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Structural Identifiability Analysis of a Cardiovascular System Model ⋆

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Abstract: A simple experimentally validated cardiovascular system model has been shown to be able to track the evolution of various diseases. The model has previously been made patient-specific by adjustment of its parameters on the basis of a minimal set of hemodynamic measurements. However, this model has not yet been shown to be structurally identifiable, which means that the adjusted model parameters may not be unique. The model equations were manipulated to show that, from a theoretical point of view, all of their parameters can be exactly retrieved from a restricted set of model outputs. However, this set of model outputs is still too large for a clinical application, because it includes left and right ventricular pressures. Consequently, further hypotheses that determine some model parameter values have to be made for the model to be clinically applicable.

1. INTRODUCTION

1.1 Background

Mathematical models of the cardiovascular system (CVS) can be used with clinical data to help monitor a patient's cardiac and circulatory state. To be clinically relevant, these models have to be made *patient-specific*, which means that their parameters have to be adjusted so that model simulations can represent a patient's individual state. The main issue is that the data necessary to adjust the model parameters can be scarce.

There exists two main approaches to model the CVS. The first approach deals with complex three-dimensional finite element models, involving millions degrees of freedom (Hunter et al. [2003]). These models can be used to gain understanding on local parts of the CVS. However, they contain many uncertainties and, consequently, identified parameters of such models are highly inter-dependent and lack uniqueness and robustness. Thus, this study focuses on the second modelling approach, namely lumped-parameter models. These models represent whole sections of the CVS as single elements (chambers or resistances, for example), hence the name *lumped*. They have significantly less parameters than finite element models, and thus, these parameters can be more readily computed from the available experimental data.

Strictly speaking, a mathematical model comprises two main elements:

- a set of ordinary differential equations describing the system behavior, called *state equations*,
- a set of *outputs*, which are algebraic expressions of the *states* (variables involved in the state equations).

The key question is: *what is the measurements set needed 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 from noise-free and continuous measurements of all model outputs. If the answer is yes, then the model is said to be *structurally globally identifiable* (Ljung [1987]). 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 unidentifiable*.

Structural identifiability is called *structural* because it only depends on the model equations (its *structure*). As a consequence, structural identifiability strongly depends on the number of model outputs, which is part of the model structure. If the number of model outputs is too low, the model is likely to be unidentifiable. The goal of this work is to determine an output set which is small enough, but sufficient for the model to be identifiable.

Taking the measurement noise and the limited number of data into account and investigating if the model parameters still can be unequivocally determined relates to a different topic, called *practical identifiability* (Pohjanpalo [1978], Docherty et al. [2011]). Obviously, structural iden-

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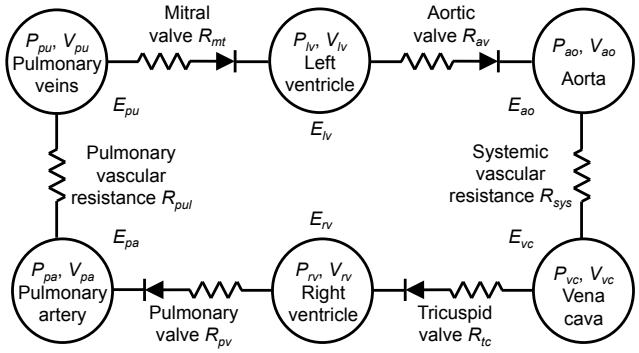

Fig. 1. Schematic representation of the six-chamber CVS model.

tifiability is a necessary condition for practical identifiability.

1.3 Methods to Test for Structural Identifiability

Since the problem of structural identifiability has been posed, various methods to test models for this property have been proposed (Walter and Pronzato [1997]). For linear time-invariant models, general conditions on the model structure exist. However, for non-linear and time-varying models, which includes realistic models of the CVS, no general method has been proposed yet, because there exist many different types of non-linearities.

Consequently, the method to test identifiability of a non-linear and time-varying model depends on the model itself. As noted, there are numerous CVS models, each with different goals and uses. In the next subsection, we briefly introduce the CVS model of interest and what is the current knowledge on its identifiability. From here on, the word "model" will be used to refer to the state equations only, which is a usual language abuse. The outputs will thus be separately referred to.

