Structural identifiability of viscoelastic mechanical systems

Adam Mahdi¹, Nicolette Meshkat¹, Seth Sullivant¹

Department of Mathematics, North Carolina State University, NC, USA

¹ These authors contributed equally to this work.

* E-mail: Corresponding amahdi@ncsu.edu

Abstract

We solve the local and global structural identifiability problems for viscoelastic mechanical models represented by networks of springs and dashpots. We propose a very simple characterization of both local and global structural identifiability based on *identifiability tables*, with the purpose of providing a guideline for constructing arbitrarily complex, identifiable spring-dashpot networks. We illustrate how to use our results in a number of examples and point to some applications in cardiovascular modeling.

Introduction

Mathematical modeling is a prominent tool used to better understand complex mechanical or biological systems [1]. A common problem that arises when developing a model of a biological or mechanical system is that some of its parameters are unknown. This is especially important when those parameters have special meaning but cannot be directly measured. Thus a natural question arises: Can all, or at least some, of the model's parameters be estimated indirectly and *uniquely* from observations of the system's input and output? This is the question of *structural identifiability*. Sometimes the uniqueness holds only within a certain range. In this case, we say that a system is only *locally* structurally identifiable. There are numerous reasons why one would be interested in establishing identifiability. The unobservable biologically meaningful parameters of a model can only be determined (or approximated) if the model is structurally identifiable. Moreover, optimization schemes cannot be employed reliably since they will find difficulties when trying to estimate unidentifiable parameters [2]. The concept of structural identifiability was introduced for the first time in the work of Belman and Åström [3]. Since then, numerous techniques have been developed to analyze the identifiability of linear and nonlinear systems with and without controls [2, 4-7]; see also [8] for a review of different approaches.

Viscoelastic mechanical models that utilize springs and dashpots in various configurations have been widely used in numerous areas of research including material sciences [9], computer graphics [10], and biomedical engineering to describe mechanical properties of biological systems [11–18]. To achieve a desirable response, networks with different numbers of springs and dashpots in various configurations have been constructed. For example, it is well-known that the simplest models of viscoelastic materials such as Voigt (spring and dashpot in parallel) or Maxwell (spring and dashpot in series) do not offer satisfactory representation of the nature of real materials [19]. Thus more complicated configurations are usually constructed and analyzed [17].

In this paper we investigate the identifiability problem of viscoelastic models represented by an arbitrarily complex spring-dashpot network. Although there exist numerous methods that can determine the type of identifiability of a system of ordinary differential equations, generally they are difficult to apply. Our results will show in a remarkably simple way how to verify whether the studied model is (locally or globally) structurally identifiable. In case it is unidentifiable, our method provides an explanation why this is the case and how to reformulate the problem. Moreover, the existing methods usually allow to establish the identifiability only *a posteriori*, i.e. after concrete systems have been established. Thus, we also introduce "identifiability tables", which allow not only to check but also to construct an arbitrarily complex *identifiable* spring-dashpot network.



Figure 1. Changing blood pressure (P) causes periodic expansion and contraction of the arterial wall. Spring-dashpot (S-D) networks are often used in order to describe the biomechanical properties of the arterial tissue as well as the strain sensed by various receptors (e.g. baroreceptors) embedded in the arterial wall. Typically a spring (representing a receptor's nerve ending) is combined in series with a S-D network (representing viscoelastic coupling of the nerves to the wall). Recently, several cardiovascular approaches have used the framework described above, in particular, choosing one of the following S-D networks: (A) Burgers model [20]; (B) three element Kelvin-Voigt body [21]; (C) generalized Kelvin-Voigt model [22].

Application to cardiovascular modeling

A particular motivation for this work comes from cardiovascular modeling [21, 22], although the results of this paper can be applied to any viscoelastic modeling approach.

Arterial wall. Changing blood pressure causes periodic expansion and contraction of the arterial wall (see Fig. 1). It is well-known that the stress-strain curves of the artery walls exhibit hysteresis, which is understood to be a consequence of the fact that the wall is viscoelastic. Another manifestation of the viscoelasticity of the arterial tissue is the stress relaxation experiments under constant stretch (strain). Spring-dashpot (S-D) networks are often used in order to describe the biomechanical properties of the arterial tissue [23–25]. Identifiable networks can be determined using the results of this paper (see Theorem 2).

Neural activity. It is common to use the spring-dashpot network to describe the neural firing of various sensors (e.g. muscle spindle, baroreceptors), see [20, 21, 26, 27]. Typically one assumes that the firing activity is proportional to the strain sensed by a spring connected in series with a spring-dashpot network, which represents a local integration of the nerve endings to the arterial wall (see Fig. 1). Then the arterial wall and neural activity models are combined. Although separately each model is structurally identifiable, there is no guarantee that the resulting viscoelastic structure is identifiable. Thus, using our results given in Theorem 4, we can establish whether the combined viscoelastic model is identifiable, and if not, what needs to be modified.



Figure 2. Simple linear viscoelastic models. (A) Maxwell element, (B) Voigt element, (C) Burgers model.

Results and Discussion

After reviewing basic concepts of viscoelasticity of systems, we present and discuss our main results related to local and global structural identifiability of such systems. Finally, we illustrate our results with a number of examples from the literature.

Spring-dashpot networks

The ideal linear elastic material follows Hooke's law $\sigma = E\epsilon$, where E is a Young's modulus (or a spring constant), which describes the relationship between the stress σ and the strain ϵ . Analogously, the relation $\sigma = \eta \dot{\epsilon}$ describes the viscous material, where $\dot{\epsilon} = d\epsilon/dt$ and η is a viscous constant [28]. In the basic linear viscoelasticity theory, the elastic and viscous elements are combined. In this work, we shall be concerned with the problem of identifiability of networks of springs and dashpots that are essentially one-dimensional. The elements can be combined either in series or in parallel. In order to obtain the relationship between the total stress (force) σ and the total strain (extension) ϵ for a given spring-dashpot network, we use two fundamental rules. For two viscoelastic elements connected in series, the stress is the same in both elements, but the total strain is the same for both elements, but the total stress is the sum of individual stresses on each element. Now we consider concrete viscoelastic networks, starting with the simplest configurations.

