Analysis of Left Ventricular Function by Optimization Models

Jari J. Hämäläinen

Helsinki University of Technology
Systems Analysis Laboratory
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Jari J. Hämäläinen

Helsinki University of Technology
Systems Analysis Laboratory
Otakaari 1 M
SF-02150 Espoo, Finland

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[I] R.P. Hämäläinen and J.J. Hämäläinen, and U. Miekkala, "Optimal control modelling of ventricular ejection - do the endpoint conditions dominate the performance criteria?" in *Modelling and Data Analysis in Biotechnology and Medical Engineering*, G.C. Vansteenkiste and P.C. Young, Eds. Amsterdam: North-Holland, 1983, pp. 151–162.

[II] R.P. Hämäläinen and J.J. Hämäläinen, "On the minimum work criterion in optimal control models of left-ventricular ejection," *IEEE Trans. Biomed. Eng.*, vol. BME–32, pp. 951–956, 1985.

[III] J.J. Hämäläinen and R.P. Hämäläinen, "Energy cost minimization in left ventricular ejection: an optimal control model," *Modeling Methodology Forum, J. Appl. Physiol.*, vol. 61, pp. 1972–1979, 1986.

[IV] J.J. Hämäläinen, "Optimal stroke volume in left ventricular ejection," Systems Analysis Lab., Helsinki Univ. Techn., Rep. A26, 1988.

[V] J.J. Hämäläinen, "A hierarchical optimization model of left ventricular ejection," Systems Analysis Lab., Helsinki Univ. Techn., Rep. A19, 1988.

PREFACE

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Helsinki, August 1988 Jari Hämäläinen

ABSTRACT

The development of a new hierarchical optimization model for explaining left ventricular function is summarized. In the model, arterial load is described by three linear time-invariant differential equations. End-diastolic volume, linear end-systolic pressure-volume relation, heart rate, and nominal ejection time are given. Under these constraints, ventricular function is described by optimality criteria that are based on minimizing an index of myocardial oxygen consumption per beat. Also forces developed during ejection and ventricular efficiency are taken into account in the cost functions of the model. The model predicts ventricular stroke volume, time courses of root aortic flow and pressure, and ejection time. These predictions are in accordance with experimental data from an isolated canine heart preparation. In the measurements analyzed, arterial load has been changed while end-diastolic volume, contractility, and heart rate have been kept constant. Thus the analysis shows that the left ventricular response to a change in arterial load can be predicted by an optimization model. The results also suggest that energy economy and efficiency are essential features of left ventricular function.

1. INTRODUCTION

The mammalian heart is composed of two atria and and two ventricles. Each atrium is connected to a ventricle through an A-V valve. In the systemic part of the circulatory system, the left ventricle is connected to the aorta through the aortic valve. The aortic valve opens at the beginning of ventricular ejection when the pressure in the contracting ventricle exceeds the pressure in the root of aorta. The mitral valve between the left ventricle and the left atrium prevents backflow of blood from the ventricle into the atrium during the systolic contraction phase. When the ejection of a certain stroke volume has occurred, the aortic valve closes due to a decrease in ventricular pressure.

During diastole the aortic valve is closed and pressure in the aorta decreases while blood flows through arterioles and capillaries into the veins (blood is stored in the compliant aorta and arteries during the ejection period). At the same time blood flowing from the left atrium fills the left ventricle to a certain end-diastolic volume from which the ventricle starts to contract after diastole. The time interval in the beginning of systole, when ventricular pressure rises while both the mitral valve and aortic valve are closed, is called the isovolumic contraction period.

Given ventricular loading conditions, stroke volume and the time courses of root aortic pressure and flow during the ejection period (the ejection pattern) are determined by the operation of the ventricle. End-diastolic volume describes preload. Arterial load can be characterized by the arterial input impedance that is determined from simultaneous measurements of root aortic pressure and flow. Given preload and arterial load, the myocardial contractile state also influences stroke volume and ejection pattern. Heart rate is the fourth important factor. For a review of factors influencing cardiac performance, see e.g. [2].

