An Integrated Model of Cardiovascular Function and Control in Normal and Diseased States - Applications in Cardiac Electrotherapy

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Abstract

To achieve highest hemodynamic benefit with rate-responsive cardiac pacing, the patient's individual pathophysiology concerning cardiovascular control as well as hemodynamics must be estimated in terms of control theory to design and adjust rate adaptation algorithms adequately. For this purpose, computer simulations are a powerful tool to investigate new sensors and develop effective algorithms prior to clinical evaluation, which is of special importance to closed-loop systems. The methodology of model development as a prerequisite for the consecutive pacemaker design will be discussed.

Introduction

One of the major development issues of cardiac pacemaker technology in the recent decade was, besides continuing reduction of weight and size as well as numerous technical improvements, to provide physiological adaptation of pacing frequency where an appropriate sinus rhythm is no longer present. The important therapeutic benefit of this enhanced functionality results from the fact that an appropriate pacing frequency is decisive for sufficient blood flow through all organs and tissues of the body at different exercise levels and other challenges of every-day life. As will be shown below, remarkable changes occur in circulatory hemodynamics even at moderate exercise levels that will soon lead to insufficient supply of oxygen and other nutrients and, therefore, reduce the patient’s physical performance when no rate adaptation is present. Rate-responsive pacing will contribute, therefore, significantly to the patient’s well-being and quality of life.
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The major difficulty of this approach is to detect the current metabolic demand of the body reliably and precisely enough. Moreover, the employed physical sensor principle must be long-term stable, easy to handle and should not bring about disadvantages to the whole pacing system, e.g. regarding additional power consumption, additional efforts for initial programming and pacemaker follow-up etc. that can not be justified by the therapeutic benefit.

A whole number of very different sensor principles for rate-adaptive pacing have been developed and employed so far, meeting the above requirements to very different degrees. These include acceleration sensors, thermistors for measurement of central venous blood temperature, the measurement of the QT interval, pressure sensors and blood oxygen sensors in the pacemaker electrode (experimental), different kinds of impedance measurements for quantification of respiration and intracardiac unipolar impedance measurement to quantify heart dynamics (i.e. contractility). Further sensors are currently investigated; e.g., the measurement of heart potentials with fractally-coated pacing electrodes, such as ventricular evoked response or monophasic action potential, shows promising results since no additional sensor is required (which is also true for unipolar intracardiac impedance measurement). An overview of all major principles can be found in the literature (e.g. Schaldach\(^1\), Lau\(^2\), Urbaszek\(^3\)).

From the control theory point of view, the different sensor principles can be classified into two groups: open-loop and closed-loop systems, depending on whether the „output“ of the adaptive system (pacing rate) has a feedback effect on the sensor signal or not. E.g. the acceleration sensor is clearly an open-loop system, while, e.g., unipolar intracardiac impedance measurement provides closed-loop control which will be discussed in more detail below. As it is known from control theory, closed-loop control is superior due to the fact that the hemodynamic result of the rate response may be observed with the sensor signal, which is not possible in open-loop systems.

On the other hand, the design of a closed-loop system requires a detailed mathematical description of the controlled system, which is the human cardiovascular system in the case of cardiac pacemaker design. The following paper will outline the methodology of this system design process and discuss more deeply the modelling of the relevant physiological systems involved in cardiovascular hemodynamics regulation.

**General considerations**

The design goal of closed-loop pacing rate adaptation or, more general, of every closed-loop adaptive implant is depicted in Figure 1: The control algorithm of the implant has to be designed in a way that the implant sends some output signal (e.g. pacing frequency) to maintain the controlled system (e.g. the circulation) in some optimum state. The output signal is continuously adapted...
in the controller unit as a function of one or several input signals, which are measured and processed in a measurement unit.

Figure 1: General design approach of closed-loop adaptive implants.

In order to define the functional design of the rate-adaptive pacemaker, the following tasks must be solved:

- provide a mathematical description of the physiological system to be controlled (i.e. heart and circulation),
- find a measurement principle which allows to monitor relevant system variables to get the required information about, e.g., the metabolic demand and design a signal measurement and processing unit,
- design the controlling element (normally an algorithm which is performed on dedicated hardware in the implant) to achieve some optimum behaviour of the controlled system.

The following section focuses on the first step, i.e. the definition of a mathematical model of the human cardiovascular system.

**Model definition**

As shown in Figure 2, model definition of complex systems encompasses several stages: Based on functional relationships of the involved physiological mechanisms and quantitative experimental data, a mathematical description is set up which in most cases allows to perform numerical simulations, but is too complex for being directly employed for controller design. Therefore, it has to be simplified and linearized to come to a description having the required structure to apply one of the standard controller design methods. Once the con-
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trol algorithm is designed, each of the two model stages can serve as a „virtual patient“ to verify the controller behaviour in tests and simulation runs, which may result in modifications of the model, the controller or both.