Example 1 (Maxwell element). The series combination of a spring, denoted by its constant E, and a dashpot, denoted by its constant η , is known as a Maxwell element (see Fig. 2(A)). Since the elements are connected in series, the stress σ is the same on both elements and the total strain ϵ is the sum of strains ϵ_E and ϵ_η corresponding to the spring and dashpot, respectively. Now, the relationship between the total strain and stress for this system is

$$\dot{\epsilon} = \dot{\sigma}/E + \sigma/\eta. \tag{1}$$

Example 2 (Voigt element). Another simple example is the Voigt element (also known as Kelvin or Kelvin-Voigt) given in Fig. 2(B). Following the steps outlined in the previous example, we obtain the $\sigma - \epsilon$ relationship

$$E\epsilon + \eta \dot{\epsilon} = \sigma. \tag{2}$$

Example 3 (Burgers model). In our third example we consider a particularly popular four-element model, represented by a Maxwell element combined in series with a Voigt element, and known as the Burgers model (Fig. 2(C)). Denote by subscript m and v the spring and viscous constants of the Maxwell and Voigt elements, respectively. Note that the stress σ is the same on all three elements connected in

series (Voigt, spring and dashpot). Eliminating the corresponding local strains, we obtain the following relationship

$$E_m \ddot{\epsilon} + \frac{E_m E_v}{\eta_v} \dot{\epsilon} = \ddot{\sigma} + \left[\frac{E_m}{\eta_m} + \frac{E_m}{\eta_v} + \frac{E_v}{\eta_v}\right] \dot{\sigma} + \frac{E_m E_v}{\eta_m \eta_v} \sigma.$$
(3)

Identifiability characterization

First note (cf. Examples 1, 2, and 3) that for any configuration of springs $\overline{E} = (E_1, ..., E_N)$ and dashpots $\overline{\eta} = (\eta_1, ..., \eta_M)$, the total strain-stress relationship can always be written as the following (n+1)-th order linear ordinary differential equation

$$a_{n+1}\epsilon^{(n+1)} + a_n\epsilon^{(n)} + \dots + a_0\epsilon = b_n\sigma^{(n)} + \dots + b_0\sigma,$$
(4)

where the coefficients $a_j = a_j(\bar{E}, \bar{\eta})$ and $b_k = b_k(\bar{E}, \bar{\eta})$ are functions of the spring and dashpot constants. The precise value of n and the forms of $a_j(\bar{E}, \bar{\eta})$ and $b_k = b_k(\bar{E}, \bar{\eta})$ will depend on the particular structure of the spring-dashpot model. Equation 4 is known as the *constitutive equation*. In the context of springdashpot networks, identifiability concerns whether or not it is possible to recover the unknown parameters $(\bar{E} \text{ and } \bar{\eta})$ of the system from the governing equation of the model, given only the total stress σ and strain ϵ . In order to uniquely fix the coefficients of the constitutive equation (4), we require that (4) be *normalized* so that the leading term (in σ or ϵ , depending on the situation) is monic. Thus, letting the d non-monic coefficients of (4) be represented by the vector $\mathbf{c} = (\mathbf{a}(\bar{E}, \bar{\eta}), \mathbf{b}(\bar{E}, \bar{\eta}))$, we have the following formal definition of identifiability.

Definition 1. Let **c** be a function $\mathbf{c} : \Theta \to \mathbb{R}^d$, where $\Theta \subseteq \mathbb{R}^{N+M}$ is the parameter space. The model is *globally identifiable* from **c** if and only if the map **c** is one-to-one. The model is *locally identifiable* from **c** if and only if the map **c** is *unidentifiable* from **c** if and only if the map **c** is infinite-to-one. The model is *unidentifiable* from **c** if and only if the map **c** is infinite-to-one.

Note that local identifiability is equivalent to saying that around each point in parameter space there exists a neighborhood on which the function \mathbf{c} is one-to-one. For example, for the Burgers model considered in Example 3, the coefficient function $\mathbf{c} : \mathbb{R}^4 \to \mathbb{R}^4$ is defined as

$$\mathbf{c}: (E_m, E_v, \eta_m, \eta_v) \to \Big(E_m, \frac{E_m E_v}{\eta_v}, \frac{E_m}{\eta_m} + \frac{E_m}{\eta_v} + \frac{E_v}{\eta_v}, \frac{E_m E_v}{\eta_m \eta_v}\Big).$$

Technically speaking, in this paper we will consider the slightly weaker notion of *generic global identifiability* (or generic local identifiability, or generic unidentifiability), where *generic* means that the property holds almost everywhere. We will omit the use of the term generic when speaking of identifiability.

Definition 1 implies that if there are more parameters than non-monic coefficients, then the system must be unidentifiable. Thus, a necessary condition for structural identifiability is that the number of parameters $\bar{E}, \bar{\eta}$ (elements of the network) is less than or equal to the number of non-monic coefficients in the constitutive equation (4). We will strengthen this to a sufficient condition in the following theorem:

Theorem 2 (Local identifiability). A viscoelastic model represented by a spring-dashpot network is locally identifiable if and only if the number of non-monic coefficients of the corresponding constitutive equation (4) equals the total number of its moduli E_j and viscosity parameters η_k .

Note that although the constitutive equation (4) is a linear differential equation, its coefficients considered as functions of spring and viscous constants are not linear functions of the parameters (see (3)). Thus, Theorem 2 allows to reduce the difficult problem of checking one-to-one or finite-to-one behavior of nonlinear functions to simply counting the number of parameters (springs and dashpots) and coefficients of the constitutive equation and asking whether the two numbers are equal. The positive answer



Figure 3. (A) Multi-parameter linear viscoelastic model considered by Dietrich et al. [19]. (B) Ten element viscoelastic model studied in [13], (C) A viscoelastic model of used to describe the baroreceptor nerve ending coupling to the arterial wall (see [21] and [22,29]).

implies local identifiability, whereas a negative answer implies unidentifiability. Consider, for example, the Maxwell and Voigt elements, and the Burgers model. We note that the constitutive equations (1), (2), and (3) for all three models are already in the normalized form. Now, simply by counting the number of parameters and the non-monic coefficients of the constitutive equations, we see that the two are equal for each model. Thus, by the above theorem, all three models are locally structurally identifiable.

Constructing identifiable models

Now we examine when combining two identifiable models results also in an identifiable model. This will allow us to construct arbitrarily complex and identifiable spring-dashpot networks.

We start with an observation, which we prove in the following section, related to the possible form of any differential equation that describes a spring-dashpot network.

Proposition 3. Every spring-dashpot network, given by equation (4), has one of the four possible types

Type A:
$$b_0 b_n \neq 0$$
, $a_{n+1} = 0$, $a_0 a_n \neq 0$
Type B: $b_0 b_n \neq 0$, $a_0 = 0$, $a_1 a_{n+1} \neq 0$
Type C: $b_0 b_n \neq 0$, $a_0 a_{n+1} \neq 0$
Type D: $b_0 b_n \neq 0$, $a_{n+1} = a_0 = 0$, $a_1 a_n \neq 0$.
(5)

Table 1. Identifiability Tables.