1.4 Six-Chamber CVS Model

The CVS model used in this work is a simple lumped-parameter model that describes the whole CVS using only six chambers and six state equations (*cf.* Figure 1). The model itself has been used in several animal studies to track the evolution of different conditions, such as pulmonary embolism (Revie et al. [2011]) and sepsis (Revie et al. [2013]). However, no formal identifiability analysis has been made to put these results in context.

To our knowledge, the only proof of structural identifiability of this CVS model has been made by Hann et al. [2006]. These authors developed a specific parameter identification method for this model. This method consists in integrating the differential equations defining the model, which results in a system of algebraic equations. As a result, this particular parameter identification problem is made linear and convex, which also proves that the model is structurally globally identifiable.

The main drawback of this proof is that it requires a large output set, including simultaneous measurements of flow at six different points of the CVS (through the four heart valves and through the systemic and pulmonary

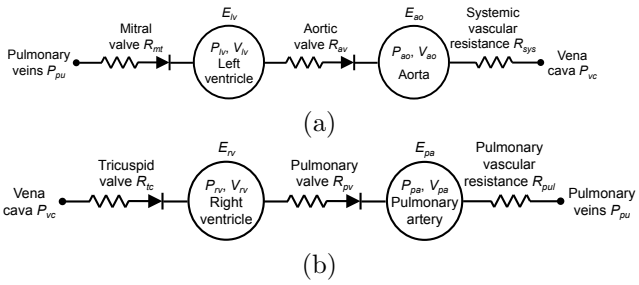

Fig. 2. Two-chamber CVS models.

circulations). This requirement is unrealistic for two reasons. First, it is currently impossible to simultaneously record flow through all heart valves. Second, "systemic and pulmonary circulations" do not correspond to actual physical locations in the body, thus making it impossible to measure flow at these places. Finally, Hann et al. [2006] did not investigate the identifiability of the total stressed blood volume. This is an important parameter, as it represents the total pressure-generating blood volume that is introduced in the model.

Since then, to our knowledge, no further study has investigated the identifiability of this CVS model despite its wider usage. In a previous work, Pironet et al. [2012] demonstrated the structurally global identifiability of simple two-chamber CVS models (*cf.* Figure 2) derived from the six-chamber CVS model. Identifiability was demonstrated from a smaller output set than the one used by Hann et al. [2006]. In this work, this procedure is extended to the full six-chamber CVS model to show that the model is structurally globally identifiable from a limited output set.

In the following sections, the six-chamber CVS model is first described including the equations it contains in detail. Its identifiability is then analyzed. The implications of model identifiability on the practical parameter identification procedure are then discussed.

2. CVS MODEL STATE EQUATIONS

The CVS model that is the focus of this work has been previously presented by Smith et al. [2004] and is shown in Figure 1. As mentioned before, it has been validated in several animal experiments (Revie et al. [2011, 2013]). In this work, ventricular interaction is not considered. The model then becomes similar to the one presented by Burkhoff and Tyberg [1993].

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, pu) and the two ventricles ($i = lv$ and rv). The arterial and venous chambers are passive, which means that there is a constant linear relationship between pressure P_i and (stressed) volume V_i:

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

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

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

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

In the previous equations, the parameters E_i are called the elastances of the chambers. Ventricular chambers are active. Thus, the relationship between pressure and volume is time-varying:

$$P_{lv}(t) = E_{lv} \cdot e_{lv}(t) \cdot V_{lv}(t) \tag{5}$$
$$P_{rv}(t) = E_{rv} \cdot e_{rv}(t) \cdot V_{rv}(t). \tag{6}$$

In Equations (5) and (6), the 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 represent the function of the CVS, they have (at least) to be periodic and range from 0 (diastole) to 1 (end-systole). In these equations, for simplicity, we assumed end-diastolic pressure-volume relationships to be zero.