The problem analyzed in this paper is to predict stroke volume and ejection pattern when preload, arterial load, contractility, and heart rate are given. Especially the effects of changes in arterial load and end-diastolic volume on stroke volume and ejection pattern will be studied in detail. It is assumed that the response of the ventricle to a change in its load can be described by an optimization model. The optimality criteria developed are based on the assumption of energetically economical and efficient performance of the ventricle.

This paper is organized as follows. Firstly, the use of optimization models in physiology is briefly discussed. Secondly, a definition of the set of feasible solutions for a dynamic optimization problem is described and an example is given of a model for the inspiratory airflow in breathing. Then the set of feasible solutions is defined for an optimization model of left ventricular ejection. The elastance model that is frequently used to describe the operation of the ventricle is also presented. Then an optimization approach for modeling left ventricular function is outlined. After these introductory sections the five papers describing the models developed in [I]-[V] are summarized.

1.1 Optimization Models in Physiology

In pure science, the concept of optimality is used to characterize the way in which a natural process does occur, out of all the ways it could occur [14]. The problem how a natural process occurs in various environmental conditions is solved by carrying out suitable experiments. How a natural process could occur can only be defined theoretically.

A mathematical optimization problem is formally stated as follows:

> Let U be a set of elements and $J : U \rightarrow R$ a cost (objective) function. The optimization problem is to find an optimal u^* that minimizes (maximizes) $J(u)$ subject to $u \in U$.

In the analysis of a physiological process by an optimization model, U is defined to contain all feasible solutions. Suppose that parameters p describe the properties of the system and the environmental conditions, and that p influences a certain quantity u describing the behavior of the system. For all $p \in S_p \subset R^q$, the corresponding u must be elements of U. S_p is the set of physiologically feasible values of p.

If we would like to construct an optimization model that predicts u for a given p, we should find a cost function J the minimization of which gives u^* when p is given. The optimal u^* should resemble the experimentally observed u for all $p \in S_p$.

Examples of cost functions used in optimization models of physiological and biomechanical systems have been given by Hämäläinen, R.P. [8], Hatze [5], and Rosen [15]: minimize the time spent for a specified movement, maximize efficiency, minimize energy expenditures, maximize stability, or take several criteria into account. Swan [24] also gives references of several biomedical optimization models.

It has been suggested that the phenomenon of natural selection is a qualitative argument justifying the use of optimality principles in biological sciences [15]. When such biological interpretations are given for the models, one should remember that the cost functions in mathematical optimization problems are not unique. Several optimization criteria can give the same solution.

Theoretically one can always try to construct a model only based on curve fitting for predicting u for a given p. In fact, there is no general benefit in using an optimization model for predicting purposes if methods based on curve fitting work equally well. However, in certain applications the optimization approach is the only method that is feasible in practice (see e.g. [5, 6]). On the other hand, the analysis of the optimality criterion may give us insight of the physiological processes involved.

1.2 Dynamical Systems

Consider a dynamical system described by the model

$$\dot{x}(t) = f(x(t), u(t), p, t) \tag{1}$$

$$y(t) = g(x(t), u(t), p, t) \tag{2}$$

where $t \in [t_0, t_1]$ is time, $x(t) \in R^n$ is the system state, $u(t) \in R^m$ is the input, $y(t) \in R^s$ is the output, and $p \in S_p \subset R^q$ is the parameter vector. Let $u \in U$ where U is the set of piecewise continuous functions from $[t_0, t_1]$ into R^m. Assume that f and g are continuous functions from $R^n \times R^m \times S_p \times [t_0, t_1]$ into R^n and R^s, respectively, and that the partial derivative of f with respect to x is continuous.

Suppose that t_0, the initial state $x(t_0)$, and p are given. Given $u(t)$, (1) is an initial-value problem that has a unique solution (see e.g. [1]).

Suppose that $x(t_0)$ is not known, but w equations of the following form are given

$$r(x(t_0), x(t_1), u(t_0), u(t_1), p) = 0 \tag{3}$$

where r is a function from $R^n \times R^n \times R^m \times R^m \times S_p$ into R^w. When t_0, t_1, $u(t)$, and p are given, and $w = n$, the differential equations (1) and boundary conditions (3) constitute the standard form of the two-point boundary-value problem. This problem can have a unique solution, several solutions, or no solution (see e.g. [18]).