(a) Parallel connection				ection			(b) S	(b) Series connection			
\oplus	\mathbf{A}	в	\mathbf{C}	D	u	\odot	A	в	\mathbf{C}	\mathbf{D}	u
Α	u	С	u	А	u	A	u	D	Α	u	u
В	С	u	u	В	u	В	D	u	В	u	u
\mathbf{C}	u	u	u	С	u	\mathbf{C}	A	В	С	D	u
D	Α	В	С	D	u	D	u	u	D	u	u
u	u	u	u	u	u	u	u	u	u	u	u

When connecting two identifiable spring-dashpot networks of one of the types A, B, C, D, or an unidentifiable u either in series or in parallel, the above tables establish the type of the resulting identifiable system. If the resulting structure is unidentifiable it is indicated by u. For example, a parallel connection of two networks of types A and D gives rise to an identifiable network of type A (see (a)), but the series connection results in an unidentifiable structure (see (b)).

Note that according to the above proposition, the spring, dashpot, Voigt, and Maxwell elements are of Types A, B, C, and D, respectively.

Theorem 4 (Local identifiability). Consider two locally identifiable spring-dashpot systems N_1 and N_2 of one of the four types A, B, C, D. Then the new model resulting in joining N_1 and N_2 either in parallel or in series is of the type indicated by the Identifiability Tables (Table 1). The letter u indicates that the network is unidentifiable, otherwise it is identifiable of the given type.

There are several ways one could use the above theorem. One way is to establish the local identifiability of a given spring-dashpot network. Contrary to our similar result given in Theorem 2, this can be done without actually calculating the constitutive equation. We will show how to apply Theorem 4 to establish structural identifiability after first introducing some notation. Given any two spring-dashpot models Mand N, we use the following notation $(M \vee N)$ and $(M \wedge N)$ to denote respectively the parallel and series combination of M and N. Let \mathcal{F} denote the function that takes a spring and dashpot model M and outputs its type (A, B, C, D) if it is locally identifiable, and u if it is unidentifiable. To apply \mathcal{F} to a complicated model built up from springs and dashpots using series and parallel connections, we replace any springs and dashpots with their respective types A and B as well as the operations \vee and \wedge with \oplus and \odot , respectively. Then we apply the operations in the Identifiability Tables (see Table 1).

Example 4 (Local identifiability of the Maxwell element). Note that the Maxwell model shown in Fig. 2(A) can be symbolically written as

$$M = E \wedge \eta.$$

In this formula, we simply replace the spring and the dashpot with A and B, respectively, as well as the operations \vee and \wedge with \oplus and \odot , respectively, to obtain

$$\mathcal{F}(M) = (A \odot B) = D.$$

Thus we conclude that the Maxwell model is locally identifiable and is of type D.

Example 5 (Local identifiability of the Burgers model). Similarly, the Burgers model shown in Fig. 2(C) can be symbolically written as

$$M = (E_v \vee \eta_v) \wedge (E_m \wedge \eta_m).$$

To check the local identifiability, we find $\mathcal{F}(M)$ and use Table 1 to obtain

$$\mathcal{F}(M) = \overbrace{(A \oplus B)}^{C} \odot \overbrace{(A \odot B)}^{D} = C \odot D = D.$$

We conclude that the Burgers model is locally identifiable and of type D.

In the next example we show how we can easily establish local structural identifiability of a more complicated network.

Example 6 (Dietrich et al. [19]). Consider a viscoelastic material studied in [19] and represented by a spring-dashpot network shown in Fig. 3(A). It can be symbolically represented by

$$M = \left[\left(\left(\left(\left(\left(E_1 \lor \eta_1 \right) \land E_2 \right) \land \eta_2 \right) \lor \eta_3 \right) \land E_3 \right) \lor \eta_4 \right] \land E_4.$$
(6)

Again, we can verify the local identifiability of the above model using Table 1 and obtain

$$\mathcal{F}(M) = \left[(((((A \oplus B) \odot A) \odot B) \oplus B) \odot A) \oplus B \right] \odot A$$
$$= \left[(((((C \odot A) \odot B) \oplus B) \odot A) \oplus B \right] \odot A$$
$$= \left[((((A \odot B) \oplus B) \odot A) \oplus B \right] \odot A = \dots = D$$

This simple computation confirms that the model is locally structurally identifiable.

Our method can also verify if a network is unidentifiable, providing the reason for the lack of its identifiability. Consider the following example.

Example 7 (Unidentifiable model). Consider a viscoelastic model used in [13] and shown in Fig. 3(B). Using the notation previously introduced, it can symbolically be written as

$$M = \left[\left(\left((E_1 \land \eta_1) \lor (E_2 \land \eta_2) \right) \land E_3 \land \eta_3 \right) \lor \left(E_4 \land \eta_4 \right) \right] \land E_5 \land \eta_5$$

Now applying Table 1, we obtain

$$\mathcal{F}(M) = \left[((\overbrace{(A \odot B)}^{D} \oplus \overbrace{(A \odot B)}^{D}) \odot \overbrace{(A \odot B)}^{D}) \oplus \overbrace{(A \odot B)}^{D} \right] \odot \overbrace{A \odot B}^{D}$$
$$= \left[(\overbrace{(D \oplus D)}^{D} \odot D) \oplus D \right] \odot D$$
$$= \left[(\overbrace{(D \odot D)}^{u} \oplus D \right] \odot D = u.$$

Whenever Table 1 indicates u (i.e. the corresponding substructure is unidentifiable), this inevitably leads to the whole model being unidentifiable. Moreover, our method can also explain what is the reason for the lack of identifiability. In this example the situation is simple: joining in series a Maxwell element (type D) with a generalized Maxwell model leads to an unidentifiable network.

So far we have considered only *local* identifiability of mechanical systems. Now we complete the presentation and discussion of our results by introducing a criterium, which establishes when a given network is *globally* structurally identifiable.

Theorem 5 (Global identifiability). A viscoelastic model represented by a spring-dashpot network is globally identifiable if and only if it is locally identifiable and the network is constructed by adding either in parallel or in series exactly one basic element (spring or dashpot) at a time.

Note that the network given in Fig. 3(A) and considered in Example 6 was deemed locally structurally identifiable. We note that it can be constructed by adding just one element at a time and therefore it is *globally* structurally identifiable. Similarly, all the simple models shown in Fig. 2 can also by constructed adding only one element at a time, and since they are locally identifiable, we conclude that they are also globally structurally identifiable. Now consider a model which is locally, but not globally, structurally identifiable.

