiratory activity. The influence of carbon dioxide and hydrogen ions through the peripheral chemoreceptors is very small compared with their effects on the chemosensitive area.

Since the blood flow through the carotid and aortic bodies is very high, the oxygen partial pressure of the tissues in the carotid and aortic bodies remains at all times almost equal to that of arterial blood. As a consequence, it is the arterial $P_{O_2}$ which determines the degree of stimulation of the chemoreceptors and not the venous $P_{O_2}$.

A changed blood $P_{O_2}$ does not affect alveolar ventilation significantly until it falls almost to half the normal value. Why does oxygen play such a small role in the control of respiration? The reason is that under normal conditions the alveolar $P_{O_2}$ is higher than the level needed to saturate almost all of the hemoglobin in the arterial blood. Therefore, it does not matter if alveolar ventilation is normal or ten times normal or even almost as small as one half normal, for the blood will still be essentially saturated. In other words, alveolar ventilation can be changed tremendously without significantly affecting $O_2$ transport to the tissues.

During normal respiration the $CO_2$ and pH feedback control mechanisms are extremely
powerful in relation to the $O_2$ feedback control. In many situations, the $CO_2$ and pH control mechanisms oppose the $O_2$ feedback control. But whenever the oppository effects of $CO_2$ and hydrogen ion control are absent, a diminished oxygen concentration can rise alveolar ventilation tremendously, such as at high altitudes.
Chapter 2

The respiratory part of the model

The model for the respiratory system is based on the two compartment model developed by Khoo et al. [30] (see also the related papers by Khoo [31] and [32], and Khoo et al. [35]).

2.1 The model structure

The model for the respiratory system comprises two compartments, lungs and lumped body tissue, which are connected by the circulating blood. Figure 2.1 shows the model structure. We will in the following derive the mass balance equations for CO₂ and O₂ for both compartments. For present purposes, any transport delays are ignored. For numerical values see Appendix B.

2.2 The lung compartment

We assume a single homogeneous lung (alveolar) compartment which is ventilated by a continuous unidirectional stream of gas. The events of the respiratory circle are ignored.

The change of CO₂ volume in the lung compartment is at every instant $t$ determined by a balance between the net rate of CO₂ expired from the lungs and the net rate of CO₂ diffusing into the lungs from the blood. Therefore, the mass balance equation for CO₂ reads

$$V_{ACO_2} \dot{F}_{ACO_2}(t) = \dot{V}_A(F_{ICO_2} - F_{ACO_2}(t)) + c F_p(t)(C_{vCO_2}(t) - C_{aco_2}(t)).$$

(2.1)

Generally, "·" denotes derivation with respect to time $t$. An exception is the alveolar ventilation which is denoted as $\dot{V}_A$. Here we use the conventional notation from respiratory physiology where $\dot{V}_A = fV_A$, with respiratory frequency $f$ and (constant) alveolar volume $V_A$. For the time being, $\dot{V}_A$ is regarded as a parameter.

$V_{ACO_2}$ is the effective CO₂ storage volume of the lung compartment. It is larger than the gaseous lung volume because there is also CO₂ dissolved in lung tissue, pulmonary capillary
blood, and extravascular lung water (compare Khoo et al. [30], or Longobardo et al. [43]). $F_{ACO_2}$ and $F_{ICO_2}$ are the fractional concentrations of $CO_2$ in the alveolar and inspired gas mixture, respectively (see Appendix A, (A.6), for a definition of fractional concentrations). $C_{aco_2}$ and $C_{vco_2}$ are the concentrations of total (i.e., bound and dissolved) $CO_2$ in arterial and mixed venous blood, respectively.

We have taken into account that $V_{ACO_2}$ and $\dot{V}_A$ are usually measured under BTPS (body temperature and pressure, saturated) conditions whereas the concentrations $C_{aco_2}$ and $C_{vco_2}$ are usually measured under STPD (standard temperature and pressure, dry) conditions (see also Appendix A.5). For this reason we have introduced the factor $c = \frac{863}{P_a - 47}$ to convert the concentrations from STPD to BTPS conditions (for a description of the different measuring conditions see Appendix A.4). Here $P_a$ is the ambient pressure and 47 mmHg is the vapor pressure of water at body temperature. The ambient pressure and the vapor pressure of water will, however, cancel out of the model equations as soon as we express the fractional concentrations through partial pressures.

$F_p$ denotes pulmonary blood flow. In most respiratory models blood flow is a general parameter (see, for instance, Grodins [14] or Khoo et al. [30]). In this case no distinction...
Chapter 2. The respiratory part of the model

is made between pulmonary blood flow \( F_p \), systemic blood flow \( F_s \), left and right cardiac output \( Q_l \) and \( Q_r \). It is assumed that \( F_p = F_s = Q_l = Q_r \) which is actually only true during a steady state. In the present model, these blood flows are distinguished. Cardiac outputs, \( Q_l \) and \( Q_r \), will be defined in Section 3.3. Systemic and pulmonary blood flows, \( F_s \) and \( F_p \), will be connected to blood pressure and vascular resistance via Hagen-Poiseuille’s law (see Section 3.4). Systemic and pulmonary blood flows will be links between the respiratory and the cardiovascular part of the model.

For present purposes we regard the storage volume \( V_{A_{CO_2}} \), the carbon dioxide concentration in inspired air, \( F_{ICO_2} \), and the ambient pressure \( P_a \) as parameters.

A similar mass balance equation with analogous notation holds for \( O_2 \),

\[
V_{AO_2} \frac{dA_{O_2}}{dt} = \dot{V}_A(F_{tO_2} - F_{AO_2}(t)) + c F_p(t)(C_{VO_2}(t) - C_{aO_2}(t)).
\] (2.2)

We assume that the storage volume for oxygen, \( V_{AO_2} \), is equal to the gaseous lung volume (see Khoo et al. [30] or Longobardo et al. [43]).

The fractional concentrations can be expressed through the corresponding partial pressures (see Appendix A, relation (A.9)),

\[
\begin{align*}
P_{A_{CO_2}}(t) &= F_{A_{CO_2}}(t)(P_a - 47), \\
P_{AO_2}(t) &= F_{AO_2}(t)(P_a - 47), \\
P_{ICO_2} &= F_{ICO_2}(P_a - 47), \\
P_{IO_2} &= F_{IO_2}(P_a - 47).
\end{align*}
\] (2.3)

Here \( P_{A_{CO_2}} \) and \( P_{AO_2} \) are the partial pressures of \( CO_2 \) and \( O_2 \) in the alveolar gas mixture, and \( P_{ICO_2} \) and \( P_{IO_2} \) are the partial pressures of \( CO_2 \) and \( O_2 \) in inspired air (the latter are assumed constant). The diffusion of \( CO_2 \) and \( O_2 \) between pulmonary capillaries and alveoli is a very rapid process compared to other processes considered in this model (see, e.g., Netter [48], p.65). Therefore, we may assume that the alveolar gas tensions are instantly equilibrated with the arterial gas tensions of \( CO_2 \) and \( O_2 \),

\[
\begin{align*}
P_{A_{CO_2}}(t) &= p_{a_{CO_2}}(t), \\
P_{AO_2}(t) &= p_{a_{O_2}}(t),
\end{align*}
\] (2.4)

where \( p_{a_{CO_2}} \) and \( p_{a_{O_2}} \), respectively, are the partial pressures of \( CO_2 \) and \( O_2 \) in the arterial blood. (We neglect the fact that \( p_{a_{O_2}} \) is smaller than \( p_{a_{CO_2}} \) due to venous admixture from the bronchial circulation. Fincham and Tehrani [7], for instance, assume an alveolar-arterial difference of 4 mmHg). Finally, the mass balance equations for the lung compartment read

\[
\begin{align*}
V_{A_{CO_2}} \frac{dA_{CO_2}}{dt} &= \dot{V}_A(P_{tCO_2} - p_{a_{CO_2}}(t)) + 863 F_p(t)(C_{vCO_2}(t) - C_{aCO_2}(t)), \\
V_{AO_2} \frac{dA_{O_2}}{dt} &= \dot{V}_A(P_{tO_2} - p_{a_{O_2}}(t)) + 863 F_p(t)(C_{VO_2}(t) - C_{aO_2}(t)).
\end{align*}
\] (2.5) (2.6)
Chapter 2. The respiratory part of the model

2.3 The tissue compartment

We assume all body tissues lumped together in one single, homogeneous compartment. In particular, the brain tissue is also contained in this compartment.

In the tissues, the change of \( \text{CO}_2 \) (\( \text{O}_2 \)) volume is determined by a balance between the net rate of carbon dioxide (oxygen) transported to the tissues by the blood and the net rate at which carbon dioxide is produced (oxygen is utilized) by the tissues,

\[
V_{T\text{CO}_2} \dot{C}_{\text{T}\text{CO}_2}(t) = MR_{\text{CO}_2} + F_s(t)(C_{a\text{CO}_2}(t) - C_{v\text{CO}_2}(t)), \quad (2.7)
\]

\[
V_{T\text{O}_2} \dot{C}_{\text{T}\text{O}_2}(t) = -MR_{\text{O}_2} + F_s(t)(C_{a\text{O}_2}(t) - C_{v\text{O}_2}(t)). \quad (2.8)
\]

Here \( V_{T\text{CO}_2} \) and \( V_{T\text{O}_2} \) are the effective tissue storage volumes for \( \text{CO}_2 \) and \( \text{O}_2 \), respectively. \( MR_{\text{CO}_2} \) is the metabolic rate of carbon dioxide production, and \( MR_{\text{O}_2} \) is the metabolic oxygen consumption rate. For the moment we will regard them as parameters.

\( F_s \) is the systemic blood flow (i.e., the blood flow perfusing the tissue compartment). It will be specified in Section 3.4.

\( C_{T\text{CO}_2} \) and \( C_{T\text{O}_2} \) are the concentrations of \( \text{CO}_2 \) and \( \text{O}_2 \) in the tissue compartment. Since diffusion of \( \text{CO}_2 \) and \( \text{O}_2 \) between the capillaries and the interstitium happens rapidly, we may assume that the gas tensions in the body tissues are uniform and at every instant equal to those in the mixed venous blood returning to the lungs,

\[
C_{T\text{CO}_2}(t) = C_{v\text{CO}_2}(t),
\]

\[
C_{T\text{O}_2}(t) = C_{v\text{O}_2}(t). \quad (2.9)
\]

Therefore, the mass balance equations for the tissue compartment can be written in the form

\[
V_{T\text{CO}_2} \dot{C}_{v\text{CO}_2}(t) = MR_{\text{CO}_2} + F_s(t)(C_{a\text{CO}_2}(t) - C_{v\text{CO}_2}(t)), \quad (2.10)
\]

\[
V_{T\text{O}_2} \dot{C}_{v\text{O}_2}(t) = -MR_{\text{O}_2} + F_s(t)(C_{a\text{O}_2}(t) - C_{v\text{O}_2}(t)). \quad (2.11)
\]

2.4 Brain tissue and cerebral blood flow

The chemosensitive area of the respiratory center responds to the carbon dioxide tension in the brain tissue (compare Section 1.10). We will therefore also derive a mass balance equation for the brain tissue.

As before, the rate of change of \( \text{CO}_2 \) volume is determined by a balance between the net rate of carbon dioxide transported to the brain tissue by the blood and the net rate at which carbon dioxide is produced in the brain tissue,

\[
V_{B\text{CO}_2} \dot{C}_{B\text{CO}_2}(t) = MR_{B\text{CO}_2} + F_B(t)(C_{a\text{CO}_2}(t) - C_{vB\text{CO}_2}(t)). \quad (2.12)
\]
Here $V_{BCO_2}$ is the effective brain tissue storage volume for $CO_2$. $C_{BCO_2}$ is the concentration of total $CO_2$ in the brain tissue and $C_{vBCO_2}$ is the total $CO_2$ concentration in the venous blood leaving the brain tissue. $MR_{BCO_2}$ is the metabolic rate of carbon dioxide production in the brain. $MR_{BCO_2}$ and $V_{BCO_2}$ are assumed to be constant.

As above, we may assume that the $CO_2$ concentration in brain tissue is equilibrated with the $CO_2$ concentration in the venous blood leaving the brain,

$$C_{BCO_2}(t) = C_{vBCO_2}(t). \tag{2.13}$$

For cerebral blood flow $F_B$ we will for present purposes take only the influence of carbon dioxide into account (compare Section 1.5). As long as the carbon dioxide partial pressure in arterial blood stays around its normal value of 40 mmHg we may assume a linear relationship,

$$F_B(t) = F_{B_0}(1 + 0.03(P_{aCO_2}(t) - 40)). \tag{2.14}$$

Compare also Guyton [17] p. 339, or Khoo [36]. The parameter $F_{B_0}$ indicates the "normal" brain blood flow for $P_{aCO_2} = 40$ mmHg. We assume that a change in $P_{aCO_2}$ implies a rapid change in $F_B$, therefore we regard this relationship to be valid at every instant.

### 2.5 The dissociation relations

The dissociation relations describe the dependence of total gas concentration on the corresponding partial pressure (see Sections 1.7 and 1.8). We assume that the dissociation relations hold in arterial blood and venous blood as well as in the body tissues. For simplicity, we will use the general abbreviations $C_{CO_2}$ for carbon dioxide concentration, $P_{CO_2}$ for carbon dioxide partial pressure, and analogous notations for oxygen. We will apply these dissociation laws also during a non-steady state. This is admissible since the oxy-hemoglobin dissociation time is short compared to the transit time of the blood through the capillaries (0.01 s versus approximately 1 s, cf. Huntsman et al. [21]).

For the S-shaped oxygen dissociation curve we will use the relation

$$CO_2(t) = K_1(1 - e^{-K_2P_{O_2}(t)})^2. \tag{2.15}$$

This relation was also used by Fincham and Tehrani [7] or Nugent [52]. Khoo et al. [30] implemented a piecewise linear relationship.

For $CO_2$, considering the narrow working range of $P_{CO_2}$, we assume a linear dependence of $C_{CO_2}$ on $P_{CO_2}$,

$$C_{CO_2}(t) = K_{CO_2}P_{CO_2}(t) + k_{CO_2}. \tag{2.16}$$

A linear relationship was also used by Khoo et al. [30].
Chapter 2. The respiratory part of the model

2.6 An empirical formula for the ventilation

During rest, ventilation is mainly controlled by carbon dioxide and oxygen. The following empirical formula describes the steady-state response of total ventilation to changes in $\text{CO}_2$ and $\text{O}_2$ concentrations in arterial blood,

$$
\dot{V}_E = G_p e^{-0.05P_{a\text{O}_2}}(P_{a\text{CO}_2} - I_p) + G_c(P_{a\text{CO}_2} - I_c).
$$

(2.17)

This formula taken from Khoo [30] is based on experimental observations presented in the Handbook of Physiology [70], p.491. It contains total ventilation $\dot{V}_E$ rather than alveolar ventilation because total ventilation can be experimentally better determined. Total ventilation and alveolar ventilation are related via

$$
\dot{V}_E = \dot{V}_A + \dot{V}_D,
$$

(2.18)

where $\dot{V}_D$ denotes the dead space ventilation. Dead space ventilation is regarded as constant. Obviously, relation (2.17) is reasonable only for $\dot{V}_A = \dot{V}_E - \dot{V}_D > 0$.

The first term in (2.17) corresponds to the peripheral reflexes ("peripheral controller") exerted by $\text{CO}_2$ and $\text{O}_2$ (see Section 1.11). The second term corresponds to the influence of $\text{CO}_2$ upon the chemosensitive area ("central controller"; compare Section 1.10). According to (2.17) the peripheral and central controller interact additively and the peripheral interaction of $\text{CO}_2$ and $\text{O}_2$ is multiplicative. The empiric factors $G_p$ and $G_c$ determine the peripheral and central controller gain, respectively. $I_p$ and $I_c$ are empirical constants. The formula does not take the so-called "dogleg" phenomenon into account which means a probable threshold value for $P_{a\text{CO}_2}$ below which ventilation is unaffected by changes of $P_{a\text{CO}_2}$ (cf. Khoo [35] or Handbook of Physiology [70], p.496).

The central chemosensitive area responds most probably to the partial pressure of $\text{CO}_2$ in brain tissue rather than to that in arterial blood (see Guyton [17], p. 507). It has been observed that ventilation and cerebral venous $\text{CO}_2$ partial pressure reach their steady state values at about the same time (after 10 to 20 minutes) if the inspired $\text{CO}_2$ is increased. On the other hand, arterial $P_{\text{CO}_2}$ achieves its steady state value within 2 to 3 minutes (see Berne et al. [3], p.628 and p.632). To account for this we express $P_{a\text{CO}_2}$ in the central controller part of (2.17) in terms of the $\text{CO}_2$ partial pressure in the brain tissue, $P_{B\text{CO}_2}$. The steady-state relation between $P_{a\text{CO}_2}$ and $P_{B\text{CO}_2}$ is obtained with the help of (2.12), (2.13), and (2.16),

$$
P_{a\text{CO}_2} = P_{B\text{CO}_2} - \frac{MR_{B\text{CO}_2}}{K_{\text{CO}_2}F_B}.
$$

(2.19)

By inserting this into (2.17), we obtain the steady-state ventilatory response expressed in terms of $P_{B\text{CO}_2}$,

$$
\dot{V}_E = G_p e^{-0.05P_{a\text{O}_2}}(P_{a\text{CO}_2} - I_p) + G_c(P_{B\text{CO}_2} - \frac{MR_{B\text{CO}_2}}{K_{\text{CO}_2}F_B} - I_c).
$$

(2.20)
Chapter 3

The cardiovascular part of the model

The cardiovascular part of the model is based on the four compartment model by Grodins [15] and [16]. It was modified and adapted by Kappel and Peer [23] and in related papers (Kappel and Peer [24], Kappel et al. [25], Lafer [41], and Peer [55]). We will in the following describe the basic ideas of the model and revise it in view of a combination with the respiratory system.

3.1 The model structure

The cardiovascular part of the model consists of two circuits (systemic and pulmonary) which are arranged in series, and two pumps (left and right ventricle) (see Figure 3.1). The bewildering complex of arteries and veins, arterioles, and capillary networks of each circuit is lumped into three components: a single elastic artery, a single elastic vein, and a single resistance vessel (including the arterioles and the capillary net where the gas exchange occurs). Furthermore, each cardiac atrium is lumped with its corresponding vein.

A fixed blood volume $V_0$ is distributed among the systemic and pulmonary arteries and the systemic and pulmonary veins. The pumps and the resistance vessels are assumed to represent a negligibly small volume.

We ignore the events of the cardiac circle and assume unidirectional non-pulsatile blood flow through the left and right ventricle. Hence, during a steady state, left and right cardiac output $Q_l$ and $Q_r$, respectively, and the blood pressures $P_{as}$, $P_{va}$, $P_{ap}$, and $P_{vp}$ in the different parts of the circuits are constant. Their values correspond to the respective mean values over the length of a pulse (”a” refers to ”arterial”, ”v” to ”venous”, ”s” to ”systemic”, and ”p” to ”pulmonary”).
3.2 The mass balance equations

We derive a continuity equation for each of the four compartments which are the systemic artery, the systemic vein, the pulmonary artery, and the pulmonary vein. To this aim we mentally replace the pressure-dependent ventricles by mechanic pumps whose arbitrary outputs are independent of blood pressures ("isolated circuits").

Let us start with the systemic arterial compartment. Here, the rate of change of blood volume contained in the systemic artery, denoted by $\dot{V}_{as}$, is the difference between inflow $Q_l$ and outflow $F_s$,

$$\dot{V}_{as}(t) = Q_l(t) - F_s(t).$$  \hspace{1cm} (3.1)

Next, we wish to express the blood volume $V_{as}$ in terms of the blood pressure $P_{as}$. Since we are not going to model the sympathetic influence upon the unstressed vessel volume we may assume that this volume is zero. As a consequence, the blood volume contained in the vessel is always equal to the vessel volume. For this reason we may use the same notation for both, vessel volume and blood volume contained in the vessel. In case of the systemic arterial compartment, both will be denoted by $V_{as}$. 
The volume \( V_{as} \) of the arterial vessel depends on the transmural pressure. We will assume that the extravasal pressure is zero, i.e., the transmural pressure is equal to the mean arterial blood pressure \( P_{as} \). If the transmural pressure increases, the volume of the vessel increases. We will use the simple relation

\[
c_{as} P_{as}(t) = V_{as}(t), \tag{3.2}
\]

i.e., the blood pressure is at every instant proportional to the blood volume contained in the compartment. Furthermore, we will neglect myogenic changes in vessel volume which occur particularly in arterial vessels (Bayliss effect) and assume that the compliance \( c_{as} \) is constant. The compliance of the arterial system plays an important role. Dilatation of the vessels during the systole and relaxation during the diastole damps the flow pulse generated by the pumps ("Windkessel effect"). The very same mechanism is also used in water reservoirs to obtain continuous water flow. The compliance of the veins is much larger than the compliance of the arteries. As a consequence, the venous blood pressure increases only slightly if the venous blood volume is increased.

Finally, the mass balance equation for the arterial systemic compartment can be written in the form

\[
c_{as} \dot{P}_{as}(t) = Q_{l}(t) - F_{s}(t). \tag{3.3}
\]

Analogous equations can be derived for each of the other three compartments,

\[
\begin{align*}
c_{vs} \dot{P}_{vs}(t) &= F_{s}(t) - Q_{r}(t), \\
c_{ap} \dot{P}_{ap}(t) &= Q_{r}(t) - F_{p}(t), \\
c_{vp} \dot{P}_{vp}(t) &= F_{p}(t) - Q_{l}(t). \tag{3.4}
\end{align*}
\]

Since the total blood volume \( V_{0} \) is constant, we can eliminate one of the differential equations (3.4). We will choose the arterial pulmonary compartment and replace the differential equation for \( P_{ap} \) by the algebraic relation

\[
P_{ap}(t) = \frac{1}{c_{ap}} \left( V_{0} - c_{as} P_{as}(t) - c_{vs} P_{vs}(t) - c_{vp} P_{vp}(t) \right). \tag{3.5}
\]

### 3.3 The dependence of ventricle output on the blood pressures

During a steady state, left cardiac output \( Q_{l} \) is constant and defined as the mean blood flow over the length of a pulse,

\[
Q_{l} = H V_{str,l}, \tag{3.6}
\]
where $H$ is the heart rate and $V_{str,l}$ the stroke volume of the left ventricle. We will use this definition also during a non-steady state, where the heart rate and the stroke volume may vary with time. In this case, $Q_l(t)$ may be interpreted as an averaged left cardiac output. Analogous notations and considerations hold for the right ventricle.

The arterial and venous blood pressures depend on the cardiac outputs via the continuity equations (3.3) and (3.4). In turn, the cardiac outputs depend on the blood pressures. To derive these relationships, we will regard the venous filling pressure, the arterial load pressure (pressure opposing the ejection of blood) and the heart rate as constant inputs which can be set arbitrarily. This way, the influence of each of them upon cardiac output and ventricular volumes can be studied ("isolated heart"). We will analyze the steady state operation of the isolated ventricle in terms of a filling and an emptying process. Since the investigations are analogous for the systemic and the pulmonary circuit we will in the following omit the subscripts for "right" and "left" and for "systemic" and "pulmonary".