As mentioned before, the six chambers are linked by resistive vessels, representing the four heart valves ($j = mt$, av, tc and pv) and the systemic and pulmonary circulations ($j = sys$ and pul). In these last two vessels, flow Q_j is given by Poiseuille's equation:

$$Q_{sys}(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_{sys}} \tag{7}$$
$$Q_{pul}(t) = \frac{P_{pa}(t) - P_{pu}(t)}{R_{pul}}, \tag{8}$$

where R_j denotes the resistance of the vessel. In the case of the valves, there is flow only if the pressure gradient through the valve is positive. Hence, one has:

$$Q_{mt}(t) = \frac{\mathrm{r}\left[P_{pu}(t) - P_{lv}(t)\right]}{R_{mt}} \tag{9}$$
$$Q_{av}(t) = \frac{\mathrm{r}\left[P_{lv}(t) - P_{ao}(t)\right]}{R_{av}} \tag{10}$$
$$Q_{tc}(t) = \frac{\mathrm{r}\left[P_{vc}(t) - P_{rv}(t)\right]}{R_{tc}} \tag{11}$$
$$Q_{pv}(t) = \frac{\mathrm{r}\left[P_{rv}(t) - P_{pa}(t)\right]}{R_{pv}} \tag{12}$$

where $r(\cdot)$ denotes the ramp function, defined by:

$$\mathrm{r}(x) = \begin{cases} x \text{ if } x > 0 \\ 0 \text{ otherwise.} \end{cases} \tag{13}$$

Finally, volume change in any of the model chambers is given by the difference between flow going in and coming out of the chamber:

$$\dot{V}_{lv}(t) = Q_{mt}(t) - Q_{av}(t) \tag{14}$$
$$\dot{V}_{ao}(t) = Q_{av}(t) - Q_{sys}(t) \tag{15}$$
$$\dot{V}_{vc}(t) = Q_{sys}(t) - Q_{tc}(t) \tag{16}$$
$$\dot{V}_{rv}(t) = Q_{tc}(t) - Q_{pv}(t) \tag{17}$$
$$\dot{V}_{pa}(t) = Q_{pv}(t) - Q_{pul}(t) \tag{18}$$
$$\dot{V}_{pv}(t) = Q_{pul}(t) - Q_{mt}(t). \tag{19}$$

Since the model is a closed loop, total (stressed) blood volume SBV is constant. This point can also be seen by summing Equations (14) to (19). This assumption that total stressed blood volume is a constant is true for short time periods. In reality, total stressed blood volume can change due to the influence of the nervous system (Guyton and Hall [2006]). As mentioned before, the value of SBV is an important model parameter.

The model parameter set $\mathbf{p}$ counts a total of 13 elements:

$$\mathbf{p} = \{E_{ao}, E_{vc}, E_{pa}, E_{pu}, E_{lv}, E_{rv}, R_{sys}, R_{pul}, R_{mt}, R_{av}, R_{tc}, R_{pv}, SBV\}. \tag{20}$$

In the following section, all the previously listed model equations are manipulated to determine whether this six-chamber CVS model is structurally globally identifiable, *i.e.* if all 13 model parameters can be computed from a limited output set.

3. STRUCTURAL IDENTIFIABILITY ANALYSIS

To perform the structural identifiability analysis of a model, it is usually assumed that the outputs can be perfectly and continuously measured (Pohjanpalo [1978]). Consequently, they can be differentiated as much as necessary. The same hypothesis will hold here. For the rest of this text, the outputs are chosen to be:

- pressure in the left ventricle $P_{lv}(t)$,
- pressure in the right ventricle $P_{rv}(t)$,
- pressure in the aorta $P_{ao}(t)$,
- pressure in the pulmonary artery $P_{pa}(t)$ and
- stroke volume SV.

Furthermore, it will also be assumed that the left and right driver functions $e_{lv}(t)$ and $e_{rv}(t)$ are known. The practical validity of these assumptions is discussed in section 4.1.