Example 8 (Local but not global identifiability). Consider a generalized Kelvin-Voigt model shown Fig. 3(C) and used in [21,29]) in the context of cardiovascular modeling. It can be symbolically represented by

 $M = E_0 \wedge (E_1 \vee \eta_1) \wedge (E_2 \vee \eta_2) \wedge (E_3 \vee \eta_3).$

Thus the local identifiability can be checked by computing

$$\mathcal{F}(M) = A \odot (A \oplus B) \odot (A \oplus B) \odot (A \oplus B) = A \odot C \odot C \odot C = A.$$

We immediately conclude that the network is locally identifiable. In order to verify whether it is also globally identifiable, note that this network *cannot* be constructed by adding only one element at a time. Thus the system is only locally, but not globally, identifiable. However, in this case the non-global identifiability arises from merely permuting the parameters among the three Voigt elements.

Analysis

In this section, we prove the main results from the previous section. To do this requires a careful analysis of the structure of the constitutive equation after combining a pair of systems in series or in parallel.

Let N_1 and N_2 be spring-dashpot models whose respective constitutive equations are $L_1\epsilon = L_2\sigma$ and $L_3\epsilon = L_4\sigma$, where L_i represent linear differential operators. We can write the differential operators (in general form) as:

$$L_{1} = a_{n_{1}}d^{n_{1}}/dt^{n_{1}} + \dots + a_{m_{1}}d^{m_{1}}/dt^{m_{1}}$$

$$L_{2} = b_{n_{2}}d^{n_{2}}/dt^{n_{2}} + \dots + b_{m_{2}}d^{m_{2}}/dt^{m_{2}}$$

$$L_{3} = c_{n_{3}}d^{n_{3}}/dt^{n_{3}} + \dots + c_{m_{3}}d^{m_{3}}/dt^{m_{3}}$$

$$L_{4} = e_{n_{4}}d^{n_{4}}/dt^{n_{4}} + \dots + e_{m_{4}}d^{m_{4}}/dt^{m_{4}}$$
(7)

Remark. Table 2 shows that there are restrictions on the values of the n_i and m_i , e.g. the differential order of the lowest order term in σ is always zero and the differential order of the lowest order term in ϵ is zero or one, but we leave the operators in general form for simplicity.

We now show the form of the resulting constitutive equation after combining these systems in series or in parallel, in terms of these differential operators. In what follows, we will treat the differential operators L_i as polynomial functions in the variable d/dt. For example, L_1 can be thought of as a polynomial $a_{n_1}x^{n_1} + \ldots + a_{m_1}x^{m_1}$.

Series connection

Suppose that $M = N_1 \wedge N_2$ is a series connection of models N_1 and N_2 , whose constitutive equations are $L_1\epsilon_1 = L_2\sigma_1$ and $L_3\epsilon_2 = L_4\sigma_2$, respectively. Then the stresses (σ) are the same for the two systems while the strains (ϵ) are added. If L_1 and L_3 are relatively prime, then the constitutive equation of M is:

$$L_1 L_3 \epsilon = (L_1 L_4 + L_2 L_3) \sigma, \quad \epsilon = \epsilon_1 + \epsilon_2, \quad \sigma = \sigma_1 = \sigma_2.$$
(8)

Type	Shape in σ	Shape in ϵ
А	[n,0]	[n,0]
В	[n,0]	[n+1,1]
С	[n,0]	[n+1,0]
D	[n, 0]	[n, 1]

Table 2. Possible types of constitutive equations

The four possible types of constitutive equations, defined by the shapes of the linear operators acting on σ and ϵ , written in brackets.

We assume that $a_{n_1} = c_{n_3} = 1$, so that the constitutive equation is monic. If L_1 and L_3 have a common factor, then the constitutive equation of M is obtained by dividing (8) by the greatest common divisor of L_1 and L_3 .

Parallel connection

Suppose that $M = N_1 \vee N_2$ is a parallel connection of models N_1 and N_2 , whose constitutive equations are $L_1\epsilon_1 = L_2\sigma_1$ and $L_3\epsilon_2 = L_4\sigma_2$ respectively. Then the strains (ϵ) are the same for the two systems while the stresses (σ) are added. If L_2 and L_4 are relatively prime, then the constitutive equation is:

$$(L_1L_4 + L_2L_3)\epsilon = L_2L_4\sigma, \quad \epsilon = \epsilon_1 = \epsilon_2, \quad \sigma = \sigma_1 + \sigma_2.$$
(9)

We assume that $b_{m_2} = e_{m_4} = 1$, so that the constitutive equation is monic. If L_2 and L_4 have a common factor, then the constitutive equation is obtained by dividing (9) by the greatest common divisor of L_2 and L_4 .

Types of networks

Now we prove Proposition 3, that is, we show that every spring-dashpot network, given by equation (4), has one of the four possible types displayed in Table 2, which are defined by the *shapes* of the linear operators L_i acting on σ and ϵ . We make this notion precise:

Definition 6. The *shape* of a linear operator L_i is a pair of numbers, written $[n_i, m_i]$, where n_i is the highest differential order and m_i is the lowest different order.

We note that a spring is of type A and a dashpot is of type B. A Voigt is formed by a parallel extension of types A and B, which forms type C, and a Maxwell is formed by a series extension of types A and B, which forms type D. The properties of these four types are displayed in Table 2. We can now form the 10 possible combinations of pairing two of these types in series and the 10 possible combinations of pairing two of these types in parallel. In Tables 3 and 4, we show the 20 total possibilities and demonstrate that each pairing results in a type A, B, C, or D. Since every spring-dashpot network can be written as a combination, in series or in parallel, of springs and dashpots, then we have shown by induction that joining any two spring-dashpot networks in series or in parallel results in one of these four types.

Remark. We note that if a type B or D is combined in series with a type B or D, then L_1 and L_3 have a common factor (since both lacked a constant term), so the equation $L_1L_3\epsilon = (L_1L_4 + L_2L_3)\sigma$ is divided by $gcd(L_1, L_3) = d/dt$ to arrive at the shapes listed in the table.

