TEKST NR 295 1995

A Review of Mathematical Modeling of the Controled Cardiovascular System

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TEKSTER fra
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IMFUFA tekst nr. 295/95 46 pages ISSN 0106-6242

Abstract

In this paper a comprehensive review of mathematical modeling of the control mechanism in the cardiovascular system of the human body is presented. The presentation includes a brief review of the different models of the cardiovascular system. The mechanical elements of the cardiovascular system include the heart, the arteries, the arterioles, the capillaries and the veins. The purpose of applying control theory is to gain information on the nature of the controller. We point out weakness and possible improvements which could and will be made.

Contents

I venture to think, however, that the essential aims of physiology are better served by an attempt, however hopeless it may appear, to find causal explanations ...

– August Krogh, 1922

1 Introduction

In this paper we review and discuss the mathematical modeling of the control mechanisms in the cardiovascular system of the human body. The major purpose of applying control theory is to gain information on the nature of the controller. However, it is also useful to investigate predictions which are suggested from the models, although these may be very sensitive to variation of parameters. We emphasize that when a model which describes the system is found its value should be judged on the basis of its ability to describe the system under all circumstances. Moreover, the model should be physiologically based and the equations describing the model should have a minimal number of parameters and each of the parameters should be sensitive to change in a particular system characteristic. Many models of the cardiovascular system, with or without feedback mechanisms, do not fulfil these criteria. We return to these questions in the various discussions.

The mechanical elements of the cardiovascular system include the heart, the arteries, the arterioles, the capillaries and the veins. The heart consists of two pumps, a left and a right ventricle, and the rest of the system of two sections, a systemic and a pulmonary part, arranged in series to perform a closed circuit. Both the systemic and the pulmonary systems consist of many distributed parallel elements. The walls of the heart are muscular and contract in rhythmic motions which result in the forcing of blood through the vascular system. Venous blood enters the right atrium and passes into the right ventricle. During a contraction of the heart blood is pushed into the pulmonary artery. Simultaneously, the tricuspid valve, between the right atrium and the right ventricle, closes. The pulmonary artery branches to the right and left lungs, where the blood is oxygenated and carbon dioxide is extracted. The pulmonary veins are the outlets from the lungs and blood passes through them back into the left half of the heart. Blood flows from the left atrium into the left ventricle. Contraction of the heart pushes the blood into the aorta and hence into the arterial and venous system. The periodic contractions of the heart result in a pulsatile flow of blood into aorta. More specifically, as a consequence of the contraction of the left ventricle, there is a pressure and a flow wave through the systemic part of the vascular system. The arterial pressure in humans is maintained within narrow limits over a wide range of the body condition in spite of the fact that many factors and functions are involved. In the human body there are distributed a number of receptors. The receptors are divided into two groups, the baroreceptors and the chemoreceptors. The baroreceptors are sensitive to pressure while the chemoreceptors are sensitive to the chemical contents of the blood. There are baroreceptors in two general areas, the carotid sinus and the aortic arch, which are believed to be main respon-

sible for the control of the arterial pressure. The blood pressure, in arteries and partly in arterioles, is altered based on information obtained from the baroreceptors and chemoreceptors. This information is processed in the brain and results in one or a combination of three possible responses. First, the heart rate can be increased or decreased. Second, the stroke volume can be increased or decreased. Third, the peripheral blood vessel diameters can be increased or decreased locally, called vasodilation and vasoconstriction, respectively. Hence, there are three distinct control mechanisms controlling the arterial blood pressure, heart rate, stroke volume, and vasomotor control. For further physiological details see for example [36] or [33].

In the following sections 2-7 and A-G we review 13 different models: In sections 2-7 we focus on how to model the baroreflex. We bring the review in chronologically order. In section 8 we bring a discussion of the baroreflex models together with a short summary and outlook. For completeness we review 5 more models in the appendixlike sections A-G, focusing on other control mechanisms than the baroreflex. These review also appear in chronologically order.

Each model can be classified in several ways. We are primarily interested in knowing whether the models are pulsatile or non-pulsatile, use open loop, closed loop or optimal control, and finally the choice of control variables. Each of the review sections start with a classification. For an overview we bring the following list:

The pulsatile models appear in sections 2, 3, B, C, E, F.
The non-pulsatile models appear in sections 4, 5, 6, 7, A, D.
The open loop control modelling appear in section 2 only.
The closed loop control modelling appear in sections 5, 7, A, B.
The optimal control modelling appear in sections 3, 4, 6, C, D, E, F.
The baroreflex models appear in sections 2, 3, 4, 5, 6, 7.

2 Warner (1962)

In this section we review a pulsatile compartment model and an open loop model of the myoneural junction, describing a part of the baroreflex. The heart rate is the control variable, it depends on the efferent action potentials of the sympathetic nerve endings going to the heart. The models are physiologically based.

In 1962 H.R. Warner [4] approaches the study of regulation and control of the circulation by use of an analogue computer. The work is based on an earlier analysis [1] from 1958 by Warner himself. Warner discusses the use of analogue

computers in analyzing and testing of mathematical models, quite general, using the case mentioned above. In the paper he does not refer to anyone but himself. Warner uses a pulsatile model for the cardiovascular system. Eight equations are used to describe each half of the uncontrolled circulation. The two halves differ only in the values of the parameters.

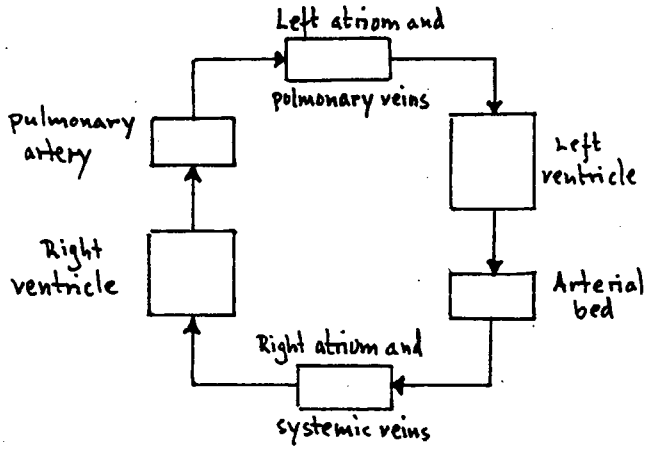

Figure 1: Warner's model.

The volume (V_1) of the left atrium and large pulmonary veins, see figure 1, is equal to its initial volume ($V_1(0)$) plus the difference between flow into the atrium (F_1) and out of the atrium (F_2) integrated with respect to time

$$V_1 = V_1(0) + \int (F_1 - F_2)dt$$

The pressure (P_1) in the left atrium and pulmonary veins is treated as a power function of the volume divided by the capacitance (C_1) of that chamber (this is to account for the well-known convexity toward the volume axis of the volume pressure curve of veins)

$$P_1 = \frac{V_1^n}{C_1}$$

where $n \geq 1$. The flow out of the left atrium and into the left ventricle is zero during systole

$$F_2 = 0 \qquad \text{(systole)}$$

and during diastole the flow is equal to the pressure gradient across the valve divided by the resistance to flow (R_1), minus an inertia term which depends on the rate of change of flow

$$F_2 = \frac{P_1 - P_2}{R_1} - L_1 \frac{dF_2}{dt} \qquad \text{(diastole)}$$

Here P_2 denotes the pressure in the left ventricle during diastole and L_1 the inductance (inertia) of blood. During diastole the pressure in the left ventricle is, similarly to the left atrium, expressed as a power function of the volume (V_2) of the left ventricle divided by the diastolic capacitance of the ventricle (C_2)

$$P_2 = \frac{V_2^m}{C_2}$$

The volume of the left ventricle may be expressed as some initial volume ($V_2(0)$) plus the integral of inflow minus outflow (F_3) of the ventricle

$$V_2 = V_2(0) + \int (F_2 - F_3) dt$$

The outflow from left ventricle is zero during diastole

$$F_3 = 0 \qquad \text{(diastole)}$$

During systole the flow depends upon the volume of the ventricle divided by its systolic capacitance ($C_{2,s}$) and the resistance (R_2) to flow, on the friction which limits the rate of contraction depending on the inductance divided by the resistance, and on the pressure in the aorta given by the volume of the aorta (V_3) divided by the aortic capacitance (C_3) and resistance

$$F_3 = \frac{V_2}{R_2 C_{2,s}} - \frac{L_2}{R_2} \frac{dF_2}{dt} - \frac{V_3}{R_2 C_3} \qquad \text{(systole)}$$

The volume of the aorta depends on the initial value ($V_3(0)$) plus the integral of inflow minus outflow (F_4)

$$V_3 = V_3(0) + \int (F_3 - F_4) dt$$

And, finally, the outflow from aorta is, similar to the outflow from the ventricle, a function of the aortic volume, the aortic capacitance, and the resistance to flow

out of the arterial bed (R_3), the inductance, the volume (V_4) and capacitance (C_4) of the systemic veins and the right atrium

$$F_4 = \frac{V_3}{R_3 C_3} - \frac{L_3}{R_3}\frac{dF_4}{dt} - \frac{V_4}{R_3 C_4}$$

To complete the loop, eight more analogoues equations must be added. These describe the properties of the large systemic veins and the right atrium, the right ventricle, and the pulmonary arterial bed.

Warner validates this model by examining its response to transient disturbances from the equilibrium state. By comparing this to the response of its biological counterpart he finds sufficient agreement.

Then Warner discusses the nerveous control. Through the central nervous system and based on information regarding the pressure in the large arteries this control mechanism modify flow and resistance to flow. The controller describes the relationship between heart rate and frequency of efferent action potentials on the sympathetic nerves going to the heart. More specific, Warner describes, what today is known to be the myoneural or neuromuscular junction, i.e. the interrelationship between the sympathetic nerve fiber endings and the heart muscle fibers, which causes the heart contraction. This control is an open loop, which may be described in the following steps:

1) The changes in noradrenalin concentration $[A_0]$ just beyond the sympathetic nerve endings is given by a term proportional to the frequency of sympathetic nerve stimulation f_1 and the number of fibers n responding to the stimulus, minus a term proportional to the concentration gradient $[A_0] - [A_1]$ in noradrenalin. The last term describes the amount of noradrenalin which diffuses to the S.A. node (Sinus Arterial node) from the sympathetic nerve endings.

2) The change in noradrenalin concentration at the S.A. node $[A_1]$ is given by a term proportional to the rate of noradrenalin which diffuses to it, minus a term describing the change in concentration due to the reaction $A_1 + B \rightleftharpoons AB$. At the time when Warner made this model, one did not knew what kind of substance B was. Today it is known to be noradrenalin receptors placed at the cell membranes of the muscles.

3) A_1 reacts with the noradrenalin receptors B in a reversible second order process to form a compound AB.

4) The quantity of noradrenalin receptors B present is limited, and thereby a maximum in the concentration of the compound AB is established.

5) The heart rate is proportional to the concentration of the compound AB.

This results in the following equations

$$\frac{d[A_0]}{dt} = k_1 n f_1 - k_2([A_0] - [A_1])$$

$$
\begin{aligned}
\frac{d[A_1]}{dt} &= k_2([A_0]-[A_1]) - \frac{d[AB]}{dt} \\
\frac{d[AB]}{dt} &= k_3[A_1][B] - k_4[AB] \\
[AB] &\leq \max[B] = \max[AB] \\
H &= H_0 + k_5[AB]
\end{aligned}
$$

Note that the "concentration" $[B]$ is, in fact, the number of free noradrenalin receptors. This submodel includes a description of the characteristic delay appearing in the control mechanism, due to the kinematics in the S.A. node described in 2) and 3) above. The parameters of the equations are adjusted to obtain the best possible fit to measured heart rates, and this agreement is the only validation of the model: First Warner shows measurements of the heart rate on a dog anesthetized with Nembutal caused by a step frequency, then he makes computer simulations using the same step frequency as in the experiment. Hereby the parameters of the model are adjusted to obtain the best possible fit. Finally the curves are superimposed, and they seem to agree pretty well. We emphasize that there appear no further validation of the model.