3.1 During Cardiac Ejection

When the aortic valve opens (t_{AVO}), aortic pressure equals left ventricular pressure:

$$P_{ao}(t_{AVO}) = P_{lv}(t_{AVO}) \tag{21}$$

Using Equation (5) gives:

$$\begin{aligned} P_{ao}(t_{AVO}) &= E_{lv} \cdot e_{lv}(t_{AVO}) \cdot V_{lv}(t_{AVO}) \\ \Leftrightarrow V_{lv}(t_{AVO}) &= \frac{P_{ao}(t_{AVO})}{E_{lv} \cdot e_{lv}(t_{AVO})} \end{aligned} \tag{22}$$

This last quantity is the end-diastolic volume. Similarly, at the time of aortic valve closing (t_{AVC}), aortic pressure once again equals left ventricular pressure:

$$\begin{aligned} P_{ao}(t_{AVC}) &= P_{lv}(t_{AVC}) \\ &= E_{lv} \cdot e_{lv}(t_{AVC}) \cdot V_{lv}(t_{AVC}) \\ \Leftrightarrow V_{lv}(t_{AVC}) &= \frac{P_{ao}(t_{AVC})}{E_{lv} \cdot e_{lv}(t_{AVC})} \end{aligned} \tag{23}$$

This is the end-systolic volume. By definition, the stroke volume SV is equal to the difference between the end-diastolic and end-systolic volumes:

$$\begin{aligned} SV &= V_{lv}(t_{AVO}) - V_{lv}(t_{AVC}) \\ &= \frac{P_{ao}(t_{AVO})}{E_{lv} \cdot e_{lv}(t_{AVO})} - \frac{P_{ao}(t_{AVC})}{E_{lv} \cdot e_{lv}(t_{AVC})} \\ &= \frac{1}{E_{lv}} \left(\frac{P_{ao}(t_{AVO})}{e_{lv}(t_{AVO})} - \frac{P_{ao}(t_{AVC})}{e_{lv}(t_{AVC})} \right) \end{aligned} \tag{24}$$

$$\Leftrightarrow E_{lv} = \frac{1}{SV} \left(\frac{P_{ao}(t_{AVO})}{e_{lv}(t_{AVO})} - \frac{P_{ao}(t_{AVC})}{e_{lv}(t_{AVC})} \right) \tag{25}$$

Once E_{lv} is known, from $P_{lv}(t)$ and the driver function, using Equation (5), one can obtain:

$$V_{lv}(t) = \frac{P_{lv}(t)}{E_{lv} \cdot e_{lv}(t)}. \tag{26}$$

Integrating Equation (10) during ejection (when $P_{lv}(t) > P_{ao}(t)$, *i.e.* between $t = t_{AVO}$ and $t = t_{AVC}$) gives:

$$\int_{t_{AVO}}^{t_{AVC}} Q_{av}(t)\ dt = \int_{t_{AVO}}^{t_{AVC}} \frac{P_{lv}(t) - P_{ao}(t)}{R_{av}}\ dt. \tag{27}$$

Since, during ejection, all flow going out of the heart goes through the aortic valve,

$$\int_{t_{AVO}}^{t_{AVC}} Q_{av}(t)\ dt = SV. \tag{28}$$

Consequently, using the previous two equations gives:

$$\Leftrightarrow R_{av} = \frac{\int_{t_{AVO}}^{t_{AVC}} [P_{lv}(t) - P_{ao}(t)]\ dt}{SV}. \tag{29}$$

The reasoning that has been exposed in this section for the left side of the circulation can be transposed to the right side. Consequently, pulmonary valve resistance R_{pv} and right ventricular elastance E_{rv} are identifiable, which allows computation of $V_{rv}(t)$.

3.2 During Ventricular Filling

Focusing now on (right) ventricular filling ($P_{vc}(t) > P_{rv}(t)$ and $P_{rv}(t) < P_{pa}(t)$), the combination of Equations (11), (12) and (17) gives:

$$\dot{V}_{rv}(t) = \frac{P_{vc}(t) - P_{rv}(t)}{R_{tc}}. \tag{30}$$

Differentiating this equation yields:

$$\ddot{V}_{rv}(t) = \frac{\dot{P}_{vc}(t) - \dot{P}_{rv}(t)}{R_{tc}}. \tag{31}$$

Using Equations (2), (7), (11) and (16), Equation (31) becomes (dependencies with respect to time being omitted for clarity):

$$\ddot{V}_{rv} = \frac{1}{R_{tc}} \left(E_{vc} \left(\frac{P_{ao} - P_{vc}}{R_{sys}} - \frac{P_{vc} - P_{rv}}{R_{tc}} \right) - \dot{P}_{rv} \right). \tag{32}$$