In addition to the type of equation that results after combining two equations of types $\{A, B, C, D\}$, we have in Tables 3 and 4 the resulting identifiability properties of each equation, which we will obtain

Type	Shape in σ	Shape in ϵ	Non-monic	Parameters	Identifiable?	Type
			coefficients			
(A,A)	$[n_1 + n_2, 0]$	$[n_1+n_2,0]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 2$	Not Id	A
(A,B)	$[n_1+n_2+1,0]$	$[n_1+n_2+1,1]$	$2n_1 + 2n_2 + 2$	$2n_1+2n_2+2$	Id	D
(A,C)	$[n_1 + n_2 + 1, 0]$	$[n_1+n_2+1,0]$	$2n_1 + 2n_2 + 3$	$2n_1+2n_2+3$	Id	A
(A,D)	$[n_1+n_2,0]$	$[n_1+n_2,1]$	$2n_1 + 2n_2$	$2n_1+2n_2+1$	Not Id	D
(B,B)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 1]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 2$	Not Id	В
(B,C)	$[n_1 + n_2 + 1, 0]$	$[n_1 + n_2 + 2, 1]$	$2n_1 + 2n_2 + 3$	$2n_1 + 2n_2 + 3$	Id	В
(B,D)	$[n_1 + n_2, 0]$	$[n_1 + n_2, 1]$	$2n_1 + 2n_2$	$2n_1 + 2n_2 + 1$	Not Id	D
(C,C)	$[n_1 + n_2 + 1, 0]$	$[n_1 + n_2 + 2, 0]$	$2n_1 + 2n_2 + 4$	$2n_1 + 2n_2 + 4$	Id	С
(C,D)	$[n_1 + n_2 + 1, 0]$	$[n_1 + n_2 + 1, 1]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 2$	Id	D
(D,D)	$[n_1 + n_2 - 1, 0]$	$[n_1 + n_2 - 1, 1]$	$2n_1 + 2n_2 - 2$	$2n_1 + 2n_2$	Not Id	D

Table 3. Series connection

Two systems of types A, B, C, or D are combined in series, where in the first system $n = n_1$ and in the second system $n = n_2$.

Table 4.	Parallel	connection
----------	----------	------------

(type,	Shape in σ	Shape in ϵ	Non-monic	Parameters	Identifiable?	Type
type)			coefficients			
(A,A)	$[n_1 + n_2, 0]$	$[n_1 + n_2, 0]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 2$	Not Id	А
(A,B)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 0]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 2$	Id	С
(A,C)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 0]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 3$	Not Id	С
(A,D)	$[n_1 + n_2, 0]$	$[n_1 + n_2, 0]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 1$	Id	A
(B,B)	$[n_1 + n_2, 0]$	$[n_1+n_2+1,1]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 2$	Not Id	В
(B,C)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 0]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 3$	Not Id	C
(B,D)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 1]$	$2n_1 + 2n_2 + 1$	$2n_1 + 2n_2 + 1$	Id	В
(C,C)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 0]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 4$	Not Id	С
(C,D)	$[n_1 + n_2, 0]$	$[n_1 + n_2 + 1, 0]$	$2n_1 + 2n_2 + 2$	$2n_1 + 2n_2 + 2$	Id	С
(D,D)	$[n_1 + n_2, 0]$	$[n_1 + n_2, 1]$	$2n_1 + 2n_2$	$2n_1 + 2n_2$	Id	D

Two systems of types A, B, C, or D are combined in parallel, where in the first system $n = n_1$ and in the second system $n = n_2$.

in the next section. Note that Definition 1 implies that if there are more parameters than non-monic coefficients, then the system must be unidentifiable. The tables show that the number of non-monic coefficients is bounded by the number of parameters, thus a necessary condition for identifiability is that the number of parameters equals the number of non-monic coefficients in the constitutive equation (4). In the next section, we show that this is also a sufficient condition.

Local identifiability

Consider a spring-dashpot system M whose final step connection is a series connection of two systems N_1 and N_2 , i.e. $M = N_1 \wedge N_2$. Since the number of non-monic coefficients in any spring-dashpot model is always less than or equal to the number of parameters in that model, we know that a necessary condition for this system to be locally identifiable is that N_1 and N_2 are both locally identifiable.

Let $L_1\epsilon_1 = L_2\sigma_1$ be the constitutive equation for N_1 and $L_3\epsilon_2 = L_4\sigma_2$ be the constitutive equation for N_2 . Each of the operators L_1 , L_2 , L_3 , and L_4 will have a fixed shaped determined by the structure of N_1 and N_2 . Assuming that N_1 and N_2 are locally identifiable, we can choose parameters in each of the models N_1 and N_2 so that the coefficients of these constitutive equations are arbitrary numbers. Thus, deciding identifiability of this system amounts to determining whether the map that takes the pair of equations $(L_1\epsilon_1 = L_2\sigma_1, L_3\epsilon_2 = L_4\sigma_2)$ to the constitutive equation for the system M, given in (8) is finite-to-one or not. The same reasoning works *mutatis mutandis* for parallel connections, where we now concern ourselves with the map from the pair of equations $(L_1\epsilon_1 = L_2\sigma_1, L_3\epsilon_2 = L_4\sigma_2)$ with generic coefficients to the constitutive equation for $M = N_1 \vee N_2$ given in (9).

Definition 7. The shape factorization problem for a quadruple of shapes

$$Q = ([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$$

is the following problem: for a generic pair of polynomials (f, g) with f monic such that the shape $(f) = [n_1 + n_3, m_1 + m_3]$ and shape $(g) = [\max(n_1 + n_4, n_2 + n_3), \min(m_1 + m_4, m_2 + m_3)]$, do there exist finitely many quadruples of polynomials (L_1, L_2, L_3, L_4) with shape $(L_i) = [n_i, m_i]$, L_1 and L_3 are monic, and such that $f = L_1 L_3$ and $g = L_1 L_4 + L_2 L_3$? A quadruple of shapes Q is said to be good if the shape factorization problem for that quadruple has a positive solution.

The language of shape factorization problems and the remarks in the preceding paragraphs allow us to reduce the local identifiability problem for a spring-dashpot system to determining whether a certain quadruple is a good quadruple.

Proposition 8. Let $M = N_1 \wedge N_2$ be a spring-dashpot model joined in series from N_1 and N_2 , where N_1 has constitutive equation $L_1\epsilon_1 = L_2\sigma_1$ of shapes $[n_1, m_1]$ and $[n_2, m_2]$ respectively and N_2 has constitutive equation $L_3\epsilon_2 = L_4\sigma_2$ of shapes $[n_3, m_3]$ and $[n_4, m_4]$ respectively. Then the model M is locally identifiable if and only if

- 1. N_1 and N_2 are locally identifiable, and
- 2. $([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$ is a good quadruple.

Similarly, if $M = N_1 \vee N_2$ is a spring-dashpot model joined in parallel from N_1 and N_2 , then M is locally identifiable if and only if

- 1. N_1 and N_2 are locally identifiable, and
- 2. $([n_2, m_2], [n_1, m_1], [n_4, m_4], [n_3, m_3])$ is a good quadruple.