The model could easily be extended to a close loop control model by assuming a specific connection between the frequency of the sympathetic nerve stimulation and the arterial pressure when coupled with a model of the uncontrolled cardiovascular system, but Warner does not discuss this possibility. Moreover, he does not include the decomposition of noradrenalin due to enzymes. Therefore an acumullation in noradrenalin appear in this model. However, in another work [3] by Warner and Cox also from 1962 and in a later work [10] by Warner and Russell a term, $-k_6([A_2]-[A_0])$, is included in the two first equation above, describing the decomposition of noradrenalin.

3 Noldus (1976)

In this section we review a pulsatile optimal electrical analogue model, which includes Starling's law of the heart. The pressure in the left ventricle is the control variable. The optimal strategy is given by minimizing the potential energy and the mechanical flow work of the ventricle per cycle. Hereby a baroreflex mechanism, describing how the heart rate depend on the arterial pressure, is obtained.

The paper by E.J. Noldus [11] from 1976 is, to our knowledge, the first attempt to use optimal control theory to model the regulation of the ventricle. The model is based on physiologically considerations and an optimization concept by Milsum

[9] from 1968. Loosely speaking, the concept of Milsum is as follows, it is assumed that a selective survival advantage is gained by those organisms whose subsystems operate in an optimal fashion on some energetic basis, and that as a result living system have evolved towards optimal performance when executing a given task. Noldus emphasizes that it is by no means clear which performance criterion is the relevant one for a given biological system, but optimization seems to be a worthwhile viewpoint, both for theoretical analysis and for suggesting new experiments. However, we doubt whether this concept holds in all cases, for example, if the brain for some reason does not get enough oxygen we expect that the heart will increase the blood circulation for almost any energetic prize.

The purpose of Noldus paper is to approach the problem of developing a ventricular pumping model, which relye on an optimization criterion in agreement with Milsum's concept. Hereby Noldus determine an elastance function $E(t) = P(t)/V(t)$, where $P(t)$ and $V(t)$ represent the instantaneous values of left ventricular pressure and volume.

Noldus use an electrical analogue model, originally proposed by Suga [30] in 1971. This describes the pulsatile cardiovascular system, together with a version of Starling's law, which states that the stroke volume V_{stroke} increases with end-diastolic volume and decreases with increasing arterial pressure

$$V_{\text{stroke}} = a + (c - d \cdot \overline{P_a}) \cdot V_0$$

The end-diastolic volume V_0 equals the ventricular volume at the beginning of ejection. $\overline{P_a}$ is the average aortic pressure during ejection and a,c and d are positive constants.

The dynamic equations for the model in figure 2 are

$$V(t) = V_0 - \int_0^t i(s)ds \tag{1}$$

$$P(t) = P_a(t) + ri(t) + L\frac{di(t)}{dt} \tag{2}$$

and

$$i(t) = \frac{1}{R}P_a(t) + C\frac{dP_a(t)}{dt} \tag{3}$$

Where $V(t)$ is the left ventricular volume, $P(t)$ is the left ventricular pressure, P_a is the aortic blood pressure, $i(t)$ is the flow rate ejected from the ventricle, r is the aortic valvular resistance, L is the blood inertia, R is the peripheral resistance and C is the compliance of the lumped arterial Windkessel load. Rewriting these equations one ends up with the following state equations

$$\frac{dV(t)}{dt} = -i(t) \tag{4}$$

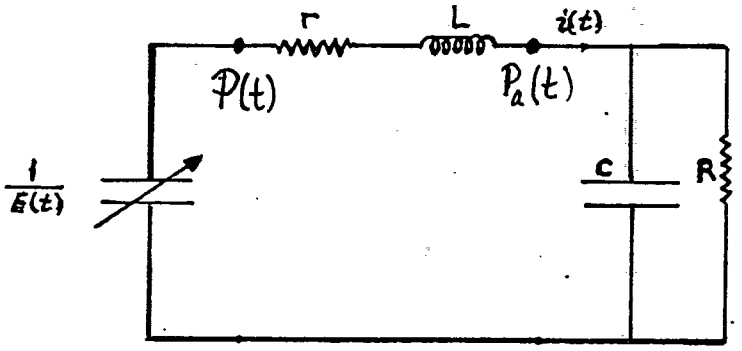

Figure 2: Noldus electrical analogue model.

$$\frac{di(t)}{dt} = \frac{1}{L}(P(t) - P_a(t) - ri(t)) \tag{5}$$

and

$$\frac{dP_a(t)}{dt} = -\frac{1}{RC}P_a(t) + \frac{1}{C}i(t) \tag{6}$$

where $P(t)$ is the control variable. There are of cause certain boundary conditions for each variable, which ensure that the solution to the following optimal control problem is non-trivial. Noldus seeks the optimal solution with respect to the performance index

$$J = \int_0^{t_e} \left(P^2(t) + \alpha P(t)i(t)\right) dt \tag{7}$$

α is a unknown positive weighting constant (it turns out that the simulations are rather insensitive to the precise choice of α) and $[0, t_e]$ represents the ejection period of the ventricle. Minimization of J may be interpreted as minimizing the mechanical work required for blood flow ejection, while at the same time penalizing the buildup of high pressure peaks over time. Alternatively one may interpret J as a weighted sum of mean stored potential energy and mechanical flow work. By use of Pontryagin's maximum principle Noldus are able to derive an analytical expressions for the state variable, and hence for the elastance, see [11]. Moreover, if one considers t_e to be free one also gets the heart rate (in terms of t_e).

The validation criterion of Noldus is to obtain qualitative agreement between measurements and simulations, when varying some of the parameters. A standard

estimate of the parameters is taken from Defares et al. [28]. The model is capable of correctly reproducing many classical experiments, in a qualitative sense, including the change in left ventricular pressure curves in response to varying preload (V_0) and afterload ($\overline{P_a}$) conditions. The family of elastance curves, depending on V_0 and $\overline{P_a}$, agrees qualitatively with the result of Greene et al. [34], but is in contrast with those of Suga [31], [32]. When the ejection period is allowed to change, it decreases for decreasing V_0 and increasing $\overline{P_a}$, also in agreement with experimental findings. However, the model is not reproducing the time cause of blood flow during ejection satisfactory. Possibly, this can be attributed to an oversimplification in simulating the characteristics of the aortic valve as a constant resistance. Some evidence supporting this conjecture is included in the paper of Noldus.

4 Ono et al. (1982)

In this section we review a non-pulsatile optimal electrical analogue model, which includes the baroreflex. The control variables are the ventricular outflow and the peripheral resistance, both with and without the heart compliance. They depend on the arterial pressure. The optimal strategy is given by minimizing the deviation in the arterial pressure and the control variables from some set point values over an infinite time horizon.

In the paper from 1982 K. One, T.Uozumi, C. Yoshimoto and T. Kenner [22] made an attempt to establish a theoretical framework for relating the optimal regulatory behavior to the responses of individual component. They used a Windkessel model with time variant resistance ($R(t)$) and constant compliance (C) for the non-pulsatile arterial system. The heart is assumed to be a mechanical pump whose output ($Q(t)$) is independent of the arterial pressure. The system has the medullary cardiovascular center as its decision maker under which the heart and arterial system are subordinated. The center accepts regular feedback information about the pressure, sensed by the baroreceptors in the carotid sinus and in the aortic arch through the afferent fiber. The information is processed at the center and its decisions are distributed to the effectors through the efferent fiber, see figure 3.

The system equation is as follows

$$\frac{dP(t)}{dt} = C^{-1}G(t)P(t) + C^{-1}Q(t)$$

where $P(t)$ denotes the arterial pressure and $G(t)$ the inverse quantity of the resistance, called the conductance. Ono et al. change to new variables, expressed

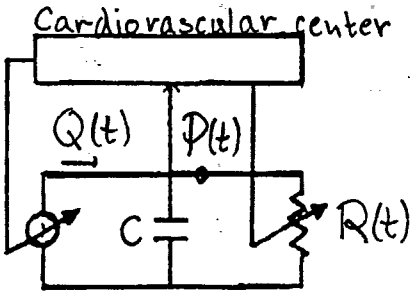

Figure 3: The model of Ono et al.

as the relative deviation from some reference values

$$\begin{aligned} x(t) &= (P(t) - P_0)/P_0 \\ u_1(t) &= (Q(t) - Q_0)/Q_0 \\ u_2(t) &= (G(t) - G_0)/G_0 \end{aligned}$$

Here $x(t)$ is considered as the state variable and $u_1(t)$ and $u_2(t)$ as the control variables. Moreover, Ono et al. change the time-scale, $t \to tG_0/C$, thus there is a constrain on the reference values $P_0G_0/Q_0 = 1$. Hence the state equation becomes

$$\frac{dx(t)}{dt} = -(1 + u_2(t))(1 + x(t)) + (1 + u_1(t))$$

This equation is linear in both the state and the control variables each taken separately, but not jointly in both. Then Ono et al. assume that the optimal regulation is such that it keeps the arterial pressure fluctuation close to zero without excessive control responses of the heart and the arteries, from an energetic point of view. Consequently, Ono et al. demand the following criterion function to be minimized

$$J = \int_0^\infty \left(x^2(t) + q_1 u_1^2(t) + q_2 u_2^2(t)\right) dt$$

where q_1 and q_2 are weighting factors. One may use the maximum principle of Pontryagin to obtain numerical results. However, linearization of the state equation near steady state, i.e. neglecting the nonlinear term $u_2(t)x(t)$, gives some analytical information. The linearized state equation become

$$\frac{dx(t)}{dt} = -x(t) + u_1(t) - u_2(t)$$

Now Ono et al. define $u(t)$ as $\sqrt{u_1^2(t) + \frac{q_2}{q_1}u_2^2(t)}$ and by Pontryagin's maximum principle they get

$$u(t) = -K_1 x(t) - K_2 \int_0^t x(s)ds$$

where K_1 and K_2 are given constants depending on q_1 and q_2. The system based on the optimal principle then turns out to be a parametric proportional plus integral control system which tends to eliminate the steady state error. According to the equation they can predict that faster recovery of the pressure is achieved by smaller values of the weighting factors q_1 and q_2. Ono et al. discusses the different weighting values and conclude that the arterial response plays the dominant role in the pressure control, but the pressure recovery is indeed accelerated when the cardiac response participate. The optimal values of the weighting factors are $q_1 = q_2 = 1/300$.

The model validation is made by comparing measurements to the curves for arterial pressure, cardiac output and arterial conductance, and they show the right characteristics.

Furthermore, Ono et al. analyzes the contractile process of the heart from an optimal control point of view. This model is an extension of the above model, and here Ono et al. include the following description of the ventricle. The ventricle is composed of two elements, the contractile component and the series elastic component. This is the same idea as Robinson used in 1965, see section B. The contractile component is expressed by the time variant compliance (C_x). It is assumed that the contractile component stretches the series elastic component (C_e) and that the total contractile force is generated by a combination of them. Two diodes are used for the mitral valve and the aortic valve, respectively. The right heart is lumped into the venous system and the arterial system is composed according to the Windkessel model, see figure 4.

