Investigating the Structural Identifiability Analysis by Extended Observability Method

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Abstract:
The usefulness of structural identifiability analysis by extended observability is investigated. The theoretical framework of both structural identifiability and observability is presented in an intuitive fashion, e.g. through examples. The theory is first explained in the linear case and then extrapolated to the nonlinear. The method is applied to different iterations of a case model and are analysed for structural identifiability, as well as correlated parameters and states. It is concluded that as long as it is feasible to perform the computations, a structural identifiability analysis is worth performing. Furthermore, it is shown that the method can pinpoint the conditions under which a model can become structurally identifiable, even if the model is not initially. With some assumptions made it is shown which parameters in the case model were correlated and resulted in the model being structurally unidentifiable. It is found that the method has some limitations, mainly due to how computationally demanding the implementation is, when analysing large models. It is however not clear for the case model, whether the limitations are due to a lack of memory, a property of the method, or the implementation.
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Preface

This report was written as a combined subject module project and bachelor thesis at Roskilde University. We would like to thank our supervisor Johnny T. Ottesen for all his help. Furthermore we would also like to thank Rasmus K. Pedersen and Heine Larsen for their assistance and consultations.

Even though Roskilde University won’t acknowledge Karl Nordentoft’s contribution to this report, we would like to stress that his contribution has been absolutely equal to that of the rest of the authors.
Reading Guide

Each chapter in the report begins with a metatext, in which the purpose and structure of the chapter is presented. Within the theory chapter, metatexts are also present for each section and subsection. Within the analysis, metatexts are included for the sections. The discussion only has a metatext for the chapter itself. Metatexts are denoted by *italics* and as such are easily distinguishable from regular text.

The target audience of this report is natural science bachelor students on fifth or sixth semester in their studies. The project is meant to be written as a coherent text, but assumes some background in linear algebra, and calculus. Some experience in mathematical modelling is also an advantage, but is not a prerequisite.

Note that we included a list of abbreviations and a list of some selected equations in the back of the report. This might be of some help to the reader.
1. Introduction

With the advent of computers it has become feasible to make larger and larger mathematical models through which we can gain new insight into the inner workings of systems. Therefore the interest in studying these models has been increasing, and increasing complexity in the models pose new challenges in investigating them.

It is interesting to analyse mathematical models, to see what information we can get of the whole system when we can only observe a smaller part of the system. When we have a given mathematical model and we know that we can only observe some part of the system, we might ask the question: "What can we learn about the parameters in the model, from what we can observe?" This is called identifiability and is a problem of great relevance in a variety of subjects that utilise mathematical models.

Identifiability analysis is often done numerically a posteriori of parameter estimation (DiStefano, 2013). It is however also possible to do an identifiability analysis a priori. Such analysis will usually investigate the very structure of the model and is called structural identifiability (SI). SI thus concerns a more fundamental question than the one posed above: "What is it theoretically possible to learn about the parameters in the model, from what we can observe?".

Whether a model is structurally identifiable has wide implications for the usability of the model, as well as for the quantification of the model. For novice modellers, the problems they are facing may stem from these implications, without the modeller realising that this is the cause (DiStefano, 2013). Some modellers who do recognise said problems, attempt to circumvent the problem by leaving the model unquantified, thereby arguing that the need to analyse for structural identifiability is removed, as a parameter estimation is never performed (Gutenkunst et al., 2007). Even in these cases, structural identifiability is worth analysing for, as an unidentifiable (unID) model can compromise its ability to provide insight into the system, even if the model is never quantified (Villaverde, 2019).
One challenge of analysing identifiability structurally is that the approaches for doing so are quite limited in scope in terms of how large systems it is feasible to compute on (Villaverde, Barreiro et al., 2016b). This is partly a consequence of the methods being much less widespread than numerical identifiability (NI) analysis, and thus having had much less work dedicated to finding effective approaches. Interest in structural identifiability is however currently increasing and recently a new method has been develop to perform the analysis.

This method is called "structural identifiability analysis by extended observability" (ObsID). Observability is a concept that stems from control theory which investigates whether states can be determined from the input and output of a model. Observability is then expanded in ObsID, to investigate the parameters along with the states thereby also studying the SI of the model. ObsID does not test for global SI, but only local SI. Hence references to SI will implicitly denote structural local identifiability. ObsID is relevant because it is supposedly capable of working upon larger models than previous methods (Villaverde, Barreiro et al., 2016b). A potential case model is the Cancitis model (Sajid et al., 2019). This leads us to the following research question:

1.0.1 Research Question

How useful is structural identifiability analysis by extended observability at providing new information about a given mathematical model? How can this information be applied in an analysis of the Cancitis model?

1.0.2 Method and Problem Boundaries

The main focus of this report is upon the mathematical aspect of the problem. Therefore the biological intricacies of the Cancitis model will be largely ignored. The report is written with the intent of providing an intuitive explanation of theory and its applications.

In the analysis we will perform ObsID analysis on the cancitis model, using the matlab-package STRIKE-GOLDD (Villaverde, Barreiro et al., 2016a).
2. Theory

In this chapter the theory of observability, SI and ObsID will be presented. The method of ObsID is built on the theory of observability and SI and will thus be explained lastly. To give the reader an intuitive sense of the theory, examples will be given throughout the chapter. They are chosen so as to illustrate the discussed methods.

ObsID analysis is done through generalised observability analysis, which does not require linearity. The theory in the observability and SI sections will however be presented so that the linear case is shown first. This done to illustrate the method in an intuitive framework, which is then generalised for the nonlinear case. Lastly the generalised method for observability, is combined with SI, to define the method of ObsID.

