Medical Engineering and Physics 38 (2016) 433–441

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

Structural identifiability analysis of a cardiovascular system model

Antoine Pironet[a,*], Pierre C. Dauby[a], J. Geoffrey Chase[b], Paul D. Docherty[b], James A. Revie[b], Thomas Desaive[a]

[a] University of Liège (ULg), GIGA-In Silico Medicine, Liège, Belgium
[b] University of Canterbury, Department of Mechanical Engineering, Christchurch, New Zealand

ARTICLE INFO

Article history:
Received 25 September 2014
Revised 22 December 2015
Accepted 7 February 2016

Keywords:
Identifiability
Parameter identification
Lumped-parameter model
Physiological model

ABSTRACT

The six-chamber cardiovascular system model of Burkhoff and Tyberg has been used in several theoretical and experimental studies. However, this cardiovascular system model (and others derived from it) are not identifiable from any output set.

In this work, two such cases of structural non-identifiability are first presented. These cases occur when the model output set only contains a single type of information (pressure or volume).

A specific output set is thus chosen, mixing pressure and volume information and containing only a limited number of clinically available measurements. Then, by manipulating the model equations involving these outputs, it is demonstrated that the six-chamber cardiovascular system model is structurally globally identifiable.

A further simplification is made, assuming known cardiac valve resistances. Because of the poor practical identifiability of these four parameters, this assumption is usual. Under this hypothesis, the six-chamber cardiovascular system model is structurally identifiable from an even smaller dataset.

As a consequence, parameter values computed from limited but well-chosen datasets are theoretically unique. This means that the parameter identification procedure can safely be performed on the model from such a well-chosen dataset. Thus, the model may be considered suitable for use in diagnosis.

1. Introduction

1.1. Background

Accurately determining cardiac parameters in the intensive care unit is difficult since only indirect data of the patient's cardiovascular state is available and this state is also rapidly changing. Mathematical models of the cardiovascular system (CVS) have been developed to provide clinicians with additional information regarding the overall picture of the cardiac and circulatory state. To be clinically relevant, these models have to be patient-specific, which means that their parameters have to be identified so that simulations represent a patient's individual state. This task is not obvious due to the indirect nature of the necessary clinical data.

The CVS can be modelled using very different approaches, including finite element models [1], pulse-wave propagation models [2], and lumped-parameter models [3]. The present study focuses on one such lumped-parameter model. Lumped-parameter models represent whole sections of the CVS as single elements (chambers or resistances, for example). An important advantage of these models is that they have few parameters, and thus, these parameters can be more readily identified from clinical data. The main drawback of lumped-parameter models is that they cannot be used to gain local spatial information on the CVS.

The CVS model used in this work has been developed by Burkhoff and Tyberg [3]. It is a simple lumped-parameter model that describes the whole CVS using six state equations and thirteen parameters (*cf.* Fig. 1). This model is the simplest model to consider systemic and pulmonary circulations. This model has allowed theoretical studies assessing the consequences of left ventricular dysfunction [3] and ventricular interaction [4].

From an experimental point of view, a similar model has been used for hemodynamic monitoring during septic shock [5] and pulmonary embolism [6,7]. The model parameters, such as systemic and pulmonary vascular resistances, ventricular end-systolic elastances and pulmonary arterial elastance, are needed by clinicians to assess the severity of a condition. The model has also recently been used to compute total stressed blood volume [8], an index of fluid responsiveness [9]. Furthermore, many other models, more complex, can be seen as extensions of this simple model [4,10–13]. One of these more complex models has been used to investigate

Abbreviations: CVS, cardiovascular system.

* Corresponding author. Tel.: +32 4 366 33 56.
E-mail address: a.pironet@ulg.ac.be (A. Pironet).

http://dx.doi.org/10.1016/j.medengphy.2016.02.005
1350-4533/

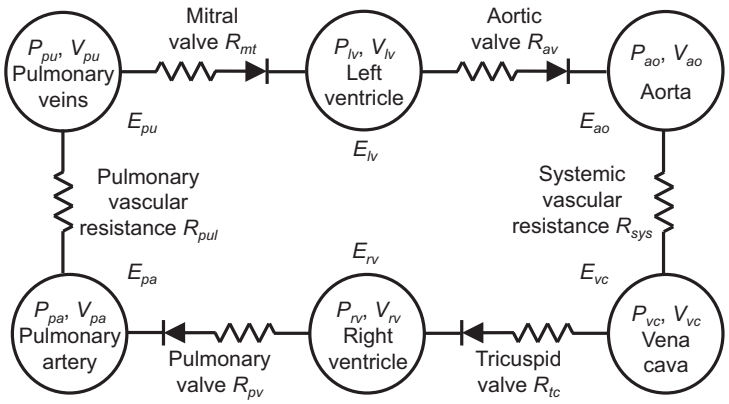

Fig. 1. Schematic representation of the six-chamber CVS model.

the haemodynamic state of patients after mitral valve replacement surgery [14].