So what remains to show is that, for the shapes that arise in spring-dashpot models, whether a quadruple of shapes is a good quadruple only depends on the types (A, B, C, or D) of the systems being combined. The proof of this statement will occupy the rest of this section.

Let f and g be two polynomials. Note that for given fixed shapes, $[n_1, m_1]$ and $[n_3, m_3]$ there are at most finitely many factorizations $f = L_1 L_3$, where L_1 has shape $[n_1, m_1]$ and L_3 has shape $[n_3, m_3]$ and both are monic. This is because there are at most finitely many ways to factorize a monic polynomial into monic factors. Once we fix one of these finitely many choices for L_1 and L_3 , the equation $g = L_1 L_4 + L_2 L_3$ is a linear system in the (unknown) coefficients of L_2 and L_4 .

Let L_i have shape $[n_i, m_i]$. The coefficients of L_1L_4 can be written in vector form as

$$[L_1L_4] = \begin{pmatrix} a_{n_1} & 0 & \cdots & 0 \\ \vdots & a_{n_1} & \cdots & 0 \\ a_{m_1} & \vdots & \cdots & \vdots \\ 0 & a_{m_1} & \cdots & 0 \\ \vdots & 0 & \cdots & a_{n_1} \\ \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & a_{m_1} \end{pmatrix} \begin{pmatrix} e_{n_4} \\ \vdots \\ e_{m_4} \end{pmatrix}$$

We will refer to this product as $G'[L_4]$, where G' is a $n_1 + n_4 - m_1 - m_4 + 1$ by $n_4 - m_4 + 1$ matrix. Likewise, the coefficients of L_2L_3 can be written in vector form as

$$[L_{2}L_{3}] = \begin{pmatrix} c_{n_{3}} & 0 & \cdots & 0 \\ \vdots & c_{n_{3}} & \cdots & 0 \\ c_{m_{3}} & \vdots & \cdots & \vdots \\ 0 & c_{m_{3}} & \cdots & 0 \\ \vdots & 0 & \cdots & c_{n_{3}} \\ \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & c_{m_{3}} \end{pmatrix} \begin{pmatrix} b_{n_{2}} \\ \vdots \\ b_{m_{2}} \end{pmatrix}$$

We will refer to this product as $H'[L_3]$, where H' is a $n_2 + n_3 - m_2 - m_3 + 1$ by $n_2 - m_2 + 1$ matrix. Then we call the *matrix factored form* of $[L_1L_4 + L_2L_3]$ the expression:

$$G[L_2] + H[L_4]$$
 (10)

where the matrices G and H are the matrices G' and H' padded with rows of zeros so that coefficients corresponding to monomials of the same degree appear in the same row. This makes $(G \ H)$ a max $\{n_1 + n_4, n_2 + n_3\} - \min\{m_1 + m_4, m_2 + m_3\} + 1$ by $n_2 - m_2 + n_4 - m_4 + 2$ matrix.

We can now state a criteria for determining if the shape factorization problem has finitely many solutions:

Proposition 9. The quadruple $([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$ is a good quadruple if and only if the matrix $(G \ H)$ is generically invertible.

Proof. We can write the shape factorization problem of type $([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$ in matrix factored form as $G[L_2] + H[L_4] = [g]$ (see (10)), so that

$$\begin{pmatrix} G & H \end{pmatrix} \begin{pmatrix} L_2 \\ L_4 \end{pmatrix} = [g]$$

Example 10. Suppose that our quadruple $([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$ is ([2, 0], [2, 0], [3, 0], [3, 1]) which is a special case of joining models of types A and D in parallel. The resulting matrix $(G \ H)$ is the matrix

1	a_2	0	0	c_3	0	0
	a_1	a_2	0	c_2	c_3	0
	a_0	a_1	a_2	c_1	c_2	c_3
	0	a_0	a_1	c_0	c_1	c_2
	0	0	a_0	0	c_0	c_1
	0	0	0	0	0	c_0

We now determine when this matrix $(G \ H)$ is generically invertible, i.e. square and full rank. The Sylvester matrix associated to two polynomials $p(z) = p_0 + p_1 z + p_2 z^2 + ... + p_m z^m$ and $q(z) = q_0 + q_1 z + q_2 z^2 + ... + q_n z^n$ is the n + m by n + m matrix that has the coefficients of p(z) repeated n times as columns and the coefficients of q(z) repeated m times as columns in the following way:

p_m	0	• • •	0	q_n	0	• • •	0 \
1	p_m		0	÷	q_n		0
p_0	÷		÷	q_0	÷		÷
0	p_0	• • •	0	0	q_0		0
:	0		p_m	÷	0		q_n
	÷		÷	÷	÷		÷
0	0		p_0	0	0		q_0
		~			-~-		,
		n			m		

The determinant of the Sylvester matrix of the two polynomials p and q is the *resultant*, which is zero if and only if the two polynomials have a common root. In particular, for generic polynomials p and q, the Sylvester matrix is invertible [30, Chapter 3].

We will use the Sylvester matrix in the following way. We will show that there are submatrices of $(G \ H)$ that correspond to the Sylvester matrix associated to L_1 and L_3 .

Proposition 11. If the matrix $(G \ H)$ is square, then it is generically invertible.

Proof. We claim that the columns of $(G \ H)$ can be ordered so that the resulting matrix has the shape

$$\begin{pmatrix} S' & 0 & 0 \\ X & S & Y \\ 0 & 0 & S'' \end{pmatrix}$$
 (11)

where S is the Sylvester matrix associated to the nonzero coefficients of L_1 and L_3 . Note that this means that we might shift the coefficients down if necessary so there are no extraneous zero terms of low degree (i.e. if the shape is $[n_i, m_i]$ with $m_i \neq 0$). The matrix S' is a square lower triangular matrix with nonzero entries on the diagonal, and S'' is a square upper triangular matrix with nonzero entries on the diagonal. This will prove that $(G \ H)$ is invertible, since its determinant will be the product of the determinants of S, S' and S'', all of which are nonzero. To prove that claim requires a careful case analysis. The number of columns of $(G \ H)$ is $n_4 - m_4 + n_2 - m_2 + 2$ and the number of rows is $\max(n_1 + n_4, n_2 + n_3) - \min(m_1 + m_4, m_2 + m_3) + 1$. Without loss of generality, we can assume that the maximum is attained by $n_1 + n_4$. We need to distinguish between the two cases where the minimum is attained by $m_1 + m_4$ and by $m_2 + m_3$.

Case 1: $\min[m_1 + m_4, m_2 + m_3] = m_1 + m_4$. Since $(G \ H)$ is a square matrix, this implies that $n_1 - m_1 = n_2 - m_2 + 1$. In this case we group the columns of $(G \ H)$ in the following order.