If the previous equation is differentiated twice more and the derivatives of $P_{vc}(t)$ are eliminated using Equations (2), (7), (11) and (16), the result is two more equations of the form:

$$\dddot{V}_{rv}(t) = f\Big(R_{tc}, E_{vc}, R_{sys}, P_{ao}(t), \dot{P}_{ao}(t), P_{vc}(t), P_{rv}(t), \dot{P}_{rv}(t), \ddot{P}_{rv}(t)\Big) \tag{33}$$

$$\ddddot{V}_{rv}(t) = g\Big(R_{tc}, E_{vc}, R_{sys}, P_{ao}(t), \dot{P}_{ao}(t), \ddot{P}_{ao}(t), P_{vc}(t), P_{rv}(t), \dot{P}_{rv}(t), \ddot{P}_{rv}(t), \dddot{P}_{rv}(t)\Big). \tag{34}$$

The algebraic system formed by Equations (30), (32), (33) and (34) counts four equations and four unknowns $P_{vc}(t)$, R_{sys}, R_{tc} and E_{vc} (since $V_{rv}(t)$ is known, *cf.* the last paragraph of section 3.1). Solving this system with a symbolic computation software (Mathematica Version 8.0, Wolfram Research, Inc., Champaign, IL) shows that it has a unique solution at each time step. This, in turn, guarantees the identifiability of the three parameters R_{sys}, R_{tc} and E_{vc} (Anguelova [2004]). This outcome also provides the curve of $P_{vc}(t)$ during filling, which will be useful further in this demonstration.

During filling, aortic and pulmonary valves are closed. Hence, the volume comprised in the three chambers between these two valves is conserved and the sum of the flows is zero:

$$\dot{V}_{ao}(t) + \dot{V}_{vc}(t) + \dot{V}_{rv}(t) = 0. \tag{35}$$

This relationship allows to obtain the time curve of $\dot{V}_{ao}(t)$ during filling:

$$\dot{V}_{ao}(t) = -\dot{V}_{vc}(t) - \dot{V}_{rv}(t) = -\frac{\dot{P}_{vc}(t)}{E_{vc}} - \dot{V}_{rv}(t) \tag{36}$$

since $P_{vc}(t)$ is now available. Thus, using $\dot{V}_{ao}(t)$ and $\dot{P}_{ao}(t)$, E_{ao} can be computed as:

$$E_{ao} = \frac{\dot{P}_{ao}(t)}{\dot{V}_{ao}(t)}. \tag{37}$$

As done in the previous section, the approach applied here can be transposed to the other side of the circulation to prove the identifiability of the parameters R_{pul}, R_{mt}, E_{pu} and E_{pa} and the availability of the curve $P_{pu}(t)$ during filling.

Finally, SBV can be computed from its definition:

$$\begin{aligned} SBV = {} & V_{lv}(t) + V_{ao}(t) + V_{vc}(t) \\ & + V_{rv}(t) + V_{pa}(t) + V_{pu}(t). \end{aligned} \tag{38}$$

Using the fact that E_{ao}, E_{pa}, E_{vc} and E_{pu} are known, as well as $P_{vc}(t)$ and $P_{pu}(t)$ (during filling), yields:

$$\begin{aligned} SBV = {} & V_{lv}(t) + \frac{P_{ao}(t)}{E_{ao}} + \frac{P_{vc}(t)}{E_{vc}} \\ & + V_{rv}(t) + \frac{P_{pa}(t)}{E_{pa}} + \frac{P_{pu}(t)}{E_{pu}}. \end{aligned} \tag{39}$$

4. RESULTS AND DISCUSSION

The demonstration performed in the previous section shows that all 13 model parameters R_{mt}, R_{av}, R_{sys}, R_{tc}, R_{pv}, R_{pul}, E_{lv}, E_{ao}, E_{vc}, E_{rv}, E_{pa}, E_{pu} and SBV can be uniquely retrieved from $P_{lv}(t)$, $P_{rv}(t)$, $P_{ao}(t)$, $P_{pa}(t)$ and SV measurements and knowledge of the driver functions $e_{lv}(t)$ and $e_{rv}(t)$. This outcome, in turn, proves that the six-chamber CVS model is structurally globally identifiable from these output signals. Consequently, given all required measurements of the outputs, there exists one and only one possible parameter set corresponding to these measurements. The parameter identification process thus theoretically possesses a unique global minimum.