The symbols used in the model in figure 4 are as follow; R_p denote the resistance of pulmonary vein, R_v the resistance of aortic valve, and R_s the viscous resistance of myocardium. The symbols V and P with index x, e and a denote the volume and pressure of the contractile component, the series elastic component and the arterial system. In this paper we will not include the equations which describes the dynamics of the ejection phase, instead we refer to [22]. However, the problem is treated as an optimal control problem, the ventricle is assumed to eject as much blood as possible within a systole and at the same time the work done by the contractile component is assumed minimized.

The model is validated by the fact that, the pressure, volume and flow waves together with the valvular movement and driving force are in good agreement with those adopted in textbooks of physiology.

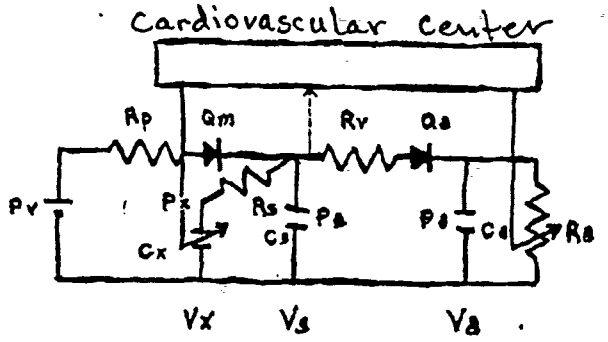

Figure 4: The left ventricular model of Ono et al.

Ono et al. makes an important concluding remark, which we quote: "Even through the theoretical results exhibit good agreement with real situation, one cannot conclude that the existing phenomena are essentially explained by the performance criteria and therefore by the maximum principle. The principle provides only the sufficiency condition but not the necessary condition. It may be said that the mechanism found in our study is but a part of more general control mechanisms."

5 Wesseling et al. (1982)

In this section we review a non-pulsatile closed loop electrical analogue model, which includes the cardio-pulmonary reflex and the baroreflex. The venous unstretched volume, the ventricular maximal elastance, the heart rate, the peripheral resistance and the stroke volume are the control variables. They depend on each orther, on the arterial pressure, on the systemic venous pressure and on the pulmonary venous pressure.

In the paper [23] K.H. Wesseling, J.J. Settels, H.G. Walstra, H.J. van Esch and J.J.H. Donders discuss the so-called "10 s rhythm", an almost sinusoidal oscillation of frequency 0.1 Hz, observed in the short term variability of continuous registrated blood pressure in normal subjects. This is done in term of the following non-pulsatile model of the cardiovascular system with closed loop control. The model is compiled from many literature sources (for reference, see [23]). Wesseling et al. describe the model in terms of an electrical analogue model and standard control diagrams. The symbols in the figures below are explained together with normal

values of the parameters and variables in the table 4 below. In figure 5 we sketch the circulation system.

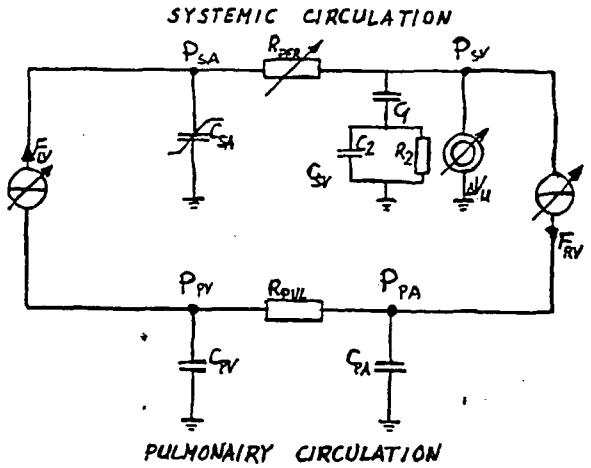

Figure 5: The circulation system of Wesseling et al.

The left and right ventricles have been indicated symbolically as flow sources. The arterial compliance is a non-linear function of pressure, and is given in tabular form.

The systemic venous compliance is visco-elastic, and shows a delay in the compliance. The unstrectched venous volume control has been modeled as a volume source. Both ventricles, peripheral resistance and unstretched venous volume are varible, as indicated in figure 5. The baroreflex and the cardio-pulmonary reflex are modeled as shown in figure 6.

In figure 6 inputs are on the left, the controlled parameter or variable output on the right. The cardio-pulmonary reflex is shown to modulate, inhibit, the baroreflex. Four reflex effectors are shown. The BFC box (in figure 6) is given in tabular form too.

The heart model is shown in figure 7

The heart model is the non-pulsatile part of the model and it is only the vegal (parasympathetic) control of the heart rate which is included. The stroke volume, shown explicit in figure 7, multiplied by heart rate determines the cardiac output. The PVD box in figur 7 is also displayed in tabular form.

Finally, in figure 8 of the integrated model, three (pressure) variables are shown to modulate four hemodynamic parameters via the two interacting reflexes.

The only validation of this model is that it seems to agree well with the 10 s rhythm from continuous measurements. We find the model very interesting,

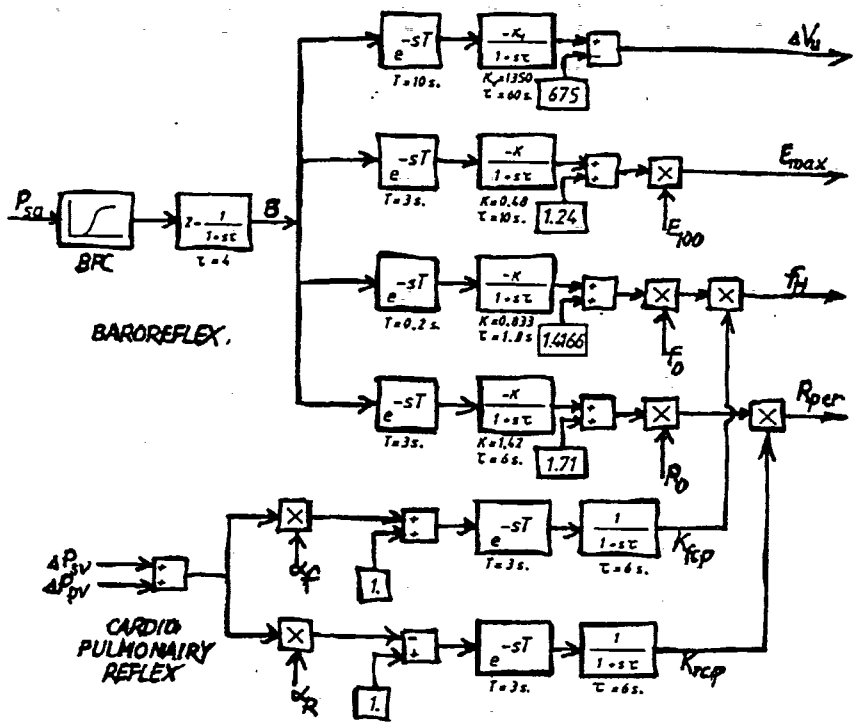

Figure 6: The reflex model of Wesseling et al.

especial the detailed integrated reflex model.

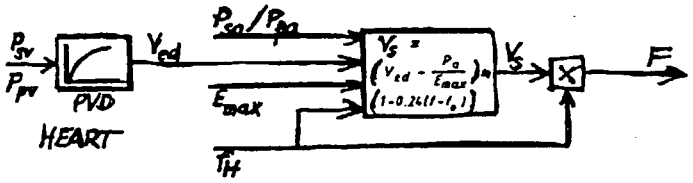

Figure 7: The heart model of Wesseling et al.

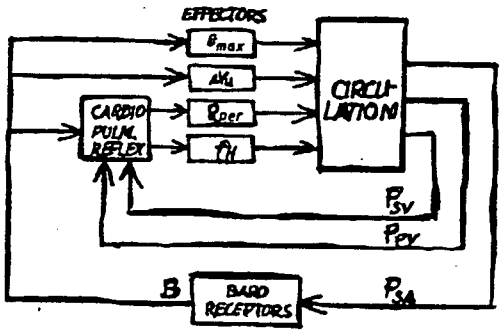

Figure 8: The integrated model of Wesseling et al.

6 Kappel et al. (1993)

In this section we review a non-pulsatile optimal compartment model, which includes the baroreflex. The control variable is the change in heart rate, it depends on the arterial pressure. The optimal strategy is given by minimizing the deviation in the systemic arterial pressure from a set point value and, at the same time, the deviation in the control variable from zero, over an infinite time horizon. The model includes closed loop submodels of Starling's law of the heart, the Bowditch effect, and the autoregulation in peripheral regions.

Based on a four compartment model F. Kappel and R.O. Peer [25] in 1993 developed a model for the response of the controlled cardiovascular system to a short term submaximal workload. The four compartment model is non-pulsatile and is originally due to Grodins [5]. Starling's law of the heart, the Bowditch effect and the autoregulation in the peripheral regions are all included in the model. It is assumed that the feedback control is represented by the baroreceptor loop and that it minimizes a quadratic cost functional. Kappel and Peer state that their model differs from those of Doubek (see section C), Kenner and Pfeiffer (see section F), Noldus (see section 3) and Ono et al. (see section 4) since their investigations are global in the sense that it models all essential subsystems. But they do not mention the similarities with the previous work by Wesseling et al. (see section 5), which also is global in the same sense. However, we like to point out that this paper apparently is the first which covers a mathematical investigation of the stability of the controlled model. Kappel and Peer made their model as a tool for studying the reaction of the cardiovascular system to a constant ergometric workload imposed on a test person on a bicycle-ergometer after a period of rest.

Following Grodins [5], Kappel and Peer restate the four compartment model shown in figure 9 below. They emphasizes the underlying assumptions. The first assumption is, that the variation of volume in time in each compartment equals the difference between the inflow and outflow of the compartment. The second assumption is, that the system is closed, i.e. blood flow only occurs between compartments. These two assumptions gives rise to the following equations

$$\begin{aligned}
\frac{dV_{as}}{dt} &= Q_l - F_s \\
\frac{dV_{vs}}{dt} &= F_s - Q_r \\
\frac{dV_{ap}}{dt} &= Q_r - F_p \\
\frac{dV_{vp}}{dt} &= F_p - Q_l
\end{aligned} \tag{8}$$

where V_{as}, V_{vs}, V_{ap}, and V_{vp} denote the volumes of the four compartments, the arterial systemic part, the venous systemic part, the arterial pulmonary part and the venous pulmonary part of the circulatory system, Q_l and Q_r denote the cardiac output for the left and right ventricle, whereas F_s and F_p denote the blood flows through the systemic and the pulmonary part of the peripheral regions. Likewise use $P_{as}, \ldots, P_{vp}$ denote the pressures and $c_{as}, \ldots, c_{vp}$ the compliances of the four compartments. Note that the total volume of blood is constant

$$V_{as}(t) + V_{vs}(t) + V_{ap}(t) + V_{vp}(t) = V_0 \tag{9}$$

The third assumption is concerned with the peripheral system. They assume that the flow in the cardiovascular system is laminar, proportional to the pressure difference and directed from higher to lower pressure. This assumption immediately gives

$$\begin{aligned}
F_s &= (P_{as} - P_{vs})/R_s \\
F_p &= (P_{ap} - P_{vp})/R_p
\end{aligned} \tag{10}$$

where the pulmonary peripheral resistance R_p is constant, whereas the systemic peripheral resistance R_s may be regulated. It is determined in the process of autoregulation. The fourth assumption is, that the flow generated by the ventricle, i.e. the average cardiac output, is given by