2.1 Observability

This section will introduce the concept and methodology of observability. The section will start with an explanation of the properties and purpose of observability. This explanation will then be related to the mathematical definition and criteria for observability.

Afterwards the case of linear time-invariant systems will be reviewed more thoroughly. This is then extrapolated to the nonlinear case.

Observability is a concept in which knowledge of model inputs and outputs are related to knowledge of the states of the model. Observability can be described by:

“In order to see what is going on inside the system under observation, the system must be observable” (Liu, 2018).

This description serves as an intuitive understanding of the concept. An observable system is simply a system that is structured in such a way that information about the system itself can be gained from its outputs and in-
puts. Strictly speaking however, observability is not an inherent property of the system that is investigated but rather of the model that is used to describe the system. This distinction matters, since the same system can be described with both observable and unobservable models (DiStefano, 2013).

Formally, observability is usually expressed by the notion that if the initial state can be uniquely determined from the outputs and inputs, then the model is observable. This leads us to a broad definition that holds for both linear and nonlinear cases based on the model:

\[
\begin{align*}
\dot{x} &= f(x, u, p, t) \\
y &= g(x, u, p, t) \\
x_0 &= x(t_0)
\end{align*}
\]

Where \( t \in \mathbb{R} \) is time, \( x \in C^1(\mathbb{R}, \mathbb{R}^n) \) the state variables, \( y \in C^0(\mathbb{R}, \mathbb{R}^m) \) the outputs, \( u \in C^0(\mathbb{R}, \mathbb{R}^r) \) the inputs and \( p \in \mathbb{R}^q \) the constant parameters. Furthermore \( f \in C^{n-2}(\mathbb{R}^{n+r+q+1}, \mathbb{R}^n) \) and \( g \in C^{n-1}(\mathbb{R}^{n+r+q+1}, \mathbb{R}^m) \). \( t_0 \) denotes the initial timepoint, and \( x_0 \in \mathbb{R}^n \) here denotes the values of the state variables at the initial timepoint \( t_0 \).

Under the assumption of complete knowledge of model structure, observability can then be defined generally as:

**Definition 2.1.1.** A state \( x_i(\tau) \) is said to be observable if it can be determined from the output \( y(t) \) and any known inputs \( u(t) \) of the model in the interval \( t_0 \leq \tau \leq t \leq t_1 \) for a finite \( t_1 \). Otherwise, it is unobservable. A model is observable if all its states are observable (Villaverde, Tsiantis et al., 2019).

Where \( x_i \in \mathbb{R} \) denotes the value of a single state\(^1\), \( x_i \in x \). \( \tau \in t \) denotes some specific time.

So at some specific time \( \tau \), the state \( x_i \) is observable if it is possible to determine the value of the state at the time, \( x_i(\tau) \), from the inputs and outputs of the model at the time greater than or equal to \( \tau \), while still being finite. If this is true for all states in the model, the model itself is observable.

\(^1\)Note that even though this is the same notation as for the initial values of the state vector, \( x_0 \), they denote different things. When the index is zero we denote a state vector at initial conditions. Otherwise the index denote a element of \( x \). For time \( t \) the index always refers to a specific time.
2.1.1 Linear Observability

This subsection will begin by introducing a state-space representation of the model, from which it will be shown that a specific sequence of derivatives can be found. It will then be shown how this sequence can be used to analyse the observability of the system by arranging the derivatives in a matrix. The method is then applied to a physics example.

An LTI system with constant coefficients is the simplest case to analyse for observability and for that reason is used to exemplify the process. In this case it is unnecessary to define an interval to test for observability in, since if the model is observable at a time \( \tau \), it is for all \( t \). Thus, the test will tell whether the model is either completely observable or not at all (DiStefano, 2013).

We consider the state-space representation of a system, as the set of inputs, outputs and variables related by first order differential equations. The state-space representation of equation (2.1) is:

\[
\begin{align*}
\dot{x} &= Ax + Bu \\
y &= Cx \\
t_0 &= 0
\end{align*}
\]  

(2.2)

where \( x \in C^1(\mathbb{R}, \mathbb{R}^n) \), \( y \in C^0(\mathbb{R}, \mathbb{R}^m) \), \( u \in C^0(\mathbb{R}, \mathbb{R}^r) \). \( A \) is a coefficient state matrix, where \( A \in \mathbb{R}^{n \times n} \), \( B \), the input coefficient matrix, where \( B \in \mathbb{R}^{n \times r} \), \( C \) is the output coefficient matrix, where \( C \in \mathbb{R}^{m \times n} \).

The question to be answered at this stage is: is it possible to uniquely determine the state vector \( x(t) \), at any given time \( t \), from known outputs?

The state-vector can at any specific point in time, \( \tau \), be interpreted as a point, \( x(\tau) \), in the n-dimensional state-space and the state vector function \( x(t) \) can be interpreted as the responses that traces out a trajectory in the state-space. By this interpretation it is evident that complete knowledge about the model at some state \( x(\tau) \) is sufficient for determining \( x(t) \) at any time \( t \). This can be verified analytically by finding the particular solution for \( x(t) \). Equation (2.2) can be written as \( \dot{x} = Ax + Bu \implies \dot{x} + (-A)x = Bu \).