This result can be linked to previous work done on simplified versions of the six-chamber CVS model. Simple two-chamber CVS models can be derived from the six-chamber model of Figure 1. Doing so, the model is split in two equivalent two-chamber models, representing the systemic and

pulmonary circulations (see Figure 2), previously shown to be structurally globally identifiable from a specific output set. In the present work, it was shown that the union of these two submodels was structurally globally identifiable from the union of the two output sets needed to identify the two submodels.

The six-chamber CVS model is thus structurally globally identifiable from a limited output set containing ventricular and arterial pressures and stroke volume. But this does not imply that this limited set can not be reduced. It would be useful to investigate the structural identifiability of the model from other output sets, either smaller (for example, not containing ventricular pressures) or containing different outputs.

Another way to reduce the size of the output set is to fix some model parameters to population values. For instance, valve resistances R_{mt}, R_{av}, R_{tc} and R_{pv} were observed not to exert a large influence on the model's overall behavior. If these valve resistances are kept constant and are not identified, it can be shown, using the same kind of procedure as above, that the remaining parameters can be identified only from $P_{ao}(t)$, $P_{pa}(t)$ and SV. In this case, ventricular pressures $P_{lv}(t)$ and $P_{rv}(t)$ do not have to be included in the outputs.

4.1 Practical Considerations

In this section, the implications of the results on the practical parameter identification process are discussed. In the meantime, the validity of the assumptions made in section 3 is assessed.

One of these assumptions was that the left and right driver functions were known. Practical determination of the driver functions requires simultaneous measurements of left and right ventricular pressures and volumes at different loads (Suga et al. [1973]). This is of course impossible in a clinical setting. However, the driver function has been found to be relatively similar for any human heart (Senzaki et al. [1996]). This makes *a priori* generic driver functions a sensible assumption for any individual.

Practically speaking, the fact that ventricular pressures $P_{lv}(t)$ and $P_{rv}(t)$ need to be part of the output set is quite problematic. Indeed, these values are typically not recorded in a clinical setting. If further work shows that these pressures cannot be omitted for the model to remain identifiable, more assumptions would have to be made for the model to be clinically applicable. For instance, as mentioned previously, if valve resistances are assumed to be constant, the need for ventricular pressures vanishes. In that case, the remaining parameters are theoretically identifiable from a clinically available output set.

In the demonstration, the third derivative of ventricular pressure is used to prove model identifiability (Equation 34). It is of course practically impossible to use such a signal, because it would be too noisy. Thus, assumption of perfect and noise-free data does not hold in practice and the equations developed in section 3 cannot be used to practically compute the model parameters. Now that the model is shown to be structurally identifiable, it is also necessary to determine if specific supplementary data is needed to *practically* compute the model parameters.

Another reason causing the equations of section 3 not to be usable in practice is that the model is not perfectly valid, because of unmodelled elements. For instance, to derive Equation (25), it is assumed that the left ventricular and aortic pressures were equal at the time of aortic valve closing. This is one of the assumptions underlying the model, but in a real ventricle the blood has inertia, causing the aortic valve to close when ventricular pressure is actually lower than aortic pressure. However, Equation (25) could still be used to get a reasonable approximation of left ventricular end-systolic elastance.

5. CONCLUSION

The CVS model of Smith et al. [2004] has been used to track the evolution of diseases in animal experiments. However, only one study demonstrated the structural *a priori* identifiability of this model, but did so using a large output set. In this work, a specific output set is chosen containing only a limited number of measurements. Then, by manipulating the model equations involving these outputs, it is demonstrated that the CVS model is structurally globally identifiable. This means that the model parameters are unique and can theoretically be identified from the specified limited output set. However, this limited output set is still too large from a clinical point of view, as it requires ventricular pressures, which are typically not available at a patient's bedside. Consequently, if the demonstration presented in this work cannot be improved, further simplifying assumptions may have to be made for the clinical use of this CVS model.

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