- 1. The first $n_1 + n_4 n_2 n_3$ columns of G
- 2. Then the next $n_3 m_3$ columns of G
- 3. Then all $n_2 m_2 + 1 (= n_1 m_1)$ columns of *H*
- 4. Then the remaining $m_2 + m_3 m_1 m_4$ columns of G.

This choice has the property that the middle two blocks of columns together have the desired form, since we have chosen to start including columns from G and H precisely when they both have nonzero entries in the same rows, and stopping the formation of these when they stop having nonzero entries in the same rows, which has the correct form. Note we have used all columns of G since

$$n_1 + n_4 - n_2 - n_3 + n_3 - m_3 + m_2 + m_3 - m_1 - m_4 = (n_1 - m_1) + (n_4 - m_4) - (n_2 - m_2) = (n_4 - m_4 + 1).$$

Case 2: min $[m_1 + m_4, m_2 + m_3] = m_2 + m_3$. Note that since $(G \ H)$ is square, this implies that $n_1 - m_3 = n_2 - m_4 + 1$. In this case, we do not need to reorder the columns to obtain the desired form. We mention how to block the columns to obtain the desired form.

- 1. The first $n_1 + n_4 n_2 n_3$ columns of G
- 2. Then the next $n_3 m_3$ columns of G
- 3. Then the first $n_1 m_1$ columns of H
- 4. Then the remaining $m_1 + m_4 m_2 m_3$ columns of H.

Note that we have the desired number of columns from the second and third blocks, and we have chosen them so that that those columns have nonzero entries at exactly the same rows. Furthermore, we have used all columns of G since

$$n_1 + n_4 - n_2 - n_3 + n_3 - m_3 = n_1 + n_4 - n_2 - m_3 = n_4 - m_4 + 1$$

and all columns of H since

$$n_1 - m_1 + m_1 + m_4 - m_2 - m_3 = n_1 + m_4 - m_2 - m_3 = n_2 - m_2 + 1.$$

In Example 10, the 5×5 matrix in the upper lefthand corner is the Sylvester matrix, the matrix S' is the empty matrix, and the matrix S'' is the 1×1 matrix in the lower righthand corner.

Proof of Theorem 2. We will show that if the number of parameters equals the number of non-monic coefficients, then the matrix $(G \ H)$ is square. By Propositions 9 and 11, this will imply that the model is locally identifiable.

Let $M = N_1 \wedge N_2$ be a spring-dashpot model joined in series from N_1 and N_2 , where N_1 has constitutive equation $L_1\epsilon_1 = L_2\sigma_1$ of shapes $[n_1, m_1]$ and $[n_2, m_2]$ respectively and N_2 has constitutive equation $L_3\epsilon_2 = L_4\sigma_2$ of shapes $[n_3, m_3]$ and $[n_4, m_4]$ respectively. By induction, we can assume that the number of parameters equals the number of non-monic coefficients for the systems models N_1 and N_2 , i.e. there

are $n_1 - m_1 + n_2 - m_2 + 1$ parameters in the first and $n_3 - m_3 + n_4 - m_4 + 1$ in the second. Assume the number of parameters equals the number of non-monic coefficients in this full system, i.e.

$$n_1 - m_1 + n_2 - m_2 + n_3 - m_3 + n_4 - m_4 + 2 = \max\{n_1 + n_4, n_2 + n_3\} - \min\{m_1 + m_4, m_2 + m_3\} + 1 + n_1 - m_1 + n_3 - m_3.$$

Subtracting $n_1 - m_1 + n_3 - m_3$ from both sides, we get that

$$n_2 - m_2 + n_4 - m_4 + 2 = \max\{n_1 + n_4, n_2 + n_3\} - \min\{m_1 + m_4, m_2 + m_3\} + 1.$$

From the definition of $(G \ H)$, this means the number of rows equals the number of columns, so that $(G \ H)$ is square.

The argument for the parallel extension is identical and is omitted.

Proof of Theorem 4. Theorem 2 shows that the model is locally identifiable if and only if the number of parameters equals the number of non-monic coefficients. Thus the identifiability properties of the 20 cases in Tables 3 and 4 are determined by checking the if the numbers in the columns corresponding to the number of parameters and the number of non-monic coefficients are equal. \Box

Global identifiability

We now determine necessary and sufficient conditions for global identifiability.

Proposition 12. Let $M = N_1 \wedge N_2$ be a spring-dashpot model joined in series from N_1 and N_2 , where N_1 has constitutive equation $L_1\epsilon_1 = L_2\sigma_1$ of shapes $[n_1, m_1]$ and $[n_2, m_2]$ respectively and N_2 has constitutive equation $L_3\epsilon_2 = L_4\sigma_2$ of shapes $[n_3, m_3]$ and $[n_4, m_4]$ respectively. Then the model M is globally identifiable if and only if

- 1. N_1 and N_2 are globally identifiable,
- 2. The shape factorization problem for the quadruple $([n_1, m_1], [n_2, m_2], [n_3, m_3], [n_4, m_4])$ generically has a unique solution.

Similarly, if $M = N_1 \vee N_2$ is a spring-dashpot model joined in parallel from N_1 and N_2 , then M is globally identifiable if and only if

- 1. N_1 and N_2 are globally identifiable, and
- 2. The shape factorization problem for the quadruple $([n_2, m_2], [n_1, m_1], [n_4, m_4], [n_3, m_3])$ generically has a unique solution.

Proof. We handle the case of series extensions, parallel extensions being identical. Let $M = N_1 \wedge N_2$. Clearly, N_1 and N_2 must be globally identifiable otherwise we could give two sets of parameters yielding the same constitutive equation for N_1 , which could then be combined with parameters for N_2 to get two sets of parameters for M yielding the same constitutive equation.

Now if the shape factorization problem has a unique solution, there is a unique way to take the constitutive equation for M and solve for the constitutive equations for N_1 and N_2 , since N_1 and N_2 are globally identifiable, there is a unique way to solve for parameters of those models giving a unique solution for parameters for M. Conversely, if there were multiple solutions to the shape factorization problem, then by global identifiability of N_1 and N_2 , we could solve all the way back to get multiples parameter choices for the same parameter choice for M.

Note that in our analysis of the shape factorization problem in the previous section, we saw that once L_1 and L_3 are chosen among all their finitely many values, when the model is locally identifiable there is a unique way to then construct L_2 and L_4 . Hence, the shape factorization problem has a unique solution when there is a unique way to factor $f = L_1 L_3$. This happens if and only if either $n_1 = m_1$ or $n_3 = m_3$, otherwise, generically, we can exchange roots of L_1 and L_3 giving multiple solutions.