Equations of this form, \( \dot{w} + h_1(s)w = h_2(s) \), can be solved analytically through the following equation:

\[
w(t) = e^{H_1(t)} \int_{t_0}^{t_1} e^{-H_1(s)} h_2(s) \ ds + ce^{H_1(t)}
\]  

(2.3)
Which for equation (2.2) becomes:

$$x(t) = e^{At} \int_{t_0}^{t_1} e^{-A(u)} Bu \, du + ce^{At}$$  (2.4)

Observability of a LTI system depends on the two coefficient matrices $A$ and $C$ as we consider zero input response. Even if inputs are present the properties remain unchanged as knowing the input is a precondition for conducting the test, and the effect of the input can be subtracted in the end. Omitting the input term $Bu$ from equation (2.2) simplifies it to the following form:

$$\dot{x} = Ax$$
$$y = Cx$$
$$t_0 \equiv 0$$  (2.5)

This also means that equation (2.4) can be simplified significantly:

$$x(t) = e^{At} \int_{t_0}^{t_1} 0 \, du + ce^{At} = ce^{At}$$  (2.6)

It is usually most convenient to evaluate the system for the initial states. Equation (2.6) then becomes:

$$x(t_0) = ce^{A0} = c \equiv x_0$$  (2.7)

A unique sequence of initial states, if they exists, can then be found by solving the equation:

$$y_0 = Cx_0$$  (2.8)

For $x_0$, when considering zero inputs (DiStefano, 2013). At this point it is evident that whilst the model simply requires, $x \in C^1(\mathbb{R}, \mathbb{R}^n)$ and $y \in C^0(\mathbb{R}, \mathbb{R}^m)$, it follows from the structure of (2.5) that $x$ and $y$ become infinitely differentiable. With the assumption that the system is complete (Hermann and Krener, 1977) and that the time-derivatives of $y$ can be determined, a sequence of $i+1$ continuous-time outputs are generated by taking the derivative of equation (2.5) $i$ times:

$$y_0 = Cx_0$$
$$y_0 = Cx_0 = CAx_0$$
$$\dot{y}_0 = CAx_0 = CA^2x_0$$
$$\vdots$$
$$y_0^{(i)} = CA^ix_0$$  (2.9)
Due to the time-invariance of LTI systems, complete knowledge of the model's observability is available from analysis at any single time. Equation (2.9) can thus also be expressed in a generalised form:

\[
\begin{align*}
  y &= Cx \\
  \dot{y} &= C\dot{x} = CAx \\
  \ddot{y} &= C\ddot{x} = CA^2x \\
  &\vdots \\
  y^{(i)} &= Cx^{(i)} = CA^ix
\end{align*}
\] (2.10)

Observability analysis of model (2.5) is then done by arranging the sequence of its output derivatives (2.10) as submatrices in a matrix $O_L$, called the linear observability matrix.

\[
O_L = \begin{pmatrix}
C \\
CA \\
CA^2 \\
\vdots \\
CA^{n-1}
\end{pmatrix}
\] (2.11)

Where $O_L \in \mathbb{R}^{n \times m} \times \mathbb{R}^n$ with $n$ being the amount of states in the system, and $m$ being the amount of output equations. The structure of $O_L$ means that it is sufficient to build the observability matrix from $n$ equations. The reasoning for this is based on the Cayley-Hamilton theorem, which states that:

**Theorem 2.1.1** (Cayley-Hamilton theorem). Given a square matrix $A$ with dimension $n \times n$ and corresponding characteristic polynomial $p(\lambda) = \det(\lambda I - A)$, with $I$ being the identity matrix with equal dimensions, then $A$ is a root in the equation $p(A) = 0$, where $p(A)$ is a matrix polynomial corresponding to $p(\lambda)$.

So if we have a matrix $A$ with dimensions $n \times n$, the characteristic polynomial of $A$ is given by:

\[
\lambda^n + a_{n-1}\lambda^{n-1} + \ldots + a_2\lambda^2 + a_1\lambda + a_0 = 0
\] (2.12)

the matrix $A$, would satisfy the equation:

\[
A^n + a_{n-1}A^{n-1} + \ldots + a_2A^2 + a_1A + a_0 = 0
\] (2.13)

Solving this equation for $A^n$ we get:

\[
A^n = -a_{n-1}A^{n-1} - \ldots - a_2A^2 - a_1A - a_0I
\] (2.14)
so we can write $A^n$ as a linear combination of $A$ raised to a power lower than $n$.

$$A^n = \sum_{j=0}^{n-1} -a_j A^j$$  (2.15)

This argument also holds for powers greater than $n$. This can be seen in equation 2.14 if we multiply by $A$ on both sides

$$A^{n+1} = -a_{n-1}A^n - \ldots - a_2 A^3 - a_1 A^2 - a_0 A$$  (2.16)

The first term on the right hand side, $-a_{n-1}A^n$, has already been shown to be a linear combination of $A$ raised to a power lower than $n$, so the left hand side, $A^{n+1}$, is therefore also a linear combination of terms with power lower than $n$. The same argument would apply for even higher powers. Therefore $A$ raised to an arbitrary power can be described by a matrix polynomial with $A$ raised up to $n - 1$ power.