Our goal is to derive the dependence of the stroke volume $V_{str}$ on the venous (filling) pressure and the arterial (load) pressure. We will start with the filling process.

At its beginning the ventricle has a residual volume, $V_r$. It fills for $t_d$ minutes and at the end its volume will be the end-diastolic volume $V_d$. The filling of the ventricle is driven by a constant venous pressure $P_v$ and opposed by visco-elastic forces $R$ generated within the heart. We assume that the filling process can be described by a first-order differential equation,

$$R\dot{V}(t) + \frac{1}{c}V(t) = P_v, \quad V(0) = V_r. \tag{3.7}$$

Here $c$ denotes the compliance of the relaxed ventricle. We have assumed that the unstressed volume of the relaxed ventricle is zero. The solution to this differential equation is

$$V(t) = (V_r - cP_v)e^{-\frac{t}{Rc}} + cP_v. \tag{3.8}$$

It describes the momentary volume of the ventricle during diastole. Especially, after $t_d$ minutes, the volume of the ventricle is the end-diastolic volume $V_d = V(t_d)$, which is given by

$$V_d = (V_r - cP_v)e^{-\frac{t_d}{Rc}} + cP_v. \tag{3.9}$$

Let us now turn to the emptying process. At the beginning of the emptying process, the ventricle contains the end-diastolic volume $V_d$. It ejects the stroke volume $V_{str}$ against the arterial blood pressure $P_a$ and leaves behind the residual volume $V_r$,

$$V_{str} = V_d - V_r. \tag{3.10}$$

For the relationship between stroke volume $V_{str}$, arterial load pressure $P_a$, and end-diastolic volume $V_d$ we use a simple model based on Starling’s law (cf. Section 1.6),

$$V_{str} = S \frac{V_d}{P_a}. \tag{3.11}$$
In doing so we neglect the dynamics of the ejection process and look only at its beginning and end. The proportionality constant $S$ describes the strength of the ventricle and is called contractility. Obviously, relation (3.11) makes only sense for

$$\frac{S}{P_a} \leq 1,$$

(3.12)

since otherwise more blood volume would be ejected than has been contained in the ventricle. To make (3.11) meaningful for all pairs of $S$ and $P_a$, we replace $S$ in (3.11) by the function $f(S, P_a)$,

$$V_{str} = f(S, P_a) \frac{V_d}{P_a},$$

(3.13)

where $f$ is defined as (cf. Kappel et al. [25])

$$f(s, p) = 0.5(s + p) - 0.5((p - s)^2 + 0.01)^{1/2}. $$

(3.14)

This function is in principle equal to the minimum function $\min(s, p)$. The term $0.01$ is introduced to smooth $f(s, p)$ around $s = p$.

Using relations (3.9), (3.10), and (3.13) we get the dependence of $V_{str}$ upon $P_v$, $P_a$, and $S$,

$$V_{str} = \frac{cP_v f(S, P_a)(1 - e^{-\frac{t_d}{P_a}})}{P_a(1 - e^{-\frac{t_d}{P_a}}) + f(S, P_a)e^{-\frac{t_d}{P_a}}}. $$

(3.15)

For the duration of the diastole we assume

$$t_d = \frac{60}{P} - \kappa \left(\frac{60}{P}\right)^{1/2},$$

(3.16)

with the empirical factor $\kappa = 0.4$ (see Kappel and Peer [24]). We can now write the left and right cardiac output as

$$Q_l = H \frac{c_l P_{sv} f(S_l, P_{as})(1 - e^{-\frac{t_d}{P_{as}}})}{P_{as}(1 - e^{-\frac{t_d}{P_{as}}}) + f(S_l, P_{as})e^{-\frac{t_d}{P_{as}}}}, $$

$$Q_r = H \frac{c_r P_{vs} f(S_r, P_{ap})(1 - e^{-\frac{t_d}{P_{ap}}})}{P_{ap}(1 - e^{-\frac{t_d}{P_{ap}}}) + f(S_r, P_{ap})e^{-\frac{t_d}{P_{ap}}}}.$$  

(3.17)

The substance of these rather complicated looking expressions can be seen as follows. If we would neglect the dynamics of the filling process by assuming a negligibly small resistance $R$
opposing the filling process, then the end-diastolic volume would be \( V_d = cP_e \). In consequence, the stroke volume would become (with Starling’s law)

\[
V_{str} = S \frac{cP_e}{P_a}.
\]

(3.18)

(Here we have also omitted the substitution \( S \rightarrow f(S, P_a) \).) This would yield simpler expressions for the cardiac outputs,

\[
Q_l = H S_l \frac{c_P_{vp}}{P_{as}},
\]

\[
Q_r = H S_r \frac{c_P_{vs}}{P_{ap}}.
\]

(3.19)

These relations are obtained from (3.17) by letting \( t_d \rightarrow \infty \).

3.4 Hagen-Poiseuille’s law

We assume that blood is a homogeneous fluid whose flow depends on the driving pressure difference and on the opposing viscous resistance via Hagen-Poiseuille’s law,

\[
F_s(t) = \frac{P_{as}(t) - P_{vs}(t)}{R_s},
\]

\[
F_p(t) = \frac{P_{ap}(t) - P_{vp}(t)}{R_p}.
\]

(3.20)

(3.21)

Here \( F_s \) and \( F_p \) denote the systemic and pulmonary blood flow, respectively, and \( R_s \) and \( R_p \) are the corresponding resistances.

If the pressure inside a vessel increases, then the radius of the vessel increases and therefore the resistance decreases. That is, the resistance depends upon blood pressure (passive dependence, cf. Klinke [37], p. 149). However, to simplify matters, we will neglect any passive or active (myogenic) reactions of the resistance vessels and consider \( R_s \) and \( R_p \) independent of blood pressure (see also Section 1.3). For a model considering the dependence of resistance upon blood pressure and flow see, e.g., Kenner and Bergmann [27], and Kenner and Ono [28]. Metabolic autoregulation will be taken into account when modeling exercise. So far, by regarding \( R_s \) and \( R_p \) as parameters, we have modeled the resistance vessels as rigid tubes.

3.5 Relationship between heart rate and contractilities

Most descriptions of cardiac function concentrate on three major controlling mechanisms. These are the Frank-Starling mechanism ("length-tension-relationship"), neural and other
influences that affect cardiac force independently of muscle length (inotropic mechanisms),
and the influence of afterload ("force-velocity relationship").

However, there is a missing component for the understanding of cardiac function. If an
isolated strip of cardiac muscle is fixed at its two ends and electrically stimulated to contract
at different rates and rhythms the force developed is not identical in each contraction. It
varies in a complicated but reproducible way with the pattern of stimulation. Since the
three factors mentioned above are held constant in such an experiment, and cardiac muscle
responds to stimulation with an all or nothing contraction, this sensitivity to the interval
between contractions must be and intrinsic property of the muscle. It is known as the force-
interval or strength-interval relation. The original observations on this topic were made by
Bowditch [4] more than 100 years ago (compare Seed and Walker [62] and see also Section
1.6).

We take the Bowditch effect into account by assuming that the contractility of the car-
diac muscle is increased if heart rate is increased. Studies conducted by Kappel and Peer
[23] showed that a better adaption of the model to experimental data is obtained if the
contractility follows the heart rate with a second order delay,

\[ \ddot{S}(t) + \gamma \dot{S}(t) + \alpha S(t) = \beta H. \]  

(3.22)

For simplicity we have omitted the subscripts for "left" and "right". The constants \( \alpha, \beta \)
and \( \gamma \) must be determined by parameter identification.

The steady state and therefore the asymptotic behavior is determined by the quotient of
\( \beta \) and \( \alpha \),

\[ S = \frac{\beta}{\alpha} H. \]  

(3.23)

If heart rate is suddenly changed to the constant value \( H \) (step-input) then the dynamics of
\( S(t) \) depends on the damping-ratio \( \delta = \frac{\gamma}{\sqrt{\alpha}} \). For \( 0 < \delta < 1 \) the contractility \( S \) oscillates
around its final value \( \frac{\beta}{\alpha} H \) before settling down. In case of greater damping, if \( \delta \geq 1 \), contrac-
tility follows the increased heart rate more or less slowly to its new steady state value. The
greater the damping the closer is the dominating eigenvalue to zero and therefore the longer
will it take until \( S \) reaches its final value.

To obtain differential equations of first order we introduce

\[ \sigma = \dot{S}. \]  

(3.24)

Then (3.22) yields

\[ \dot{S}(t) = \sigma(t), \]
\[ \dot{\sigma}(t) = -\gamma \sigma(t) - \alpha S(t) + \beta H. \]  

(3.25)
Chapter 4

The general cardiovascular and respiratory model

If we combine the model equations for the respiratory and the cardiovascular part that have been derived in the preceding Chapters we get a model structure as shown in Figure 4.1. This combined model is described by the following set of differential equations,

\[ \begin{align*}
    c_{as} \dot{P}_{as}(t) &= Q_l(t) - F_s(t), \\
    c_{vs} \dot{P}_{vs}(t) &= F_s(t) - Q_r(t), \\
    c_{vp} \dot{P}_{vp}(t) &= F_p(t) - Q_l(t), \\
    V_{A\text{CO}_2} \dot{C}_{a\text{CO}_2}(t) &= 863F_p(t)(C_{v\text{CO}_2}(t) - C_{a\text{CO}_2}(t)) + \dot{V}_A(P_{\text{ICO}_2} - P_{a\text{CO}_2}(t)), \\
    V_{A\text{O}_2} \dot{C}_{a\text{O}_2}(t) &= 863F_p(t)(C_{v\text{O}_2}(t) - C_{a\text{O}_2}(t)) + \dot{V}_A(P_{\text{IO}_2} - P_{a\text{O}_2}(t)), \\
    V_{B\text{CO}_2} \dot{C}_{B\text{CO}_2}(t) &= MR_{B\text{CO}_2} + F_B(t)(C_{a\text{CO}_2}(t) - C_{B\text{CO}_2}(t)), \\
    V_{T\text{CO}_2} \dot{C}_{v\text{CO}_2}(t) &= MR_{\text{CO}_2} + F_s(t)(C_{a\text{CO}_2}(t) - C_{v\text{CO}_2}(t)), \\
    V_{T\text{O}_2} \dot{C}_{v\text{O}_2}(t) &= -MR_{\text{O}_2} + F_s(t)(C_{a\text{O}_2}(t) - C_{v\text{O}_2}(t)), \\
    \dot{S}_l(t) &= \sigma_l(t), \\
    \dot{S}_r(t) &= \sigma_r(t), \\
    \dot{\sigma}_l(t) &= -\gamma_l \sigma_l(t) - \alpha_l S_l(t) + \beta_l H, \\
    \dot{\sigma}_r(t) &= -\gamma_r \sigma_r(t) - \alpha_r S_r(t) + \beta_r H.
\end{align*} \]

(4.1)

Arterial pulmonary pressure is given by the algebraic equation,

\[ P_{ap}(t) = \frac{1}{c_{ap}}(V_0 - c_{as}P_{as}(t) - c_{vs}P_{vs}(t) - c_{vp}P_{vp}(t)). \]

(4.2)
The systemic and pulmonary blood flows are defined by

\[ F_s(t) = \frac{P_{as}(t) - P_{as}(t)}{R_s}, \quad (4.3) \]

\[ F_p(t) = \frac{P_{ap}(t) - P_{vp}(t)}{R_p}. \quad (4.4) \]

Brain blood flow is given by

\[ F_B(t) = F_{B0}(1 + 0.03(P_{aCO_2}(t) - 40)). \quad (4.5) \]

Left and right cardiac output depend on the blood pressures and the heart rate via

\[ Q_l(t) = H \frac{c_l P_{vp}(t)f(S_l(t), P_{as}(t))(1 - e^{-\frac{t_d}{\pi_{cl}}})}{P_{as}(t)(1 - e^{-\frac{t_d}{\pi_{cl}}}) + f(S_l(t), P_{as}(t))e^{-\frac{td}{\pi_{cl}}}}, \quad (4.6) \]

\[ Q_r(t) = H \frac{c_r P_{vp}(t)f(S_r(t), P_{ap}(t))(1 - e^{-\frac{t_d}{\pi_{cr}}})}{P_{ap}(t)(1 - e^{-\frac{t_d}{\pi_{cr}}}) + f(S_r(t), P_{ap}(t))e^{-\frac{td}{\pi_{cr}}}}. \quad (4.7) \]

The duration of the diastole is given by

\[ t_d = \left(\frac{60}{P_a}\right)^{1/2}\left(\left(\frac{60}{P_a}\right)^{1/2} - \kappa\right). \quad (4.8) \]

The function \( f(s, p) \) has been defined in (3.14). Moreover, the gas concentrations and the corresponding partial pressures are related by the dissociation laws

\[ C_{aO_2}(t) = K_1(1 - e^{-K_2P_{aO_2}(t)})^2, \]
\[ C_{vO_2}(t) = K_1(1 - e^{-K_2P_{vO_2}(t)})^2, \]
\[ C_{aCO_2}(t) = K_{CO_2}P_{aCO_2}(t) + k_{CO_2}, \quad (4.9) \]
\[ C_{vCO_2}(t) = K_{CO_2}P_{vCO_2}(t) + k_{CO_2}, \]
\[ C_{BCO_2}(t) = K_{CO_2}P_{BCO_2}(t) + k_{CO_2}. \]

Total ventilation during rest can be described by the empirical feedback relationship

\[ \dot{V}_E = G_p e^{-0.05P_{aO_2}(P_{aCO_2} - I_p)} + G_c(P_{aCO_2} - I_c), \quad (4.10) \]

and alveolar ventilation is obtained by

\[ \dot{V}_A = \dot{V}_E - \dot{V}_D. \quad (4.11) \]

In particular, \( H, MR_{CO_2}, MR_{O_2}, \) and \( R_s \) are regarded as parameters.
Figure 4.1: The cardiovascular and respiratory model
Chapter 5

The model for exercise

We are going to model the situation where a person performs exercise (e.g., a bicycle ergometer test). In particular, a constant ergometric workload $W$ will be imposed. We will only treat the case of exercise below the anaerobic threshold. In this case, the amount of energy consumed by the muscles is equal to the aerobic energy supply and a new steady state can be reached. The limit for aerobic exercise for an average male test person in good physical condition lies between 110 and 130 Watt (compare Stegemann [63], p. 283). A concise treatment of exercise physiology is given by Falls [6], Rowell [60], or Stegemann [63].

5.1 Aerobic and anaerobic exercise

The basic source of energy for muscle contraction is adenosine triphosphate (ATP). It is present in almost all living cells. ATP delivers energy, e.g., for ion transport against a concentration gradient, for biosynthesis, and, last but not least, it supplies the energy for muscle contraction.

At the onset of exercise, suddenly a large amount of energy is needed. The amount of ATP present in the muscles is sufficient to sustain maximal muscle power for only 5 to 6 seconds. However, there is another energy reservoir, creatin phosphate (CP), whose concentration in the muscle cells is two or three times the concentration of ATP. The feature of the CP energy supply is that it can anaerobically furnish energy for the resynthesis of ATP within a small fraction of a second. Therefore, all the energy stored in the muscle CP is instantaneously available for muscle contraction, just as the energy stored in ATP. Cell CP together with ATP can provide maximal muscle power for a period of 10 to 15 seconds (e.g., enough for a 100 meter dash).

As the increasing blood flow supplies the tissues with more nutrients and oxygen more energy can be supplied aerobically. The aerobic energy system means the oxidation of foodstuff in the mitochondria to provide energy. Here, glucose, fatty acids, and amino acids combine
Chapter 5. The model for exercise

with oxygen to release tremendous amounts of energy that are used for the resynthesis of ATP. The waste products are water and carbon dioxide. If the imposed workload is not too high, a steady state can finally be reached, where all the needed energy is supplied by the aerobic mechanism.

However, if the blood flow is not high enough to supply the needed oxygen and nutrients, or if the oxygen consumption exceeds an upper limit $\dot{V}_{O_{2}}_{\text{max}}$, additional energy must be furnished (the value of $\dot{V}_{O_{2}}_{\text{max}}$ is determined by enzyme kinetics in the muscle tissue and depends on the training level). This third mechanism of metabolic energy supply is the glycogen-lactic acid system. Usually, the stored glycogen in the muscle is split into glucose which, in turn, is split into pyruvic acid and ATP. This process occurs entirely without the use of oxygen (anaerobic glycolysis). Now, if there is sufficient oxygen, the pyruvic acid enters the mitochondria and reacts with oxygen to form still more ATP (aerobic energy production). If, however, there is insufficient oxygen for the aerobic stage of the glucose metabolism, the pyruvic acid is converted in lactic acid, which diffuses out of the muscle cells into the blood.

Anaerobic muscle metabolism usually leads to fatigue and exhaustion, for different reasons. If the blood flow through the muscles is too slow to remove lactate as fast as it is formed it will accumulate in the muscle and inhibit further muscle contractions. Another reason is the accumulation of lactic acid and therefore the development of acidosis. A third reason may be the wearing down of the glycogen stores.

The anaerobic breakdown of glucose is less effective. It furnishes only 2 mole ATP per mole of glucose whereas the aerobic breakdown produces 36 mole of ATP. On the other hand, the anaerobic breakdown of glycogen forms ATP more rapidly as the oxidative mechanism of the mitochondria, and can therefore provide energy for 30 to 40 seconds of maximal muscle activity in addition to the 10 to 15 seconds provided by the initial breakdown of the ATP and CP stores.

In the first period after the onset of exercise, where the ATP and CP stores are exhausted, the organism makes a so-called oxygen debt. This debt has to be repaid after cessation of exercise, that is, an extra amount of oxygen must be taken into the body to restore all the metabolic systems back to their initial state. Part of this debt results from usage of oxygen that is already stored in the body (oxygen bound to myoglobin and to hemoglobin, oxygen in the air of the lungs and in the body fluids). Most of this oxygen can be used by the muscles during exercise and must be repaid after exercise is over. Additional oxygen debt can result from the need to metabolize lactic acid and refill the exhausted ATP and CP stores of the body.
5.2 The metabolic rates during exercise

In our model, the metabolic rates show up in the oxygen and carbon dioxide balance equations (see Section 2.3),

\[
\begin{align*}
VT_{\text{O}_2} & \dot{C}_{\text{vO}_2}(t) = -MR_{\text{O}_2} + F_s(t)(C_{\text{aO}_2}(t) - C_{\text{vO}_2}(t)), \\
VT_{\text{CO}_2} & \dot{C}_{\text{vCO}_2}(t) = MR_{\text{CO}_2} + F_s(t)(C_{\text{aCO}_2}(t) - C_{\text{vCO}_2}(t)).
\end{align*}
\] (5.1)

For the brain tissue we have only considered a carbon dioxide balance (2.12), since it was assumed that the brain blood flow depends only on the carbon dioxide concentration. According to Lambertsen [42], on an average for the entire brain, no detectable changes in its \(O_2\) (and \(CO_2\)) metabolism occur over a wide range of physiologic stresses, including muscular exercise. We will therefore assume that brain metabolism remains constant during exercise.

As far as the tissue compartment is concerned, the oxygen consumption of the working muscles increases manifold during exercise and so does the carbon dioxide production. However, in the first minutes after the onset of exercise the delivery of oxygen to the muscles by the blood flow cannot keep up with the energy demands (see the preceding section). During this short period, some part of the needed energy is supplied anaerobically. In other words, the oxygen demand \(MR_{\text{O}_2}^e\) of the muscles is made up by an aerobic term, the oxygen supply \(MR_{\text{O}_2}(t)\) of the muscles, and an anaerobic term \(M_{sp}(t)\),

\[
MR_{\text{O}_2}^e = MR_{\text{O}_2}(t) + M_{sp}(t).
\] (5.2)

In case of a constant workload below the anaerobic threshold the aerobic term increases exponentially and the anaerobic term decreases exponentially.

There are two possibilities to model the initial anaerobic energy supply. First, we may assume that the metabolic oxygen consumption rate \(MR_{\text{O}_2}(t)\) rises exponentially from the constant initial value \(MR_{\text{O}_2}^r\) to the new constant value \(MR_{\text{O}_2}^e\),

\[
MR_{\text{O}_2}(t) = MR_{\text{O}_2}^r + (MR_{\text{O}_2}^e - MR_{\text{O}_2}^r)(1 - e^{-t/\tau_a}).
\] (5.3)

The time constant \(\tau_a\) of the exponential function can be chosen according to Stegemann [63], p. 51, \(\tau_a = 0.5\). After \(4\tau_a\) minutes the momentary oxygen supply has reached 98% of the total oxygen demand. In this case, the oxygen balance equation attains the following form during exercise,

\[
VT_{\text{O}_2} \dot{C}_{\text{vO}_2}(t) = -MR_{\text{O}_2}(t) + F_s(t)(C_{\text{aO}_2}(t) - C_{\text{vO}_2}(t)),
\] (5.4)

with \(MR_{\text{O}_2}(t)\) as given in (5.3).

An alternative is the approach chosen by Kappel and Peer [23]. It is assumed that the anaerobic part of energy supply increases as the venous (the tissue) oxygen concentration decreases,

\[
M_{sp}(t) = -K \dot{C}_{\text{vO}_2}(t).
\] (5.5)
Substitution for $MR_{O_2}(t)$ in (5.1) using $MR_{O_2}(t) = MR^e_{O_2} - M_{sp}(t)$, yields the following differential equation for $C_{vo_2}(t)$,

$$(V_{T_{O_2}} + K)\dot{C}_{vo_2}(t) = -MR^e_{O_2} + F_s(t)(C_{ao_2}(t) - C_{vo_2}(t))$$

(5.6)

The term on the left hand side indicates the change of volume of stored oxygen in the tissue and of the stored high energy phosphates. The value of the constant $K$ must be determined by parameter identification, e.g., $K = 19.2$ liters in Kappel and Peer [24].

The increase in metabolic rate is proportional to the workload. As in Kappel and Peer [24], we use the relationship

$$MR^e_{O_2} = MR_{O_2} + \rho W.$$  
(5.7)

Here the parameter $\rho$ characterizes the physical condition of the exercising person. We will furthermore assume that the rate of carbon dioxide production, $MR_{CO_2}(t)$, is at every instant related to the oxygen consumption $MR_{O_2}(t)$ by

$$MR_{CO_2}(t) = RQ MR_{O_2}(t),$$

(5.8)

where $RQ$ denotes the constant respiratory quotient.

### 5.3 Vessel resistance during exercise

The increased sympathetic activity during exercise has a constrictory effect on the blood vessels. However, in organs with increased metabolic activity, there is a need for more blood flow in order to supply the necessary oxygen and to remove the excess carbon dioxide. This is achieved by a local vasodilatation (metabolic autoregulation). In consequence, in the exercising muscles, metabolic vasodilatation more or less predominates over the vasoconstrictor influence of the nervous vegetative system.

The net vasoconstriction depends on the conditions under which the exercise is performed (cf. Guyton [17], p. 337, or Klinke et al. [37], p. 165). When a person exercises very tensely but uses only a few muscles (e.g., arm exercise when nailing on the ceiling or cutting the hedge), the sympathetic response occurs everywhere in the body and vasodilatation occurs only in the exercising muscles. Therefore, the net effect is mainly vasoconstriction, with the consequence that the mean arterial pressure may increase as high as 180 mmHg. On the other hand, when a person performs whole body exercise, the extreme vasodilatation in large muscle masses leads to an increase in mean arterial pressure by only 20 to 40 mmHg.