The admissible inputs $u(t)$ for the model defined by (1)-(3) must be such that the boundary conditions (3) are satisfied. When the model is used to describe a biomechanical or a physiological system, physiological conditions are often described by parameters p. In order to predict the system behavior when p is changed, one should be able to describe the effects of p on the input $u(t)$.

1.3 An Example: Model for the Inspiratory Airflow in Breathing

In order to clarify the general formulation above, let us consider a model for the inspiratory airflow in breathing. The dynamical behavior of the lung-ribcage system can be described by a first order differential equation (see [11])

$$P_l(t) = E_l V_l(t) + R_l \dot{V}_l(t) \tag{4}$$

where $t \in [0, t_1]$. $P_l(t)$ is the total driving pressure produced by the respiratory muscles, $V_l(t)$ is the increase in lung volume from the resting equilibrium volume, E_l is the total elastance, and R_l is the total resistance of the airways, lung tissue, and thoracic wall. When the duration of inspiration t_1, V_l^0, and tidal volume V_l^1 are given, the following boundary conditions must be satisfied:

$$V_l(0) = V_l^0 \tag{5}$$

$$V_l(t_1) = V_l^0 + V_l^1 \tag{6}$$

$$\dot{V}_l(0) = 0 \tag{7}$$

$$\dot{V}_l(t_1) = 0. \tag{8}$$

Conditions (5)-(6) fix the tidal volume and (7)-(8) say that the inspiratory airflow is zero at the beginning and at the end of the inspiratory period. In this case the state of the system is $V_l(t)$, the input is $P_l(t)$, the parameter vector is $p_l = [E_l\ R_l\ V_l^0\ V_l^1\ t_1]'$ (the superscript $'$ denotes the transpose), $n = 1$, and $w = 4$. It is easy to see that the model is of the form (1)-(3).

Assume that p_l and $P_l(t)$ are known for a patient being at rest. Thus the airflow pattern $\dot{V}_l(t)$ is obtained by solving the initial value problem (4)-(5). Since $P_l(t)$ is admissible, the boundary conditions (6)-(8) are satisfied.

Assume that p_l is changed. For example, R_l can be increased artificially or p_l may change due to a change in physiological conditions (e.g. exercise). In order to predict the new $\dot{V}_l(t)$, the new $P_l(t)$ must also be predicted. The predicted $P_l(t)$ should be such that (4)-(8) are satisfied and that the flow pattern $\dot{V}_l(t)$ resembles the measurements.

Hämäläinen, R.P. et al. have presented an optimal control formulation of the problem, where an optimal operation of the respiratory control system is assumed [7, 9, 10, 11]. The optimality criteria suggested in these papers are based on minimizing the oxygen cost of breathing and on avoiding rapid muscular movements.

1.4 Feasibility Conditions for Theoretical Left Ventricular Ejection Patterns

In left ventricular ejection, arterial load (input impedance) can be described by a set of linear time-invariant differential equations (see e.g. [4, 25]). In [V] a four-element model is used

$$\frac{d}{dt}P_a(t) = -\frac{1}{RC}P_a(t) + \frac{1}{C}i(t) \tag{9}$$

$$\frac{d}{dt}i(t) = -\frac{1}{L}P_a(t) - \frac{r}{L}i(t) + \frac{1}{L}P(t) \tag{10}$$

where $t \in [t_0, t_1]$. t_0 denotes the beginning and t_1 the end of ejection. The electric analog of the system is shown in Fig. 1. C is arterial compliance, R is peripheral resistance, L is inertance, and r is a small resistance which represents the characteristic impedance of the ascending aorta [4]. $P(t)$ is the pressure in the root of aorta and $i(t)$