Since the state coefficient matrix $A$ from equation (2.2) is square, theorem 2.1.1 applies to it. Thereby it is sufficient to build $O_L$ as an $m \cdot n \times n$ matrix, since it is certain that adding the $n$th output derivative to the observability matrix has no purpose, as it would be a linear combination of the prior derivatives. This is an essential property of the observability matrix, since observability analysis is based on determining the rank of $O_L$, as stated in theorem 2.1.2:

**Theorem 2.1.2 (Linear Observability Rank Condition).** Given a linear time-invariant model $M_L$ as defined in (2.2), a necessary and sufficient condition for complete observability is that rank($O_L = n$), where $O_L = (C|C \cdot A|C \cdot A^2| \ldots |C \cdot A^{n-1})^T$ (Villaverde, 2019).

which states that the rank of the observability matrix $O_L$ must be of rank $n$ for the system to be observable. If the rank is less than $n$ the model is said to be unobservable and this implicates that some states are correlated. Since the full observability matrix has dimensions $m \cdot n \times n$, a minimum of $\frac{n}{m}$ output derivatives must be taken\(^2\), before it can have rank $n$. Further output derivatives can then be added, until the maximum of $n$ derivatives, at which theorem 2.1.1 implies that the rank can no longer increase.

In such a case, it is possible to extract information in regards to identifying the unobservable states, from the observability matrix. We can examine this\(^2\) Otherwise the matrix will have fewer rows than $n$. 

\[\text{\footnotesize 8}\]
property of the states, by removing a column of the observability matrix. If the rank of the matrix is reduced as a result of this, the state corresponding to the removed column is observable. In converse, if the rank remains the same, the state is unobservable.

**Theorem 2.1.3** (Linear Observability Condition). *Given a model $M$ defined by equation (2.1), its $i$th state $x_i$ is observable if $\text{rank}(O^{i*}(\tilde{x})) < \text{rank}(O(\tilde{x}))$, where $O(\tilde{x})$ is the observability matrix, and $(O^{i*}(\tilde{x}))$ is the matrix found by removing the column corresponding to $x_i$ from $O(\tilde{x})$ (Villaverde, 2019).*

The observability matrix maps from the initial state $x_\tau$ into the resulting output trajectory, shown in equation (2.10), and the evaluation verifies if it is possible to retrace the trajectory back to the origin. By finding the inverse of $O_L$ and multiplying equation 2.10 with the inverse, $x_\tau$ is isolated. In the cases where there is more than one output, the left inverse of $O_L$ is used to isolate $x_\tau$.

### 2.1.2 Linear Observability Analysis Example

The model is adapted from the article "Coupled spring equations" (Fay and Graham, 2003) and is a system with two connected springs as shown in figure 2.1.
Figure 2.1: Model of two connected springs. $x_1$ denotes the position of the mass $m_a$ and $x_2$ (not shown on the figure) denotes the velocity of $m_a$. $x_3$ denotes the position of the mass $m_b$ and $x_4$ (not shown in the figure) denotes the velocity of $m_b$.

We assume these springs obey Hooke’s law, meaning we can write the restoring force as $F = -kl$ where $k$ is the spring constant, and $l$ is the elongation of the spring.

We denote the change in position from the equilibrium point of the first mass $m_a$ by $x_1$, and $x_2 = \dot{x}_1$ is its velocity. Likewise $x_3$ is the change in position of the second mass $m_b$ relative to its equilibrium point, and $x_4 = \dot{x}_3$ is its velocity.

In this system, there are two forces acting on the upper mass. A restoring force, from the elongation of the upper spring $-k_a x_1$ and a force $-k_b (x_1 - x_3)$ from the compression of the other spring. On the second mass, we will have the restoring force $-k_b (x_3 - x_1)$. Letting $\ddot{x}_2$ and $\ddot{x}_4$ denote the acceleration and using Newton’s second law, we get a system of four equations:

\begin{align}
\dot{x}_1 &= x_2 \\
\dot{x}_2 &= -\frac{k_a}{m_a} x_1 - \frac{k_b}{m_a} (x_1 - x_3) \\
\dot{x}_3 &= x_4 \\
\dot{x}_4 &= -\frac{k_b}{m_b} (x_3 - x_1)
\end{align}

(2.17)
We can rearrange this into matrix form, using state-space representation notation, since it is a state determined model:

\[
\dot{x} = Ax = \begin{pmatrix}
0 & 1 & 0 & 0 \\
\frac{k_a + k_b}{m_a} & 0 & \frac{k_b}{m_a} & 0 \\
0 & \frac{k_b}{m_a} & 0 & 1 \\
\frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0
\end{pmatrix}
\begin{pmatrix}
x_1 \\
x_2 \\
x_3 \\
x_4
\end{pmatrix}
\]  
(2.18)

Assuming that only the position of the second mass can be observed is this system then observable? In this case our output coefficient matrix is simply a row vector:

\[
C = \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix}
\]  
(2.19)

and the observability matrix:

\[
O_L = \begin{pmatrix} C \\ CA \\ CA^2 \\ CA^3 \end{pmatrix}
\]  
(2.20)

\(CA\) is the third row of \(A\), that is \(CA = (0 0 0 1)\). Similarly \(CA^2 = (CA)A\) is the fourth row of \(A\), \(CA^2 = \left(\frac{k_b}{m_b} 0 - \frac{k_b}{m_b} 0\right)\). \(CA^3 = (CA^2)A\) is then:

\[
CA^3 = \left(\frac{k_b}{m_b} 0 - \frac{k_b}{m_b} 0\right)
\begin{pmatrix}
0 & 1 & 0 & 0 \\
\frac{k_a + k_b}{m_a} & 0 & \frac{k_b}{m_a} & 0 \\
0 & \frac{k_b}{m_a} & 0 & 1 \\
\frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0
\end{pmatrix}
\]  
(2.21)

\[
CA^3 = \begin{pmatrix} 0 & \frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} \end{pmatrix}
\]

Inserting our calculated submatrices, we obtain the observability matrix:

\[
O_L = \begin{pmatrix}
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1 \\
\frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0 \\
0 & \frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b}
\end{pmatrix}
\]  
(2.22)

We see that \(\text{rank}(O_L) = 4\), which is full rank and our system is therefore observable.
2.1.3 Nonlinear Observability

In this subsection observability will be generalised to the nonlinear case. The method is based on the use of Lie derivatives to build what is called the general observability matrix. We will show how the method can be used in a familiar example. We will also use the theory behind nonlinear observability to create a case that is unobservable.