$$Q = HV_{\text{stroke}} \tag{11}$$

where H is the heart rate frequency and V_{stroke} is the stroke volume. Consequently the time varying quantities in the model have to be interpreted as averaged over the length of a pulse. Until now the ventricles and the peripheral regions are

considered as non-compartments, so there are not associated any blood volume with these parts of the cardiovascular system. However, to evaluate the stoke volume and hence the flow generated by the ventricles one has to consider the pulsatile dynamic of the ventricles. The underlying assumption for this study is contained in the fifth, sixth and seventh assumption. The fifth assumption is that the stroke volume is proportional to the final diastolic volume V_d, and inversely proportional to the arterial (mean) pressure P_a

$$V_{\text{stroke}} = S\frac{V_d}{P_a} \tag{12}$$

where S is the contractibility of the ventricle and measure the strength of contraction. The sixth assumption is that, during diastole, the venous pressure P_v acting on the ventricle is the sum of the viscous filling pressure and the ventricle pressure

$$P_v = R\frac{dV(t)}{dt} + \frac{1}{c}V(t) \tag{13}$$

Hence

$$V(t) = (V(0) - cP_v)e^{-\frac{t}{cR}} + cP_v \tag{14}$$

where R is the total viscous resistance and c is the compliance of the relaxed ventricle. The seventh assumption is, that the ventricle resistances depend on the peripheral resistance according to

$$R_l(R_s) = 1.0547R_s - 0.0008 \tag{15}$$

$$R_r(R_s) = 0.1563R_s + 0.0042 \tag{16}$$

The coefficients are obtain by interpolating data in [5] and [27]. From the fifth, sixth and seventh assumption one get

$$V_{\text{stroke}} = S\frac{cP_v\left(1 - e^{-\frac{t_d(H)}{cR(R_s)}}\right)}{P_a\left(1 - e^{-\frac{t_d(H)}{cR(R_s)}}\right)} + Se^{-\frac{t_d(H)}{cR(R_s)}} \tag{17}$$

where t_d is the duration of the diastole. In contrast to Grodins, Kappel and Peer use the empirical formula

$$t_d(H) = \left(\frac{60}{H}\right)^{1/2}\left(\left(\frac{60}{H}\right)^{1/2} - \kappa\right) \tag{18}$$

where κ a constant between 0.3 and 0.5, when the time unites are minutes. Hence they get an expression for the non-pulsatile flow, in (11), generated by the ventricle

$$Q = H\frac{cSP_v\left(1-e^{-\frac{t_d(H)}{cR(R_s)}}\right)}{P_a\left(1-e^{-\frac{t_d(H)}{cR(R_s)}}\right)} + Se^{-\frac{t_d(H)}{cR(R_s)}} \tag{19}$$

Finally, they need an eighth assumption connecting blood volume and pressure in a compartment. This assumption says that the blood volume V is proportional to the pressure P in the compartment

$$V = cP \tag{20}$$

where c is the compliance of the compartment. Moreover, it is assumed that c is constant. Hence, by substitution equation (10), (19) and (20) into equation (8) they obtain the following system of nonlinear ordinary differential equations describing the variation of the pressure in the four compartments

$$\begin{aligned}
c_{as}\frac{dP_{as}}{dt} &= -(p_{as}-P_{vs})/R_s + H\frac{c_lS_lP_{vp}\left(1-e^{-\frac{t_d(H)}{c_lR_l(R_s)}}\right)}{P_{as}\left(1-e^{-\frac{t_d(H)}{c_lR_l(R_s)}}\right)} + S_le^{-\frac{t_d(H)}{c_lR_l(R_s)}} \\
c_{vs}\frac{dP_{vs}}{dt} &= (p_{as}-P_{vs})/R_s - H\frac{c_rS_rP_{vs}\left(1-e^{-\frac{t_d(H)}{c_rR_r(R_s)}}\right)}{P_{ap}\left(1-e^{-\frac{t_d(H)}{c_rR_r(R_s)}}\right)} + S_re^{-\frac{t_d(H)}{c_rR_r(R_s)}} \\
c_{ap}\frac{dP_{ap}}{dt} &= -(p_{ap}-P_{vp})/R_p + H\frac{c_rS_rP_{vs}\left(1-e^{-\frac{t_d(H)}{c_rR_r(R_s)}}\right)}{P_{ap}\left(1-e^{-\frac{t_d(H)}{c_rR_r(R_s)}}\right)} + S_re^{-\frac{t_d(H)}{c_rR_r(R_s)}} \\
c_{vp}\frac{dP_{vp}}{dt} &= (p_{ap}-P_{vp})/R_p - H\frac{c_lS_lP_{vp}\left(1-e^{-\frac{t_d(H)}{c_lR_l(R_s)}}\right)}{P_{as}\left(1-e^{-\frac{t_d(H)}{c_lR_l(R_s)}}\right)} + S_le^{-\frac{t_d(H)}{c_lR_l(R_s)}}
\end{aligned} \tag{21}$$

The equations in (21) essentially constitute the model given by Grodins in [5] for the mechanical part of the cardiovascular system. Notice that there is a relation

between the state variables due to equation (20) and (9), for example $P_{ap} = P_{ap}(P_{as}, P_{vs}, P_{vp}, V_0)$.

The Bowditch effect is modeled as in [15]. Kappel and Peer state that there are essential two possibilities for a ventricle to change the cardiac output, either to change the heart rate or the contractibility. But the heart rate and contractibility are related through the Bowditch effect. Therefore the contractibility is proportional to the heart rate. For each ventricle the Bowditch effect is modeled as follows

$$\frac{d^2S}{dt^2} + \gamma\frac{dS}{dt} + \alpha(S)S = \beta(S)H \tag{22}$$

where γ is a positive constants and α and β are simple positive functions, in fact, Kappel and Peer choose them as constant in a broad range around the normal values of S.

Consider the baroreceptor loop. Kappel and Peer claim that the task of the baroreceptor mechanism is to stabilize, sufficiently fast, the regulated variable P_{as} to a somehow predefined debit-value P_{as}^{deb}. Thus the nervous reflex loop can be considered as a stabilizing and optimizing feedback, the regulated quantity being P_{as}. The optimization is based on the assumption that the control $u = \frac{dH}{dt}$ is chosen to minimize

$$J(u) = \int_0^\infty \left(q(P_{as}(s) - P_{as}^{\text{deb}})^2 + (u(s) - u^{\text{deb}})^2\right) ds \tag{23}$$

where q is a weighting factor and the debit-value of u is $u^{\text{deb}} = 0$.

Another fundamental regulation mechanism in the model of Kappel and Peer is autoregulation, which is very important during phases of exercise. The role of autoregulation is to guarantee a sufficient blood flow in the relevant muscles and parts of tissue. This is done essentially by lowering R_s in the relevant tissue. Under autoregulation R_s is a function of the venous O_2-concentration $[O_2]_v$. Thus Kappel and Peer assume that the peripheral resistance R_s is directly proportional to the venous O_2-concentration, called the metabolic dilation

$$R_s = A \cdot [O_2]_v \tag{24}$$

A is assumed to be a positive constant during periods of constant workload, i.e. it is load-dependent. The second assumption on the mechanism of autoregulation is an modification of Fick's law on energy balance, which states that the complete consumed energy flow is equal to the delivered O_2-energy flow plus the biochemical energy flow M_{sp}

$$M = ([O_2]_a - [O_2]_v) \cdot F_s + M_{sp} \tag{25}$$

where $[O_2]_a$ denote the arterial O_2-concentration. The third assumption on autoregulation states that a positive amount of M_{sp} is delivered whenever $[O_2]_v$ is lowered, or more specifically, the storage energy flow M_{sp} supplied in a phase of exercise, is directly proportional to the variation of the venous O_2-concentration in time

$$M_{sp}(t) = -K\frac{d([O_2]_v(t))}{dt} \tag{26}$$

where K is a positive constant. Differentiating equation (24) and combining it with (25), (26) and the first equation of (10), one obtains

$$\frac{dR_s}{dt} = \frac{1}{K}\left(P_{vs} - P_{as} + A\left(\frac{P_{as} - P_{vs}}{R_s}[O_2]_a - M\right)\right) \tag{27}$$

Hence, equations (19), (22), (27) and the equation $u = \frac{dH}{dt}$ constitute the model of Kappel and Peer for the cardiovascular system. A diagram for the model is drawn in figure 9.

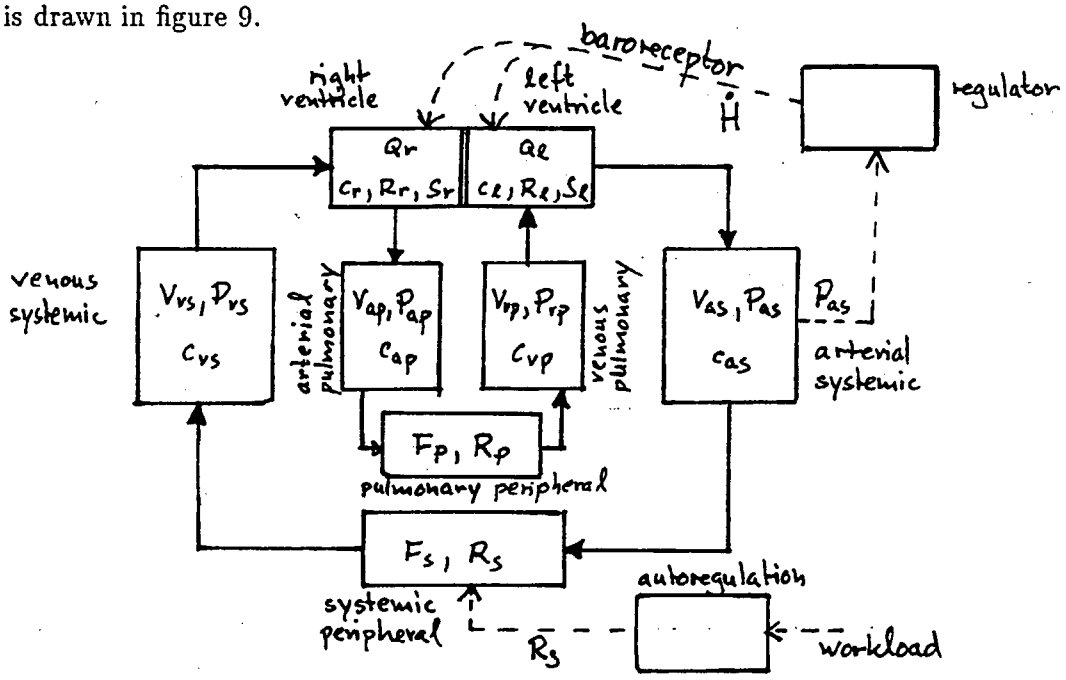

Figure 9: The model of Kappel et al.

Then Kappel and Peer analyze the state equations, which they write as

$$\frac{dx}{dt} = \mathcal{F}(x, u; p) \tag{28}$$

where the state vector $x = x(t) \in \mathbf{R}^9$, the control vector $u = u(t) \in \mathbf{R}$ and the parameter vector $p \in \mathbf{R}^{26}$, but only three of the components in p depend on the different phases of the experiments (rest and exercise): M, which characterizes the workload, H^{stat}, which determines the specific stationary solution, and A, which describes the metabolic dilation. The stationary solution is that of equation (28) for $u = 0$. From the theory of non-linear control systems, see [35], it follows that a stabilizing feedback law of the corresponding linearized control system also locally stabilizes the non-linear control system. Thus the trajectory of the non-linear control system may be approximated by the solution of the corresponding non-linear differential equation. This is obtained from the non-linear control system by substituting the control law from the linearized control system. Moreover, Kappel and Peer also discuss a dynamical observer for the feedback system.