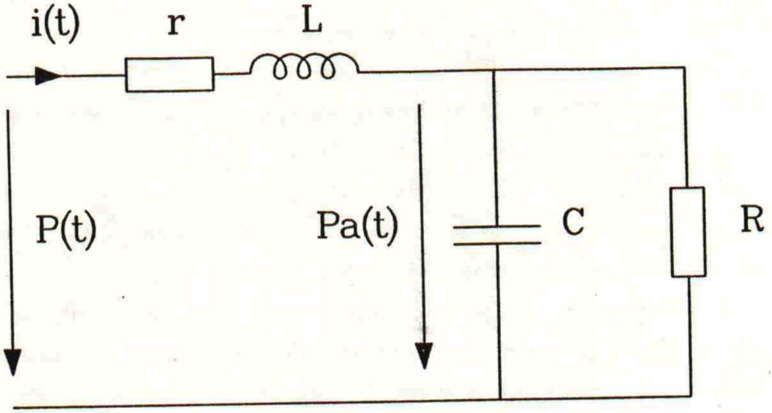

Fig. 1. *The electric analog of the arterial load model (9)-(11). In the analog, $P(t)$ and $P_a(t)$ represent voltages, $i(t)$ is current, r and R are resistances, L is inductance, and C is capacitance.*

the root aortic flow. $P_a(t)$ does not have a specific counterpart in the real system during the ejection period. The rate of change of the left ventricular volume $V(t)$ is given by

$$\frac{d}{dt}V(t) = -i(t). \tag{11}$$

When $P(t)$ is the input, i.e. $u(t) := P(t)$, and $x(t) := [P_a(t)\ i(t)\ V(t)]'$, the model (9)-(11) is in the form of (1).

If the inertial component L is neglected, the model becomes the so-called three-element windkessel model [25] that is often used to describe the arterial input impedance. When also r is neglected, the classical windkessel load is obtained (see e.g. [13]).

The theoretical ejection patterns should satisfy certain feasibility conditions in order to be physically realistic. At the beginning of ejection

$$V(t_0) = V_{ed} \tag{12}$$

$$i(t_0) = 0 \tag{13}$$

$$\frac{d}{dt}i(t_0) = 0 \tag{14}$$

where V_{ed} is the end-diastolic volume. At the end of ejection

$$V(t_1) = V_{ed} - V_s \tag{15}$$

$$i(t_1) = 0 \tag{16}$$

$$\frac{d}{dt}i(t_1) = 0. \tag{17}$$

Equations (12) and (15) say that a stroke volume V_s is ejected while the aortic valve is open. The root aortic flow is zero at the beginning and at the end of ejection due to (13) and (16) (opening and closing of the aortic valve). According to (14) and (17) it is required that the first time derivative of $i(t)$ is zero at t_0 and t_1. Since $i(t) \equiv 0$ during diastole, these are natural assumptions. During diastole (9)-(10) give an exponential decay of pressure in the aorta. Thus

$$P(t_0) = kP(t_1) \tag{18}$$

where $k = \exp(-t_d/(RC))$. The duration of diastole t_d is defined to include the duration of isovolumic contraction: $t_d = T - t_e$, where $t_e = t_1 - t_0$ is the duration of ejection (s) and T is the duration of cardiac cycle (s).

The parameter vector is $p = [r\ L\ C\ R\ V_{ed}\ V_s\ t_0\ t_1\ T]'$. Assume that a nominal solution [$P(t)$ and $i(t)$] for a certain p is known. For example, the value of peripheral resistance R can be different in different physiological conditions. In order to predict the effect of a change in R on $i(t)$, it is not enough to change R in the system equations (9)-(11), since the left ventricle reacts to a change in arterial load such that also the input pressure $P(t)$ changes. In fact, also V_s, t_e, and t_d change when R is changed in an isolated heart preparation while V_{ed} and T are kept constant. The predicted new $P(t)$ should be admissible, i.e. (9)-(18) should be satisfied. On the other hand, the new $P(t)$ and $i(t)$ should resemble the experimentally observed root aortic pressure and flow curves.

1.5 The Time-Varying Elastance Model

The time-varying elastance model [19, 22] or some modification of it (see e.g. [3, 17]) has been used to describe the operation of the left ventricle. The model is based on the assumption that the ventricular elastance curve $e(t)$ is independent of ventricular loading conditions when contractility and heart rate remain constant. Ventricular pressure $P_v(t)$ is given by

$$P_v(t) = e(t)[V(t) - V_d] \tag{19}$$

where $V(t)$ is the ventricular volume and V_d is an experimentally estimated correction volume (originally assumed to be a constant, but in some models V_d is a function of time, see [3]). Model (19) can be combined with arterial load models of the form (1)-(2) (e.g. (9)-(11)) for predicting the effects of changes in load on $P(t)$, $i(t)$, V_s, and t_e (often it is assumed that $P_v(t) = P(t)$).