Observability analysis of a nonlinear model is an extension of the linear method and as such depends similarly on the rank of the observability matrix and should yield identical results. To test for observability of nonlinear models, it is however necessary to revamp the approach as the derivatives of the outputs cannot be expressed in terms of the coefficient matrices $A$, $B$ and $C$ (Villaverde, 2019). In the nonlinear case we take the Lie derivatives, which for a smooth function $g(x)$ and vectorfield $f(x)$ (Villaverde, Barreiro et al., 2016a), we write:

$$L_f g(x) = \frac{\partial g(x)}{\partial x} f(x) \quad (2.23)$$

Note that we consider an input free system and have omitted the term from the equation.

When we write $\frac{\partial g(x)}{\partial x}$ this is the Jacobian$^3$. The Jacobian has dimensions $m \times n$ where $m$ is the number of outputs and $n$ is the number of states. In the case where $m = 1$ the Jacobian is a row gradient.

Lie derivatives can be defined recursively (Röbenack and Reinschke, 2000). For $k = 1$ the Lie derivative is:

$$L_f^1 g(x) = \frac{\partial g(x)}{\partial x} f(x) \quad (2.24)$$

and for $k = 2$:

$$L_f^2 g(x) = \frac{\partial L_f^1 g(x)}{\partial x} f(x) \quad (2.25)$$

and so for higher order Lie derivatives we get (Röbenack and Reinschke, 2000):

$$L_f^k g(x) = \frac{\partial L_f^{k-1} g(x)}{\partial x} f(x) \quad \text{with} \quad L_f^0 g(x) = g(x) \quad (2.26)$$

$^3$It is worth noting here, that we use a notation, that is used commonly throughout the relevant litterature, but is not often seen outside.
By using this we can build the generalised observability matrix for nonlinear systems (Villaverde, Barreiro et al., 2016a):

$$\mathcal{O}_{NL}(x) = \begin{pmatrix}
\frac{\partial g(x)}{\partial x} \\
\frac{\partial}{\partial x} (L_1^1 g(x)) \\
\frac{\partial}{\partial x} (L_1^2 g(x)) \\
\vdots \\
\frac{\partial}{\partial x} (L_1^n g(x))
\end{pmatrix} \tag{2.27}$$

and by the given theorem 4:

**Theorem 2.1.4** (Nonlinear Observability Rank Condition). A nonlinear model \( M_{NL} \) as defined in (2.1), with constant input \( u \) satisfies \( \text{rank}(\mathcal{O}_{NL}(x_0)) = n \), where \( \mathcal{O}_{NL} \) is defined by (2.27), then it is locally observable around \( x_0 \) (Villaverde, 2019).

Local observability means that it is possible to distinguish between two adjacent states, but there might still exist distant states that are indistinguishable. Often, if a model is locally observable it is also globally observable (Villaverde, 2019).

### 2.1.4 Nonlinear Observability Analysis Example

Looking again at our model for the system of two springs, we can build the nonlinear observability matrix and see that the result is the same. In this model we have:

$$f(x) = \begin{pmatrix}
-\frac{(k_a + k_b)x_1}{m_a} + \frac{k_bx_3}{m_a} \\
\frac{k_bx_1}{m_b} - \frac{k_bx_3}{m_b} \\
x_4 \\
x_2
\end{pmatrix} \tag{2.28}$$

$$g(x) = x_3$$

Forming the first submatrix of the observability matrix, we find:

$$\frac{\partial g(x)}{\partial x} = \begin{pmatrix}
\frac{\partial x_3}{\partial x_1} & \frac{\partial x_3}{\partial x_2} & \frac{\partial x_3}{\partial x_3} & \frac{\partial x_3}{\partial x_4}
\end{pmatrix} = \begin{pmatrix}
0 & 0 & 1 & 0
\end{pmatrix} \tag{2.29}$$

\(^4\text{An actual proof of the theorem is done in the article (Hermann and Krener, 1977)}\)
Multiplying this by \( f(x) \) we can find the first Lie derivative:

\[
L_1^f g(x) = \frac{\partial g(x)}{\partial x} f(x)
\]

\[
= \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} -\frac{(k_a + k_b)x_1}{m_a} & -\frac{k_b x_3}{m_a} & \frac{x_2}{m_a} \\ -\frac{k_b x_1}{m_b} & -\frac{k_b x_3}{m_b} & \frac{x_4}{m_b} \end{pmatrix} = x_4
\]

(2.30)

Repeating the procedure we find the second submatrix:

\[
\frac{\partial}{\partial x} (L_1^f g(x)) = \begin{pmatrix} \frac{\partial x_4}{\partial x_1} & \frac{\partial x_4}{\partial x_2} & \frac{\partial x_4}{\partial x_3} & \frac{\partial x_4}{\partial x_4} \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 & 1 \end{pmatrix}
\]

(2.31)