Kappel and Peer simulate the reaction of the cardiovascular system to an activity test, i.e. after a period of rest a constant workload is imposed on a test person. Eight of the parameters (in p) is found in the literature and the last sixteen parameters were fitted to measurements by the method of least square in the range of stationary situations. The simulations agree very well with measurements of P_{as} and $H(t)$. Furthermore, the values of the other components of the state vector were within a physiologically realistic range. However, we have to point out that calculation of the blood volume in each compartment results in very unrealistic values. Moreover, we belive that the large number of estimated parameters in the model is a considerable weakness.

7 Frello et al. (1994)

In this section we review a non-pulsatile closed loop compartment model of the baroreflex. The control varible is the change in heart rate, it depend on the arterial pressure. The baroreflex model consists of two submodels, one giving the change in heart rate as a function of the sympathetic and parasympathetic tone and one giving the sympathetic and parasympathetic tone, as functions of the arterial pressure. These submodels are physiologically based. The model is closed by coupling the feedback model and the model of the uncontrolled cardiovascular system, described in the paper of Kappel and Peer.

In the report [26] from 1994 by S. Frello, R.U. Johansen, M.P.C. Hansen and

K.D. Jensen, supervised by V. Andreasen, the authors adapt the Model of Kappel and Peer, except for the part concerning the central nervous regulation, i.e. the baroreceptor loop. Instead the feedback is modeled explicitly, on the basis of qualitative physiological theory. But, Frello et al. express some doubt about the validity of the model of Kappel and Peer. We will only sketch a few problems: First of all they were not able to find any physiological reason or data supporting the modeling of the Bowditch effect (Kappel and Peer's refers to Ranft [15] who refers to a paper of Koch-Weser, which they were not able to find). Secondly, the linear equations, which Kappel and Peer get for the dependence of the ventricle resistances to the peripheral resistance, see equation (16), are obtained by linear extrapolation of two points (measurements from [5]). Besides these problems, Frello et al. also add on the problems mention above when we discused the paper of Kappel and Peer. The results obtained by Frello et al. agree with measurement to the same degree as those of Kappel and Peer, and further it gives an understanding of the physiological mechanisms being modeled. We emphasize that the model of the central nervous regulation made by Frello et al. is in fact independent of the choice of the model of the uncontroled cardiovascular system, except for the fact that the arterial pressure has to be a state variable.

Frello et al. assume that the heart rate is a function of the activity of the autonome nerve system, both sympathetic and parasympathetic (vegal). It is described by the tones T_s, a measure for the activity of the sympathetic nerve system, and T_p, a measure for the activity of the parasympathetic nerve system. These tones depends primarily on the arterial pressure P_{as}. Hence

$$\frac{dH}{dt} = f\left(T_s(P_{as} - P_{as}^*), T_P(P_{as} - P_{as}^*)\right) \tag{29}$$

where f denotes a yet unknown function and P_{as}^* a set-point which depends on external factors such as exercise or anaesthesica. It is assumed that the control attempts to steer P_{as} to some ideal state, the set-point. Based on experiments it is further assumed that the tones, as function of the arterial pressure, may be described by the tangent hyperbolic function. Each curve on figure 10 is fitted using of two parameters, β which fixes the tones when the pressure equals the set-point, and α which describs the slope when the tones are fifty percent of their maximal values. Hence one arrives at the following expressions

$$\begin{aligned} T_p(P_{as} - P_{as}^*) &= \frac{1}{2}\{1 + \tanh[\alpha_p(P_{as} - P_{as}^* - \beta_p)]\} \\ T_s(P_{as} - P_{as}^*) &= \frac{1}{2}\{1 - \tanh[\alpha_s(P_{as} - P_{as}^* - \beta_s)]\} \end{aligned} \tag{30}$$

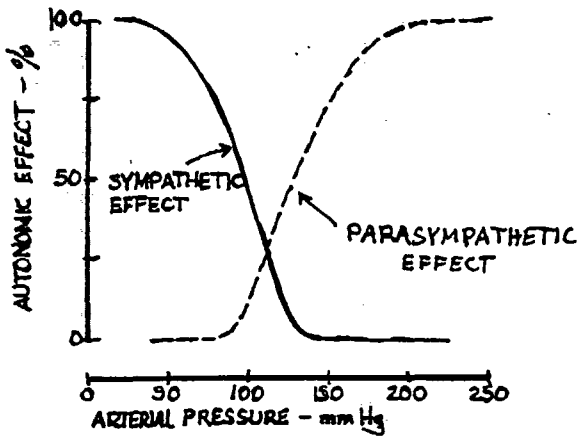

Figure 10: The sympathetic and the parasympathetic (vegal) activity level, tones, as function of the arterial pressure.

of cause this is an ad-hoc choice of quantitative connections. Similar Frello et al. model the change in heart rate as a function of tones. Based on the experiments of Levy and Zieske [29], they catch the qualitative physiological characteristics by the following quantitative ad-hoc choice of functional dependents

$$\frac{dH}{dt} = \frac{\alpha_H T_s}{1 + \beta_H T_p} - \gamma_H T_p \tag{31}$$

Note that this model seems to be in better agreement with the physiological theory than the one suggested by Levy and Zieske in [29]. The constants α_H, β_H and γ_H are positive and have the following physiological interpretation, $\frac{dH}{dt} \approx \alpha_H$ for $P_{as} \ll P^*_{as}$, i.e. for $T_p \approx 0$ and $T_s \approx 1$, $\frac{dH}{dt} \approx -\gamma_H$ for $P_{as} \gg P^*_{as}$, i.e. for $T_p \approx 1$ and $T_s \approx 0$, and β_H defines the strength of the damping from the parasympathetic tone of the influence of the sympathetic tone on the heart rate. Since one demands that $\frac{dH}{dt} = 0$ for $P_{as} = P^*_{as}$, the change in heart rate as a function of the arterial pressure depends on six parameters. These parameters are fitted to match measurements made by Levy and Zieske, see figure 11.

It turns out that the change in heart rate is globally decreasing with the arterial pressure and, that the model is stable when coupled with a slight modification of the compartment model of Kappel and Peer. The modification mentioned consists of the additional assumption that the stroke volume for the left and the right ventricles are equal. It would be interesting to analyze the model when this additional assumption is dropped. Finally Frello et al. simulate the same activity

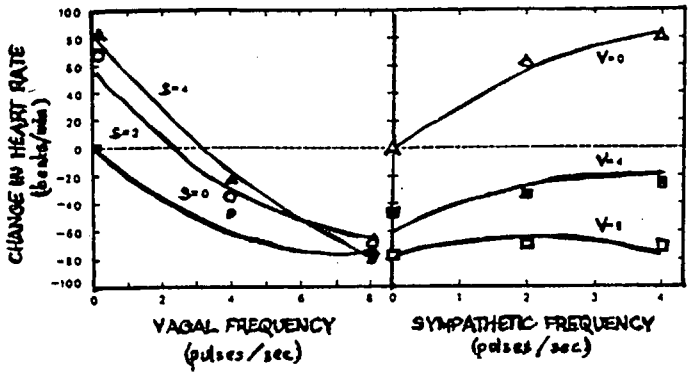

Figure 11: The change in heart rate due to variation in sympathetic and parasympathetic (vegal) activity level.

test as Kappel and Peer did. They get agreement to the same degree with the experimental data. This agreement indicates that the value of the cost functional of Kappel and Peer, using the arterial pressure and change in heart rate obtained by Frello et al., is nearly optimal. However, it would be interesting to calculate it explicit. Moreover, we would prefer an algebraic expressions instead of the above use of the tangent hyperbolic function.

8 Discussion of the baroreflex models

In this section we discuss the modeling of the baroreflex.

Warner describes a pulsatile compartment model of the cardiovascular system and an independent open loop model of a part of the baroreflex describing the myoneural junction, i.e. how the heart rate, as the control variable, depends on the efferent action potentials of the sympathetic nerves going to the heart. However, Warner does not couple the two independent models.

The input to the open loop control model is the frequency of the sympathetic nerve stimulation. The baroreflex model incorporate the characteristic time delay, that appears in the physiological control mechanism.

The model parameters are fitted to measurements of the heart rate, and the simulation then agree to a heigh degree of accuracy to these measurements. There is no further validation of the model.

However, This model could be turned into a closed loop control model by assuming a specific connection between the frequency of the sympathetic nerve stimulation and the pressure in aorta.

Noldus describes a pulsatile electrical analogue model of the systemic part of the cardiovascular system. This model was originally proposed by Suga in 1971. He incorporates Starling's law and extends the model by using optimal control theory to arrive at a baroreflex mechanism. This is done by minimizing the potential energy and the mechanical flow work of the ventricle per cycle using the ventricle pressure as control variable, whereby the heart rate becomes dependent on the aortic pressure. Hence, the model primarily describes a single heart beat.

The model reproduces many classical experiments, in a qualitative sense, using parameter values taken from the literature. Moreover, the model determines the elastance curve of the ventricle which agrees well with measurements. However, it does not satisfactory reproduce the time course of the blood flow during systole.

Ono et al use a non-pulsatile electrical analogue model to describe the systemic part of the cardiovascular system and extend the model using optimal control theory with the ventricular outflow and the peripheral conductance as control variables. Hereby, they develop a baroreflex and a vasomotor reflex mechanism. This is done by minimizing the deviation in the arterial pressure, the ventricular outflow, and the peripheral resistance from some set point values over an infinite time horizon. Thus the control variables become dependent on the arterial pressure. They also discuss the inclusion of the compliance of the ventricle as a control variable.

The validation of the model is that the curves for the arterial pressure, the cardiac output, and the arterial conductance show the right characteristics.

Wesseling et al present a non-pulsatile closed loop electrical analogue model of the cardiovascular system including the cardiopulmonary reflex and the baroreflex. The non-pulsatile part of the model is the submodel of the heart, and only the parasympathetic control of the heart is included. The control variables are the venous unstretched volume, the ventricular contractibility, the peripheral resistance, the heart rate, and the stroke volume. The first two depend on the systemic arterial pressure, the next two depend also on the systemic and pulmonary pressure, and the last one depends on all the venous and arterial pressures, both systemic and pulmonary, partly through the heart rate and the ventricle contractibility.

The only validation of the model is, that it agrees well with the 10 s rhythm obtained from continuous measurements, which was the topic for their study.

Based on a four compartment model, originally proposed by Grodins in 1963, **Kappel and Peer** develop a non-pulsatile model for the response of the cardiovascular system to a constant short term submaximal workload.

The basic mechanisms included in the model are Starling's law of the heart, the Bowditch effect (relating the heart rate to the contractibility of the ventricle), and the autoregulation in the peripheral regions, as closed loop control mechanisms.

A fundamental assumption is, that the action of the feedback control is represented by the baroreceptor reflex and minimizes a quadratic cost functional. Hereby, they minimize the deviation in the systemic arterial pressure and in the change in heart rate from some set point values over an infinite time horizon. Hence, the change in heart rate, as the control variable, becomes dependent on the arterial pressure.

There are 26 parameters in the model and 18 of these are estimated from the arterial pressure and the heart rate data obtained in a bicycle ergometer test. They use the same data to validate the model, which indeed is a considerable weakness. Furthermore, they state that the values of, for example, the systemic venous pressure, the systemic resistance, and the ventricle contractibility are within a physiologically realistic range. However, calculations of the blood volume of each compartment give very unrealistic values.

Recently **Frello et al** studied the model described by Kappel and Peer. Instead of using optimal control theory they were modeling the baroreflex directly based on physiology.