Figure 2: From model definition to system design.

**Detailed heart and circulation model**

A detailed descriptive, quantitative model of the human cardiovascular system has been developed and published earlier (Urbaszek⁴). It was hierarchically structured to involve circulatory hemodynamics, myocardial contraction and even excitation-contraction coupling at the cellular level. Moreover, the important short-term control mechanisms, such as the baroreceptors or the autonomic nervous system were also included. This detailed approach was necessary to consider all relevant physiological subsystems not only for the hemodynamic adaptations during exercise and other challenges, but also the mechanisms having an influence on the measured sensor signal, i.e., unipolar intracardiac impedance.

Simulations allowed to study the response of various hemodynamic parameters, such as systolic and diastolic arterial blood pressure, cardiac output or stroke volume to different pacing frequencies for different loads and pathophysiological conditions. The results correlated very well with clinical data and gained important insight into physiological relationships, e.g. the changes of
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cardiac mechanics upon neurohumoral stimulation, which were modelled in detail. On the other hand, this model could not directly be used for controller design due to its complexity. Therefore, a new model had to be created which should be based on the detailed one containing only the most important relationships in a very simple and transparent form. Before this model will be discussed in the next section, the pacemaker principle which it is made for will be summarized briefly.

Rate-responsive pacing based on unipolar intracardiac impedance

Cardiac output (CO), which is the amount of blood pumped through the body every minute, may vary from 5 l/min under resting conditions up to 25 l/min for heavy physical exercise. This is achieved most of all by a remarkable increase in heart rate, which can be increased from about 70 beats per minute (bpm) at rest up to a maximum value which is estimated to 220 - age/years (bpm). Compared to this, stroke volume may increase only moderately by about 50%.

In chronotropic incompetent patients, e.g. due to sick sinus syndrome or other diseases, heart rate (chronotropic) adaptation is no longer present, leading to insufficient blood supply even for moderate exercise, since stroke volume adaptation, which results from enhanced myocardial contractility or heart dynamics (inotropic adaptation) has only limited effects. This leads to a drop in mean arterial blood pressure (MABP) due to the lowered peripheral resistance (TPR), meaning that a sufficient perfusion pressure may not be maintained.

Figure 3: Principle of the ANS-controlled pacemaker (see text for abbreviations).
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quiring no additional sensor element. As has been shown in previous studies (Schaldach⁵,⁶), intracardiac impedance maps geometry changes of ventricular myocardium in the near vicinity of the electrode tip in the right ventricular apex. The signal morphology is determined by heart dynamics, allowing to extract a parameter correlating to the inotropic state with a suitable algorithm. This principle provides a very physiological rate response, since the same neurohumoral control signals that normally adjust the sinus rate are utilized to adapt the pacing rate, which was demonstrated in numerous clinical trials (e.g. Witte⁷).

The required mathematical model of the cardiovascular system must therefore emphasize - besides all relevant parameters of circulatory hemodynamics - the contraction and relaxation dynamics of the heart itself, i.e. the influence of heart rate and contractility on cardiac output and venous return.

Design of a simplified heart and circulation model

The simplified model was constructed based on the results and experience obtained with the detailed model. The most important simplification is that the pulsatile nature of blood flow will be no longer considered, since it is sufficient to track the course of the mean or effective values of pressures, volumes and flows. Furthermore, it is practical to consider the sub-units ‘peripheral circulation’ and ‘heart and pulmonary system’ separately and to employ different relationships due to the different roles they play in cardiovascular adaptation.

Peripheral circulation

This part of the model must comprise at least the following quantities and relationships:

- mean arterial blood pressure (MABP), which is often considered as the main controlled quantity in cardiovascular control,
- mean central venous pressure, which is responsible for right atrial filling,
- the variation of total peripheral resistance (TPR) due to muscular exercise on one hand and vasoconstrictory effects of neurohumoral control on the other,
- the variation of central venous compliance due to neurohumorally mediated vasoconstriction, which increases right atrial filling,
- the pooling of blood in lower parts of the body during orthostasis, i.e. the change from supine to upright position, with its hemodynamic consequences.

These requirements are met by a 4-chamber compartmental representation according to Figure 4 (lower part).