Multiplying this submatrix by \( f(x) \) we can find the second Lie derivative:

\[
L_2^f g(x) = \begin{pmatrix} 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} -\frac{(k_a + k_b)x_1}{m_a} + \frac{k_b x_3}{m_a} & \frac{x_2}{m_a} \\ \frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b} & \frac{x_4}{m_b} \end{pmatrix} = \frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b}
\]

(2.32)

From which the third submatrix can be found as:

\[
\mathcal{O}_{3,*} = \begin{pmatrix} \frac{\partial}{\partial x_1} \begin{pmatrix} k_b x_1 - k_b x_3 \\ m_b \end{pmatrix} \\ \frac{\partial}{\partial x_2} \begin{pmatrix} k_b x_1 - k_b x_3 \\ m_b \end{pmatrix} \\ \frac{\partial}{\partial x_3} \begin{pmatrix} k_b x_1 - k_b x_3 \\ m_b \end{pmatrix} \\ \frac{\partial}{\partial x_4} \begin{pmatrix} k_b x_1 - k_b x_3 \\ m_b \end{pmatrix} \end{pmatrix}^T
\]

(2.33)

\[
\mathcal{O}_{3,*} = \begin{pmatrix} k_b & 0 & -k_b & 0 \\ m_b & 0 & m_b & 0 \end{pmatrix}
\]
where $O_{3,*}$ denotes the third row of $O$.

The last submatrix is then found through the third Lie derivative which is:

$$L^3_{j}g(x) = \begin{pmatrix} k_b/m_b & 0 & -k_b/m_b & 0 \end{pmatrix} \begin{pmatrix} -(k_a + k_b)x_1/m_a + k_b x_3/m_a \\ x_2 \\ 0 \\ k_b x_1/m_b - k_b x_3/m_b \end{pmatrix}$$

$$L^3_{j}g(x) = \frac{k_b x_2}{m_b} - \frac{k_b x_4}{m_b}$$

And the fourth submatrix is then:

$$O_{4,*} = \begin{pmatrix} \partial \left( \frac{k_b x_2}{m_b} - \frac{k_b x_4}{m_b} \right) \\ \partial \left( \frac{k_b x_2}{m_b} - \frac{k_b x_4}{m_b} \right) \\ \partial \left( \frac{k_b x_2}{m_b} - \frac{k_b x_4}{m_b} \right) \\ \partial \left( \frac{k_b x_2}{m_b} - \frac{k_b x_4}{m_b} \right) \end{pmatrix}$$

$$O_{4,*} = \begin{pmatrix} 0 & k_b/m_b & 0 & -k_b/m_b \end{pmatrix}$$

These submatrices then form the nonlinear observability matrix for our spring model\(^5\) as in equation (2.27):

$$O = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ k_b/m_b & 0 & -k_b/m_b & 0 \\ 0 & k_b/m_b & 0 & -k_b/m_b \end{pmatrix}$$

The matrix looks familiar since it is identical to the observability matrix we got, using the method for linear systems. Obviously, since the matrix is the same, we can draw the same conclusion; the system is observable.

---

\(^{5}\)This computation was also performed using the Computer Algebra System (CAS) Sage (The Sage Developers, 2017), the script can be seen in section A.2.1.
2.1.5 Unobservable Nonlinear Model Example

Consider the case for equation (2.1), where \( f(x_1, x_2) \) is a vector function of two states, \( f : \mathbb{R}^2 \rightarrow \mathbb{R}^2 \). The output function \( g(x_1, x_2) \), has one output, \( g : \mathbb{R}^2 \rightarrow \mathbb{R}^1 \).

The first Lie derivative will be:

\[
L^1_fg(x) = \frac{\partial g(x)}{\partial x_1} \cdot f(x)_1 + \frac{\partial g(x)}{\partial x_2} \cdot f(x)_2
\]

(2.37)

where \( f(x)_1 \) and \( f(x)_2 \) denotes the first and second element of \( f(x) \), respectively.

An obvious case where the model is not observable, is when \( \text{rank}(\mathcal{O}) \neq n \), is if the first Lie derivative is zero. Setting the first Lie derivative to zero, we get:

\[
\frac{\partial g(x)}{\partial x_1} \cdot f(x)_1 + \frac{\partial g(x)}{\partial x_2} \cdot f(x)_2 = 0
\]

(2.38)

Which we can solve for \( f(x)_1 \):

\[
f(x)_1 = -\left( \frac{\frac{\partial g(x)}{\partial x_1}}{\frac{\partial g(x)}{\partial x_2}} \right) \cdot f(x)_2
\]

(2.39)

Example of non-observable

If we now consider a model where we have \( g(x) = f(x)_2 \) and \( f(x)_2 = \cos(x_1) + \sin(x_2) \)

A model which would satisfy equation (2.39) is then:

\[
f(x) = \begin{pmatrix}
\cos(x_1) + \sin(x_2) \\
\sin(x_1) \\
\cos(x_1) + \sin(x_2)
\end{pmatrix}
\]

(2.40)

As previously mentioned, the Jacobian is equal to a row gradient when \( m = 1 \). In this case the row gradient is:

\[
\left( \frac{\partial g(x)}{\partial x_1} \quad \frac{\partial g(x)}{\partial x_2} \right) = \left( -\sin(x_1) \quad \cos(x_2) \right)
\]

and its field is shown alongside the function vector field in figure 2.2.
Figure 2.2: The gradient field in red alongside the function vector field shown in blue. The two vector fields are perpendicular everywhere. The figure was created using Sage (The Sage Developers, 2017), the script can be seen in appendix A.2.2.