Their model of the baroreflex is independent of the model of the uncontrolled cardiovascular system, except that it uses the arterial pressure as an input to determine the heart rate, which is the control variable. When coupled with a model of the uncontrolled cardiovascular system, it becomes a closed loop model.

The baroreflex model consists of two submodel: One describing how the sympathetic and parasympathetic tones (nerve activity) depend on the arterial pressure, which is qualitatively based on physiology. The parameters have physiological interpretation. The other submodel describes how the change in heart rate depends on the sympathetic and parasympathetic tones. This submodel is also qualitatively based on physiology and the parameters do also have physiological interpretation. As in the former submodel, the parameter values are determined by fitting the final model to measurements.

Together these submodels describe how the change in heart rate, as the control variable, depend on the arterial pressure, and qualitatively the curve show the right characteristic behavior.

The parameters of the integrated model are fitted to the data used in the paper

by Kappel and Peer. As in the simulations by Kappel and Peer, agreement to the same degree is achieved, describing the transition from rest to exercise. Further, the systemic venous pressure, the systemic peripheral resistance and the ventricle contractibility shows the right characteristic behavior.

Conclusion: The model of **Warner** should be closed. However, it includes time delay and is physiologically based. The validation of the model is poor. The model by **Frello et al** is compounded of two physiologically based submodels, but does not include time-delay. However, it is validated to some degree. These two models should be compared using the same model for the uncontrolled cardiovascular system. Both are non-pulsatile.

The model of **Kappel and Peer** is also non-pulsatile but they use optimal control theory as a fundamental principle. However, we doubt this concept to hold in all situations, for example, if the brain for some reason does not get enough oxygen we expect the heart to increase the blood circulation for almost any energetic prize. The model is validated to some degree, but it gives some unrealistic value for the volume of the blood compartments. However, it would be interesting to calculate the cost functional, used by Kappel and Peer, using the arterial pressure and the change in heart rate obtained by Warner and by Frello et al. respectively.

The models of **Ono et al.** and **Wesseling et al.** describe more than one feedback mechanism. The model of Wesseling is very complex and is not very well explained. Hence, they are not so easy to analyse.

The model of **Noldus** is pulsatile and is used for study one cycle of the heart. It is very well validated and includes a detailed discussion of the model.

As an **outlook** we will improve and close the feedback model of Warner. Moreover, we will analyse the model mathematically and couple it with different models of the uncontroled system. We will also expand the model and couple it with pulsatile models of the uncontroled system. Further, we want to improve the model of Frello et al. for example by including time delay and by making it pulsatile. We also want to analyse the model in greater details. In all cases it would be nice to compare the models with corresponding models using optimal control theory and discuss the possible deviations. Finally, we plan to inverstigate the model of Wesseling et al. partly by simplifying it such that mathematical analyse becomes possible.

A Grodins (1959)

In this section we review a non-pulsatile closed loop compartment model with stroke volume as control variable. The latter is dependent on the arterial pressure through Starling's law.

In the fifties physiologists made an intensive reexamination of the ideas about cardiac output regulation. The first to give an comprehensive mathematical treatment was F.S. Grodins [2] in his classical paper from 1959. Grodins described the non-pulsatile cardiovascular system by a compartment model composed by the right ventricle, the pulmonary arteries, the pulmonary peripheral resistant, the pulmonary veins, the left ventricle, the systemic arteries resistant, the systemic peripheral and the systemic veins. In the model the dependent variables are the cardiac output, the ventricular volumes and work, the systemic arterial and venous pressures, the pulmonary arterial and venous pressures, the systemic and pulmonary blood volumes and their distribution between artery and vein. The independent variables are the cardiac frequency, strength, viscance, and compliance of each ventricle, systemic and pulmonary arteriolar resistances, systemic arterial and venous compliances, pulmonary arterial and venous compliance and total blood volume. The feedback regulator appears in the following version of Starling's law, $v_{\text{stroke}} = (S/P_A)v_d$, where v_{stroke} denote the stroke volume, S the strength of the ventricle, P_A the mean arterial pressure and v_d the diastolic volume. The mathematical model so derived appeared capable of accounting reasonably well for a variety of experimental observations, for example the relationship between systemic venous pressure and 1) mean systemic arterial pressure, 2) the cardiac output and 3) the cardiac frequency.

We will not go into further detail of the model of Grodins, but only mention that the major contribution of his analysis perhaps was an inspiration to further mathematical treatment of the regulation of the cardiovascular system. However, in the earlier section 6 we described a further developed compartment model of Grodins [5], when discussing the paper of Kappel and Peer.

B Robinson (1965)

In this section we review a pulsatile closed loop hydraulic analogue model, which include the homeometric autoregulation. The intraventricular pressure is the control variable, and it depends on the isometric ventricle pressure during systole.

In 1965 D.A. Robinson, inspired by Grodins [2] and Warner [4], continues the idea of using control theory to regulate the left ventricle. In the paper [6] Robinson makes a hydraulic analogue model of the left ventricle and the arterial systemic part of the circulatory system. The main point is to consider the ventricle conceptually divided into two chambers in series corresponding to the contractile and the elastic part of myocardium. Then the intraventricular pressure regulates the isometric pressure during systole, modeling the so-called homeometric autoregulation. In contrast to Grodins' model the one of Robinson is pulsatile, as Warner's was.

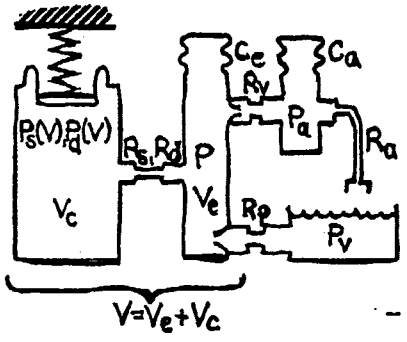

Figure 12: Robinson's hydraulic analogue model.

The symbols used in figure 12 are as follows: P is the intraventricular pressure, $P_s(V)$ is the isometric pressure during systole, V is the total volume of the ventricle, R_s is the coefficient of myocardial viscosity during systole, $\frac{dV}{dt}$ is the rate of change of volume, i.e. the flow, it is the cardiac output during systole and the pulmonary venous return during diastole, C_e is the compliance of that portion of the ventricular volume contributed by the series elastic component of the myocardium, C_a is the compliance of the elastic of the arterial tree, R_a is the systemic resistance, R_v is the small resistance of the aortic valve and the ascending aorta, $P_d(V)$ is the isometric pressure of the ventricle during diastole, R_d is the coefficient of myocardial viscosity during diastole, τ is the relaxation time constant of the myocadial viscosity, P_a is the arterial pressure, P_v is the filling pressure in the pulmonary venous reservoir, and R_p is the resistance of the pulmonary veins, the atrium and the mitral valve.

From the analogue model in figure 12 one arrives at the following set of equa-

tions, describing the ventricle and the arterial load respectively. During the systole

$$P = P_s(V) + R_s\frac{dV}{dt} - R_sC_e\frac{dP}{dt} \tag{32}$$

and

$$P + C_aR_a\frac{dP}{dt} + R_vC_aR_a\frac{d^2V}{dt^2} + (R_v + R_a)\frac{dV}{dt} = 0 \tag{33}$$

During the diastole

$$P = P_d(V) + [(R_s - R_d)e^{-t/\tau} + R_d]\frac{dV}{dt} - [(R_s - R_d)e^{-t/\tau} + R_d]C_e\frac{dP}{dt} \tag{34}$$

$$C_aR_a\frac{dP_a}{dt} + P_a = 0 \tag{35}$$

and

$$P = P_v - R_p\frac{dV}{dt} \tag{36}$$

The term in the squared bracket in equation (34) is a submodel of how the resistance of the aortic valve changes when going from systole to diastole, using a time constant $\tau = 0.05$ second. The expressions for $P_s(V)$ and $P_d(V)$, for the uncontrolled system, are given by ad-hoc choices, according to some parameters fitted to measurements. For the controlled system Robinson use homeometric autoregulation, i.e. he add to the uncontrolled $P_s(V)$ the deviation between a weight averaging of the intraventricular pressure and the mean pressure (using the weight function $e^{-(t-s)/1.5}$, where s denote the integration variable).

Robinson's simulations are made using data from a 10 kg dog and the validation is qualitative focusing on the fact that when introducing the homeometric autoregulation the Starling's law is obeyed. In contrast to the work of Grodins [2] and Warner [4] Starling's law follows from Robinson's model.

C Doubek (1978)

In this section we review a pulsatile optimal electrical analogue model, which include the vasomotor reflex. The peripheral resistance is the control variable and the optimal strategy is given by minimizing the expended energy per cycle.

In the paper [13] of E. Doubek from 1978 the vasomotor control is investigated. Doubek's paper is based on a complex model of the pulsatile cardiovascular system described by Weygandt et al. in [12]. The model consists of an electrical network

with two different types of "elements", the longitudinal sections and the vascular beds, for further details see [13].

The mathematical model consists of 24 state equations relating pressures and flows, and one control variable, the peripheral resistance. Doubek then apply optimal control theory and calculate an optimal control, assuming a parametric proportional plus rate set point controller of the carotid sinus pressure. This is done by formulating the problem like a Riccati state regulator problem, and assuming that the optimization criterion is the minimization of expended energy per cycle.

Doubek simulates some very nice "normal" waveforms in the uncontrolled case, using the criterion that the carotid sinus pressure at the beginning of the 5th heartbeat should differ sufficient little from the pressure at the end of the 5th heartbeat (steady state). Then Doubek manipulate some arbitrary constants to get the controlled waveforms to agree with the "normal" one. Finally, Doubek conclude that the simulations verifies the chosen form of the controller.

However, we shall note that Swan, see section G, in [24] points out some very fatal problems in the analysis of Doubek, which seems to casts doubt on the validity of his conclusions.

D Taylor (1978)

In this section we review a non-pulsatile optimal mechanical analogue model, which includes the vasomotor reflex and Starling's law of the heart. A sympathetic arterial constrictor signal is the control variable and it depends on a sympathetic constrictor signal. The model is studied both with and without a sympathetic venous constrictor signal as an additional control variable, it depends on some unspecified control signal. The optimal strategy is given by minimizing the deviations in the arterial pressure from its final value, the venous pressure from its initial value, and the control signals from their final equilibrium values over a given time period.

In a nice paper [16] from 1978, M.G. Taylor discussed the use of the method of quasilinearization to solve a set of non-linear ordinary differential equations with two-point boundary values. They arise from the use of the maximum principle of Pontryagin to solve an optimal control problem. Taylor demonstrates the method on two examples, one of these is the vasomotor control of the cardiovascular system, thus there is no attempt to include autonomic influence on the heart. A diagram of the model is illustrated in figure 13.