We distinguish in the model between the resistance of the pulmonary vessels, $R_p$, and the resistance of the systemic vessels, $R_s$. According to e.g., Fung [11], p. 341, or Falls [6], p. 101, pulmonary resistance decreases during exercise. We will for present purposes not investigate
the underlying control but simply assume that $R_p$ decreases exponentially from a given ”rest” value $R_p^r$ to a given ”exercise” value $R_p^e$ according to

$$R_p(t) = R_p^r + (R_p^e - R_p^r)(1 - e^{-t/\tau_p}).$$  \hspace{1cm} (5.9)

In Kappel and Peer [23], $R_p$ was taken as a parameter whose value changed as soon as the workload was imposed. The values of $R_p$ for ”rest” and ”excise” were obtained by parameter identification.

As far as the systemic resistance $R_s$ is concerned, we consider that in most cases a net decrease of total systemic resistance occurs during exercise. Therefore it seems reasonable to pay more attention to the modeling of the metabolic dilatation.

There are several biochemical indices of how hard the tissue is working. Among these are the tissue concentrations of $H^+$, $CO_2$, $O_2$, and lactic acid. These concentrations are reflected in the venous blood of a tissue. The arterial blood has the same composition for all tissues in the body, so it cannot be used in a local control mechanism. This raises a problem since the organism regulates the vessel resistance primarily on the arterial side of a tissue at the level of small arteries and arterioles. The resolution of this problem may lie in the fact that the arterioles are embedded in the tissue which they supply with blood so that the outsides of their walls sense the tissue concentrations.

Of all the different factors causing local vasodilatation, the reduction of oxygen in the muscle tissues seems to be the most important one. We will assume that systemic resistance depends on the venous $O_2$ concentration via

$$R_s(t) = A_{pesk}C_{vo2}(t).$$  \hspace{1cm} (5.10)

This relationship was originally introduced by Peskin [56]. It is based on a model for autoregulation first developed by Huntsman et al. [21]. Relationship (5.10) was also used by Kappel and Peer [23]. There, the value for $A_{pesk}$ was determined by parameter identification. In order to achieve better results for the adaption of the model to the measured data it was necessary to assume different parameter values for $A_{pesk}$ during ”rest” and ”exercise”.

We will here make the transient from the ”rest” to the ”exercise”-value continuous by the assumption that $A_{pesk}$ is a time-varying function of the form

$$A_{pesk}(t) = A_{pesk}^r + (A_{pesk}^e - A_{pesk}^r)(1 - e^{-t/\tau_s}).$$  \hspace{1cm} (5.11)

The sympathetic vasoconstrictor influence on the systemic resistance will not be considered for the time being.

5.4 The heart rate during exercise

At the onset of exercise, the heart rate is immediately increased. If the level of exercise remains below the anaerobic threshold, the heart rate reaches a new steady state after 1 to 3
Chapter 5. The model for exercise

35

minutes. This new steady state value is proportional to the increase in oxygen consumption. For instance, Stegemann and Kenner observed that, when blood flow in various muscles was occluded during rest and during exercise, the relationship between the heart rate and the oxygen debt repaid was the same regardless of the way in which the debt had been induced ([63], [64], and [65]).

It is generally accepted that at the onset of exercise the motor cortex emits impulses to the muscles as well as to the circulatory center ("central command"). These impulses are essential for the immediate increase in heart rate. Central command appears to raise the heart rate by withdrawal of vagal activity (cf., e.g., Rowell [60]). Only gradually the slower sympathetic activation of the heart becomes dominant. For a more detailed model of the influence of vagal and sympathetic stimulation on heart rate see Lafer [41]. The hypothesis of central command is supported by the observation that an unsuccessful attempt to contract paralyzed muscles is still accompanied by an increase in heart rate (see e.g., Freyschuss [10]).

However, it is doubtful that the cortical impulses are responsible for the exact adaption of the cardiovascular system to exercise. It is therefore assumed that the central command signals are modulated by feedback signals from active muscles and other reflexes. There are many studies concerning the nature of these reflexes. A comprehensive review is given by Rowell [60].

For the dynamic behavior of the heart rate, we make the same assumption as Kappel and Peer [23]. The controlling instances of the organism which determine the heart rate (vasomotor center) are lumped into one controller. The variation of the heart rate is regarded as an output of the controller,

\[ \dot{H} = u_1(t). \]  

(5.12)

The input of the controller will be information about mean blood pressure and blood gas concentrations (see Section 8.3).

5.5 Alveolar ventilation during exercise

We will also consider alveolar ventilation \( \dot{V}_A \) as a time-varying quantity, \( \dot{V}_A = \dot{V}_A(t) \). It will be defined such that during a steady state, \( \dot{V}_A(t) \) is constant and equal to the mean value \( \dot{V}_A = V_A f \). Here \( V_A \) denotes the volume of the alveolar compartment and \( f \) denotes the frequency of respiration. This definition is commonly used in respiratory physiology.

As described in Section 1.9 alveolar ventilation is adjusted by the respiratory center to maintain proper concentrations of oxygen, carbon dioxide and hydrogen ion concentration in the body fluids. During exercise, oxygen utilization and carbon dioxide formation can increase tremendously. Yet, alveolar ventilation increases almost exactly in step with the increased level of metabolism. As a consequence, the \( CO_2 \), \( O_2 \) and hydrogen ion concentrations in the blood remain almost exactly constant.
One is tempted to explain the increase in ventilation as a consequence of chemical alterations in the body fluids, including the increase of carbon dioxide and hydrogen ions, and the decrease of oxygen. However, it has been observed that alveolar ventilation increases without an initial increase in arterial $CO_2$ concentration. Furthermore, none of the chemical concentrations change significantly and certainly not enough to account for more than only a small percentage of the increase in ventilation. Experiments have shown that even if a very high $CO_2$ concentration should develop during exercise, this would be sufficient to account only for two thirds of the increased ventilation that develops during heavy muscular exercise (see Guyton [17], p. 512).

There seem to be at least two different effects that cause the increase in ventilation during exercise. First, it is assumed that the motor cortex, on transmitting impulses to the contracting muscles, transmits collateral impulses into the brain stem to excite the respiratory center. That is, at the same time that the brain excites the muscle, an anticipatory signal from the brain increases alveolar ventilation. This is analogous to the hypothesis that the higher centers of the brain stimulate the vasomotor center during exercise (see the preceding section).

Second, it is believed that the body movements, especially of the limbs, increase pulmonary ventilation by exciting proprioceptors which then transmit excitatory impulses to the respiratory center. The reason for this hypothesis is that even passive movements of the limbs often increase pulmonary ventilation severalfold. There may be other factors, such as hypoxia developing in the muscles, but since the increase of ventilation begins immediately as exercise sets in, the two factors mentioned above will probably play the most important role.

As far as the chemical factors are concerned, it is assumed that they make the final adjustments in the control of respiration whenever the anticipatory nervous signal is too strong or too weak to supply the extra oxygen and get rid of the extra carbon dioxide.

What are the factors which determine the intensity of the anticipatory signal by the brain? Many experiments indicate that the signal is partly if not entirely a learned response. With repeated periods of exercise with the same degree of strenuousness, the brain appears to become more and more able to increase ventilation the proper amount to maintain the chemical factors at their normal levels during exercise. Hence, there is reason to believe that some of the higher centers of learning (cerebral cortex) are important with regard to the brain signal. Indeed, if a person is anesthetized, and therefore the higher centers become nonfunctional, respiratory control is mediated almost entirely by the chemical factors.

Like heart rate, we will also consider the variation of alveolar ventilation as an output of the controller,

$$\dot{V}_A(t) = u_2(t).$$  \hspace{1cm} (5.13)

Here we have denoted $\frac{dV_A}{dt} = \ddot{V}_A$. 
5.6 The model equations for exercise

Figure 5.1 shows the structure of the cardiovascular and respiratory model for exercise. It consists of the following set of differential equations,

\[
\begin{align*}
\dot{c}_a s P_{as} (t) &= Q_l (t) - F_s (t), \\
\dot{c}_v s P_{vs} (t) &= F_s (t) - Q_r (t), \\
\dot{c}_v p P_{vp} (t) &= F_p (t) - Q_l (t), \\
V_{ACO_2} \dot{P}_{ACO_2} (t) &= 863 F_p (t) (C_{vCO_2} (t) - C_{aCO_2} (t)) + \dot{V}_A (t) (P_{lCO_2} - P_{aCO_2} (t)), \\
V_{AO_2} \dot{P}_{AO_2} (t) &= 863 F_p (t) (C_{vO_2} (t) - C_{aO_2} (t)) + \dot{V}_A (t) (P_{lO_2} - P_{aO_2} (t)), \\
V_{BCO_2} \dot{C}_{BCO_2} (t) &= M R_{BCO_2} + F_B (t) (C_{aCO_2} (t) - C_{BCO_2} (t)), \\
V_{TCO_2} \dot{C}_{vCO_2} (t) &= M R_{CO_2} + F_s (t) (C_{aCO_2} (t) - C_{vCO_2} (t)), \\
V_{TO_2} \dot{C}_{vO_2} (t) &= - M R_{O_2} + F_s (t) (C_{aO_2} (t) - C_{vO_2} (t)), \\
\dot{\sigma}_l (t) &= \sigma_l (t), \\
\dot{\sigma}_r (t) &= \sigma_r (t), \\
\dot{\sigma}_l (t) &= - \gamma_l \sigma_l (t) - \alpha_l S_l (t) + \beta_l H (t), \\
\dot{\sigma}_r (t) &= - \gamma_r \sigma_r (t) - \alpha_r S_r (t) + \beta_r H (t), \\
\dot{H} (t) &= u_1 (t), \\
\ddot{V}_A (t) &= u_2 (t). 
\end{align*}
\]

(5.14)

The following relationships characterize the situation "exercise". The metabolic oxygen consumption rate \( M R_{O_2} (t) \) rises exponentially from the oxygen demand during rest \( M R_{O_2}^r \) to the oxygen demand during exercise \( M R_{O_2}^e \),

\[
M R_{O_2} (t) = M R_{O_2}^r + (M R_{O_2}^e - M R_{O_2}^r) (1 - e^{-t/\tau}).
\]

(5.15)

Alternatively, one can assume

\[
M R_{O_2} (t) = M R_{O_2}^e - M s_p (t),
\]

(5.16)

with

\[
M s_p (t) = - K C_{vO_2}.
\]

(5.17)

The increase in metabolic rate is proportional to the workload,

\[
M R_{O_2}^e = M R_{O_2}^e + \rho W.
\]

(5.18)
Figure 5.1: Model for the cardiovascular and respiratory control system during exercise
Metabolic carbon dioxide production is at all times proportional to the oxygen consumption,

$$MR_{CO_2}(t) = RQ MR_{O_2}(t).$$  \hspace{1cm} (5.19)

Pulmonary resistance decreases from a given "rest" value $R_p^r$ to a given "exercise" value $R_p^e$ according to

$$R_p(t) = R_p^r + (R_p^e - R_p^r)(1 - e^{-t/\tau_p}).$$  \hspace{1cm} (5.20)

Systemic resistance is autoregulated via metabolic dilatation,

$$R_s(t) = A_{pesk} C_{VO_2}(t).$$  \hspace{1cm} (5.21)

Here $A_{pesk}$ is a time-varying function of the form

$$A_{pesk}(t) = A_{pesk}^r + (A_{pesk}^e - A_{pesk}^r)(1 - e^{-t/\tau_s}).$$  \hspace{1cm} (5.22)

Finally, the variations of heart rate and alveolar ventilation are outputs of the controller,

$$\dot{H} = u_1(t), \quad \text{and} \quad \dot{V}_A = u_2(t).$$  \hspace{1cm} (5.23)

All other relationships are the same as in Chapter 4.
Chapter 6

Steady state relationships

In this chapter we will investigate the steady state behavior of the state variables for increasing workloads.

6.1 Determination of a steady state

Due to (5.14) we have the following set of algebraic equations to determine the steady state values of $P_{as}$, $P_{vs}$, $P_{vp}$, $P_{aCO_2}$, $P_{aO_2}$, $P_{BCO_2}$, $P_{vCO_2}$, $P_{vO_2}$, $S_l$, $S_r$, $H$ and $\dot{V}_A$:

\begin{align*}
0 &= Q_l - F_s \\
0 &= F_s - Q_r \\
0 &= F_p - Q_l \\
0 &= 863F_p(C_{vCO_2} - C_{aCO_2}) + \dot{V}_A(P_{ICO_2} - P_{aCO_2}) \\
0 &= 863F_p(C_{vO_2} - C_{aO_2}) + \dot{V}_A(P_{IO_2} - P_{aO_2}) \\
0 &= MR_{BCO_2} + F_B(C_{aCO_2} - C_{BCO_2}) \\
0 &= MR_{CO_2} + F_s(C_{aCO_2} - C_{vCO_2}) \\
0 &= -MR_{O_2} + F_s(C_{aO_2} - C_{vO_2}) \\
0 &= \sigma_l \\
0 &= \sigma_r \\
0 &= -\gamma_l \sigma_l - \alpha_l S_l + \beta_l H \\
0 &= -\gamma_r \sigma_r - \alpha_r S_r + \beta_r H \\
0 &= u_1 \\
0 &= u_2.
\end{align*}
For the dependence of $F_s$, $F_p$, $F_B$, $Q_l$, $Q_r$, $C_{aCO_2}$, $C_{ao_2}$, $C_{Bco_2}$, $C_{vCO_2}$, and $C_{vo_2}$ on the variables see Chapter 4 and Chapter 5.6.

The last two equations of (6.1) express only that heart rate and alveolar ventilation are constant during a steady state. They do not give any information about the numerical values of the variables. For this reason we need two additional algebraic relations in order to determine a steady state.

It has been observed in many experiments that the increase of heart rate during exercise is proportional to the increase in oxygen demand (see Falls [6], p. 9, and also Section 5.4). Therefore we may use a linear relationship between the steady state value of the heart rate and the oxygen consumption,

$$H = aMR_O2 + b.$$  

(6.2)

The constants $a$ and $b$ must be obtained by parameter identification. For present purposes they will be chosen according to experimental data presented by Kappel and Peer [24], $a = 35$ and $b = 66$. For a second relationship we remember that it is one of the main goals of respiratory control to keep the arterial $CO_2$ tension close to 40 mmHg (Section 1.10). Therefore we may generally assume that

$$P_{aCO_2} = 40$$  

(6.3)

during a steady state. Now the number of unknowns is equal to the number of equations.

Before we are able to compute a steady state we need to determine the steady state values of $R_p$ and $A_{pesk}$ (compare (5.9) and (5.11)). We will assume that the pulmonary resistance $R_p$ decreases with increasing workload according to

$$R_p = 1.965 - 0.02091W.$$  

(6.4)

This relationship is chosen such that the values of $R_p$ for $W = 0$ and $W = 75$ coincide with the ”rest” and ”exercise” values for $R_p$ that have been identified by Kappel and Peer [24].

As far as $A_{pesk}$ is concerned we will assume that it increases with increasing workload according to

$$A_{pesk} = 177.3 + 1.17W.$$  

(6.5)

This relationship is chosen such that the ”rest” and ”exercise” values for the mean arterial pressure $P_{as}$ coincide with those obtained from measurements for $W = 0$ and $W = 75$ by Kappel and Peer [24].

In summary, the following steps for the determination of a steady state are needed.

i) Choose the workload $W$. 


ii) Determine the steady state values of \( A_{pesk}, R_p, MR_{O_2}, MR_{CO_2}, \) and \( H \) by
\[
\begin{align*}
A_{pesk} &= 177.3 + 1.17W, \\
R_p &= 1.965 - 0.02091W, \\
MR_{O_2} &= 0.350 + \rho W, \\
MR_{CO_2} &= RQMR_{O_2}, \\
H &= 35MR_{O_2} + 66, \\
P_{aCO_2} &= 40.
\end{align*}
\] (6.6)

iii) Solve the steady state system (6.1).

Before we numerically compute the steady states for different workloads we will have a closer look on the steady state relationships (6.1) to make some qualitative remarks.

6.2 Qualitative results

We see immediately that
\[
S_l = \frac{\beta_l}{\alpha_l} H \quad \text{and} \quad S_r = \frac{\beta_r}{\alpha_r} H,
\] (6.7)
that is, the contractilities are proportional to the heart rate. Remember that we have assumed that the heart rate depends linearly on the oxygen demand, which in turn depends linearly on the imposed workload. Thus, also the contractilities increase in proportion to the workload.

From the first equations in (6.1) we infer that left and right cardiac outputs and systemic and pulmonary blood flows are equal during a steady state,
\[
Q_l = Q_r = F_s = F_p.
\] (6.8)

In consequence, the fifth equation in (6.1) may be written as
\[
863Q_l(C_{aO_2} - C_{vO_2}) = \dot{V}_A(P_{lO_2} - P_{aO_2}).
\] (6.9)

This relation is known as Fick’s Principle. It allows to determine cardiac output from measurements of the oxygen concentrations in arterial and mixed venous blood and in the inspired air. Furthermore, we infer that
\[
\dot{V}_A(P_{lO_2} - P_{aO_2}) = 863MR_{O_2},
\]
\[
\dot{V}_A(P_{lCO_2} - P_{aCO_2}) = -863MR_{CO_2}.
\] (6.10)
These relations express that, during a steady state, all the oxygen inspired by the lungs is consumed by the tissues, and all the CO\textsubscript{2} formed in the tissues is expired. This is a consequence of the fact that no oxygen or carbon dioxide is stored in the body during a steady state.

If \( P_{acO_2} \) is kept constant at 40 mmHg and if we take into account that \( MR_{CO_2} = RQ MR_{O_2} \) then equations (6.10) imply that alveolar ventilation increases in proportion to the metabolic rate \( MR_{O_2} \) and hence in proportion with increasing workload. Furthermore, equations (6.10) yield that together with \( P_{acO_2} \) also \( P_{acO_2} \) has always the same steady state value. This is consistent with the observation that not only \( P_{acO_2} \) but also \( P_{acO_2} \) is regulated close to its resting level.

Equations number six, seven and eight of (6.1) can be rewritten as

\[
\begin{align*}
C_{BCO_2} &= C_{aCO_2} + \frac{MR_{BCO_2}}{F_B}, \\
C_{vO_2} &= C_{aO_2} - \frac{MR_{O_2}}{F_s}, \\
C_{vCO_2} &= C_{aCO_2} + \frac{MR_{CO_2}}{F_s}.
\end{align*}
\] (6.11)

These equations show that the venous \( O_2 \) concentration can never exceed the arterial \( O_2 \) concentration and that the arterial \( CO_2 \) concentration is a lower bound for the venous \( CO_2 \) concentration. Furthermore, since \( P_{acO_2} \) and hence cerebral blood flow \( F_B \) have always the same steady state value this is also the case for the carbon dioxide concentration in brain tissue, \( C_{BCO_2} \). Moreover, we infer that the arterio-venous oxygen and carbon dioxide differences depend on the quotient of metabolic rates and cardiac output. For instance, for fixed metabolic rates, the arterio-venous \( O_2 \)-difference is increased, and the arterio-venous \( CO_2 \)-difference is decreased if cardiac output decreases.

Finally, let’s assume for a moment that we use the empiric relationship for alveolar ventilation which has been presented in Section 2.6,

\[
\hat{V}_A = G_p e^{-0.05P_{acO_2}} (P_{acO_2} - I_p) + G_c (P_{acO_2} - I_c) - \hat{V}_D.
\] (6.14)

Then the partial pressures \( P_{acO_2} \) and \( P_{acCO_2} \) are already determined by equations (6.10) and hence it is no longer possible to choose the value for \( P_{acCO_2} \). Therefore we need another relationship to determine the remaining steady state values. In his respiratory model, Khoo [30] chose the value of cardiac output (blood flow) for the steady state. Cardiac output determines the venous gas concentrations via equations (6.12) and (6.13) but does not influence the arterial gas concentrations which follow from (6.10) and (6.14).
6.3 Steady states for increasing workloads

We increase the workload $W$ in equidistant steps, beginning at $W = 0$ and ending at $W = 75$. The used parameters are listed in Table 9.1 in Section 9.3.

Figure 6.1 shows how the mean blood pressures depend on the workload. The values of systemic mean arterial blood pressure $P_{as}$ for workloads $W = 0$ and $W = 75$ Watt coincide with the values measured by Kappel and Peer [24] in a bicycle ergometer test. The increase in systemic mean arterial blood pressure $P_{as}$ and the decrease in mean systemic venous blood pressure $P_{vs}$ with increasing workload $W$ imply an increased pressure difference. This tends to increase blood flow. On the other hand, the decrease in pulmonary arterial blood pressure $P_{ap}$ and the increase in pulmonary venous blood pressure $P_{vp}$ implies a decreased pressure difference. In order for the pulmonary blood flow (and hence cardiac output) to increase, it is necessary that the pulmonary resistance decreases, too. The quotient of preload and afterload remains for both ventricles nearly the same, since $P_{vp}$ and $P_{as}$ both increase and $P_{vs}$ and $P_{ap}$ both decrease.

The pulmonary blood pressure difference $P_{ap} - P_{vp}$, in turn, decreases with increasing workload, which tends to decrease pulmonary blood flow. However, we have assumed that pulmonary resistance decreases with increasing workload which makes possible an increase in pulmonary blood flow. In the next section we will investigate the situation where pulmonary resistance remains constant.
The increase in pulmonary venous blood pressure $P_{vp}$ means that blood is driven into the left ventricle with increased vigor. But also the pressure opposing the ejection of blood from the left ventricle, $P_{as}$, is increased during exercise. However, the left contractility $S_l$ is also increased (this is a consequence of the increased heart rate, see (6.7)) and hence the ventricle has the strength to eject an even slightly increased stroke volume. The nearly linear relationship between heart rate and cardiac output depicted in Figure 6.3 indicates that stroke volume remains almost constant and that the tremendously increased cardiac output is a consequence of the increased heart rate. Similar observations can be made for the right ventricle.

Furthermore, Figure 6.2 shows that the arterio-venous oxygen difference increases with increasing workloads. Since the arterial oxygen concentration remains constant, this means that more oxygen is extracted from the blood with increasing workload. In other words, the oxygen concentration in the tissue $C_{vO_2}$ decreases with increasing workload. This in turn implies the decrease in systemic resistance $R_s$.

Finally, Figure 6.3 shows that cardiac output and alveolar ventilation increase almost proportionally. This is also expressed by Fick’s Principle. Indeed, alveolar ventilation must increase a little bit more, since the extraction of oxygen from the blood increases, too.

6.4 Adaption to exercise if the pulmonary resistance is constant

In the previous section both, the pressure difference $P_{ap} - P_{vp}$ and pulmonary resistance $R_p$, have decreased with increasing workloads. This made possible an increase in cardiac output.

The question arises how the system adapts if we keep the pulmonary resistance constant when workload increases. This may be interpreted as the case where the lung vessels are
Figure 6.3: Left figure: the linear increase of cardiac output $Q_l$ with the heart rate $H$ indicates that the stroke volume remains relatively constant. Right figure: alveolar ventilation $\dot{V}_A$ increases almost in proportion to cardiac output $Q_l$.

considered as rigid tubes. We will in the following keep $R_p$ constant, once at the ”rest”-value, $R_p = 1.965$, and once at the value corresponding to $W = 75$, $R_p = 0.2922$.