As can be seen from figure 2.2 the gradient vector field and the function vector field are perpendicular everywhere, which makes sense because this is how we created our model. This can also be seen by creating the nonlinear observability matrix. Since we already have derived the first entry, we only need to derive the second:

\[
L_f^1 g = \left( \frac{\partial g(x)}{\partial x_1} \quad \frac{\partial g(x)}{\partial x_2} \right) \cdot \left( \frac{\left(\cos(x_1) + \sin(x_2)\right) \cos(x_2)}{\sin(x_1)} \quad \frac{\sin(x_1)}{\cos(x_1) + \sin(x_2)} \right)
= (-\sin(x_1) \quad \cos(x_2)) \cdot \left( \frac{\left(\cos(x_1) + \sin(x_2)\right) \cos(x_2)}{\sin(x_1)} \quad \frac{\sin(x_1)}{\cos(x_1) + \sin(x_2)} \right)
= \left(\cos(x_1) + \sin(x_2)\right) \cos(x_2) - \cos(x_2)(\cos(x_1) + \sin(x_2)) = 0
\]

Now we can build our observability matrix:

\[
\mathcal{O} = \left( \begin{array}{cc} -\sin(x_1) & \cos(x_2) \\ 0 & 0 \end{array} \right)
\]
For cases where the system is unobservable, theorem 2.1.3 can be generalised to the nonlinear case:

**Theorem 2.1.5 (Nonlinear Observability Condition).** Given a model $M$ defined by equation (2.1), it’s $ith$ state $x_i$ is locally observable in a neighbourhood $V(x_r)$, if $\text{rank}(\mathcal{O}^*(\vec{x}_r)) < \text{rank}(\mathcal{O}(\vec{x}_r))$, where $\mathcal{O}(\vec{x}_r)$ is the observability matrix defined in equation (2.27), generated for the statevector $x_r$, and $(\mathcal{O}^*(\vec{x}_r))$ is the matrix found by removing the column corresponding to $\frac{\partial}{\partial \vec{x}_i}$ from $\mathcal{O}(\vec{x}_r)$ (Villaverde, 2019).

By theorem (2.1.5) it can be seen that through our observability matrix (2.42) that both states are unobservable, since the rank remains the same, no matter which column we remove.

### 2.2 Structural Identifiability

In this section the concept of structural identifiability will be presented. Firstly the concept and purpose of structural identifiability will be explained. This will be related to the mathematical definition and criteria for identifiability.

The concept of linear structural identifiability will be explained to give the reader an intuitive grasp of the concept. Afterwards the problem of structural identifiability in the nonlinear case will be presented.

Structural identifiability analysis, is the act of analysing a model and assessing whether it is possible to quantify parameters given ideal noise-free input-output data. SI analysis is a qualitative modelling concept, meaning it does not need real data but rather manipulates the model symbolically. It is through these manipulations that SI analysis reveals if the given parameters are quantifiable (DiStefano, 2013).

We consider the general model from equation (2.1):

\[
\begin{align*}
\dot{x} &= f(x, u, p, t) \\
y &= g(x, u, p, t) \\
x_0 &= x(t_0)
\end{align*}
\]

Where $t \in \mathbb{R}$ is time, $x \in C^1(\mathbb{R}, \mathbb{R}^n)$ the state variables, $y \in C^0(\mathbb{R}, \mathbb{R}^m)$ the outputs, $u \in C^0(\mathbb{R}, \mathbb{R}^n)$ the inputs and $p \in \mathbb{R}^q$ the constant parameters. Furthermore $f \in C^{n-2}(\mathbb{R}^{n+r+q+1}, \mathbb{R}^n)$ and $g \in C^{n-1}(\mathbb{R}^{n+r+q+1}, \mathbb{R}^m)$. 

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With the true parameters of the system denoted by $p^* \in \mathbb{R}^q$, and some parameter guess denoted by $p_{\text{guess}} \in \mathbb{R}^q$ we have the following definition:

**Definition 2.2.1 (Structural Local Identifiability).** A parameter $p_i \in p_{\text{guess}}$ is structurally locally identifiable, if for almost\(^6\) any true parameter value $p_i^* \in p^*$, there exists a neighbourhood $V(p^*)$, where:

$$p_{\text{guess}} \in V(p^*) \text{ and } y(t, p_{\text{guess}}) = y(t, p^*) \implies p_{\text{guess}} = p^* \quad (2.43)$$

If all parameters $p_1, p_2, \ldots, p_n$ are structurally locally identifiable, the model is structurally locally identifiable (Villaverde, Barreiro et al., 2016b).

If the parameter guess $p_{\text{guess}}$ is within the neighbourhood $V(p^*)$ of the true parameter value, the model output $y(t, p_{\text{guess}})$ can only be the same as the model output for the true parameter $y(t, p^*)$, if the guess $p_{\text{guess}}$ is the true parameter value $p^*$.

The SI of both the model and the parameters can be extrapolated to global SI, if all possible parameter values fulfill the requirement of $p_{\text{guess}} \in V(p^*)$.

### 2.2.1 Linear Structural Identifiability

This subsection will explain structural identifiability in the linear case, through examples. The reader will be introduced to the concept of unidentifiable combinations of parameters, as well as a way of handling this. The concept of unidentifiable combinations of parameters is important, as it is a crucial part of the analysis.