The model consists of an arterial reservoir of capacitance C_1 leading to a pe-

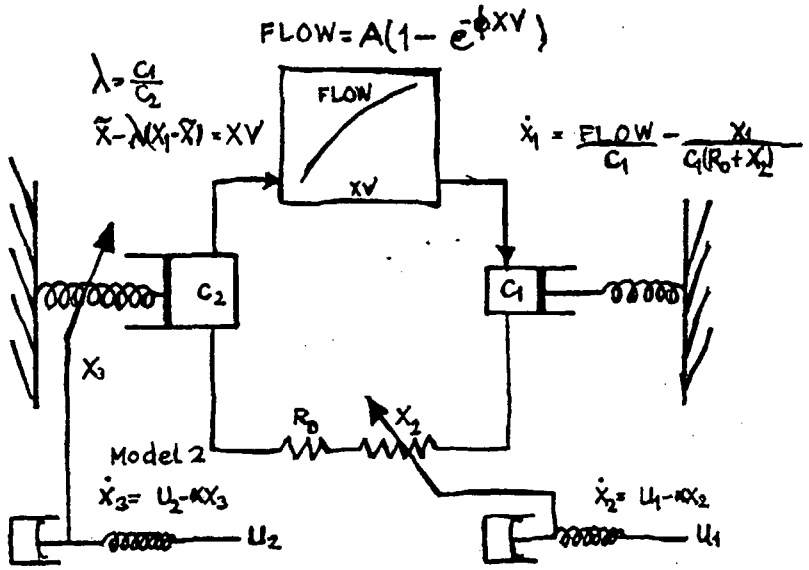

Figure 13: The model of Taylor

ripheral resistance which has two components. One is fixed, denoted R_0, and one is variable, denoted x_2. The variable component is constrained to be greater than zero, and its value is determined by the control variable u_1 acting through the spring dashpot element with a time constant $1/\alpha$ (see figure 13)

$$\frac{dx_2}{dt} = u_1 - \alpha x_2$$

This spring dashpot element represents the delay between a sympathetic constrictor signal (u_1) and the resulting smooth muscle tone of the resistance vessel (x_2). On the venous side, there is also a reservoir of capacitance C_2. Taylor does in fact study two models: One in which the venous reservoir was unregulated (model 1), and one in which it was subject to a venoconstrictor tone x_3 (model 2), regulated by a control signal u_2, acting, as in the case of the peripheral resistance, through a spring dashpot element of the same time constant $1/\alpha$

$$\frac{dx_3}{dt} = u_2 - \alpha x_3 \qquad \text{(model 2 only)}$$

The effect of this venoconstrictor tone is to divide the capacitance by x_3, thus, for

any given venous volume, the venous pressure is increased in proportion to x_3, i.e. the venous volume is given by $C_2 x_v / x_3$. We note that a spring dashpot system is mathematical equivalent to a capacitor resistance system. Finally, Taylor describes the cardiac output or flow by a sort of Frank-Starling relation between the filling pressure x_v and the flow F

$$F = A(1 - e^{-\phi x_v})$$

where A and ϕ are constants and x_v is the venous filling pressure. This venous pressure is determined by the arterial pressure (x_1) via a relationship which expresses the fact that the total storage in the two reservoir is constant

$$x_1 C_1 + x_v C_2 = \tilde{x}(C_1 + C_2)$$

where $\tilde{x}$ is a constant, describing the equilibrium pressure of the system. Rearranging this expression and putting $\lambda = C_1/C_2$, Taylor gets

$$x_v = \tilde{x} - \lambda(x_1 - \tilde{x})$$

The problem posed by Taylor is to find the optimal strategy or time course of the control signal u_1 (and in model 2, of u_2 as well) representing a pattern of sympathetic nervous activity which will take the arterial pressure x_1 from an initial value of 4.0 units at time $t = 0$ to a final value of 6.0 units at time $t = 15$. The transition subject to various costs should be accomplished as quickly as possible, during the fixed interval of time. The cost functional consists of four terms and penalize certain deviations; the arterial pressure from its final value, the venous pressure from its initial value (or equivalent the flow from its initial value) and the control signals from their final equilibrium values

$$\begin{aligned} J &= \int_0^{15} \left((x_1 - x_1(15))^2 + \beta(x_v - x_v(0))^2 + \right. \\ &\qquad \left. \gamma(u_1 - u_1(15))^2 + \kappa(u_2 - u_2(15))^2\right) dt \end{aligned}$$

where β, γ and κ represent weighting constants. Hence Taylor uses the maximum principle of Pontryagin with quasilinearization to get the optimal solution for u_1 (and in model 2 also u_2). The following values of the various constants were used, $A = 2.0$, $\phi = 0.731$, $\tilde{x} = 0.5$, $\lambda = 0.05$, $C_1 = 1.0$, $R_0 = 1.0$, $x_1(0) = 4.0$, $x_1(15) = 6.0$, $x_2(0) = 3.1845$, $x_2(15) = 5.2767$, $x_3(0) = 1.0$, $x_3(15) = 1.4444$, $u_1 < 50.0$, $u_2 < 50.0$, $\alpha = 0.2$, $\gamma = 0.2$, $\kappa = 20.0$ and $\beta = 400.0$. It is not clear how these values are determined and the units doesn't appear anywhere in the paper.

Taylor makes three simulations, the above described situation for model 1 and 2 together with a simulation where the "fixed" element of peripheral resistance

is increased suddenly from an initial value of 1.0 to 2.0 in model 2. It seems, as expected, that the models response quite nicely. Particularly interesting is the form of the control signal u_1, there is a steep rise (or fall) followed by a slower settling (with or without an overshoot or undershoot) to a new equilibrium value which is claimed to be characteristic for autonomic firing patterns found in animal experiments under circumstances such as those modeled. These pattern arise in the simulations entirely as an expression of the optimal strategy stated. Moreover, the third simulation show that the arterial pressure in the face of a 25 % change in peripheral resistance, only changes about 2.5 %.

E Yamashiro et al. (1979)

In this section we review a pulsatile optimal electrical analogue model of the aortic flow pulse counter. The ventricular outflow is the control variable, it depends on the heart rate, stroke volume, arterial compliance, peripheral resistance, valvular resistance, and end-diastolic flow. The optimal strategy is given by minimizing the power dissipating through the valvular and the peripheral resistances per cycle.

In the paper [19] by S.M. Yamashiro, J.A. Daubenspeck and F.M. Bennett from 1979 the question; what is the optimal left ventricular ejection pattern which minimizes the total power required for a given level of cardiac output. They answer the question by use of variational calculus and a model of the cardiovascular system, or rather the left ventricle load. For some reason, unknown to us, they do not use optimal control theory. The electrical analog of this model is shown in figure 14.

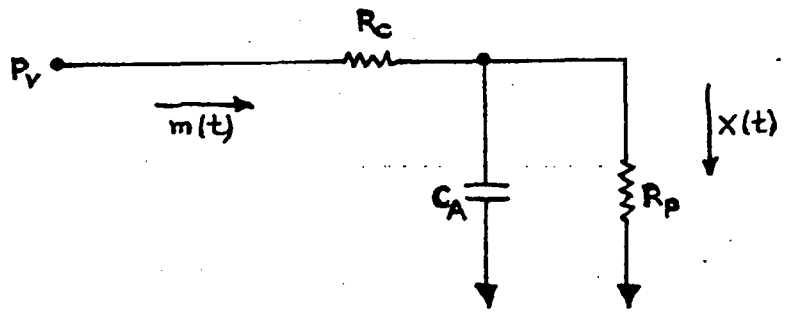

Figure 14: The electrical analog model of Yamashiro et al.

Yamashiro et al. wish to minimize the hydraulic power dissipated through the valvular resistance (R_C) and the peripheral resistance (R_P) over the cardiac period (T), see figure 14. Hence, they minimize

$$J = R_C \int_0^{t_s} m^2(t)dt + R_P \int_0^{t_s} x^2(t)dt + R_P \int_{t_s}^{T} x^2(t)dt \tag{37}$$

where t_s denotes the systole duration, $m(t)$ the aortic root flow (notice that it is indeed zero during diastole, i.e. when $t_s \leq t \leq T$) and $x(t)$ the peripheral flow. The optimization hypothesize is with t_s and T free. Moreover, they use the constraint that the delivered stroke volume (V_s) of the peripheral circulation is maintained constant

$$V_s = \int_0^{t_s} m(t)dt = \text{constant} \tag{38}$$

The linking between the control variable $m(t)$ and the peripheral flow $x(t)$ is given by the electrical network shown in figure 14

$$m(t) = \tau \frac{dx(t)}{dt} + x(t) \tag{39}$$

where $\tau = R_P C_A$. In fact, there is a third constraint on $m(t)$ due to the present of the aortic valve. It implies that the flow is proceeding out of the ventricle through R_C (defined to be the positive direction). This complication is approached by limiting the values of t_s to a range where the value of $m(t)$ is nonnegative. If one imposes the initial and final value of x, equation (39) determines the behavior of $x(t)$ in the interval $t_s \leq t \leq T$. Thus one gets an exponential decay and

$$x_{t_s} \equiv x(t_s) = x(0)e^{(T-t_s)/\tau}$$

Thus the third term in equation (37) depends on t_s, T and $x(0)$, but is independent of the course of $m(t)$. Hence it is sufficient to consider a simplification of the criterion function (37) to

$$J = R_C \int_0^{t_s} m^2(t)dt + R_P \int_0^{t_s} x^2(t)dt \tag{40}$$

Now Yamashiro et al. use calculus of variation to calculate analytically expressions for the minimum power dissipation (given by J) and the optimal aortic root flow ($m(t)$) as functions of t_s for fixed mechanical parameters, i.e. cycle duration (T) and stroke volume (V_s), and hence constant cardiac output.

By use of Robinson's parameters for a 10 kg dog, given in [6], Yamashiro et al. simulate the sensitivity of the optimal trajectories, i.e. the optimal aortic root flow

as a function of time, to changes in the heart period (T), the stroke volume (V_s), the arterial compliance (C_A), the peripheral resistance (R_P), the valvular resistance (R_C), and the end-diastolic peripheral flow ($x(0)$). Furthermore, by numerical calculations they fixed the optimal trajectories for some values of t_s. The optimal value of t_s determined from the observation that the power dissipation decreases as t_s increases and that $m(t)$ becomes negative when t_s is increased beyond 0.29 seconds.

The validation of the model is done by observing that the major shape characteristics of the predicted optimal aortic flow pulses agree with some measured flow pulses in dogs reported in literature. This does't incorporate the initial part of the systole. The present optimal pulse predictions show an instantaneous rise of flow at the beginning of the systole which of cause is never observed (it would require an infinite ventricular pressure due to the inertia of blood). At this point one should mention that in a paper from 1978, S.M. Yamashiro, J.A. Daubenspeck, F.M. Bennet, S.K. Edelman and F.S. Grodins [17] present the same model except that they do include the inertance of blood. However, then it becomes the same model as Noldus analyzed in 1976, see section 3. Yamashiro claims, in the discussion following the article, [17], that the solution obtained is independent of the value of the inertance, why they neglect it in the model equations. We disapprove with this, since a non-vanishing inertance term would prevent the instantaneous rise of flow in the beginning of the systole (this also follows by the model of Noldus).

F Kenner et al. (1980)

In this section we review a pulsatile optimal electrical analogue model of the aortic flow pulse counter. The ventricular outflow is the control variable and the optimal strategy is given by minimizing the power dissipating through the valvular and the peripheral resistances.