Corollary 13. Suppose that $M = N_1 \wedge N_2$ is globally identifiable. Then either N_1 or N_2 must have been one of a spring, a dashpot, or a Maxwell model. Suppose that $M = N_1 \vee N_2$ is globally identifiable. Then either N_1 or N_2 must have been one of a spring, a dashpot, or a Voigt model.

Proof. The four models given by the spring, dashpot, Voigt, and Maxwell are the only four locally identifiable models that have the property that at least one of the differential operators in its constitutive equation has exactly one term. This can be seen by analyzing the four types (A,B,C,D) and looking at all possibilities that arise on combining two equations. Once both operators do not have a single term, no model combined from such a model can have an operator with a single term.

The three choices for the series connection (spring, a dashpot, or a Maxwell model) are the three of four models that put a differential operator with a single term in the correct place so there could be a unique solution to the shape factorization probelm. Similarly for the parallel connection. \Box

Proof of Theorem 5. Clearly a globally identifiable model is locally identifiable. By Corollary 13, we must be able to construct such a globally identifiable model by adding at each step either a spring, dashpot, Maxwell or Voigt at each step, but when adding a Maxwell it must be used in series and when using a Voigt it must have been added in parallel. However, adding a Maxwell in series can be achieved by adding a spring and then a dashpot both in series. Similarly, adding a Voigt in parallel can be achieved by adding a spring and then a dashpot both in parallel. Hence, we can work only adding springs or dashpots at each step. \Box

Acknowledgments

Adam Mahdi was partially supported by the VPR project under NIH-NIGMS grant #1P50GM094503-01A0 sub-award to NCSU. Nicolette Meshkat was partially supported by the David and Lucille Packard Foundation. Seth Sullivant was partially supported by the David and Lucille Packard Foundation and the US National Science Foundation (DMS 0954865).

References

- Ottesen JT (2011) The mathematical microscope making the inaccessible accessible. BetaSys -Systems Biology 2: 97–118.
- [2] Chis OT, Banga JR, Balsa-Canto E (2011) Structural identifiability of systems biology models: A critical comparison of methods. PLoS ONE 6: 1–16.
- [3] Bellman R, Åström K (1970) On structural identifiability. Mathematical Biosciences 7: 329–339.
- [4] Walter E, Lecourtier Y (1981) Unidentifiable compartmental models: What to do? Mathematical Biosciences 56: 1–25.
- [5] Denis-Vidal L, Joly-Blanchard G (2000) An easy to check criterion for (un)identifiability of uncontrolled systems and its applications. IEEE Trans Automat Control 45: 768–771.
- [6] Denis-Vidal L, Joly-Blanchard G (2001) Some effective approaches to check the identifiability of uncontrolled nonlinear systems. Math Comput Simul 45: 35–44.

- [7] Little MP, Heidenreich WF, Li G (2010) Parameter identifiability and redundancy: Theoretical considerations. PLoS ONE 5: e8915.
- [8] Miao H, Xia X, Perelson AS, Wu H (2011) On identifiability of nonlinear ODE models and applications in viral dynamics. SIAM Rev 53: 3–39.
- [9] Anand L, Ames NM (2006) On modeling the micro-indentation response of an amorphous polymer. International journal of plasticity 22: 1123–1170.
- [10] Terzopoulos D, Fleiseher K (1988) Modeling inelastic deformation: Viscoelasticity, plasticity, fracture. Computer Graphics 22: 269–278.
- [11] Bland D (1965) The theory of linear viscoelasticity. Oxford, London: Pergamon Press.
- [12] Christensen RM (1971) Theory of viscoelasticity, an introduction. New York, London: Academic Press.
- [13] Rosco R (1950) Mechanical models for the representation of visco-elastic properties. Br J Appl Phys 1: 171–173.
- [14] Akyildiz F, Jones RS, Walters K (1990) On the spring-dashpot representation of linear viscoelastic behaviour. Rheologica Acta 29: 482–484.
- [15] Gandhiy F, Chopra I (1996) A time-domain non-linear viscoelastic damper model. Smart Mater Struct 5: 517–528.
- [16] Fung YC (1993) Biomechanics: Mechanical Properties of Living Tissues. New York: Springer Verlag.
- [17] Ekpenyong AE, Whyte G, Chalut K, Pagliara S, Lautenschläger F, et al. (2012) Viscoelastic properties of differentiating blood cells are fate- and function-dependent. PLoS ONE 7.
- [18] Ackerley EJ, Cavan AE, Wilson PL, Berbeco RI, Meyer J (2013) Application of a spring-dashpot system to clinical lung tumor motion data. Med Phys 40: 021713.
- [19] Dietrich L, Lekszycki T, Turski K (1998) Problems of identification of mechanical characteristics of viscoelastic composites. Acta Mechanica 126: 153–167.
- [20] Alfrey KD (2000) Characterizing the Afferent Limb of the Baroreflex. Ph.D. thesis. Houston: Rice University.
- [21] Bugenhagen SM, Cowley AWJ, Beard DA (2010) Baroreceptor dynamics and their relationship to afferent fiber type and hypertension. Physiological Genomics 42: 23–41.
- [22] Mahdi A, Sturdy J, Ottesen JT, Olufsen M (2013) Modeling the afferent dynamics of the baroreflex control system : Preprint.
- [23] Learoyd BM, Taylor MG (1966) Alterations with age in the viscoelastic properties of human arterial walls. Circ Res 18: 278–292.
- [24] Nichols WW (2011) McDonald's blood flow in arteries : theoretical, experimental and clinical principles. London: Hodder Arnold, 6th ed. / Wilmer W. Nichols, Michael f. O'Rourke, Charalambos Vlachopoulos. edition.
- [25] Kalita P, Schaefer R (2008) Mechanical models of artery wall. Arch Comput Methods Eng 15: 1–36.
- [26] Houk J, Cornew RW, Stark L (1966) A model of adaptation in amphibian spindle receptors. J Theoretical Biol 12: 196–215.

- [27] Hasan Z (1983) A model of spindle afferent response to muscle stretch. Journal of Neurophysiology 49: 989–1006.
- [28] Flügge W (1975) Viscoelasticity. New York: Springer Verlag.
- [29] Mahdi A, Ottesen JT, Olufsen M (2012) Qualitative aspects of a novel baroreceptor model. Proc Int Workshop on Innovative Simul for Health Care Backfrieder, Bruzzone, Longo, Novak, Rosen, Eds.: 89-94.
- [30] Cox DA, Little J, O'Shea D (2005) Using algebraic geometry, volume 185 of *Graduate Texts in Mathematics*. New York: Springer, second edition.