However, as will be shown further, there are several measurement sets from which the parameters of this model (and other models derived from it) cannot be uniquely computed. The key question is: *can we find a measurement set which allows to identify all model parameters*? In more theoretical terms, this question can be stated as: *what is the set of model outputs one has to include in the model definition for this model to be structurally globally identifiable*? This notion of structural identifiability is defined in the next subsection.

1.2. Structural identifiability

Structural identifiability analysis of a model determines whether all model parameters can be uniquely retrieved in the perfect conditions of noise-free and continuous measurements of the model outputs. If the answer is yes, then the model is said to be *structurally globally identifiable* [15,16]. Otherwise, if there exists multiple parameter values for the given model outputs, the model is *structurally locally identifiable*. Finally, if there is an infinite number of possible parameter values, the model is termed *structurally non-identifiable*.

Structural identifiability is called *structural* because it only depends on the model equations (its *structure*). Thus, it depends on the roles of the parameters and the nature and number of the available model outputs. For instance, if the number of model outputs is too low, the model is likely to be non-identifiable.

Taking the measurement noise and the practically finite number of data points into account and investigating if the model parameters still can be uniquely determined relates to a different topic, called *practical identifiability* [17]. The tools used to investigate practical identifiability are different and include, for instance, sensitivity analyses and parameter correlation analyses [8]. Structural identifiability is a necessary condition for practical identifiability. It is therefore risky to perform a parameter identification procedure on a model which has not been shown to be structurally identifiable.

1.3. Goal

This work aims to prove the structural identifiability of the CVS model from a clinically available output set. As said above, this structural identifiability analysis is a necessary step to ensure that results obtained when identifying the model parameters from limited clinical data are unique, and thus, relevant.

2. Methods

2.1. Six-chamber cardiovascular system model

The CVS model that is the focus of this work has been previously presented by Burkhoff and Tyberg [3] and is shown in Fig. 1. The model comprises six elastic chambers linked by resistive vessels. These six chambers represent the aorta, the vena cava, the pulmonary artery, the pulmonary veins ($i = ao$, vc, pa and pu) and the two ventricles ($i = lv$ and rv).

The arterial and venous chambers are modelled as passive chambers with a constant linear relationship between pressure P_i and (stressed) volume V_i:

$$P_{ao}(t) = E_{ao} \cdot V_{ao}(t) \tag{1}$$

$$P_{vc}(t) = E_{vc} \cdot V_{vc}(t) \tag{2}$$

$$P_{pa}(t) = E_{pa} \cdot V_{pa}(t) \tag{3}$$

$$P_{pu}(t) = E_{pu} \cdot V_{pu}(t) \tag{4}$$

where the constant parameters E_i are called the elastances of the chambers.

Ventricular chambers are active. Thus, the relationship between pressure and volume is time-varying [18]:

$$P_{lv}(t) = E_{lv} \cdot e_{lv}(t) \cdot V_{lv}(t) \tag{5}$$

$$P_{rv}(t) = E_{rv} \cdot e_{rv}(t) \cdot V_{rv}(t). \tag{6}$$

In Eqs. (5) and (6), the constant parameters E_{lv} and E_{rv} are the end-systolic elastances and the functions $e_{lv}(t)$ and $e_{rv}(t)$ are called the driver functions. These driver functions can take different forms, but for the model to correctly mimic the physiological activity of the normal heart, $e_{lv}(t)$ and $e_{rv}(t)$ have (at least) to be periodic with period T (the cardiac period), range from 0 (diastole) to 1 (end-systole) and rise and fall at approximately the same time. Equally, it has been shown that while this approach still holds in disease, there are subtle changes to driver functions based on disease sate [19]. Also note that, for simplicity, no end-diastolic pressure-volume relationships were inserted in Eqs. (5) and (6).

The six chambers are linked by resistive vessels, representing the four heart valves (mitral: *mt*, aortic: *av*, tricuspid: *tc* and pulmonary: *pv*) and the systemic and pulmonary circulations (*sys* and *pul*). In these last two vessels, flow Q is given by Ohm's law:

$$Q_{sys}(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_{sys}} \tag{7}$$