In an earlier paper from 1978 K.P. Pfeiffer and T. Kenner [14] restate the model developed by Yamashiro et al., see section E. Moreover, they make simulations and the resulting flow and pressure contours look pretty much as those mentioned in a later paper. However, in this earlier paper Pheiffer and Kenner briefly mention the work of Noldus, see section 3, which is a more preferable approach. In a later paper [20] from 1980, that will be discussed in details here, Kenner and Pheiffer improve the model of Yamashiro et al., also using the method of calculus of variations. Their validation is done in order to simulate the characteristics of the central aortic flow pulse contour, i.e. its steep ascent, which leads to a peak

flow early in the systole, its slow descent, which, together, give the pulse a more or less triangular shape, and its "shoulder". Kenner and Pfeiffer use the same model of the cardiovascular system, or rather of the left ventricular load, as Yamashiro et al., but do moreover give an explicit equation for the ventricular pressure P_V during the systole

$$P_V(t) = R_C m(t) + R_P x(t)$$

We have used the same notation as in section E. Whereas Yamashiro et al. minimizes the external loss of energy per stroke, Kenner and Pheiffer minimizes the total external stroke work

$$W = \int_0^{t_s} P_V m(t) dt$$

This is partly inspired by the work of Noldus, see section 3. Thus the model is similar to that of Yamashiro et al., except that the functional to be minimized is

$$\int_0^{t_s} \left((R_P + R_C)x^2(t) + R_P C_A (2R_C + R_P) x(t) \frac{dx(t)}{dt} + (R_P^2 C_A^2 R_C)(\frac{dx(t)}{dt})^2 \right) dt$$

The flow pulses computed according to this model have the same strange appearance as those of Yamashiro et al. insofar as the steepness of the ascent of the flow pulse is infinite in contrast to real physiological pulses. Thus Kenner and Pheiffer improve the model by impose the additional condition

$$\left. \frac{dm(t)}{dt} \right|_{t=0} = 0$$

In solving this new model Kenner and Pfeiffer first solve the original optimization problem, and then they expand the equation for $x(t)$ as

$$x(t) = A_0 + A_1 e^{-at} + A_2 e^{at} + A_3 e^{ba^2 t}$$

Finally they use an iterative procedure to compute a value of b, such that the optimization criterion is a minimum. Hence, in that sense, they find a suboptimal solution.

The new model does produce flow contours which agree much better with the characteristic physiological shapes, especially with finite ascending slope. However, the shoulder in the downslope of the flow pulses can only be seen at low values of the characteristic impedance R_C. This fact, apparently, does not agree with physiological conditions since the shoulder can be seen in vivo at normal (higher)

values of the characteristic impedance. The values of the maximal pressure slope $(dp/dt)_{\max}$ were measured and it shows the expected behavior; it increases with reduction of peripheral resistance and of capacitance, and with increased values of the valvular resistance. Furthermore, it was found that the energy saving by optimization is surprisingly small (it may not exceed 5 % of that of some triangular pulses). This indicate that, under physiological conditions, additional constraints are of equal importance for the purpose of circulatory control, or it may even indicate that, the used optimization criterion is not the appropriate one.

In 1981 Kenner and Pfeiffer restated their work in another paper [21] but in a condensed form.

G Swan (1984)

In this section we review a discussion of the pulsatile optimal electrical analogue models described in sections 5, 6 and 8.

The excellent book of Swan "Application of Optimal Control Theory in Biomedicine" [24] is devoted to several case studies and includes a nice introduction to optimal control theory, in particular chapter 7 contains a fine compound of the optimal control aspect of the circulatory system, especially it discussed the paper of Noldus [11], Yamashiro et al. [19] and Doubek [13]. Swan remark that it is rather surprising that Yamashiro et al. when writing their paper, were unaware of the 3 year earlier work by Noldus, as it seems. Swan present the analysis of Noldus as he did, see section 3, but when discussing the model of Yamashiro et al., see section E, Swan uses optimal control theory. Instead of equation (40), Swan incorporates equation (38) into the criterion functional

$$J = \int_0^{t_s} \left(R_C m^2(t) + R_P x^2(t) + \rho m(t) \right) dt \quad . \tag{41}$$

where ρ is a unknown weight and the rest of the symbols are as in section E. Straightforward use of optimal control theory gives $x(t)$, involving ρ in a linear manner, then $m(t)$ is obtained from equation (39) and finally, an linear equation for ρ is obtained by equation (38). The result and validation is the same as discussed by Yamashiro et al., see section E.

Swan elaborate the analysis of Doubek, see section C, on certain points, indicating the possibility of two failures. The first problem is that some time dependent parameters of the model equations have to fulfil a particular equation for a central derivation in the paper of Doubek to be correct. However, Doubek does not mention this problem and the matter is not yet resolved. The second problem is that

Doubek uses what appears to be a circular argument when correlating the control to changes in peripheral resistance. We will not discuss these fatal problems further but reefer to [24].

In the end of the chapter Swan use optimal control theory in the study of using microcomputers to administrate automatic drug delivery to patients suffering from hypertension.

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Below we bring a list of the publications, those numbered [1]-[26] are dealing explicitely with mathematical modeling of the control of the cardiovascular system. The publications numbered [27]-[36] are general litterature and publications also appearing in the text. Each part of the list is ordered chronologically. If one author appears as auther anywhere else in the list the name of the author has an integer as supscript, the number indicate how many times the specific author name appear in the list.

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217/92 "Two papers on APPLICATIONS AND MODELLING IN THE MATHEMATICS CURRICULUM"
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by: Lars Kadison

219/92 "RUPNOK - stationær strømning i elastiske rør"
af: Anja Boisen, Karen Birkelund, Mette Olufsen
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af: Per M.Hansen, Steffen Holm, Peter Maibom, Mads K. Dall Petersen, Pernille Postgaard, Thomas B.Schrøder, Ivar P. Zeck
Vejleder: Peder Voetmann Christiansen

228/92 "Teknologi og historie"
Fire artikler af:
Mogens Niss, Jens Høyrup, Ib Thiersen, Hans Hedal

229/92 "Masser af information uden betydning"
En diskussion af informationsteorien i Tor Nørretranders' "Mærk Verden" og en skitse til et alternativ basseret på andenordens kybernetik og semiotik.
af: Søren Brier

230/92 "Vinklens tredeling - et klassisk problem"
et matematisk projekt af
Karen Birkelund, Bjørn Christensen
Vejleder: Johnny Ottesen

231A/92 "Elektrondiffusion i silicium - en matematisk model"
af: Jesper Voetmann, Karen Birkelund, Mette Olufsen, Ole Møller Nielsen
Vejledere: Johnny Ottesen, H.B.Hansen

231B/92 "Elektrondiffusion i silicium - en matematisk model" Kildetekster
af: Jesper Voetmann, Karen Birkelund, Mette Olufsen, Ole Møller Nielsen
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232/92 "Undersøgelse om den simultane opdagelse af energiens bevarelse og især om de af Mayer, Colding, Joule og Helmholtz udførte arbejder"
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Instability in an SIR-model with age-dependent susceptibility
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- Modul 3 fysik projekt -
af: Thomas Jessen

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af: Anja Boisen, Peter Bøggild

Vejleder: Peder Voetmann Christiansen
Erland Brun Hansen

236b/93 STRØMSSAMMENBRUD AF KVANTE HALL EFFEKTEN

af: Anja Boisen, Peter Bøggild

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af: Lars Kadison

238/93 SEMIOTIK OG SYSTEMEGENSKABER (2)

Vektorbånd og tensorer

af: Peder Voetmann Christiansen

239/93 Valgsystemer - Modelbygning og analyse

Matematik 2. modul

af: Charlotte Gjerrild, Jane Hansen, Maria Hermannsson, Allan Jørgensen, Ragna Clauson-Kaas, Poul Lützen

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Om sære matematiske fisks betydning for den matematiske udvikling

af: Claus Dræby, Jørn Skov Hansen, Runa Ulsøe Johansen, Peter Meibom, Johannes Kristoffer Nielsen

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af: Bent Sørensen

242/93 Brovedligeholdelse - bevar mig vel

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af: Linda Kyndlev, Kare Fundal, Kamma Tulinius, Ivar Zeck

Vejleder: Jesper Larsen

243/93 TANKEEKSPERIMENTER I FYSIKKEN

Et 1.modul fysikprojekt

af: Karen Birkelund, Stine Sofia Korremann

Vejleder: Dorthe Posselt

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Projektrapport

af: Trine Andreasen, Tine Guldager Christiansen, Nina Skov Hansen og Christine Iversen

Vejledere: Gestur Olafsson og Jesper Larsen

245a+b /93 Time-Of-Flight målinger på krystallinske halvledere
Specialerapport

af: Linda Szkotak Jensen og Lise Odgaard Gade

Vejledere: Petr Viscor og Niels Boye Olsen

246/93 HVERDAGSVIDEN OG MATEMATIK
- LÆREPROCESSER I SKOLEN

af: Lena Lindenskov, Statens Humanistiske Forskningsråd, RUC, IMFUFA

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by: Jeppe C. Dyre

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by: B. Booss-Bavnbek, K.P.Wojciechowski

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by: B. Booss-Bavnbek

With comments by W.Abikoff, L.Ahlfors, J.Cerf, P.J.Davis, W.Fuchs, F.P.Gardiner, J.Jost, J.-P.Kahane, R.Lohan, L.Lorch, J.Radkau and T.Söderqvist

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Projektrapport af: Anja Juul, Lone Michelsen, Tomas Højgård Jensen

Vejleder: Stig Andur Pedersen

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by: Freddy Bugge Christiansen, Viggo Andreasen and Ebbe Thue Poulsen

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Projektrapport af: Birthe Friis, Lisbeth Helmgaard Kristina Charlotte Jakobsen, Marina Mosbæk Johannessen, Lotte Ludvigsen, Mette Hass Nielsen

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Teori og model

af: Lise Arleth, Kåre Fundal, Nils Kruse

Vejleder: Mogens Niss

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Materiale til et statistikkursus

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af: Peter Harremoës

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Bredde-kursus i Fysik
Eksamensopgaver fra 1976-93

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by: Lars Kadison

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af: Mogens Brun Heefelt

264/93 FOTOVOLTAISK STATUSNOTAT 2
af: Bent Sørensen

265/94 SPHERICAL FUNCTIONS ON ORDERED SYMMETRIC SPACES
To Sigurdur Helgason on his sixtyfifth birthday
by: Jacques Faraut, Joachim Hilgert and Gestur Olafsson

266/94 Kommensurabilitets-oscillationer i laterale supergitre
Fysikspeciale af: Anja Boisen, Peter Bøggild, Karen Birkelund
Vejledere: Rafael Taboryski, Poul Erik Lindelof, Peder Voetmann Christiansen

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Vejleder: Bernhelm Booss-Bavnbek

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Et projekt om modellering af aorta via en model for strømning i kloakrør
af: Anders Marcussen, Anne C. Nilsson, Lone Michelsen, Per M. Hansen
Vejleder: Jesper Larsen

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metaprojekt, fysik
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Vejleder: Jens Højgaard Jensen

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by: Jacob Jacobsen

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Opdaget eller opfundet
NAT-BAS-projekt
vejleder: Jens Højgaard Jensen

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Det praktiske elevarbejde i gymnasiets fysikundervisning, 1907-1988
af: Kristian Hoppe og Jeppe Guldager
Vejledning: Karin Beyer og Nils Hybel

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Verifikation af model
af: Lise Fabricius Christensen, Helle Pilemann, Bettina Sørensen
Vejleder: Mette Olufsen

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Vejledere: Viggo Andreasen & Jesper Larsen

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2nd Edition
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Projektrapport 1. modul
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Vejleder: Jens Højgaard Jensen

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Projektrapport udarbejdet af:
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Vejleder: Viggo Andreasen

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af: Erwin Dan Nielsen, Jan Danielsen, Niels Bo Johansen

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(èn kaotisk talgenerator)

af: Erwin Dan Nielsen og Niels Bo Johansen

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Gymnasiematematikkens begrundelsesproblem

En specialerapport af Peter Hauge Jensen

og Linda Kyndlev

Vejleder: Mogens Niss

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by: Viggo Andreasen and
Freddy B. Christiansen

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Et 3.modul matematik projekt

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Vejleder: Jesper Larsen

291/95 1st Annual Report from the project

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an example of using methods developed for the OECD/IEA and the US/EU fuel cycle externality study

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