First, we note that the flow to the tissues and hence cardiac output must increase because of the steady state relation

$$F_s(C_{aO_2} - C_{vO_2}) = MR_{O_2}. \quad (6.15)$$

For, if the additional oxygen for the tissue would only be supplied by an increased extraction of oxygen from the blood, this would imply a tremendous decrease in venous oxygen concentration $C_{vO_2}$. This in turn would decrease the systemic resistance which would increase the blood flow. Hence, cardiac output must increase (see Figure 6.4). We observe furthermore that alveolar ventilation is not affected if we keep pulmonary resistance constant. The reason is that the value of $\dot{V}_A$ is determined only by the oxygen uptake $MR_{O_2}$ (see relation (6.10)). Figure 6.5 shows how the system manages to increase cardiac output when the pulmonary

Figure 6.4: Dependence of cardiac output $Q_l$ and alveolar ventilation $\dot{V}_A$ on workload $W$ if pulmonary resistance $R_p$ is kept constant (dotted: $R_p = 1.965$, dashed: $R_p = 0.2922$) compared to the case where $R_p$ decreases (solid). If pulmonary resistance is constant the increase in cardiac output is smaller. Ventilation is unaffected by a change in pulmonary resistance.
resistance is kept constant. Obviously, now the pulmonary pressure difference \( P_{ap} - P_{vp} \) is increased. This is the only possibility to increase pulmonary blood flow and hence cardiac output if pulmonary resistance remains constant. At the same time, systemic arterial blood pressure decreases which makes possible an almost constant stroke volume out of the left ventricle. Similarly, systemic venous pressure \( P_{vs} \) in front of the right ventricle increases to obtain an almost unchanged right stroke volume.

### 6.5 Adaption to exercise if the heart rate is constant

In the previous sections the main increase in cardiac output has been brought about by an increase in heart rate. Stroke volume has only slightly increased. One could ask whether the system is able to increase cardiac output if heart rate is forced to remain constant (e.g., by a pacemaker with a programmable rate controller). Let us keep the heart rate at the "rest"-value, \( H = 78 \) beats per minute. Figure 6.6 shows that now the driving pressures into the left and right ventricle (\( P_{vp} \) and \( P_{vs} \)) increase and the pressures opposing the ejection of blood out of the ventricles (\( P_{as} \) and \( P_{ap} \)) decrease. In consequence, stroke volume is increased, as shown in Figure 6.7. This is the only way to increase cardiac output because heart rate and
hence contractilities are constant.

6.6 The influence of $A_{pesk}$

In Kappel and Peer [23], better simulation results were obtained if the parameter $A_{pesk}$ relating systemic resistance and venous oxygen concentration was allowed to have different values during rest and exercise. What happens if we assume that $A_{pesk}$ does not change with increasing workloads? We will in the following keep $A_{pesk}$ constant, once at the ”rest”-value, $A_{pesk} = 177.3$, and once at the value corresponding to $W = 75$, $A_{pesk} = 265.05$.

If $A_{pesk}$ is constant the systemic resistance $R_s$ depends linearly on the venous oxygen concentration, since $R_s = A_{pesk}C_{vO_2}$. Inserting this in (6.12) we obtain

$$C_{vO_2} = \frac{C_{aO_2}}{1 + (P_{as} - P_{vs})MR_{O_2}A_{pesk}}, \quad (6.16)$$

that is, the greater $A_{pesk}$, the smaller $C_{vO_2}$ for fixed metabolic rate $MR_{O_2}$ (and hence fixed workload). This is depicted in Figure 6.8. Figure 6.9 shows that the greater $A_{pesk}$ and hence $R_s$, the greater is the driving pressure difference $P_{as} - P_{vs}$ for fixed workload.
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Figure 6.7: Dependence of left stroke volume $V_{str,l}$ and cardiac output $Q_l$ on workload $W$ if the heart rate remains constant at $H = 78$ (dotted) compared to the case where heart rate increases with oxygen uptake according to $H = 66 + 35M R_{O_2}$ (solid). If the heart rate is kept constant the rise in cardiac output is achieved by marked increases in stroke volume.

Figure 6.8: Dependence of venous oxygen concentration $C_{vO_2}$ and systemic resistance $R_s$ on workload $W$ if the parameter $A_{pesk}$ is constant (dotted: $A_{pesk} = 177.3$; dashed: $A_{pesk} = 225.3$) compared to the case where $A_{pesk}$ increases with increasing workload (solid: $A_{pesk} = 177.3 + 0.6W$). The greater $A_{pesk}$ the smaller is the venous oxygen concentration $C_{vO_2}$ and the greater is systemic resistance $R_s$.

Figure 6.9: Dependence of systemic arterial and venous blood pressures $P_{as}$ and $P_{vs}$, respectively, on workload $W$ if the parameter $A_{pesk}$ is constant (dotted: $A_{pesk} = 177.3$; dashed: $A_{pesk} = 225.3$) compared to the case where $A_{pesk}$ increases with increasing workload (solid: $A_{pesk} = 177.3 + 0.6W$). The greater $A_{pesk}$ and hence $R_s$, the greater the pressure differences for fixed workload to obtain the same cardiac output.
Chapter 7

Results from control theory

In this chapter some important results from control theory are summarized. For proofs please refer to Knobloch and Kwakernaak [38], Kwakernaak and Sivan [40], or Russell [61].

Many systems can be described by a set of simultaneous differential equations of the form

$$\dot{x}(t) = f(x(t)).$$

(7.1)

Here $t$ denotes the time variable and $x(t)$ is a real time-varying $n$-dimensional column vector, called the state or the response of the system. The function $f$ is real and vector-valued and assumed to be arbitrarily often differentiable with respect to the components of $x$. The state differential equation (7.1) usually follows directly from the physical principles that govern the system.

We will restrict ourselves to time-invariant systems, that is, to systems whose properties are independent of time and where thus the function $f$ does not explicitly depend on time.

7.1 Stability

Definition 7.1 Let $x_e$ be an equilibrium of the system

$$\dot{x}(t) = f(x(t)).$$

(7.2)

In the following we will also refer to $x_e$ as the nominal solution. Let $x(t)$ be an arbitrary solution of (7.2). Then $x_e$ is called locally asymptotically stable if the following conditions are satisfied.

(i) (Stability in the sense of Lyapunov) For any $\epsilon > 0$ there exists a $\delta(\epsilon)$ such that $\|x(0) - x_e\| < \delta$ implies $\|x(t) - x_e\| < \epsilon$ for all $t \geq 0$.

(ii) There exists a $\rho > 0$ such that $\|x(0) - x_e\| < \rho$ implies $\|x(t) - x_e\| \to 0$ as $t \to \infty$. 

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In particular, if $\|x(t) - x_e\| \to 0$ as $t \to \infty$ for any $x(0)$ then the equilibrium is called globally asymptotically stable.

Here $\|x\|$ denotes the norm of a vector $x$. Any norm is possible because all norms in $\mathbb{R}^n$ are equivalent. For instance, the Euclidean norm,

$$
\|x\| = \sqrt{\sum_{i=1}^{n} x_i^2}
$$

may be used.

Stability in the sense of Lyapunov guarantees that the state $x(t)$ does not depart too far from the nominal solution $x_e$ if the initial state $x(0)$ is chosen close enough to $x_e$. Local asymptotic stability implies, in addition to stability in the sense of Lyapunov, that the solution $x(t)$ always approaches the nominal solution $x_e$ provided that the initial deviation is within a certain region around $x_e$. Finally, if the nominal solution $x_e$ is globally asymptotically stable, any solution (i.e., no restriction upon the initial condition is necessary) eventually approaches $x_e$.

7.2 Linear systems

We will in this thesis frequently deal with linear (time-invariant) systems of the form

$$
\dot{x}(t) = Ax(t),
$$

where $A \in M_n(\mathbb{R})$ (Here $M_n(\mathbb{R})$ denotes the vector space of $n \times n$ matrices with real-valued components). Since the solutions of a linear system may be scaled up and down without changing their qualitative behavior no distinction needs to be made between local asymptotic stability and global asymptotic stability. Furthermore, the only asymptotically stable equilibrium of a linear system can be the equilibrium $x_e = 0$. Hence we can generally speak of the asymptotic stability of a linear system.

**Definition 7.2** The linear system (7.4) is called asymptotically stable if the equilibrium $x_e = 0$ is asymptotically stable.

The solutions of a linear system can be obtained easily with the help of the transition matrix $\theta(t,0)$.

**Theorem 7.1** The solution of the linear system (7.4) can be expressed in the form

$$
x(t) = \theta(t,0)x(0),
$$
where the transition matrix $\theta(t,0)$ is the solution to

$$\frac{d}{dt} \theta(t,0) = A \theta(t,0), \quad \theta(0,0) = I. \quad (7.6)$$

Here $I$ denotes the $n$-dimensional identity matrix. Moreover, the transition matrix is

$$\theta(t,0) = e^{At}. \quad (7.7)$$

The exponential of a square matrix $M$ is defined via the series

$$e^M = 1 + M + \frac{1}{2!} M^2 + \frac{1}{3!} M^3 + ..., \quad (7.8)$$

which converges for all $M$.

If $A$ is diagonalizable an explicit form of the transition matrix can be easily obtained:

Theorem 7.2 Suppose that $A$ has $n$ distinct eigenvalues $\lambda_1, ..., \lambda_n$ with corresponding eigenvectors $e_1, ..., e_n$. Let us furthermore define the $n \times n$ matrix $T$ consisting of the eigenvectors of $A$ as columns,

$$T = (e_1, ..., e_n). \quad (7.9)$$

Then

i) $T$ diagonalizes $A$, that is,

$$T^{-1}AT = \text{diag}(\lambda_1, ..., \lambda_n). \quad (7.10)$$

ii) The transition matrix has the form

$$\theta(t,0) = T \text{diag}(e^{\lambda_1t}, ..., e^{\lambda_nt}) T^{-1}. \quad (7.11)$$

iii) The solution of (7.4) can be written as

$$x(t) = \sum_{i=1}^{n} \mu_i e^{\lambda_i t} e_i, \quad (7.12)$$

where the scalars $\mu_i$ depend on the initial condition $x(0)$ via $(\mu_1, ..., \mu_n)^T = T^{-1} x(0)$. 

This theorem shows that the response $x(t)$ of system (7.4) can be decomposed in motions along the eigenvectors of $A$. These motions are called **modes** of the system. If the initial state $x(0)$ is chosen to lie in the direction of one eigenvector, then the whole motion will be along this direction. One says, only this mode has been excited. Generally, a particular mode is excited by choosing the initial state to have a component along the corresponding eigenvector.

Even if the matrix $A$ has multiple eigenvalues, it can be diagonalized provided that the eigenvectors of $A$ span the $\mathbb{R}^n$. This is the case if the number of linear independent eigenvectors to each eigenvalue equals the multiplicity of the eigenvalue.

If $A$ does not have $n$ linearly independent eigenvectors it cannot be diagonalized but it can be brought into the Jordan normal form (cf., e.g., Kwakernaak and Sivan [40] or Lorenz [44]). In this case, the response $x(t)$ of system (7.4) may contain besides purely exponential terms of the form $e^{\lambda_i t}$ also terms of the form $t e^{\lambda_i t}, t^2 e^{\lambda_i t}, \ldots$ and so on.

The eigenvalues of $A$ are also called the poles of the system. They determine the dynamic behavior of the system to a considerable extent. Obviously, the stability properties of system (7.4) depend solely on the eigenvalues of $A$.

**Corollary 7.1** The linear system $\dot{x}(t) = Ax(t)$ is asymptotically stable if and only if all eigenvalues of $A$ have strictly negative real parts.

In this case one says that the matrix $A$ is asymptotically stable. In general, one distinguishes the so called stable and unstable subspace of $\mathbb{R}^n$.

**Definition 7.3** If $A$ is diagonalizable the linear subspace spanned by the eigenvectors corresponding to eigenvalues with strictly negative real parts is called the **stable subspace** of $A$. Similarly, the subspace spanned by the eigenvectors corresponding to eigenvalues with nonnegative real part is called the **unstable subspace** of $A$.

The whole $\mathbb{R}^n$ is the direct sum of the stable and the unstable subspace. In case of nondiagonalizable $A$ a similar decomposition of $\mathbb{R}^n$ is possible.

Assume that the system is not asymptotically stable that is, some of the eigenvalues have nonnegative real parts. Then the response will converge to the zero state only if the initial state has components only along those eigenvectors that correspond to stable poles.

**Corollary 7.2** The response $x(t)$ of system (7.4) converges to zero if and only if the initial state lies in the stable subspace.

### 7.3 Controllability

We will in the following consider linear systems containing a **control function** or input function $u(t)$

$$\dot{x}(t) = Ax(t) + Bu(t).$$

(7.13)
The function $u(t)$ is real and $k$-dimensional and assumed to be piecewise continuous. The matrix $B$ has appropriate dimensions. The response $x(t)$ of the system depends now on the choice of the control function $u(t)$. It is easy to obtain the solution of (7.13) with the help of the transition matrix $\theta(t,0) = e^{At}$.

**Theorem 7.3** The solution of (7.13) is

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-s)}Bu(s)\,ds.$$  \hspace{1cm} (7.14)

For the solution of many control problems it is important to know whether a given system can be steered from any given initial state to any other given final state. This question leads to the definition of controllability.

**Definition 7.4** System (7.13) is called (completely) controllable if for any initial state $x_0$ and any terminal state $x_1$ there exists a control function $u(t)$ which brings the system from the state $x_0$ to the state $x_1$ within finite time.

For linear time-invariant systems as considered here there is a convenient criterion to check controllability.

**Theorem 7.4** System (7.13) is completely controllable if and only if the column vectors of the controllability matrix

$$P = (B, AB, A^2B, ..., A^{n-1}B)$$  \hspace{1cm} (7.15)

span the $\mathbb{R}^n$.

Obviously, the controllability properties of the system depend only on the matrices $A$ and $B$. Thus, if the system is completely controllable we say also that the pair $(A, B)$ is completely controllable.

If the system is not completely controllable it is convenient to introduce the following terminology.

**Definition 7.5** The subspace spanned by the columns of $P$ is called the controllable subspace of the system (7.13).

The controllable subspace has the following important property.

**Theorem 7.5** Any state in the controllable subspace can be transferred to any other state in the controllable subspace within finite time.
7.4 Stabilizability

Consider the system
\[
\dot{x}(t) = Ax(t) + Bu(t). \tag{7.16}
\]
Assume furthermore that the system without control,
\[
\dot{x}(t) = Ax(t) \tag{7.17}
\]
is not asymptotically stable, that is, there exist eigenvalues of $A$ with nonnegative real parts. The question arises, whether there exists a control function $u(t)$ capable of stabilizing the system, i.e., of steering the response of (7.16) to the zero state. Of course, if the system (7.16) is completely controllable, it can in particular be steered to the zero state. But a weaker property suffices, since only the unstable components of system (7.17) need to be controlled. This leads us to the definition of stabilizability.

**Definition 7.6** System (7.16) is called stabilizable if its unstable subspace is contained in its controllable subspace.

7.5 Reconstructability and Detectability

In this section we will discuss the problem whether it is possible to determine from the behavior of the output of the system what the behavior of the state is. Consider the system
\[
\dot{x}(t) = Ax(t) + Bu(t), \tag{7.18}
\]
with output
\[
y(t) = Cx(t), \tag{7.19}
\]
where $C$ is a matrix in $M_{m,n}(\mathbb{R})$ (Here $M_{m,n}(\mathbb{R})$ denotes the vector space of $n \times m$ dimensional matrices). That means, that at time $t$, the only information we have about the state of the system is the $m$-dimensional quantity (the output) $Cx(t)$. Is it possible to reconstruct the behavior of the state $x(t)$ from the output? Consider the following simple example of a scalar output, e.g., $C = (1, 0, ..., 0)$, and $y(t) = x_1(t)$. Of course, it is not possible to reconstruct the vector $x(t)$ from its first component $x_1(t)$. But it might be possible that from the knowledge of $x_1(t)$ for all $t$ in an interval $[0, t_1]$, the vector $x(0)$ can be reconstructed with the help of the dynamical relationships (7.18). The concept of reconstructability has to do with the dynamical relationships between the components of $x(t)$ in the sense that deviations in the state at time $x(0)$ imply deviations in the output $y(t)$ for $t$ in an interval.
**Definition 7.7** Let \( x, x' \) be solutions of (7.18) with control function \( u \) and respective output \( y, y' \). Then (7.18) is called

i) **(completely) reconstructible** if there exists a \( t_- < 0 \) such that
\[
y(t) = y'(t) \quad \text{for} \quad t_- \leq t \leq 0
\]
implies \( x(t) = x'(t) \) for any control function \( u \).

ii) **(completely) observable** if there exists a \( t_+ > 0 \) such that
\[
y(t) = y'(t) \quad \text{for} \quad 0 \leq t \leq t_+
\]
implies \( x(t) = x'(t) \) for any control function \( u \).

In other words, (7.18) is completely reconstructible if the state \( x(t) \) can be uniquely determined from the observation of the output during a finite interval in the past. Similarly, it is completely observable if the state \( x(t) \) can be uniquely determined from the observation of the output during a finite interval in the future. In fact, since the system under consideration is time-invariant, the concepts of reconstructibility and observability are equivalent. This can be seen by substituting \( t \rightarrow -t \). These two concepts are only equivalent for the case of time-invariant systems.

Moreover, since the difference of two solutions of (7.18) solves the corresponding homogeneous equation \( \dot{x} = Ax \), we see that it is sufficient to examine the case of zero input.

**Corollary 7.3** System (7.18) is completely reconstructible (completely observable) if and only if for \( u = 0 \) there exists an \( \epsilon > 0 \) such that
\[
y(t) = 0, \quad 0 \leq t \leq \epsilon
\]
implies \( x(t) = 0 \).

Therefore, reconstructibility (observability) is solely a property of the homogeneous system.

A convenient criterion to check reconstructibility is given in the following theorem.

**Theorem 7.6** System (7.18) is reconstructible if and only if the row vectors of the reconstructibility matrix
\[
Q = \begin{pmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{n-1} \end{pmatrix}
\]
span the \( \mathbb{R}^n \).
If a system is not completely reconstructible, it is never possible to determine uniquely from the output what the state of the system is. The question is what uncertainty remains. In this context the definition of the unreconstructible subspace is helpful.

**Definition 7.8** The unreconstructible subspace of system (7.18) is the linear subspace consisting of those initial states \( x(0) \) for which the corresponding output to \( u = 0 \) has the property

\[
y(t) = 0, \quad t \geq 0.
\]  
(7.24)

The unreconstructible subspace can be determined with the help of the reconstructibility matrix.

**Theorem 7.7** The unreconstructible subspace of system (7.18) is the nullspace of the reconstructibility matrix (7.23).

The output of the system remains unchanged if one adds a vector from the unreconstructible subspace to the initial state.

**Corollary 7.4** Suppose that the output \( y(t) \) and the input \( u(t) \) of system (7.18) are known over an interval \( 0 \leq t \leq t_1 \). Then the (initial) state of the system at \( t = 0 \) is determined only up to the addition of an arbitrary vector from the unreconstructible subspace.

In other words, if the system is not reconstructible there is always a uncertainty about the actual state of the system. For, to any possible state one can always add an arbitrary vector from the unreconstructible subspace. The best one can hope for in this case is that for any state in the unreconstructible subspace the zero input response converges to zero. Then, whatever for the unreconstructible component of the state is guessed, the error will never grow infinitely. A system with this property is called detectable.

**Definition 7.9** The linear system (7.18) is called detectable if its unreconstructible subspace is contained in its stable subspace.

The state of a detectable system can at least be asymptotically reconstructed from the past behavior of the output.

An alternative to the criteria involving the controllability and the reconstructibility matrix is the following theorem. It is in particular useful for a numerical investigation of the system properties.

**Theorem 7.8** Consider the time-invariant system

\[
\begin{align*}
\dot{x}(t) &= Ax(t) + Bu(t) \\
y(t) &= Cx(t).
\end{align*}
\]  
(7.25)
Chapter 7. Results from control theory

i) The system is completely controllable if and only if the following is true: If \( p \) is an eigenvector of \( A^T \) then \( p^T B \neq 0 \).

ii) The system is stabilizable if and only if the following is true: If \( p \) is an eigenvector of \( A^T \) corresponding to the eigenvalue \( \lambda \) with \( \text{Re}(\lambda) \geq 0 \) then \( p^T B \neq 0 \).

iii) The system is completely reconstructible if and only if the following is true: If \( p \) is an eigenvector of \( A \) then \( C p \neq 0 \).

iv) The system is detectable if and only if the following is true: If \( p \) is an eigenvector of \( A \) corresponding to the eigenvalue \( \lambda \) with \( \text{Re}(\lambda) \geq 0 \) then \( C p \neq 0 \).

7.6 Linear state feedback control

Many control systems exhibit the feature of feedback, that is, the actual operation of the control system is compared to the desired operation. The input to the system is adjusted on the basis of this comparison. Since the actual operation is continuously compared to the desired operation, feedback control systems are able to operate satisfactorily despite adverse conditions, such as disturbances that act upon the system or variations in plant properties.

Sometimes the main goal of a feedback design is to stabilize a system which is initially unstable or to improve its stability properties if transient phenomena do not die out sufficiently fast. Consider the system

\[
\dot{x}(t) = A x(t) + B u(t).
\]

(7.26)

We assume that the complete state \( x(t) \) can be accurately measured at all times and is thus available for feedback. Then it is possible to implement a linear control law of the form

\[
u(t) = -F(t) x(t),
\]

(7.27)

where the (possibly time-varying) matrix \( F(t) \) has appropriate dimensions and is called the feedback gain matrix. Connecting this control law to system (7.26) yields the closed-loop system

\[
\dot{x}(t) = (A - B F(t)) x(t).
\]

(7.28)

In particular, if we choose a constant matrix \( F \), then the stability of the system is determined solely by the eigenvalues of \( A - BF \) (cf. Corollary 7.1).

The following theorem gives more insight into the concepts of controllability and stabilizability.
Theorem 7.9 Consider system

\[ \dot{x}(t) = A x(t) + B u(t), \quad (7.29) \]

with the time-invariant control law

\[ u(t) = -F x(t). \quad (7.30) \]

Then

i) The eigenvalues of \( A - BF \) can be arbitrarily located in the complex plane (with the restriction that complex eigenvalues occur in complex conjugate pairs) by choosing \( F \) suitably if and only if the system is completely controllable.

ii) It is possible to find a constant matrix \( F \) such that the closed-loop system is asymptotically stable if and only if the system is stabilizable.

In other words, it is always possible to stabilize a completely controllable system by state feedback, or to improve its stability, by assigning the closed-loop poles to locations in the left-half complex plane. If the system is stabilizable but not completely controllable, not all but at least the unstable poles of the system can be moved to arbitrary locations by choosing \( F \) suitably. However, this theorem gives no guidance as to where in the left-half complex plane the closed-loop poles should be located. This uncertainty is removed by optimal linear regulator theory.