In practice some class of functions must be selected to describe $e(t)$. Third order polynomials can be used [3]

$$e(t) = a_0 + a_1 t + a_2 t^2 + a_3 t^3. \tag{20}$$

The free parameters $a_0, ..., a_3$ do not have a physical interpretation and they can only be estimated by model fitting. Although the elastance model or its variations have been reported to describe the behavior of an isolated heart quite accurately [17, 21, 22], the model does not seem to be as good in predicting the effects of changes in load on the behavior of an in situ heart [3].

1.6 An Optimization Approach for Modeling Left Ventricular Function

The papers summarized in the sequel deal with the use of optimization models in predicting the left ventricular function. In [V] it is shown that given model (9)-(11) and boundary conditions (12)-(18), $P(t)$ and $\dot{\imath}(t)$ can indeed be predicted by using optimality principles. The cost function suggested is of the form

$$J(\bar{u}) = h(\bar{x}(t_1), p) + \int_{t_0}^{t_1} g(\bar{x}(t), \bar{u}(t), p)dt \tag{21}$$

where h and g are given real-valued functions. Mathematically the model is an optimal control problem (see e.g. [1]). Note that V_s and t_e are fixed in (12)-(18). However, also V_s and t_e are predicted by the hierarchical model developed in [V]. The system state and the input have been redefined in (21) and the new boundary conditions are of the form

$$\bar{r}(\bar{x}(t_0), \bar{x}(t_1), p) = 0. \tag{22}$$

The cost function developed in [V] is based on minimizing an index of ventricular oxygen consumption per beat and on avoiding high values of total axial force on the direction of blood flow through the aortic valve. Also the efficiency of ventricular response to an increase in V_{ed} is taken into account.

Since the cost function is based on several optimality criteria we are dealing with a multiple-criteria optimization problem. One method to take into account multiple criteria is to use weighting parameters by which different terms in the cost function are multiplied (see e.g. [26]). The weighting parameters used in [I], [III], and [V] cannot be given exact physical interpretations and they can only be estimated by model fitting. Thus, in order to see how accurately the model describes the operation principles of the ventricle, the model predictions must be compared with independent measurement data that have not been used in the estimation of the weighting parameters.

2. SUMMARY OF THE THESIS

In [I] the problem of predicting $P(t)$ and $i(t)$ for given stroke volume (V_s), heart rate (HR), ejection time (t_e), and arterial load is analyzed. Arterial load is described by a model consisting of a small resistance in series with the classical windkessel load. The cost function describes the external work done by the left ventricle and it also includes an additional term that penalizes rapid changes in aortic flow.

The choice of the boundary conditions for an optimal control model has not received sufficient attention in the literature. The number of boundary conditions needed depends on the structures of the system model and the cost function used. Although the boundary conditions are due to physical constraints, it may be possible to describe these constraints by several alternative boundary conditions for some state variable. However, the same optimality criterion can yield entirely different solutions with different sets of boundary conditions although the conditions do not differ much from each other [I].

The choice of the boundary conditions related to the initial and final values of $P(t)$ is studied in detail [I]. It is shown that the solution of the model analyzed is very sensitive to the choice of these conditions. A model formulation is presented that predicts an aortic flow pattern with an initial peak that is in qualitative accordance with experimental observations. However, the model (model 6 in [I]) fails to predict correctly the effects of changes in arterial compliance on the aortic pressure and flow curves (Fig. 8 in [I]).

The results of [II] suggest that the minimization of external work should be an essential component of the optimality criterion used to explain the ejection pattern. A detailed analysis of the validity of the minimum external work criterion is presented by studying theoretical ejection patterns generated by a model. The ejection patterns are required to satisfy certain feasibility and normalization conditions. Arterial load is described by the three-element windkessel model. Also HR, t_e, V_s, and mean ejection pressure $\bar{P}_e$ are given when the patterns of ejection flow and pressure are changed. The comparison of the patterns with respect to the external work shows that a pattern with the maximum flow in the first half of ejection is optimal among the patterns studied.