Each compartment is considered to have a compliance C, while the flow between two compartments is considered to go through a (purely) resistive vessel with flow resistance R.
For every compartment, volume V, flow Φ and pressure p are calculated according to the following set of formulas:

\[ p = \frac{V - V_0}{C} \quad \text{if} \quad V > V_0 \]

\[ \Phi = \frac{\Delta p}{R} \]

\[ \frac{dV}{dt} = \Phi_{\text{in}} - \Phi_{\text{out}} \]

In this notation, \( \Delta p \) means the pressure gradient \( p_1 - p_2 \) between two compartments, while between the upper and lower compartments of the arterial as well as venous side an additional hydrostatic pressure gradient \( p_h \) must be added:

\[ \Delta p = p_1 - p_2 + p_h \]

\( p_h \) has opposite signs for the arterial and the venous side.

In this set of equations, the resistance between the arterial and the venous branch is considered as TPR and is subject to workload influences and neurohumoral control, while the latter is also true for the compliance values of both venous compartments.
Heart and pulmonary system

The following quantities and effects are essential for cardiac adaptation:

- **Venous return**, which is the amount of blood that returns to the heart every minute, i.e., the flow from the upper venous compartment into the right atrium,
- The dependency of mean diastolic right atrial pressure (and, therefore, venous return) on heart rate and contractility (or lusitropy, which means that not only contraction but also relaxation is accelerated under inotropic adaptation),
- The buffer function of the pulmonary system (Guyton\(^6\)), that allows transient differences between venous return and cardiac output,
- **Cardiac output**, which is the flow from the left ventricle into the aorta (corresponding to the upper arterial compartment),
- The dependency of cardiac output on heart rate and contractility, preload (filling from the pulmonary vein) and afterload (aortic pressure against which the left ventricle has to eject blood).

The model structure as can be seen in the upper part of Figure 4 was chosen to reflect all relevant relationships: It consists of a right atrial compartment similar to the circulatory compartments, which is subject to additional influences such as heart rate and lusitropy (the ‘counterpart’ of contractility, describing a faster and more pronounced relaxation). Contractility and lusitropy are assumed to change simultaneously and to the same degree since they result from the same cellular effects, as could be also shown in the detailed model (Urbaszek\(^4\)).

The atrial compartment is followed by a pump representing the right ventricle and a second compartment representing the pulmonary vessels; a distinction between pulmonary arteries and veins is not necessary. Finally, a second pump follows which represents the left ventricle. The dependency of cardiac output on the above-mentioned factors was derived from detailed functional investigations with a roller pump model as well as with an isolated cat heart published in Westerhof\(^9\). The results have been further simplified by linearizing the obtained functional graphs resulting in the following relationship:

\[
CO = \frac{p_{pv}}{HR} \cdot K_{HR} \cdot \frac{1}{psa} \cdot K_{CY}
\]

where

- \(p_{pv}\) is the pressure in the ‘pulmonary vessel’ compartment,
- \(psa\) is the pressure in the systemic artery compartment (corresponding to MABP),
- \(CO\) is the contractility,
- \(K_{HR}\) and \(K_{CY}\) are constants.

The second pump representing the right ventricle is described in a similar way.
Results

With this simplified model, all relevant short-term cardiovascular adaptation mechanisms are described in a transparent and effective way. Figure 5 shows the simulation results for an orthostatic challenge and heavy exercise, which make the hemodynamic adaptations visible: E.g. after an abrupt change from supine to upright position, blood begins to pool in the lower parts of the body due to the additional hydrostatic gradient (cf. the decrease in the upper systemic vein volume in the lower left graph). Due to the resulting decrease of arterial pressure, cardiac output increases slightly for the first moment. But since venous return immediately decreases, cardiac output also diminishes, until both values equal again (which must be the case over any prolonged period of time).

The drop in mean arterial blood pressure is detected by the baroreceptors and leads to a neurohumoral response, which leads to increased heart rate and total peripheral resistance due to sympathetic vasoconstriction.

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**Orthostasis**

- Heart rate
- Cardiac output
- Venous return
- Total peripheral resistance
- Upper systemic vein volume

**Exercise**

- Heart rate
- Cardiac output
- Venous return
- Total peripheral resistance
- Upper systemic vein pressure

Figure 5: Simulation results.
Conclusions

A method to describe the human cardiovascular system mathematically has been demonstrated, which is necessary for the optimal design of a closed-loop rate-responsive pacemaker. The proposed level of description is simple enough to employ controller design methods known from control theory while explaining all relevant phenomena sufficiently at the same time. Furthermore, new designs of pacemaker algorithms can be tested extensively prior to clinical investigation, which reduces the number of necessary clinical tests and, therefore, development time and costs. More importantly, the risk for the patient is minimized since only extensively tested designs will be implanted.

References