7.7 The deterministic linear optimal regulator problem

In the previous section we have seen that a completely controllable time-invariant linear system can always be stabilized by a linear feedback law. The closed-loop poles can be located anywhere in the complex plane. Thus, by choosing them far to the left, the convergence to the zero state can be made arbitrarily fast. However, to make the system move fast, large input amplitudes are required. This can be seen from the following example. Consider the one-dimensional system

\[ \dot{x}(t) = -bx(t), \quad (7.31) \]

where \( b \) is a positive real number. This may be interpreted as a closed loop system, whose state would be constant in the uncontrolled case. The control (input) function is given by \( u(t) = -bx(t) \) where \( b \) is the feedback gain. The solution to this differential equation has the time-course \( \exp(-bt) \). One sees that the farther left the eigenvalue \( -b \), the faster converges the solution to zero but the greater is the input amplitude.
In any practical situation, the input amplitudes are constrained to certain maximal values. Therefore, we have to take into account not only the speed of convergence of the state to zero but also the magnitude of the input amplitudes. This leads to an optimization problem.

Let us study this optimization problem more generally for a linear time-varying system,

\[ \dot{x}(t) = A(t)x(t) + B(t)u(t), \quad (7.32) \]

with **controlled variable** \( z \in \mathbb{R}^s \),

\[ z(t) = D(t)x(t). \quad (7.33) \]

We assume that the matrix \( A(t) \) is continuous, that the matrices \( B(t) \) and \( D(t) \) are piecewise continuous functions and that all matrix functions are bounded. Consider the problem where we want to reduce the controlled variable \( z(t) \) from an arbitrary initial value to zero as quickly as possible. One criterion to express how fast \( z(t) \) is reduced to zero during the interval \([t_0, t_1]\) is the quadratic cost functional

\[ \int_{t_0}^{t_1} z^T(t)R_3(t)z(t) \, dt, \quad (7.34) \]

where \( R_3(t) \) is a positive definite symmetric matrix which is piecewise continuous with respect to \( t \). The expression \( z^T(t)R_3(t)z(t) \) is a measure of the extent to which \( z \) at time \( t \) deviates from zero. Here the weighting matrix \( R_3(t) \) determines how much weight is assigned to each of the components of \( z \). A time dependent weighting matrix makes possible that the importance attached to a component varies with time. If \( R_3 \) is diagonal, which is usually the case, \( z^T(t)R_3(t)z(t) \) is the weighted sum of the deviations of each of the components of \( z \) from zero. The integral (7.34) is a measure for the cumulative deviation of \( z(t) \) from zero during the interval \([t_0, t_1]\).

Now, minimizing the criterion (7.34) will result in infinitely large input amplitudes. Therefore, we need to include a second term into the quadratic cost criterion that prevents the input from growing infinitely. We thus consider the criterion

\[ \int_{t_0}^{t_1} \left( z^T(t)R_3(t)z(t) + u^T(t)R_2(t)u(t) \right) \, dt, \quad (7.35) \]

where the matrix \( R_2(t) \) is positive definite, symmetric and a piecewise continuous function of \( t \). If it is very important that the terminal state \( x(t_1) \) is as close as possible to the zero state, it is useful to add a third term to the criterion,

\[ \int_{t_0}^{t_1} \left( z^T(t)R_3(t)z(t) + u^T(t)R_2(t)u(t) \right) \, dt + x^T(t_1)P_1 x(t_1), \quad (7.36) \]

where \( P_1 \) is a nonnegative-definite symmetric matrix.

In summary, our optimization problem is the following.
Definition 7.10 (The deterministic linear optimal regulator problem) Consider the linear time-varying system

\[ \dot{x}(t) = A(t)x(t) + B(t)u(t), \]  

with initial condition

\[ x(t_0) = x_0, \]  

and controlled variable

\[ z(t) = D(t)x(t). \]  

The matrix \( A(t) \) is continuous, \( B(t) \) and \( D(t) \) are piecewise continuous, and all matrix functions are bounded. Determine an input \( u(t) \), \( t_0 \leq t \leq t_1 \) such that the criterion

\[ \int_{t_0}^{t_1} \left( z^T(t)R_3(t)z(t) + u^T(t)R_2(t)u(t) \right) dt + x^T(t_1)P_1x(t_1), \]  

is minimal. Here, \( P_1 \) is a nonnegative-definite symmetric matrix and \( R_2(t) \) and \( R_3(t) \) are positive-definite symmetric matrices.

The term "deterministic" emphasizes that we consider here only problems where a linear system has a disturbed initial state and it is required to return the system to the zero state as quickly as possible while the input amplitude must stay limited. In contrast, the "stochastic" linear optimal regulator problem would also consider disturbances that act uninterruptedly upon the system which tend to drive the state away from the zero state.

The following theorem gives the solution of the deterministic optimal regulator problem.

Theorem 7.10 Consider the deterministic linear optimal regulator problem. Then the optimal input \( u(t) \) can be generated through a linear control law of the form

\[ u(t) = -F(t)x(t), \]  

where

\[ F(t) = R_2^{-1}(t)B^T(t)P(t). \]  

The matrix \( P(t) \) is symmetric and nonnegative-definite and satisfies the matrix Riccati equation

\[ -\dot{P}(t) = D^T(t)R_3(t)D(t) - P(t)B(t)R_2^{-1}(t)B^T(t)P(t) + P(t)A(t) + A^T(t)P(t), \]  

with terminal condition

\[ P(t_1) = P_1. \]  

The minimal value of the cost criterion is equal to \( x_0^T P(t_0) x_0 \).
In other words, the control law \((7.41)\) automatically generates the optimal input for any initial state. Under the conditions formulated in Definition 7.10 the deterministic optimal regulator problem always has a unique solution.

In practical problems, it is often natural to consider very long control periods \([t_0, t_1]\). What happens to the solution of the deterministic regulator problem as \(t_1 \to \infty\)? Under certain restrictive conditions (cf., e.g., Kwakernaak and Sivan [40], Theorem 3.5) the following results hold.

i) As \(t_1 \to \infty\) the solution \(P(t)\) of the matrix Riccati equation \((7.43)\) with terminal condition \(P(t_1) = P_1\) converges to a steady state solution \(\bar{P}(t)\) that is independent of \(P_1\).

ii) The solution of the deterministic optimal regulator problem for \(t_1 \to \infty\) is given by the steady state control law

\[
u(t) = -F(t)x(t) \quad (7.45)
\]

with

\[
\bar{F}(t) = R_2^{-1}(t)B^T(t)\bar{P}(t). \quad (7.46)
\]

This control law stabilizes the system asymptotically.

The second property is intuitively clear. Since the integral

\[
\int_{t_0}^{\infty} \left( z^T(t)R_3(t)z(t) + u^T(t)R_2(t)u(t) \right) \, dt \quad (7.47)
\]

exists, it follows that \(z(t) \to 0\) and \(u(t) \to 0\) as \(t_1 \to \infty\). But this can generally only be true if \(x(t) \to 0\) as \(t_1 \to \infty\) which means that the closed loop system is asymptotically stable.

In particular, for a time-invariant system the following result holds.

**Theorem 7.11** Consider the time-invariant system

\[
\begin{align*}
\dot{x}(t) &= Ax(t) + Bu(t), \\
z(t) &= Dx(t),
\end{align*} \quad (7.48)
\]

and the criterion

\[
\int_0^{t_1} \left( z^T(t)R_3z(t) + u^T(t)R_2u(t) \right) \, dt + x^T(t_1)P_1x(t_1). \quad (7.49)
\]
The matrices $A$, $B$, $D$, $R_3 > 0$, $R_2 > 0$, and $P_1 \geq 0$ are constant and $R_3$, $R_2$, and $P_1$ are symmetric. The associated Riccati equation is

$$-\dot{P}(t) = D^T R_3 D - P(t) BR_2^{-1} B^T P(t) + P(t) A + A^T P(t),$$

with terminal condition

$$P(t_1) = P_1.$$  \hspace{1cm} (7.51)

Assume that system (7.48) is stabilizable and detectable. Then the following is true.

i) The solution of the Riccati equation (7.50) approaches the unique value $\bar{P}$ as $t_1 \rightarrow \infty$ which is independent of $P_1$.

ii) $\bar{P}$ is the unique nonnegative-definite symmetric solution of the algebraic Riccati equation

$$0 = D^T R_3 D - PBR_2^{-1} B^T P + PA + A^T P.$$ \hspace{1cm} (7.52)

iii) The steady state control law

$$u(t) = -F x(t),$$ \hspace{1cm} (7.53)

with

$$F = R_2^{-1} B^T \bar{P},$$ \hspace{1cm} (7.54)

minimizes

$$\int_0^\infty (z^T(t) R_3 z(t) + u^T(t) R_2 u(t)) \, dt + x^T(t_1) P_1 x(t_1)$$  \hspace{1cm} (7.55)

for all $P_1 \geq 0$. For the optimal input the criterion takes the value $x^T(0) \bar{P} x(0)$.

iv) The steady state control law (7.53) asymptotically stabilizes the control system (7.48).

7.8 Nonlinear systems

Actual systems are never linear, and the linear models used are obtained by linearization. Often systems are designed whose linear models possess good properties. The question arises, what remains of these properties when the actual nonlinear system is implemented? The following theorem shows what conclusions may be drawn from the stability of the linearized system.
Theorem 7.12 Consider the nonlinear time-invariant system

\[
\dot{x} = f(x(t)).
\]

Suppose that the system has an equilibrium \( x^e \) and that \( f \) is at least twice continuously differentiable with respect to \( x \) in \( x^e \). Consider furthermore the linearized system around \( x^e \),

\[
\dot{x} = Ax,
\]

where \( A \) denotes the Jacobian of \( f \) at \( x^e \). Then, if \( A \) is asymptotically stable, the equilibrium \( x^e \) is locally asymptotically stable for the nonlinear system (7.56).

We can not, however, conclude anything about global asymptotic stability from the linearized system. Moreover, if some of the eigenvalues of \( A \) have zero real parts while all the other eigenvalues have strictly negative real parts no conclusions about the stability of \( x^e \) for the nonlinear system can be drawn. If \( A \) has some eigenvalue with strictly positive real parts, however, \( x^e \) is not stable in any sense.

Suppose that we have an initially unstable nonlinear system and we use linearized equations to find a controller which makes the linearized system stable. Then the last theorem implies that the actual nonlinear system with this controller will at least be asymptotically stable for small deviations from the equilibrium state. We will next ask for an optimal control for a nonlinear system and in what sense it may be approximated with the help of the linearized system.

Definition 7.11 Consider the nonlinear system

\[
\dot{x}(t) = f(x(t), u(t)), \\
z(t) = Dx(t)
\]

and let without loss of generality \( x^e = 0 \) be an equilibrium of the system (with control \( u^e = 0 \)). Assume furthermore that \( f \) is at least two times continuously differentiable at \( (x^e, u^e) = (0, 0) \). The problem of finding a control \( u(t) \), \( 0 \leq t < \infty \), which minimizes the criterion

\[
\int_0^\infty ((Dx(t))^T R_3 Dx(t) + u(t)^T R_2 u(t)) \, dt
\]

subject to (7.58) is called the nonlinear quadratic optimal control problem (NLCP). Here \( R_3 \) and \( R_2 \) are positive definite symmetric weighting matrices of appropriate dimensions.

For nonlinear systems there does generally not exist an analytical closed form of a control law \( u(t) \) which solves the control problem. However, the next theorem guarantees at least local existence, uniqueness, and the possibility of linear approximation of the nonlinear feedback law.
Theorem 7.13 Consider the linearized system of (7.58),
\begin{align}
\dot{x}(t) &= Ax(t) + Bu(t), \\
z(t) &= Dx(t),
\end{align}
(7.60)
where $A$ and $B$ denote the Jacobians of $f(x,u)$ with respect to $x$ and $u$ at $(x^e,u^e) = (0,0)$. Let the linearized system be stabilizable and observable. Then there is a neighborhood $N$ of $x^e = 0$ such that the following holds.

(i) There exists a unique feedback law $u = -K(x)$ which solves the NLCP for $x \in N$.

(ii) If $x(0) \in N$ then the solution of the closed-loop system $\dot{x} = f(x,-K(x))$ always remains in $N$ and has the property
\[ \lim_{t \to \infty} x(t) = 0. \]  
(7.61)
In other words, the equilibrium $x^e = 0$ is locally asymptotically stable for the nonlinear closed-loop system.

(iii) Write $K(x)$ as
\[ K(x) = \hat{K}x + k(x), \]  
(7.62)
where $\hat{K}$ is the Jacobian of $K(x)$ at $x^e = 0$ and $k(x) = o(\|x\|)$, $x \to 0$. (Here $o(.)$ denotes the Landau symbol $f(x) = o(g(x)) \iff \|f(x)\|/\|g(x)\| \to 0$ as $x \to \infty$.) Then $A - B\hat{K}$ is a stable matrix and $\hat{K}$ is the optimal feedback matrix for the linear control problem
\begin{align}
\dot{x}(t) &= Ax(t) + Bu(t), \\
&\text{with cost functional} \\
\int_{0}^{\infty} &((Dx(t))^TR_3Dx(t) + u(t)^TR_2u(t)) \, dt.
\end{align}
(7.64)

(iv) If $x(0) \in N$ then the solution of the closed-loop system $\dot{x} = f(x,-\hat{K}x)$ always remains in $N$ and has the property
\[ \lim_{t \to \infty} x(t) = 0. \]  
(7.65)
In other words, for $x(0) \in N$ also the feedback law $u = -\hat{K}x$ stabilizes the nonlinear system.

In this sense, the optimal control for the linearized control problem is a suboptimal control for the nonlinear control problem.
Chapter 8

The control problem

8.1 Mathematical notations

We can summarize the model equations for exercise (5.14) in the following way. Let \( x(t) \in \mathbb{R}^{14} \) denote the state vector at time \( t \),

\[
x(t) = (P_{as}, P_{ve}, P_{vp}, P_{uCO_2}, P_{aCO_2}, P_{vCO_2}, P_{aO_2}, P_{vO_2}, S_l, S_r, \sigma_l, \sigma_r, H, \dot{V}_A)^T.
\]

(8.1)

For clarity we have suppressed the dependence on time \( t \). If convenient, the components of \( x \) will be also referred to as \( x_i, i = 1, \ldots, 14 \). Similarly let \( u(t) \in \mathbb{R}^2 \) denote the control vector

\[
u(t) = (u_1(t), u_2(t))^T = (\dot{H}, \ddot{V}_A)^T.
\]

(8.2)

Furthermore, let \( p \in \mathbb{R}^{37} \) contain the parameters of the model. The components of \( p \) are listed in Table 9.1. Let moreover \( U \subset \mathbb{R}^{14} \) denote the subset of physiologically meaningful state values. Since all states except \( \sigma_l \) and \( \sigma_r \) need to be positive, we have

\[
U = \mathbb{R}^{10}_+ \times \mathbb{R}^2 \times \mathbb{R}^2_+.
\]

(8.3)

We will denote the right-hand side of (5.14) with the last two components replaced by zeroes (since they refer to the control) by \( f(x; W) \). The parameter \( W \) indicates the imposed workload. Obviously, \( f(x; W) \) is a smooth function with respect to \( x \), \( f(x; W) \in C^\infty(U, \mathbb{R}^{14}) \) (Here \( C^\infty(U, \mathbb{R}^{14}) \) denotes the vector space of all functions \( f: U \rightarrow \mathbb{R}^{14} \) with derivatives of arbitrary order). Finally, we abbreviate \( \dot{x} = (\dot{x}_1, \ldots, \dot{x}_{14})^T \in \mathbb{R}^{14} \) and introduce the matrix \( B \in M_{2, 14}(\mathbb{R}) \) by

\[
B = \begin{pmatrix}
0 & 0 \\
. & . \\
. & . \\
0 & 0 \\
1 & 0 \\
0 & 1
\end{pmatrix}.
\]

(8.4)
Here $M_{n,m}(\mathbb{R})$ denotes the vector space of $n \times m$ dimensional matrices with components in $\mathbb{R}$. Then we can write (5.14) in the form

$$\dot{x}(t) = f(x(t); W) + B u(t).$$

(8.5)

The question is how to choose the control functions $u_1(t) = \dot{H}(t)$ and $u_2(t) = \ddot{V}_A(t)$?

### 8.2 The assumption of a pre-defined operating point for the baroreflex

Koch [39] was among the first who determined the stimulus response curve for the carotid sinus baroreflex. This curve describes the change in systemic arterial pressure caused by a given pressure change at the isolated carotid sinus. The "operating point" ("set point", "debit value") of the baroreceptor reflex is defined as the carotid sinus pressure at which the slope of the stimulus-response curve is maximal.

The following hypothesis about cardiovascular control during exercise is proposed by Rowell [60], p. 465. At the onset of exercise, "central command" from the cerebral cortex "resets" the arterial baroreflex to a higher operating pressure. In consequence, the prevailing value of arterial pressure at the onset of exercise is perceived by the central nervous system to be hypotensive relative to the new baroreflex operating point. Therefore, a sustained increase in sympathetic activity is needed to raise cardiac output and reduce the perceived "arterial pressure error". This way, cardiovascular regulation operates as a combined feed-forward (resetting of the operating point) and feedback control (baroreceptor reflex and other reflexes).

Any speculation that "resetting" of the baroreflex is the mechanism for blood pressure control during exercise must be viewed with care. There are many open questions. For instance, the origin of the stimulus that resets the baroreflex is not known. Moreover, it is not clear what factors determine the new operating point.

As far as the second question is concerned, many physiologists believe that the intensity of the anticipatory signal is a learned response (compare also Section 5.5). Furthermore, if the arterial baroreflex were "reset" to a higher operating point in proportion to exercise intensity, the cardiovascular responses to exercise could easily be explained on the basis of a need to correct centrally perceived "pressure errors". There are various experiments supporting the hypothesis of a reset baroreflex operating point. For instance, when the rise of arterial pressure in response to exercise is prevented, the reaction is the same as that to severe hypotension: sympathetic activity increases extremely (Walgenbach and Donald [69]).

Based on these observations we will in the following assume that the operating point for the baroreflex is reset during exercise. Kappel and Peer [23] obtained the "rest" and "exercise" operating point from the measured steady state values of $P_{as}$. Since presently no measurements are available to us, we will compute the steady state values of $P_{as}$ and take the
computed values as operating points. A steady state will be obtained from the steady state system \((6.1)\) as described in Chapter 6. We will use the observations that \(P_{acO_2}\) remains constant during exercise and that the heart rate increases in proportion with oxygen uptake. The situation we want to model is the following.

We assume that the person is at rest for \(t < 0\), that is, \(W = 0\). The corresponding steady state \(x^r\) is the solution of

\[
0 = f(x^r; 0),
\]

\[
H^r = 35M^r_R + 66,
\]

\[
P_{acO_2}^r = 40.
\]

(8.6)

Note that there is no control during a steady state. At \(t = 0\), a constant ergometric workload \(W = W^e\) is imposed. The dynamics of the system is then governed by

\[
\dot{x}(t) = f(x(t); W^e) + Bu(t), \quad x(0) = x^r.
\]

(8.7)

One basic requirement for the control to meet is that it must transfer the system from the steady state \(x^r\) to the steady state ”exercise”, \(x^e\), which is the solution to

\[
0 = f(x^e; W^e),
\]

\[
H^e = 35M^e_R + 66,
\]

\[
P_{acO_2}^e = 40.
\]

(8.8)

But still, how should this transfer be like?

### 8.3 The assumption of optimal behavior

Many physiologists assume that optimization is a basic concept in the evolution of biological systems (see, e.g., Kenner [26] or Swan [66]). One may assume that during the millions of years of evolution a biological system would have eliminated those mechanisms that involved the use of too much energy. If the energy expenditure is too large, too many basic nutrients are needed to fuel the system. Therefore, it seems reasonable to postulate that the human organism has evolved to make use of minimum energy requirements. The hypothesis of optimization can be applied to other quantities besides energy. One may, for instance, assume that the human body works in such a way that the stress upon certain organs is minimized or at least must stay within certain bounds.

Applying this concept to the situation where a constant workload is imposed, we may assume that the cardiovascular and respiratory control system transfers the organism to the steady state ”exercise” in an optimal way. What does ”optimal” mean in our case?

We assume that it is the task of the baroreceptor loop to stabilize the arterial systemic pressure \(P_{as}(t)\) to a new operating point \(P_{as}^e\). And it is the main goal of respiratory control
to keep the extracellular $CO_2$ partial pressure as close as possible to the constant value $P^e_{aCO_2}$. One possible assumption is that the variables $P_{as}$ and $P_{aCO_2}$ are stabilized such that the deviations from their debit values during the transient phase are as small as possible. In addition, we require that heart rate and alveolar ventilation must not change too fast. The last constriction corresponds to the requirement that the control effort must stay within certain bounds. This way the baroreceptor loop and the respiratory control system can be considered not only as a stabilizing but also as an optimizing feedback.

These requirements can mathematically be formulated in the following way.

**Definition 8.1 (Nonlinear control problem for exercise)** Find control functions $u_1(t)$ and $u_2(t)$ such that the quadratic cost functional

$$
\int_0^{\infty} \left( q_{as}(P_{as}(t) - P^e_{as})^2 + q_c(P_{aCO_2}(t) - P^e_{aCO_2})^2 + q_1u_1(t)^2 + q_2u_2(t)^2 \right) dt
$$

is minimized subject to the state equations

$$
\dot{x}(t) = f(x(t); W^e) + B u(t), \quad x(0) = x^r.
$$

The positive scalar weighing coefficients $q_{as}$, $q_c$, $q_1$, and $q_2$ determine the relative importance of each term of the integrand. By using the squares of $P_{as}(t) - P^e_{as}$, $P_{aCO_2}(t) - P^e_{aCO_2}$, $u_1(t)$, and $u_2(t)$ in the integrand one assures that negative and positive deviations contribute to the cost functional equivalently.
Chapter 9

A linear feedback

We will in this chapter determine a linear feedback for the nonlinear system (8.10). The linear feedback solves the nonlinear control problem for exercise (Definition 8.1) in a suboptimal way as described in Theorem 7.13.