Many of the previous models (for references, see [II]) are based on the minimum work criterion. It is shown that the main defects in the earlier analyses have been in the formulations of the boundary conditions for $P(t)$ and $i(t)$. Since the structures of the previous models are unsatisfactory, the relevance of the minimum work criterion has remained unknown.

In [III] $\bar{P}_e$ is not fixed, but V_s, HR, and t_e are given and arterial load is described by the three-element windkessel model. The optimality criterion is based on minimizing the so-called PVA index that correlates with the total ventricular oxygen consumption per beat [20]. The minimization of external work is one component of the optimality criterion. However, also a term penalizing high values of the total axial force on the direction of blood flow through the aortic valve is included in the cost function. The above two criteria are taken into account by two weighting parameters (α and β). For proper values of α and β, the ejection patterns given by the model are shown to accurately match experimental recordings of two human ejection patterns. $P(t)$ and $i(t)$ curves predicted by the model also qualitatively resemble experimental observations when the values of the arterial load model parameters are changed (while α and β are kept constant).

An optimization model for predicting V_s is developed in [IV]. End-diastolic volume (V_{ed}) and the linear end-systolic pressure-volume relation [12, 16] are given. HR and t_e are fixed and arterial load is described by the three-element windkessel model. The cost function of the model is based on minimizing PVA and on maximizing the efficiency of ventricular response to an increase in V_{ed}. The optimal V_s is very close to the experimentally observed stroke volume of an isolated heart in spite of substantial changes in arterial load.

Also previous models for an optimal arterial load are analyzed (for references, see [IV]). The difference between the optimization models for ventricular function and the optimization models for arterial load is made clear. The recent idea of matching between the ventricle and load has caused difficulties for the interpretation of the earlier models. It is shown that the previous experimental results of other authors suggest that the control of peripheral resistance in a living animal can possibly be described by an optimization model.

In [V] an inertial component is added to the arterial load model used in [III] and [IV] in order to better describe the arterial input impedance (i.e. model (9)-(11) is used). The models for an optimal stroke volume and an optimal ejection pattern are then combined. Also a model for predicting changes in ejection time is developed and included in the arising hierarchical optimization model. The predictions of the new hierarchical model are shown to match experimental data from an isolated heart preparation quite accurately. In the experiments, arterial load has been simulated by a servo-controlled loading system and contractility and V_{ed} have been kept constant (see [23] for a detailed description of the experimental setup). The results show that at least at a qualitative level the model indeed explains the response of the ventricle to a change in arterial load.

3. CONCLUSION

A hierarchical optimization model for predicting left ventricular stroke volume, time courses of root aortic flow and pressure, and ejection time has been developed. The model predictions for changes in arterial load have been shown to be in accordance with experimental data from an isolated canine heart preparation.

The minimization of energy expenditures is the basis of all the the optimality criteria suggested. However, also forces developed during ejection and ventricular efficiency are taken into account in the cost functions of the model. It should be noted that an exact correspondence between the cost functions and ventricular O_2 cost or efficiency has not been demonstrated. Still the results strongly suggest that energetically economical and efficient performance is an essential feature of left ventricular function.

In spite of difficulties in a strict interpretation of the optimality criteria, the analysis shows that the operation of the left ventricle can be predicted by optimality principles. The models developed can also be viewed as mappings from the set of parameters describing arterial load into the set of admissible root aortic pressure curves. Thus we can conclude that it is possible to describe the effects of changes in arterial load on ventricular function by an optimization model.

Most of the experimental data analyzed are from isolated heart preparations. Still the predictions of the model developed also qualitatively resemble measurements in living animals and patients. However, recent studies suggest that some of the experimental relations of the model should possibly be modified in order to better describe the behavior of an in situ heart (see [V]).

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Orders:

Helsinki University of Technology
Systems Analysis Laboratory
Otakaari 1 M, Espoo, Finland
Tel. (358-0) 451 2318
Telefax (358-0) 465077