9.1 Linearization around the final steady state

Our point of departure is the nonlinear system
\[ \dot{x}(t) = f(x(t); W^e) + Bu(t), \quad x(0) = x^r. \] (9.1)

As controlled variables we have
\[ y(t) = Dx(t) = (P_{as}(t), P_{aCO_2}(t))^T, \] (9.2)

where \( D \in M_{2,14}(\mathbb{R}) \) is given by
\[ D = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 1 & 0 & \ldots & 0 \end{pmatrix}. \] (9.3)

We want to stabilize system (9.1) around the equilibrium \( x^e \). Therefore our first step is a shift in the origin of the state space by introducing new variables \( \xi \) and \( \eta \)
\[ \xi(t) = x(t) - x^e, \]
\[ \eta(t) = y(t) - y^e. \] (9.4)

Next, we approximate \( \xi \) linearly. To this aim we express \( x \) in (9.1) by \( \xi \) and make a Taylor expansion around \( x^e \) for fixed time \( t \). This yields
\[ \dot{x} = \dot{\xi} = f(x^e + \xi; W^e) + Bu = A\xi + Bu + o(\xi). \] (9.5)
Chapter 9. A linear feedback

Here $o(.)$ denotes the Landau symbol $(f(x) = o(g(x)) :\iff \|f(x)/\|g(x)\| \to 0$ as $x \to \infty$). Note that the original state equations were already linear with respect to the control $u$. The matrix $A \in M_{14}(\mathbb{R})$ (we denote $M_{n,n}(\mathbb{R})$ by $M_n(\mathbb{R})$) is the Jacobian with respect to $x$ evaluated at $x = x^e$,

$$A = \frac{\partial f}{\partial x}(x^e; W^e).$$  \hfill(9.6)

Analogously,

$$\eta(t) = (P_{as} - P_{as}^e, P_{aCO_2} - P_{aCO_2}^e)^T = D\xi(t).$$  \hfill(9.7)

By neglecting terms of order $o(\xi)$ we get linear approximations $\xi_\ell$ and $\eta_\ell$ for $\xi$ and $\eta$, respectively,

$$\dot{\xi}_\ell(t) = A\xi_\ell(t) + Bu(t), \quad \xi_\ell(0) = x^r - x^e,$n
$$\eta_\ell(t) = D\xi_\ell(t).$$  \hfill(9.8)

### 9.2 Determination of the optimal linear feedback control

The optimal control $u_\ell(t)$ for the linearized system is determined by the requirement, that the linear-quadratic cost functional

$$\int_0^\infty (\eta_\ell^T(t)R_3\eta_\ell(t) + u^T(t)R_2u(t)) \, dt$$  \hfill(9.9)

is minimized under the constraint

$$\dot{\xi}_\ell(t) = A\xi_\ell(t) + Bu(t), \quad \xi_\ell(0) = x^r - x^e,$n
$$\eta_\ell(t) = D\xi_\ell(t).$$  \hfill(9.10)

Here, $R_3 = \text{diag}(q_{as}, q_c)$ and $R_2 = \text{diag}(q_1, q_2)$.

It is easy to show that system (9.10) is stabilizable and detectable. Then, due to Theorem 7.11, the desired control is given by

$$u_\ell(t) = -F\xi_\ell(t), \quad \text{with } F = R_2^{-1}B^TE,$$  \hfill(9.11)

where $E$ is the unique positive-definite symmetric solution of the algebraic Riccati-equation

$$EA + A^TE - EBR_2^{-1}B^TE + D^TR_3D = 0.$$  \hfill(9.12)

Substituting the linear feedback law into (9.1) yields state equations which describe a transfer from $x^r$ to $x^e$ in a suboptimal way as described in Theorem 7.13,

$$\dot{x}(t) = f(x(t); W^e) - BF(x(t) - x^e), \quad x(0) = x^r.$$  \hfill(9.13)
Here we have assumed that the complete state $x(t)$ can be accurately measured at all times and is available for feedback. In the cardiovascular model by Kappel and Peer [23] the case was also considered where only $P_{as}(t)$ can be measured. In this situation an optimal linear observer was constructed which determined an estimate $\hat{x}(t)$ of the complete state from the output $P_{as}(t)$. This estimate $\hat{x}(t)$ was then used as input for the controller, i.e., the feedback law $u$ involved $\hat{x}(t)$ instead of the exact state $x(t)$.

### 9.3 Computer simulation with *Mathematica*

The computations for solving the control problem are made with *Mathematica 3.0*. The *Mathematica* packages can be downloaded from http://www.kfunigraz.ac.at/imawww/timischl/. The parameters used for the simulation are listed in Table 9.1. They are chosen either according to the parameter values identified by Kappel and Peer [24] or from literature. For references concerning the numerical values see Appendix B. A description of the symbols is given in Appendix C.

The following steps are taken for the computation of the time courses of the variables. First, the steady states "rest" and "exercise" are computed for $W = 0$ and $W = W^e$, respectively,

$$0 = f(x^r; 0), \quad \text{and} \quad 0 = f(x^e; W^e).$$

(9.14)

Compare also (6.6). The computed steady states are listed in Table 9.2. Then the Riccati-equation (9.12) is solved and the feedback matrix $F$ is computed via (9.11). Finally, $F$ is inserted into the nonlinear system (9.13) and the differential equations are solved. The next sections present the simulation results.

### 9.4 The influence of the weights in the cost functional

In order to solve the Riccati equation we need to choose values for the weights $q_{as}, q_c, q_1$ and $q_2$ in the cost functional (8.9). 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 all weights equal to one. This means that deviations of all quantities in the cost functional by one unit are equally punished. The time courses of some variables for this choice of weights are depicted in Figures 9.1 - 9.3.

We notice that it takes $P_{aco_2}$ longer to attain its steady state value than $P_{as}$. The time until $P_{aco_2}$ reaches its steady state value can be influenced by varying the weights, especially the weight $q_c$. If we choose, for instance, $q_c = 100$, then a deviation of $P_{aco_2}$ from its debit value is punished harder in the cost functional. Figure 9.4 shows that, for $q_c = 100$, $P_{aco_2}$ reaches its steady state value already after 3 minutes (dotted line). Furthermore, $P_{aco_2}$
Table 9.1: Parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{peak, \text{steady}}$</td>
<td>177.3</td>
<td>265.1</td>
</tr>
<tr>
<td>$\alpha_l$</td>
<td>89.47</td>
<td>89.47</td>
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<tr>
<td>$\alpha_r$</td>
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<td>28.46</td>
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<td>$\beta_l$</td>
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<td>$\beta_r$</td>
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<td>1.780</td>
</tr>
<tr>
<td>$c_{ap}$</td>
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<td>0.03557</td>
</tr>
<tr>
<td>$c_{as}$</td>
<td>0.01002</td>
<td>0.01002</td>
</tr>
<tr>
<td>$c_l$</td>
<td>0.01289</td>
<td>0.01289</td>
</tr>
<tr>
<td>$c_r$</td>
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<td>0.06077</td>
</tr>
<tr>
<td>$c_{vp}$</td>
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<td>0.1394</td>
</tr>
<tr>
<td>$c_{vs}$</td>
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<td>0.643</td>
</tr>
<tr>
<td>$F_{B0}$</td>
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<td>0.800</td>
</tr>
<tr>
<td>$\gamma_l$</td>
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<td>37.33</td>
</tr>
<tr>
<td>$\gamma_r$</td>
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<td>11.88</td>
</tr>
<tr>
<td>$K_1$</td>
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<td>0.2</td>
</tr>
<tr>
<td>$K_2$</td>
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<td>0.05</td>
</tr>
<tr>
<td>$k_{CO_2}$</td>
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<td>0.244</td>
</tr>
<tr>
<td>$K_{CO_2}$</td>
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<td>0.0065</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>$MR_{BCO_2}$</td>
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<td>0.042</td>
</tr>
<tr>
<td>$MR_{CO_2, \text{steady}}$</td>
<td>0.301</td>
<td>1.010</td>
</tr>
<tr>
<td>$MR_{O_2, \text{steady}}$</td>
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<td>1.175</td>
</tr>
<tr>
<td>$P_{l_{CO_2}}$</td>
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<td>0.0</td>
</tr>
<tr>
<td>$P_{l_{O_2}}$</td>
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<td>150.0</td>
</tr>
<tr>
<td>$R_l$</td>
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<td>11.35</td>
</tr>
<tr>
<td>$P_{r_{p, \text{steady}}}$</td>
<td>1.965</td>
<td>0.3967</td>
</tr>
<tr>
<td>$RQ$</td>
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<td>0.86</td>
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<tr>
<td>$R_r$</td>
<td>4.158</td>
<td>4.158</td>
</tr>
<tr>
<td>$\rho$</td>
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<td>0.011</td>
</tr>
<tr>
<td>$\tau_p$</td>
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<td>0.5</td>
</tr>
<tr>
<td>$\tau_s$</td>
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<td>1.0</td>
</tr>
<tr>
<td>$V$</td>
<td>5.000</td>
<td>5.000</td>
</tr>
<tr>
<td>$V_{BCO_2}$</td>
<td>0.900</td>
<td>0.900</td>
</tr>
<tr>
<td>$V_{CO_2}$</td>
<td>3.200</td>
<td>3.200</td>
</tr>
<tr>
<td>$V_{O_2}$</td>
<td>2.500</td>
<td>2.500</td>
</tr>
<tr>
<td>$V_{T_{CO_2}}$</td>
<td>15.000</td>
<td>15.000</td>
</tr>
<tr>
<td>$V_{T_{O_2}}$</td>
<td>6.000</td>
<td>6.000</td>
</tr>
<tr>
<td>$W$</td>
<td>0.0</td>
<td>75.0</td>
</tr>
</tbody>
</table>
increases at the beginning rather than decreases. This is caused by the slower increase in ventilation at the onset of exercise which implies that less CO₂ is expired than diffuses into the alveoli from the blood. The behavior of the cardiovascular variables is not significantly affected if \( q_c \) is changed from 1 to 100.

Figure 9.4 shows also that \( P_{aO₂} \) reaches its steady state value only after about 10 minutes independent of the choice of \( q_c \). It can be stabilized faster if we take also \( P_{aO₂} \) as a controlled quantity. Let us include an additional term into the cost functional, \( q_o(P_{aO₂} - P_{aO₂}(t))^2 \). If we choose also \( q_o = 100 \) we see from Figure 9.5 that now \( P_{aO₂} \) reaches its steady state value sooner (dashed line) compared to the case where only \( P_{aCO₂} \) is regulated (dotted line). Also the behavior of the cardiovascular variables changes if also \( P_{aO₂} \) is regulated. The time course of cardiac output is almost unaffected. For fixed time, the heart rate is greater if \( P_{aO₂} \) is also regulated, while stroke volume is smaller. The smaller stroke volume is a consequence of an increased arterial blood pressure \( P_{as} \). The increased \( P_{as} \) and a decreased venous blood pressure \( P_{vs} \) in turn, yield a greater pressure difference. This is necessary to compensate the greater resistance \( R_s \) that is caused by the higher venous concentration of \( O₂ \) which comes from the increased ventilation.

### Table 9.2: List of Steady States

<table>
<thead>
<tr>
<th>Steady State</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{as} )</td>
<td>103.7</td>
<td>122.5</td>
</tr>
<tr>
<td>( P_{ap} )</td>
<td>16.78</td>
<td>12.76</td>
</tr>
<tr>
<td>( P_{vs} )</td>
<td>3.566</td>
<td>3.103</td>
</tr>
<tr>
<td>( P_{vp} )</td>
<td>7.687</td>
<td>9.497</td>
</tr>
<tr>
<td>( P_{aCO₂} )</td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>( P_{aO₂} )</td>
<td>103.5</td>
<td>103.5</td>
</tr>
<tr>
<td>( P_{BCO₂} )</td>
<td>48.08</td>
<td>48.08</td>
</tr>
<tr>
<td>( P_{vCO₂} )</td>
<td>50.01</td>
<td>58.91</td>
</tr>
<tr>
<td>( P_{vO₂} )</td>
<td>30.4</td>
<td>14.82</td>
</tr>
<tr>
<td>( S_l )</td>
<td>64.2</td>
<td>87.9</td>
</tr>
<tr>
<td>( S_r )</td>
<td>4.894</td>
<td>6.7</td>
</tr>
<tr>
<td>( H )</td>
<td>78.25</td>
<td>107.1</td>
</tr>
<tr>
<td>( \dot{V}_A )</td>
<td>6.494</td>
<td>21.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Steady State</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{aCO₂} )</td>
<td>0.504</td>
<td>0.504</td>
</tr>
<tr>
<td>( C_{aO₂} )</td>
<td>0.1977</td>
<td>0.1977</td>
</tr>
<tr>
<td>( C_{BCO₂} )</td>
<td>0.5565</td>
<td>0.5565</td>
</tr>
<tr>
<td>( C_{vCO₂} )</td>
<td>0.5691</td>
<td>0.6269</td>
</tr>
<tr>
<td>( C_{VO₂} )</td>
<td>0.1221</td>
<td>0.1221</td>
</tr>
<tr>
<td>( C_{aO₂} - C_{VO₂} )</td>
<td>0.07567</td>
<td>0.143</td>
</tr>
<tr>
<td>( Q_l )</td>
<td>4.625</td>
<td>8.219</td>
</tr>
<tr>
<td>( Q_r )</td>
<td>4.625</td>
<td>8.219</td>
</tr>
<tr>
<td>( R_s )</td>
<td>21.64</td>
<td>14.52</td>
</tr>
<tr>
<td>( V_{str,l} )</td>
<td>0.05911</td>
<td>0.07673</td>
</tr>
<tr>
<td>( V_{str,r} )</td>
<td>0.05911</td>
<td>0.07673</td>
</tr>
</tbody>
</table>
Figure 9.1: Dynamics of heart rate $H$ and alveolar ventilation $\dot{V}_A$.

Figure 9.2: Dynamics of mean systemic arterial and venous blood pressure $P_{as}$ and $P_{vs}$.

9.5 The influence of the dynamics of pulmonary resistance

We have chosen the time constant of pulmonary resistance to be $\tau_p = 0.5$. This time constant has the following influence on the time courses of the other states. The smaller $\tau_p$, the greater is the decrease of pulmonary resistance $R_p$ and hence the greater the initial increase of blood flow $F_p$. This in turn implies greater changes of the mean blood pressures $P_{ap}$, $P_{vp}$, $P_{vs}$, and $P_{as}$ at the onset of exercise. Furthermore, if pulmonary blood flow increases tremendously, then $P_{aCO_2}(t)$ rather increases than decreases at the onset of exercise, since then more $CO_2$ is brought by pulmonary blood flow than can be expired.

We have furthermore taken the time constant of $A_{pesk}$ to be $\tau_s = 1$. This time constant influences the initial behavior of systemic resistance. The faster $A_{pesk}$ changes at the onset of exercise the greater is the initial increase in systemic resistance, although venous oxygen concentration decreases. This implies a decrease in systemic blood flow and in consequence an immense increase in arterial systemic blood pressure $P_{as}$ and an immense decrease in venous systemic blood pressure $P_{vs}$ at the onset of exercise.
9.6 Adaption to exercise if the baroreflex operating point is not reset

Let us assume that the mean arterial blood pressure is regulated to its initial ("rest") value during exercise. In other words, there is no resetting of the baroreflex operating point.

In order to simulate this situation, we omit the relationship between heart rate and metabolic rate, \( H = 35MR_\text{O}_2 + 66 \). This is necessary because now we choose the steady state values of \( P_{\text{as}} \). We choose \( P'_{\text{as}} = P''_{\text{as}} = 103.7 \) (according to the "rest" value above). Then we obtain for unit weights \( q_{\text{as}} = q_c = q_1 = q_2 = 1 \) and for the same parameters as in Table 9.1 the dynamics as depicted in Figures 9.6 - 9.8. Fig. 9.6 shows that the heart rate attains a smaller exercise steady state value if mean arterial blood pressure is regulated to its rest value. However, cardiac output is only slightly decreased since stroke volume is increased (compare Fig. 9.8). This is a consequence of the smaller systemic arterial pressure counteracting the ejection of blood from the left ventricle.

Venous systemic pressure \( P_{\text{vs}} \) increases rather than decreases if arterial blood pressure is stabilized to its rest value (see Fig. 9.7). This implies that blood is driven into the right heart with increased vigor which in turn makes possible an increased stroke volume. The blood pressures in the pulmonary circuit are practically unaffected if the baroreflex operating point remains the same during exercise. Also, the dynamics of the blood gases are not significantly changed if the arterial pressure is not elevated during exercise.
Figure 9.4: Dynamics of arterial (alveolar) gas concentrations $P_{aCO_2}$ and $P_{aO_2}$ if deviations of $P_{aCO_2}$ from its debit value are more (dotted: $q_c = 100$) or less (solid: $q_c = 1$) punished in the cost criterion. For greater weight $q_c$, $P_{aCO_2}$ increases rather than decreases at the onset of exercise. The reason is that due to the smaller ventilation during the first minutes more $CO_2$ diffuses into the alveoli than is expired.
Figure 9.5: Dynamics of arterial (alveolar) gas concentrations $P_{aCO_2}$ and $P_{aO_2}$ if also $P_{aO_2}$ is regulated (dashed: $q_c = 100, q_o = 100$) compared to the case where only $P_{aCO_2}$ is regulated (dotted: $q_c = 100$). The oxygen partial pressure reaches its steady state value sooner if it is also controlled. In this case, the stabilization of the carbon dioxide partial pressure is no longer the primary goal of the control. Note, however, the different scaling for $P_{aCO_2}$ and $P_{aO_2}$.

Figure 9.6: Dynamics of heart rate and alveolar ventilation if mean arterial blood pressure $P_{as}$ is regulated to its "rest" value during exercise (dotted) compared to the case where $P_{as}$ is regulated to a higher pressure (solid). Heart rate is decreased if the blood pressure is not elevated during exercise. However, a concomitant increase in stroke volume makes possible an only slightly decreased cardiac output.
Chapter 9. A linear feedback

Figure 9.7: Dynamics of the blood pressures in the four compartments if mean arterial blood pressure $P_{as}$ is regulated to its "rest" value during exercise (dotted) compared to the case where $P_{as}$ is regulated to a higher pressure (solid). The smaller systemic arterial blood pressure opposing the ejection of blood from the left ventricle and an almost unchanged pulmonary venous pressure increase left stroke volume. Similarly, right stroke volume is increased by the increased systemic venous driving pressure.

Figure 9.8: Dynamics of left stroke volume and cardiac output if mean arterial blood pressure $P_{as}$ its regulated to its "rest" value during exercise (dotted) compared to the case where $P_{as}$ is regulated to a higher pressure (solid). The increase in stroke volume makes possible an only slightly decreased cardiac output despite the decreased heart rate.
Chapter 10

A nonlinear feedback

In this chapter we will design a nonlinear feedback law \( u \) for system (8.7). In doing so the nonlinear structure of the system will be considered better than by using a linear feedback. Again, we require from the control \( u \) that it transfers the system from the initial state "rest" to the final state "exercise" in an optimal way.

However, "optimal" has a different meaning now. As before, \( u \) will be chosen such that the deviations of the controlled variables \( P_{as} \) and \( P_{aCO_2} \) from their debit values are as small as possible during the transient phase. The cost of the control will again be measured by a quadratic cost criterion. But now, the integrand of the cost criterion does not involve the square of \( u \). It contains the square of a function \( v \) which is related to \( u \) by a nonlinear transformation. As a consequence, although the presence of \( v \) in the cost functional keeps the control amplitudes \( u \) bounded we can no longer attribute a physiological meaning to the control related quantity \( v \) in the cost functional.

For convenience we introduce a slightly different notation for system (8.7),

\[
\dot{x} = f(x) + g u, \quad x(0) = x^r, \tag{10.1}
\]

where \( g \in M_{14,2}(\mathbb{R}) \) is equal to the matrix \( B \) in (8.7). The columns of \( g \) will be denoted by \( g = (g_1, g_2) \), i.e.,

\[
g_1 = (0, ..., 0, 1, 0)^T \in \mathbb{R}^{14}, \quad g_2 = (0, ..., 0, 0, 1)^T \in \mathbb{R}^{14}. \tag{10.2}
\]

As before, \( f \in C^\infty(U, \mathbb{R}^{14}) \) (we have omitted the workload \( W \) in the argument of \( f \)). Again, \( U = \mathbb{R}_{+}^{10} \times \mathbb{R}^2 \times \mathbb{R}_{+}^2 \) denotes the set of physiologically meaningful states. Moreover, \( x \) is given by

\[
x = (P_{as}, P_{vs}, P_{vp}, P_{aCO_2}, P_{aO_2}, P_{BCO_2}, P_{vCO_2}, P_{vO_2}, S_l, \sigma_l, S_r, \sigma_r, H, \dot{V}_A)^T \in \mathbb{R}^{14}, \tag{10.3}
\]
Chapter 10. A nonlinear feedback

and $u \in \mathbb{R}^2$. The components of $x$ are referred to as $x_i, i = 1,...,14$. The output is written as

$$y = h(x) = (x_1, x_4)^T$$

with $h \in C^\infty(U, \mathbb{R}_+^2)$. For systems of this form we have a well-developed control theory at our disposal. In the following we will apply the results presented in Isidori [22].

10.1 A shift in the origin of the state space

As in Chapter 9.1 we introduce the coordinates

$$\xi = x - x^e, \quad \eta = y - y^e.$$ (10.5)

Substitution for $x$ in the nonlinear system (10.1) yields the transformed state equations

$$\dot{\xi} = \tilde{f}(\xi) + u_1 g_1 + u_2 g_2, \quad \xi(0) = x^r - x^e,$$

$$\eta = h(\xi) = (\xi_1, \xi_4)^T,$$ (10.6)

where $\tilde{f}(\xi)$ is defined as

$$\tilde{f}(\xi) = f(\xi + x^e).$$ (10.7)

In other words, the desired equilibrium $x = x^e$ corresponds now to the equilibrium $\xi = 0$ in the new coordinates. The initial state in the new coordinates is equal to the deviation of the steady state $x^r$ from the steady state $x^e$. Furthermore, any derivative of a component of $\tilde{f}_j(\xi)$ (or $h_k(\xi)$) with respect to a component $\xi_i$ is equal to the derivative of $f_j(x)$ ($h_k(x)$) with respect to the corresponding component $x_i$,

$$\frac{\partial \tilde{f}_j(\xi)}{\partial \xi_i} = \frac{\partial f_j(x)}{\partial x_i} \quad \text{and} \quad \frac{\partial h_k(\xi)}{\partial \xi_i} = \frac{h_k(x)}{\partial x_i}, \quad i, j \in \{1,...,14\}, k \in \{1,2\}.$$ (10.8)

10.2 Determining the relative degree

We introduce some notation first. Let $\lambda : \mathbb{R}^n \rightarrow \mathbb{R}$ be a real-valued function with continuous partial derivatives of any order. The Jacobian matrix of $\lambda$ (which in this case is the gradient) will be denoted by

$$\frac{\partial \lambda}{\partial x} = (\frac{\partial \lambda}{\partial x_1}, \frac{\partial \lambda}{\partial x_2}, \ldots, \frac{\partial \lambda}{\partial x_n}).$$ (10.9)
Furthermore, let $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$ be a vector-valued function. Then we define the linear operator $L_f$ by

$$L_f \lambda(x) = \frac{\partial \lambda}{\partial x} f(x) = \sum_{i=1}^{n} \frac{\partial \lambda}{\partial x_i} f_i(x). \quad (10.10)$$

The smooth real-valued function $L_f \lambda(x)$ is called the derivative of $\lambda$ along $f$. One can apply this operation repeatedly. If $\lambda$ is being differentiated $k$-times along $f$, we will use the notation $L^k_f \lambda$ and we have

$$L^k_f \lambda(x) = \frac{\partial (L^{k-1}_f \lambda)}{\partial x} f(x) \quad (10.11)$$

with $L^0_f \lambda(x) = \lambda(x)$. Similarly, if $g : \mathbb{R}^n \rightarrow \mathbb{R}^n$ is another vector-valued function, we can take the derivative of $\lambda$ first along $f$ and then along $g$,

$$L_g L_f \lambda(x) = \frac{\partial (L_f \lambda)}{\partial x} g(x). \quad (10.12)$$

Now we are ready to define the relative degree of a nonlinear system.

**Definition 10.1** The multi-input multi-output system

$$\begin{align*}
\dot{\xi} &= \tilde{f}(\xi) + u_1 g_1 + u_2 g_2, \\
\eta &= h(\xi),
\end{align*} \quad (10.13)$$

has the **relative degree** $r = (r_1, r_2)$ at a point $\xi^0$ if

(i) $$L_{g_j} L^k_f h_i(\xi) = 0 \quad (10.14)$$

for all $1 \leq j \leq 2$, all $\xi$ in a neighborhood of $\xi^0$, and all $k < r_i - 1$ for $i = 1$ respectively $i = 2$.

(ii) the matrix

$$\tilde{A}(\xi) = \begin{pmatrix}
L_{g_1} L^{r_1-1}_f h_1(\xi) & L_{g_2} L^{r_1-1}_f h_1(\xi) \\
L_{g_1} L^{r_2-1}_f h_2(\xi) & L_{g_2} L^{r_2-1}_f h_2(\xi)
\end{pmatrix} \quad (10.15)$$

is nonsingular at $\xi = \xi^0$.
Chapter 10. A nonlinear feedback

Applied to our system (10.6) we note first, that the action of the operator $L_g$, for $j = 1, 2$ on a function $f(x)$ is equal to derivation of $f$ with respect to the thirteenth ($j = 1$) and fourteenth ($j = 2$) component of $x$. We find immediately that

$$L_g h_1(\xi) = \frac{\partial h_1(\xi)}{\partial \xi_{13}} = 0, \quad L_g h_2(\xi) = \frac{\partial h_1(\xi)}{\partial \xi_{14}} = 0,$$

(10.16)

Furthermore,

$$L_{\tilde{f}} h_1(\xi) = \tilde{f}_1(\xi), \quad L_{\tilde{f}} h_2(\xi) = \tilde{f}_4(\xi),$$

(10.17)

and

$$L_g L_{\tilde{f}} h_1(\xi) = \frac{\partial \tilde{f}_1(\xi)}{\partial \xi_{13}}, \quad L_g L_{\tilde{f}} h_1(\xi) = \frac{\partial \tilde{f}_1(\xi)}{\partial \xi_{14}} = 0,$$

(10.18)

Hence, if we define

$$\bar{A}(\xi) = \begin{pmatrix} \frac{\partial \tilde{f}_1(\xi)}{\partial \xi_{13}} & 0 \\ 0 & \frac{\partial \tilde{f}_4(\xi)}{\partial \xi_{14}} \end{pmatrix},$$

(10.19)

then for any point $\xi^0$ with $\det \bar{A}(\xi^0) \neq 0$ the nonlinear system (10.6) has relative degree $r = (2, 2)$. In particular, for the parameters listed in Table 9.1 the point $\xi^0 = 0$ (which corresponds to $x = x^e$) satisfies this condition.

How can this property be interpreted? If we assume that the system at some time $t^0$ is in the state $\xi^0$ then $r_i$ is exactly the number of times one has to differentiate the $i$-th output $\eta_i$ at $t = t^0$ in order to have at least one component of the input vector $u(t^0)$ explicitly appearing. This is not hard to see. Let $i \in \{1, 2\}$. Then

$$\eta_i(t^0) = h_i(\xi(t^0)) = h_i(\xi^0),$$

(10.20)

and using (10.6),

$$\dot{\eta}_i(t) = \frac{\partial h_i}{\partial \xi} \frac{d \xi}{dt} = \frac{\partial h_i}{\partial \xi} (\tilde{f}(\xi(t)) + u_1(t)g_1 + u_2(t)g_2)$$

$$= L_{\tilde{f}} h_i(\xi(t)) + u_1(t) L_{g_1} h_i(\xi(t)) + u_2(t) L_{g_2} h_i(\xi(t)).$$

(10.21)
Now, due to (10.16), for all $t$ such that $\xi(t)$ is near $\xi^0$, i.e., for all $t$ near $t^0$, we have $L_{g_j} h_i(\xi(t)) = 0$, $j = 1, 2$, and therefore
\[
\dot{\eta}_i(t) = L_{\bar{j}} h_i(\xi(t)).
\] (10.22)
This in turn implies
\[
\dot{\eta}_i(t) = \frac{\partial (L_{\bar{j}} h_i)}{\partial \xi} \frac{d\xi}{dt} - \frac{\partial (L_{\bar{j}} h_i)}{\partial \xi} (\dot{\bar{j}}(\xi(t)) + u_1(t)g_1 + u_2(t)g_2)
\]
\[= L_{\bar{j}}^2 h_i(\xi(t)) + u_1(t)L_{g_1} L_{\bar{j}} h_i(\xi(t)) + u_2(t)L_{g_2} L_{\bar{j}} h_i(\xi(t)). \] (10.23)

Now, by virtue of (10.18), we have $(L_{g_1} L_{\bar{j}} h_i(\xi(t))), L_{g_2} L_{\bar{j}} h_i(\xi(t)) \neq (0, 0)$ at $t = t^0$, therefore at least one of the inputs $u_1(t^0), u_2(t^0)$ explicitly appears in the second derivative of the output $\eta_i$ at $t = t^0$. In particular,
\[
\dot{\eta}_1(t) = L_{\bar{j}}^2 h_1(\xi(t)) + u_1(t)L_{g_1} L_{\bar{j}} h_1(\xi(t)),
\]
\[
\dot{\eta}_2(t) = L_{\bar{j}}^2 h_2(\xi(t)) + u_2(t)L_{g_2} L_{\bar{j}} h_2(\xi(t)). \] (10.24)

### 10.3 Transformation to normal form

Due to Isidori [22], Lemma 5.1.2, the four row vectors
\[
\frac{\partial h_1}{\partial \xi}, \frac{\partial (L_{\bar{j}} h_1)}{\partial \xi}, \frac{\partial h_2}{\partial \xi}, \frac{\partial (L_{\bar{j}} h_2)}{\partial \xi}
\] (10.25)
are linearly independent at $\xi = \xi^0$. Therefore they qualify as a partial set of new coordinate functions around the point $\xi^0$. We set
\[
\phi_1(\xi) = h_1(\xi) = \xi_1,
\]
\[
\phi_2(\xi) = L_{\bar{j}} h_1(\xi) = \tilde{f}_1(\xi),
\]
\[
\phi_3(\xi) = h_2(\xi) = \xi_4,
\]
\[
\phi_4(\xi) = L_{\bar{j}} h_2(\xi) = \tilde{f}_4(\xi). \] (10.26)

Using Proposition 5.1.3 of Isidori [22], it is possible to find ten more functions $\phi_5, \ldots, \phi_{14}$ such that the set $\phi_1(\xi), \ldots, \phi_{14}(\xi)$ has a Jacobian matrix which is nonsingular at $\xi^0$. Moreover, it is possible to choose the remaining functions $\phi_i$, $i = 5, \ldots, 14$, such that $L_{g_j} \phi_i(\xi) = 0$, $i = 5, \ldots, 14$, $j = 1, 2$, for all $\xi$ in a neighborhood of $\xi^0$. The value at $\xi^0$ of these additional functions can be fixed arbitrarily. We will choose $\phi_i(\xi^0) = 0$, $i = 5, \ldots, 14$. Then the equilibrium $\xi^0 = 0$ in the original coordinates corresponds to the equilibrium $\phi(0) = 0$ in the new coordinates.
Let us denote the new coordinates by $z_i(t) = \phi_i(\xi(t))$, $i = 1, \ldots, 14$. Then the system described in the new coordinates can be obtained easily. We have, evoking \((10.22)\) and \((10.24)\),

\[
\dot{z}_1 = \frac{\partial \phi_1}{\partial \xi} \frac{d \xi}{dt} = \frac{\partial h_1}{\partial \xi} \frac{d \xi}{dt} = L_f h_1(\xi) = \phi_2(\xi) = z_2,
\]

\[
\dot{z}_2 = \frac{\partial \phi_2}{\partial \xi} \frac{d \xi}{dt} = \frac{\partial L_f h_1}{\partial \xi} \frac{d \xi}{dt} = L_f^2 h_1(\xi) + u_1 L_{g_1} L_f h_1(\xi),
\]

\[
\dot{z}_3 = \frac{\partial \phi_3}{\partial \xi} \frac{d \xi}{dt} = \frac{\partial h_2}{\partial \xi} \frac{d \xi}{dt} = L_f h_2(\xi) = \phi_4(\xi) = z_4,
\]

\[
\dot{z}_4 = \frac{\partial \phi_4}{\partial \xi} \frac{d \xi}{dt} = \frac{\partial L_f h_2}{\partial \xi} \frac{d \xi}{dt} = L_f^2 h_2(\xi) + u_2 L_{g_2} L_f h_2(\xi).
\]

(10.27)

On the right-hand side of the second and fourth equation we have to replace $\xi$ as a function of $z$, that is, $\xi = \phi^{-1}(z)$. Hence, by defining

\[
a_i(z) = L_{g_i} L_f h_i(\phi^{-1}(z)),
\]

\[
b_i(z) = L_f^2 h_i(\phi^{-1}(z)),
\]

(10.28)

for $1 \leq i \leq 2$, the corresponding equations can be written in the form

\[
\begin{align*}
\dot{z}_2 &= b_1(z) + u_1 a_1(z), \\
\dot{z}_4 &= b_2(z) + u_2 a_2(z),
\end{align*}
\]

(10.29)

or, more compactly,

\[
\begin{pmatrix} \dot{z}_2 \\ \dot{z}_4 \end{pmatrix} = b(z) + A(z) u.
\]

(10.30)

Here we have defined

\[
A(z) = \begin{pmatrix} a_1(z) & 0 \\ 0 & a_2(z) \end{pmatrix}, \quad b(z) = (b_1(z), b_2(z))^T.
\]

(10.31)

Note that the components of $A(z)$ are exactly those of the matrix $\tilde{A}(\xi)$ in \((10.19)\), with $\xi$ expressed as a function of $z$,

\[
A(z) = \tilde{A}(\phi^{-1}(z)).
\]

(10.32)

In particular, $A(z)$ is regular at $z^0 = \phi(\xi^0)$. Of course, $A(z)$ and $b(z)$ depend upon the choice of $\phi_5, \ldots, \phi_{14}$. If we choose them such that $L_{g_i} \phi_i(\xi) = 0$, $i = 5, \ldots, 14$, $j = 1, 2$ for all $\xi$ in a neighbourhood of $\xi_0$, then we obtain for the remaining state equations

\[
\dot{z}_i = \frac{\partial \phi_i}{\partial \xi} \frac{d \xi}{dt} = L_f \phi_i(\xi) + u_1 L_{g_1} \phi_i(\xi) + u_2 L_{g_2} \phi_i(\xi) = L_f \phi_i(\xi),
\]

(10.33)
for $i = 5, ..., 14$. Setting $q_i(z) = L\dot{\phi}_i(\phi^{-1}(z))$ the system in the new coordinates reads
\begin{align*}
\dot{z}_1 &= z_2, \\
\dot{z}_2 &= b_1(z) + u_1 a_1(z), \\
\dot{z}_3 &= z_4, \\
\dot{z}_4 &= b_2(z) + u_2 a_2(z), \\
\dot{z}_5 &= q_5(z), \\
&\vdots \\
\dot{z}_{14} &= q_{14}(z).
\end{align*}
(10.34)
Furthermore, the output of the system is related to the new state variables by
\[ \eta = h(\xi) = (z_1, z_3)^T. \]
(10.35)
Thus, by means of a suitable change of coordinates, we have arrived at a very simple and clear description of the nonlinear system. System (10.34) is said to be in normal form.

### 10.4 Partial linearization

We will in the following achieve a partial linearization of the nonlinear system (10.34) by means of a nonlinear transformation for $u$. Consider the state feedback
\[ u = A^{-1}(z)(-b(z) + v), \]
(10.36)
with new input $v = (v_1, v_2)^T$. The matrix $A(z)$ and the vector $b(z)$ have been defined in (10.31). Moreover, $A^{-1}(z)$ is well-defined in a neighbourhood of $z^0 = \phi(\xi^0)$. More explicitly, we have
\begin{align*}
    u_1 &= \frac{1}{a_1(z)}(-b_1(z) + v_1), \\
    u_2 &= \frac{1}{a_2(z)}(-b_2(z) + v_2).
\end{align*}
(10.37)
Substituting this into the normal form (10.34) of the equations we obtain
\begin{align*}
\dot{z}_1 &= z_2, \\
\dot{z}_2 &= v_1, \\
\dot{z}_3 &= z_4, \\
\dot{z}_4 &= v_2, \\
\dot{z}_i &= q_i(z), \quad i = 5, ..., 14.
\end{align*}
(10.38)
Note that both the change of coordinates and the feedback (10.36) are defined only locally around \( z^0 = \phi(\xi^0) \). In particular, they are not defined at points \( z \) where \( A(z) \) is singular.

Suppose that the new input \( v \) is chosen such that it does not depend upon \( z_i, i = 5, \ldots, 14 \). Then we have arrived at a system which is decomposed into a linear subsystem (with respect to the input \( v \)) of dimension 4 which is the only responsible for the input-output behavior, and a possibly nonlinear system of dimension 10 whose behavior does not affect the output variables. In this context we will in the following use the notation \( z = (z_\ell, z_{n\ell})^T \) with \( z_\ell = (z_1, \ldots, z_4)^T \) and \( z_{n\ell} = (z_5, \ldots, z_{14})^T \). Furthermore, we will abbreviate \( q(z) = (q_1(z), \ldots, q_{14}(z))^T \).

**Definition 10.2** From the representation in normal form, the so-called **zero dynamics** can immediately be read off. The zero dynamics describes the "internal" behavior of the system when input and initial conditions have been chosen such that the output of the system is identically zero. It can easily be seen that for each set of initial data \( z_\ell(0) = 0 \) and arbitrary \( z_{n\ell}(0) = z_{n\ell,0} \) the unique input which is capable to keep the output \( \eta(t) = 0 \) for all times \( t \) is given by

\[
u(t) = -A^{-1}(0, z_{n\ell}(t)) b(0, z_{n\ell}(t)). \quad (10.39)\]

In this case the system evolves on the subset \( z_1 = z_2 = z_3 = z_4 = 0 \) according to its zero dynamics

\[
\dot{z}_{n\ell} = q(0, z_{n\ell}), \quad z_{n\ell}(0) = z_{n\ell,0}. \quad (10.40)
\]

**10.5 Implementation of a linear feedback**

Our final step is the design of a suitable input \( v \) which stabilizes system (10.38) at the equilibrium point \( z^0 = 0 \) (which corresponds to \( x = x^e \)).

Let us rewrite the nonlinear system (10.38) in the form

\[
\begin{align*}
\dot{z}_\ell &= \hat{A} z_\ell + \hat{B} v, \\
\dot{z}_{n\ell} &= q(z_\ell, z_{n\ell}),
\end{align*} \quad (10.41)
\]

with

\[
\hat{A} = \begin{pmatrix}
0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0
\end{pmatrix}, \quad \hat{B} = \begin{pmatrix}
0 & 0 \\
1 & 0 \\
0 & 0 \\
0 & 1
\end{pmatrix}. \quad (10.42)
\]

The initial condition \( z(0) = \phi^{-1}(x^r - x^e) \) must lie sufficiently close to \( z^0 = 0 \). The controlled variables are

\[
\eta = (z_1, z_3)^T = \hat{D} z_\ell, \quad (10.43)
\]
with

\[ \hat{D} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}. \]  

(10.44)

Consider the feedback law

\[ v = -Kz, \]  

(10.45)

with a constant matrix \( K \in M_{2,4}(\mathbb{R}) \) whose components have yet to be determined. This choice of feedback yields a closed loop system

\[ \dot{z}_\ell = (\hat{A} - \hat{B}K)z_\ell, \]
\[ \dot{z}_{n\ell} = q(z_\ell, z_{n\ell}). \]  

(10.46)

The matrix \( K \) must necessarily be chosen such that the eigenvalues of \( \hat{A} - \hat{B}K \) have negative real parts. Then the linear subsystem is asymptotically stable.

What about the behavior of the nonlinear subsystem? Since \( z_\ell \to 0 \) as \( t \to \infty \), we expect that the nonlinear part behaves according to

\[ \dot{z}_{n\ell} = q(0, z_{n\ell}), \quad \text{and} \quad u = -A(0, z_{n\ell})^{-1}b(0, z_{n\ell}), \]  

(10.47)

for large \( t \). Note that this is exactly the zero dynamics of system (10.41). In fact, the following result holds (cf. Isidori [22], Proposition 4.2).

**Theorem 10.1** If the zero dynamics of system (10.41) is asymptotically stable at \( z_{n\ell}^0 = 0 \) and the eigenvalues of \( \hat{A} - \hat{B}K \) are in the left-half complex plane, then the feedback law (10.45) asymptotically stabilizes system (10.41) at \( z^0 = 0 \).

The next question is how the feedback gain matrix \( K \) should be chosen. The most reasonable way would be to consider the components of \( K \) as parameters and to determine their values by parameter identification. This was done by Kappel et al. [25] and Lafer [41] for the cardiovascular system. However, up to this date no experimental data are available to us for the combined cardiovascular and respiratory system. Therefore parameter identification cannot be applied and we have to resort to other considerations.

As before, we require that the controlled variables attain their steady state values such that the deviations from their debit values are as small as possible during the transient phase. This suggests again the use of a quadratic cost criterion. We determine the linear feedback control \( v \) by the requirement that

\[ \int_0^\infty \left( q_{as}z_1^2(t) + q_c z_3^2(t) + q_1v_1^2 + q_2v_2^2 \right) dt \]  

(10.48)
is minimized under the constraint
\[ \dot{z}_\ell = \hat{A}z_\ell + \hat{B}v, \]
\[ \eta = (z_1, z_3)^T = \hat{D}z_\ell. \] (10.49)

It is easily seen that system (10.49) is controllable and reconstructible (compare Theorems 7.4 and 7.23). This implies in particular that the system is stabilizable and detectable. Hence, according to Theorem 7.48 the desired control \( v \) is given by
\[ v = -Kz_\ell, \]
where \( E \) is the unique positive-definite symmetric solution of the algebraic Riccati equation
\[ E\hat{A} + \hat{A}^T E - E\hat{B}R_2^{-1}\hat{B}^T E + \hat{D}^T R_3 \hat{D} = 0. \] (10.51)

Here \( R_3 = \text{diag} (q_{as}, q_c) \) and \( R_2 = \text{diag} (q_1, q_2) \). Note that the controlled variables are the same as before, \( \eta = (z_1, z_3)^T = (\xi_1, \xi_4)^T \). However, the control functions \( v_1 \) and \( v_2 \) can no longer be interpreted physiologically.

In general, there are 16 solutions to the Riccati equation, which have the form
\[ E = \begin{pmatrix} * & * & 0 & 0 \\ * & * & 0 & 0 \\ 0 & 0 & * & * \\ 0 & 0 & * & * \end{pmatrix}. \] (10.52)

If we compute \( K \) via (10.50) and check the eigenvalues of the closed-loop matrix \( \hat{A} - \hat{B}K \), we find (as expected) that only one solution of the Riccati equation corresponds to the case where the eigenvalues of \( \hat{A} - \hat{B}K \) lie in the left-half complex plane. This solution furnishes explicitly
\[ K = \begin{pmatrix} \left(\frac{q_{as}}{q_1}\right)^{\frac{1}{2}} & \left(4\frac{q_{as}}{q_1}\right)^{\frac{1}{4}} & 0 & 0 \\ 0 & 0 & \left(\frac{q_c}{q_2}\right)^{\frac{1}{2}} & \left(4\frac{q_c}{q_2}\right)^{\frac{1}{4}} \end{pmatrix}. \] (10.53)

The corresponding eigenvalues of \( \hat{A} - \hat{B}K \) are
\[ -\frac{1}{\sqrt{2}} \left(\frac{q_{as}}{q_1}\right)^{\frac{1}{4}} (1 + i), -\frac{1}{\sqrt{2}} \left(\frac{q_{as}}{q_1}\right)^{\frac{1}{4}} (1 - i), -\frac{1}{\sqrt{2}} \left(\frac{q_c}{q_2}\right)^{\frac{1}{4}} (1 + i), -\frac{1}{\sqrt{2}} \left(\frac{q_c}{q_2}\right)^{\frac{1}{4}} (1 - i). \] (10.54)

Finally, we want to express \( v \) and \( u \) in terms of \( x \). Recalling \( z \) as a function of \( \xi \), the feedback \( v \) can be written as
\[ v = -K \begin{pmatrix} \xi_1 \\ \tilde{f}_1(\xi) \\ \xi_4 \\ \tilde{f}_4(\xi) \end{pmatrix}, \] (10.55)
or, expressed in terms of $x$,

$$
v = -K \begin{pmatrix}
x_1 - x_1^e \\
f_1(x) \\
x_4 - x_4^e \\
f_4(x)
\end{pmatrix} = -\begin{pmatrix}
\left(\frac{q_{as}}{q_1}\right)^\frac{1}{2}(x_1 - x_1^e) + (4\frac{q_{as}}{q_1})^\frac{1}{2}f_1(x) \\
\left(\frac{q_c}{q_2}\right)^\frac{1}{2}(x_4 - x_4^e) + (4\frac{q_c}{q_2})^\frac{1}{2}f_4(x)
\end{pmatrix}. \tag{10.56}
$$

Next, we obtain the control $u$ as a function of $\xi$ by using (10.37) and (10.28),

$$u_1 = \frac{1}{L_{g_1} L_f h_1(\xi)}(-L_f^2 h_1(\xi) + v_1),$$

$$u_2 = \frac{1}{L_{g_2} L_f h_2(\xi)}(-L_f^2 h_2(\xi) + v_2). \tag{10.57}$$

At last, by evoking (10.8) we can express $u$ in terms of $x$,

$$u_1 = \frac{1}{L_{g_1} L_f h_1(x)}(-L_f^2 h_1(x) + v_1),$$

$$u_2 = \frac{1}{L_{g_2} L_f h_2(x)}(-L_f^2 h_2(x) + v_2). \tag{10.58}$$

It remains to solve system (10.1)

$$\dot{x} = f(x) + g u, \quad x(0) = x^r. \tag{10.59}$$

### 10.6 Simulation results

Figure 10.1 shows the dynamics of some of the variables. The weights in the cost functional need to be determined by parameter identification which will be a concern of future projects. We have chosen special weights ($q_{as} = 100$, $q_c = 10$, $q_1 = 1$ and $q_2 = 0.0001$) because a bad choice might cause the relative degree to drop during time evolution.

The assumption that $A_{pesk}$ and $R_p$ vary continuously is essential for the nonlinear feedback. Would we take them as parameters with different values during rest and exercise, then heart rate and ventilation rate would decrease abruptly at the onset of exercise. For certain weight values, alveolar ventilation would initially even become negative which is rather unrealistic from the physiological point of view.
Figure 10.1: Dynamics of the heart rate $H$, the alveolar ventilation $\dot{V}_A$, the controlled variables mean arterial blood pressure $P_{as}$ and carbon dioxide partial pressure in arterial blood $P_{aco_2}$, cardiac output $Q_t$, and carbon dioxide partial pressure in arterial blood $P_{ao_2}$ obtained with a nonlinear feedback.
Chapter 11

Critical remarks and perspectives

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. In particular, the short-term reaction of the cardiovascular and respiratory system to exercise can be modeled by a two-input-two-output control system. The feedback can be approximated by the solution of a linear quadratic regulator problem. The nonlinear feedback furnishes comparable results.

There are various details which need improvement and further investigations. For instance:

- Experimental data are needed in order to perform a parameter identification.

- It would be desirable to have an improved model for the process of metabolic autoregulation, which takes into account a more complex relationship between oxygen and vessel resistance. Also the influence of other vasodilator agents could be investigated.

- The action of pulmonary stretch receptors and the passive decrease of vessel resistance in reaction to an increased blood flow should be taken into account.

- The influence of the sympathetic nervous system on the compliances of the venous compartments during exercise should be considered.

- The brain could be treated as separate compartment (cf., e.g., Fincham and Tehrani [7] or Grodins [14]).

- What factors determine the new operating value for the arterial blood pressure? Right now it is determined indirectly from an empirical relationship between heart rate and metabolic rate or from measurements. It would be desirable to have another quantity which is regulated within very narrow limits during exercise, as $P_aCO_2$ is. Then it would be possible to model exercise with varying workloads.
Moreover, the model can be adapted to simulate other situations. For example:

- The short-term regulatory mechanisms following hemorrhage or transfusion could be studied. For instance, if the systemic arterial compartment is the source of hemorrhage, the blood loss at rate $Q_H$ can be modeled by

$$c_{as} \dot{P}_{as} = Q_i - F_s - Q_H.$$  \hfill (11.1)

- The model can be used to study the consequences of a suddenly increased systemic resistance (e.g., after infusion of a vasoconstrictor substance).

- Delays could be considered in the model. This may lead to the phenomenon of periodic breathing which occurs in a number of disease conditions, such as cardiac failure. Periodic breathing has been extensively studied for instance by Batzel and Tran [1] or Khoo et al. [30].

- At the moment, only short-term regulatory effects are considered. By including long term control mechanisms (such as control of blood volume by the kidneys) the model could be used to simulate the hemodynamics during a dialysis process.
Appendix A

Physical background

A.1 The ideal gas law

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 (O₂) and carbon dioxide (CO₂) follow the
ideal gas law,

\[ PV = nRT, \]

where \( P \) is pressure, \( V \) is volume, \( n \) is the number of moles of the gas, and \( T \) is temperature.
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 volumina
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 intermolecular 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 ($P_0 = 760 \text{ mmHg}$, $T_0 = 273K$)

$$\frac{V}{n} = R \frac{T_0}{P_0} = 22.4 \text{ l} \cdot \text{mole}^{-1}.$$  \hspace{1cm} (A.2)

The $CO_2$ mole volume under standard conditions is $22.6 \text{ l} \cdot \text{mole}^{-1}$ which shows that the deviation from the "ideal" mole volume is quantitatively insignificant.

## A.2 Gas mixtures and Dalton’s law

If the (A.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 $i$, $i = 1, ..., N$, in a container with volume $V$ at temperature $T$. Then the ideal gas law reads

$$PV = (n_1 + ... + n_N)RT,$$  \hspace{1cm} (A.3)

where $P$ is the pressure exerted by the gas mixture. The pressure $P_i$ defined by

$$P_i = \frac{n_iRT}{V},$$  \hspace{1cm} (A.4)

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 (A.3) and (A.4) 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,

$$P = P_1 + P_2 + ... + P_N \text{ \hspace{1 cm} (Dalton’s law).}$$  \hspace{1cm} (A.5)

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 (A.3) and (A.4) that the partial pressure $P_i$ exerted by gas $i$ is related to the total pressure $P$ of the gas mixture by

$$P_i = \frac{n_i}{n}P.$$  \hspace{1cm} (A.6)
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

$$F_i = \frac{n_i}{n}.$$  \hspace{1cm} (A.7)

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

## A.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

$$(P - P_{H_2O})V = nRT.$$  \hspace{1cm} (A.8)

where $P_{H_2O}$ denotes the partial pressure of the water particles. 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

$$P_i = F_i(P - P_{H_2O}).$$  \hspace{1cm} (A.9)

The partial pressure of water vapor depends solely on temperature. At body temperature ($37^\circ C$), 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,

$$P_i = F_i \cdot 713.$$  \hspace{1cm} (A.10)

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,

$$P_i = F_i \cdot 760.$$  \hspace{1cm} (A.11)

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 particles.
A.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

\[
V_I = \frac{nRT_I}{(P_I - P_{H_2O,I})}, \quad (A.12)
\]

\[
V_{II} = \frac{nRT_{II}}{(P_{II} - P_{H_2O,II})}. \quad (A.13)
\]

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

\[
\frac{V_I}{V_{II}} = \frac{(P_{II} - P_{IIH_2O})}{(P_I - P_{IIH_2O})} \frac{T_I}{T_{II}}. \quad (A.14)
\]

The following conditions are often used in respiratory physiology.

- **BTPS** (body temperature and pressure, saturated): \( T = 37{^\circ}C = 310K \), \( P_a = \) ambient pressure, \( P_{H_2O} = 47 \) mmHg. These are the conditions inside the body.

- **STPD** (standard temperature and pressure, dry): \( T_0 = 0{^\circ}C = 273K \), \( P_0 = \) barometric pressure at sea level = 760 mmHg, \( P_{H_2O} = 0 \) mmHg. These are the so called standard conditions.

Using (A.14) we obtain

\[
\frac{V_{BTPS}}{V_{STPD}} = \frac{863}{P_a - 47} = 1.21, \quad (A.15)
\]

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

\[
V_{STPD} = \frac{nRT_0}{P_0}. \quad (A.16)
\]
As soon as this dry air enters the respiratory passage 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

\[ P_0 V_{BTPS} = (n + n_{H_2O}) R (T_0 + 37), \]  

or, if we mentally remove the water particles,

\[ (P_0 - 47) V_{BTPS} = n R (T_0 + 37). \]

Hence, \( V_{BTPS} \) can be on the one hand regarded as the volume occupied by the dry particles and the water particles at pressure \( P_0 \). On the other hand, it can be interpreted as the volume occupied by the dry particles alone at pressure \( P_0 - 47 \).

### A.5 Gases dissolved in liquids. 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,

\[ C_i = \alpha_i P_i \quad \text{(Henry’s law)}. \]

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 specie. \( P_i \) 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\text{STPD} of \( O_2 \) are dissolved in 1 l of plasma: \( C_{O_2} = 21.3 \text{ ml\text{STPD} \cdot l}^{-1} \). 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 the chemically bound molecules.
Appendix B

Numerical values from literature

The following numerical values have been collected from literature. They are obtained by different methods, such as measurements, empiric estimation, or parameter fitting. They should be understood as average values under resting conditions.

We do not give values for all quantities used in the model at this place. In particular, many numerical values for quantities corresponding to the cardiovascular part of the model are not specified here. They can be found in the papers by Kappel and Peer [23], [24], Kappel et al. [25], and Lafer [41].

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{aCO_2}$</td>
<td>0.493</td>
<td>lSTPD · l$^{-1}$</td>
<td>[37], p. 253</td>
</tr>
<tr>
<td>$C_{aO_2}$</td>
<td>0.197</td>
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<td>[37], p. 253</td>
</tr>
<tr>
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</tr>
<tr>
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<td>[37], p. 253</td>
</tr>
<tr>
<td>$F_B$</td>
<td>0.5</td>
<td>1 · (min · kg brain tissue)$^{-1}$</td>
<td>[35]; [37], p. 745</td>
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<tr>
<td></td>
<td></td>
<td>0.750</td>
<td>1 · min$^{-1}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-15% of resting cardiac output</td>
<td></td>
</tr>
<tr>
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<td>1 · (min · mmHg)$^{-1}$</td>
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</tr>
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<td></td>
<td></td>
<td>3.2</td>
<td>1 · (min · mmHg)$^{-1}$</td>
</tr>
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<td>1 · (min · mmHg)$^{-1}$</td>
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<td></td>
<td></td>
<td>26.5</td>
<td>1 · (min · mmHg)$^{-1}$</td>
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<tr>
<td>$H$</td>
<td>70</td>
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<td>[37], p. 144</td>
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<tr>
<td>$I_c$</td>
<td>35.5</td>
<td>mmHg</td>
<td>[30]; [31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>$I_p$</td>
<td>35.5</td>
<td>mmHg</td>
<td>[30]; [31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>$k_{CO_2}$</td>
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<td></td>
<td></td>
<td>0.0057</td>
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<td>$K_1$</td>
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</tr>
<tr>
<td>$K_2$</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>0.05</td>
<td>mmHg$^{-1}$</td>
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</table>
### Appendix B. Numerical values from literature

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<th>Unit</th>
<th>Source</th>
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<td></td>
<td>0.031</td>
<td>$l_{STPD} \cdot \text{min}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>$l_{STPD} \cdot \text{min}^{-1}$</td>
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<td>$MR_{O_2}$</td>
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<tr>
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<td>[37], p. 249</td>
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<tr>
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<td>[37], p. 239</td>
</tr>
<tr>
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<td>[37], p. 239</td>
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<td>[37], p. 239</td>
</tr>
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<tr>
<td>$Q_l = Q_r = F_p = F_s$</td>
<td>6</td>
<td>$l \cdot \text{min}^{-1}$</td>
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</tr>
<tr>
<td></td>
<td>6.2</td>
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<td>[37], p. 239</td>
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<td>5</td>
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<td>[37], p. 239</td>
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<tr>
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<tr>
<td>$R_{Q}$</td>
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<td>-</td>
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</tr>
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<td></td>
<td>0.81</td>
<td>-</td>
<td>[30]; [34]</td>
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</tr>
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<td>[30]</td>
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<td>3.0</td>
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<td>[14]</td>
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<td>$l_{BTPS}$</td>
<td>[37], p. 1011</td>
</tr>
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<td>$V_{CO_2}$</td>
<td>3.2</td>
<td>$l_{BTPS}$</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>$l_{BTPS}$</td>
<td>[35]; [14]</td>
</tr>
<tr>
<td>$\dot{V}_E$</td>
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<td>$l_{BTPS} \cdot \text{min}^{-1}$</td>
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<tr>
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<td>1</td>
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<td>[30]; [35]; [31]</td>
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<td>1</td>
<td>[30]; [35]; [31]</td>
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<td>1</td>
<td>[17], p. 1011</td>
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<td>[7]</td>
</tr>
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<td>$\dot{V}_D$</td>
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<td>2.28</td>
<td>$l_{BTPS} \cdot \text{min}^{-1}$</td>
<td>[30]</td>
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# Appendix C

## Glossary of notation

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>slope of the relationship between heart rate and metabolic rate</td>
<td>l STPD · min⁻²</td>
</tr>
<tr>
<td>$\alpha_l$</td>
<td>coefficient of $S_l$ in the differential equation for $\sigma_l$</td>
<td>mmHg · min⁻¹</td>
</tr>
<tr>
<td>$\alpha_r$</td>
<td>coefficient of $S_r$ in the differential equation for $\sigma_r$</td>
<td>mmHg · min⁻¹</td>
</tr>
<tr>
<td>$A_{\text{peak}}$</td>
<td>$R_s = A_{\text{peak}}C_{vO_2}$</td>
<td></td>
</tr>
<tr>
<td>$A_{\text{peak}}'/c$</td>
<td>steady state value of $A_{\text{peak}}$ during rest / exercise</td>
<td></td>
</tr>
<tr>
<td>$b$</td>
<td>constant relating heart rate and metabolic rate</td>
<td>mmHg · min⁻¹</td>
</tr>
<tr>
<td>$\beta_l$</td>
<td>coefficient of $H$ in the differential equation for $\sigma_l$</td>
<td>mmHg · min⁻¹</td>
</tr>
<tr>
<td>$\beta_r$</td>
<td>coefficient of $H$ in the differential equation for $\sigma_r$</td>
<td>mmHg · min⁻¹</td>
</tr>
<tr>
<td>$c$</td>
<td>factor converting from STPD to BTPS conditions, $c = 1.21$</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_a$</td>
<td>compliance of the arterial part of the systemic circuit</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_p$</td>
<td>compliance of the arterial part of the pulmonary circuit</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_l$</td>
<td>compliance of the relaxed left ventricle</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_r$</td>
<td>compliance of the relaxed right ventricle</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_v$</td>
<td>compliance of the venous part of the systemic circuit</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$c_{vp}$</td>
<td>compliance of the venous part of the pulmonary circuit</td>
<td>1 · mmHg⁻¹</td>
</tr>
<tr>
<td>$C_{aCO_2}$</td>
<td>concentration of bound and dissolved $CO_2$ in arterial blood</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{aO_2}$</td>
<td>concentration of bound and dissolved $O_2$ in arterial blood</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{BCO_2}$</td>
<td>concentration of bound and dissolved $CO_2$ in brain tissue</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{CO_2}$</td>
<td>general symbol for carbon dioxide concentration</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{O_2}$</td>
<td>general symbol for oxygen concentration</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{TCO_2}$</td>
<td>concentration of bound and dissolved $CO_2$ in lumped body tissue</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{TO_2}$</td>
<td>concentration of bound and dissolved $O_2$ in lumped body tissue</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{vBCO_2}$</td>
<td>concentration of bound and dissolved $CO_2$ in the venous blood leaving the brain tissue</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{vCO_2}$</td>
<td>concentration of bound and dissolved $CO_2$ in the mixed venous blood entering the lungs</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>$C_{vO_2}$</td>
<td>concentration of bound and dissolved $O_2$ in the mixed venous blood entering the lungs</td>
<td>l STPD · l⁻¹</td>
</tr>
<tr>
<td>Symbol</td>
<td>Meaning</td>
<td>Unit</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>$F_{ACO_2}$</td>
<td>fractional concentration of $CO_2$ in the alveolar gas mixture</td>
<td>-</td>
</tr>
<tr>
<td>$F_{AO_2}$</td>
<td>fractional concentration of $O_2$ in the alveolar gas mixture</td>
<td>-</td>
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<tr>
<td>$F_B$</td>
<td>blood flow perfusing the brain tissue compartment</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$F_{Bo}$</td>
<td>cerebral blood flow for $P_{acO_2} = 40$</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$F_{ICO_2}$</td>
<td>fractional concentration of $CO_2$ in the inspired gas mixture</td>
<td>-</td>
</tr>
<tr>
<td>$F_{IO_2}$</td>
<td>fractional concentration of $O_2$ in the inspired gas mixture</td>
<td>-</td>
</tr>
<tr>
<td>$F_p$</td>
<td>blood flow perfusing the lung compartment</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$F_s$</td>
<td>blood flow perfusing the tissue compartment</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$H$</td>
<td>heart rate</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$G_c$</td>
<td>central controller gain factor</td>
<td>$1 \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$</td>
</tr>
<tr>
<td>$G_p$</td>
<td>peripheral controller gain factor</td>
<td>$1 \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$</td>
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<tr>
<td>$\gamma_e$</td>
<td>coefficient of $\sigma_i$ in the differential equation for $\sigma_l$</td>
<td>$\text{min}^{-1}$</td>
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<tr>
<td>$\gamma_r$</td>
<td>coefficient of $\sigma_r$ in the differential equation for $\sigma_r$</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$I_c$</td>
<td>constant for central drive of ventilation</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$I_p$</td>
<td>constant for peripheral drive of ventilation</td>
<td>$\text{lSTPD} \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$K_1$</td>
<td>constant for the $O_2$ dissociation curve</td>
<td>$\text{mmHg}^{-1}$</td>
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<tr>
<td>$K_2$</td>
<td>constant for the $O_2$ dissociation curve</td>
<td>$\text{lSTPD} \cdot \text{min}^{-1}$</td>
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<tr>
<td>$K_{CO_2}$</td>
<td>slope of the physiological $CO_2$ dissociation curve</td>
<td>$\text{sec}^{1/2}$</td>
</tr>
<tr>
<td>$k_{CO_2}$</td>
<td>constant for the physiological $CO_2$ dissociation curve</td>
<td>$\text{sec}$</td>
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<tr>
<td>$\kappa$</td>
<td>duration of the systole = $\kappa \cdot \sqrt{\text{duration of the heart cycle}}$</td>
<td>$\text{lSTPD} \cdot \text{min}^{-1}$</td>
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<tr>
<td>$t_d$</td>
<td>duration of the diastole</td>
<td>$\text{lSTPD} \cdot \text{min}^{-1}$</td>
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<tr>
<td>$MR_{BCO_2}$</td>
<td>metabolic rate of $CO_2$ production in brain tissue</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$MR_{OE}^{/}$</td>
<td>steady state metabolic $CO_2$ production rate during rest/exercise</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$MR_{OE}^{/c}$</td>
<td>steady state metabolic $O_2$ consumption rate during rest / exercise</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{ICO_2}$</td>
<td>partial pressure of $CO_2$ in inspired air</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{IO_2}$</td>
<td>partial pressure of $O_2$ in inspired air</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_a$</td>
<td>ambient pressure</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{acO_2}$</td>
<td>partial pressure of $CO_2$ in arterial blood</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{aoO_2}$</td>
<td>partial pressure of $O_2$ in arterial blood</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{ACO_2}$</td>
<td>partial pressure of $CO_2$ in alveolar air</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{AO_2}$</td>
<td>partial pressure of $O_2$ in alveolar air</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{as}$</td>
<td>mean blood pressure in the arterial region of the systemic circuit</td>
<td>$\text{mmHg}$</td>
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<tr>
<td>$P_{ap}$</td>
<td>mean blood pressure in the arterial region of the pulmonary circuit</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{BCO_2}$</td>
<td>partial pressure of $CO_2$ in brain tissue</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>general symbol for partial pressure of $CO_2$</td>
<td>$\text{mmHg}$</td>
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<tr>
<td>$P_{O_2}$</td>
<td>general symbol for partial pressure of $O_2$</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{vCO_2}$</td>
<td>partial pressure of $CO_2$ in mixed venous blood entering the lungs</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{vO_2}$</td>
<td>partial pressure of $O_2$ in mixed venous blood entering the lungs</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
<td>$P_{as}$</td>
<td>mean blood pressure in the venous region of the systemic circuit</td>
<td>$\text{mmHg}$</td>
</tr>
<tr>
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<td>mean blood pressure in the venous region of the pulmonary circuit</td>
<td>$\text{mmHg}$</td>
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<tr>
<td>$q_{as}$</td>
<td>weighting factor of $P_{as}$ in the cost functional</td>
<td>$\text{mmHg}^{-2}$</td>
</tr>
<tr>
<td>$q_c$</td>
<td>weighting factor of $P_{acO_2}$ in the cost functional</td>
<td>$\text{mmHg}^{-2}$</td>
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<tr>
<td>$q_o$</td>
<td>weighting factor of $P_{aoO_2}$ in the cost functional</td>
<td>$\text{mmHg}^{-2}$</td>
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<tr>
<td>$q_1$</td>
<td>weighting factor of $u_1$ in the cost functional</td>
<td>$\text{min}^4 \cdot \text{LTPS}^{-1}$</td>
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<tr>
<td>$q_2$</td>
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<td>$\text{min}^4 \cdot \text{LTPS}^{-1}$</td>
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<tr>
<td>$Q_l$</td>
<td>left cardiac output</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>$Q_r$</td>
<td>right cardiac output</td>
<td>$1 \cdot \text{min}^{-1}$</td>
</tr>
<tr>
<td>Symbol</td>
<td>Meaning</td>
<td>Unit</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
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<tr>
<td>$R^{r/e}$</td>
<td>steady state value of pulmonary resistance during rest / exercise</td>
<td>mmHg · min$^{-1}$</td>
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<tr>
<td>$R_p$</td>
<td>resistance in the peripheral region of the pulmonary circuit</td>
<td>mmHg · min$^{-1}$</td>
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<tr>
<td>$R_l$</td>
<td>viscus resistance of the left ventricle</td>
<td>mmHg · sec$^{-1}$</td>
</tr>
<tr>
<td>$R_r$</td>
<td>viscus resistance of the right ventricle</td>
<td>mmHg · sec$^{-1}$</td>
</tr>
<tr>
<td>$R_Q$</td>
<td>respiratory quotient of the chemical reactions in the tissues</td>
<td>-</td>
</tr>
<tr>
<td>$R_{p_{res}}$</td>
<td>resistance in the peripheral region of the pulmonary circuit</td>
<td>mmHg · min$^{-1}$</td>
</tr>
<tr>
<td>$R_{p_{vis}}$</td>
<td>visous resistance of the left ventricle</td>
<td>mmHg · sec$^{-1}$</td>
</tr>
<tr>
<td>$R_{r_{vis}}$</td>
<td>visous resistance of the right ventricle</td>
<td>mmHg · sec$^{-1}$</td>
</tr>
<tr>
<td>$R_{Q}$</td>
<td>respiratory quotient of the chemical reactions in the tissues</td>
<td>-</td>
</tr>
<tr>
<td>$\rho$</td>
<td>constant relating imposed workload and metabolic rate</td>
<td>l · (min · Watt)$^{-1}$</td>
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<tr>
<td>$S_l$</td>
<td>contractility of the left ventricle</td>
<td>mmHg</td>
</tr>
<tr>
<td>$S_r$</td>
<td>contractility of the right ventricle</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\sigma_l$</td>
<td>derivative of $S_l$</td>
<td>mmHg · min$^{-1}$</td>
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<tr>
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<td>derivative of $S_r$</td>
<td>mmHg · min$^{-1}$</td>
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<td>$\tau_a$</td>
<td>time constant of $MR_{O_2}$</td>
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<td>time constant of $A_{peak}$</td>
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<td>$u_1$</td>
<td>control function, $u_1 = H$</td>
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<tr>
<td>$u_2$</td>
<td>control function, $u_2 = V_A$</td>
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<tr>
<td>$V_A$</td>
<td>alveolar gas volume</td>
<td>lBTPS</td>
</tr>
<tr>
<td>$V_{A_{vent}}$</td>
<td>alveolar ventilation</td>
<td>lBTPS</td>
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<tr>
<td>$V_{A_{vent}}$</td>
<td>time derivative of alveolar ventilation</td>
<td>lBTPS</td>
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<tr>
<td>$V_{A_{vent}}$</td>
<td>blood volume in pulmonary arterial compartment</td>
<td>lBTPS</td>
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<td>$V_{A_{vent}}$</td>
<td>blood volume in systemic arterial compartment</td>
<td>lBTPS</td>
</tr>
<tr>
<td>$V_{A_{CO_2}}$</td>
<td>effective $CO_2$ storage volume of the lung compartment</td>
<td>lBTPS</td>
</tr>
<tr>
<td>$V_{A_{O_2}}$</td>
<td>effective $O_2$ storage volume of the lung compartment</td>
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<tr>
<td>$V_{B_{CO_2}}$</td>
<td>effective brain tissue storage volume for $CO_2$</td>
<td>lBTPS</td>
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<tr>
<td>$V_{d,l}$</td>
<td>end-diastolic volume of the left ventricle</td>
<td>lBTPS</td>
</tr>
<tr>
<td>$V_{d,r}$</td>
<td>end-diastolic volume of the right ventricle</td>
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</tr>
<tr>
<td>$V_D$</td>
<td>dead space ventilation</td>
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<tr>
<td>$V_E$</td>
<td>total ventilation</td>
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<td>rest volume of the left ventricle</td>
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<tr>
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<td>rest volume of the right ventricle</td>
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<td>$V_{str,l}$</td>
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<td>stroke volume of the right ventricle</td>
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<tr>
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<td>blood volume in systemic venous compartment</td>
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</tr>
<tr>
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<tr>
<td>$W$</td>
<td>imposed workload</td>
<td>Watt</td>
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Bibliography