Consider the model:

$$\dot{x} = x + k \quad (2.44)$$

where $x$ is output and $k$ is an unknown parameter. In relation to the general model form shown in equation (2.1), it would be a model where $y = x$, $u = 0$ and $p = k$. SI analysis of equation (2.44) follows by isolating $k$ in the

\(^6\)Excepting a set of measure 0. We will not elaborate on this, as it is beyond the scope of this report.
equation if possible. The resulting equation would be:

\[ k = \dot{x} - x \]  \hspace{1cm} (2.45)

Since we have the unknown parameter \( k \) expressed as a function of the output and the derivative of the output, which are both known, equation (2.44) is SI.

Consider the same model, but with another added parameter \( k_3 \):

\[ \dot{x} = x + k_1 + k_2 \]  \hspace{1cm} (2.46)

With the same process from before, the equation is manipulated:

\[ \dot{x} - x = k_1 + k_2 \]  \hspace{1cm} (2.47)

\( k_1 \) and \( k_2 \) cannot be expressed as a function of only known quantities in the model. This is because in order to determine one of the parameters it would always be necessary to determine the other parameter. It is also possible to show that the parameters are not SI, using definition 2.2.1. If we say that the true parameter vector \( p^* \) of the model is the parameter vector:

\[ p^* = \begin{pmatrix} a \\ b \end{pmatrix} \]  \hspace{1cm} (2.48)

The output of the model, with regards to the true parameter vector would then be:

\[ x = \dot{x} - a - b \]  \hspace{1cm} (2.49)

If we then denote the parameter guess \( p_{guess} \) by the parameter vector:

\[ p_{guess} = \begin{pmatrix} c \\ d \end{pmatrix} \]  \hspace{1cm} (2.50)

The output of the model, with regards to the parameter guess vector would then be:

\[ x = \dot{x} - c - d \]  \hspace{1cm} (2.51)

For the model to be SI, it is not possible to find some parameter guess, which is close to but not equal to the true parameters, where the output is the same. For this model however, we can choose the parameter guesses \( c = a + \epsilon \) and \( d = b - \epsilon \) for an arbitrarily small \( \epsilon > 0 \), which would result in identical output:

\[ \dot{x} - c - d = \dot{x} - (a + \epsilon) - (b - \epsilon) = \dot{x} - a - b \]  \hspace{1cm} (2.52)
Therefore it is not possible to find a neighbourhood $V(p^*)$ in which identical outputs implies identical parameters, as $\epsilon$ was arbitrary. Equation (2.46) is therefore structurally unidentifiable by definition 2.2.1.

In other terms, it is only possible to determine $k_1 + k_2$, because for every $x$ there are infinitely many combinations of $k_1 + k_2$, namely all pairs $(k_1, k_2)$ such that $k_1 + k_2 = \dot{x} - x$ (DiStefano, 2013).

If a system is unID, as equation (2.46) was shown to be, then there exist identifiable combinations of parameters and these combinations are either unique or have a finite number of solutions (DiStefano, 2013). In the case of equation (2.46), even though the parameters were not possible to identify independently, a parameter $k_3$ can be created, defined by $k_3 = (k_1 + k_2)$, which transforms the problem into the same form as equation (2.44) which was shown to be SI. Such reparameterisations in terms of SI combinations (COMBOS), can always be performed for unID systems and will lead to a simplified system which is SI (DiStefano, 2013).

COMBOS are relevant because even if a model is unID, then COMBOS create a submodel that can sometimes be sufficient in answering the problem at hand. It is however not possible to gain information about the parameters that constitute the COMBOS. So if the interest is within determining a specific unID parameter, this technique is of no help (DiStefano, 2013).

2.2.2 Nonlinear Structural Identifiability

In this subsection, the problems of studying the SI of nonlinear are outlined. The earliest method for analysing the property is presented, as well as the problems involved.

When studying the SI of nonlinear models, the aforementioned methods are not applicable. The problem of defining a structured and widely applicable method of determining whether a nonlinear system is SI, has been long-standing. The earliest developed method for the purpose, is through Taylor series expansion and has been widely used since, even though it is not a perfect solution (DiStefano, 2013).

Taylor series expansion assumes that the output function is infinitely differentiable in a neighbourhood of $t = 0$, that the output function is known, and that the starting condition $x(0)$ is known. With these assumptions, the output function $y = g(x, u, t, p)$ and its successive derivatives can be
expanded in a Taylor series at the initial condition \( t = 0 \), in terms of the parameters \( p \):

\[
y = g(x, u, t, p) = \sum_{i=0}^{n} \frac{d^i g(x(0), u(0), 0, p)}{dt^i} \frac{t^i}{i!}
\]  

(2.53)

This taylor series can then be expanded until all parameters can be seen to be SI in the series.

The problem of the method, is that there does not exist a condition for determining that a parameter is unID. It is only possible to conclude that the method has not determined that a parameter was SI at the point where the taylor series was expanded to, but nothing can be said for whether it would be shown to be SI, had the series been expanded further. Therefore new methods have been developed since, which are not hampered by the same limitations, to propose solutions to the problem of determining whether a nonlinear model was SI. One of these proposed methods is...

2.3 Structural Identifiability Analysis by Extended Observability

This section ties the prior theory together and culminates in the concept of ObsID. We will give an example of how we can use this technique to investigate whether a given mathematical model is SI. We will also illustrate how manipulating the ObsID matrix provides information about parameters along with states. The method is applied to a familiar example.

It is possible to investigate whether a system is SI, using extended observability, where identifiability is considered a specific case of observability (Villaverde, Barreiro et al., 2016a; Villaverde, 2019). This is done by appending the parameters \( p \) to our state vector so we get \( \tilde{x} = \left( \begin{array}{c} x \\ p \end{array} \right)^T \). \( \tilde{x} \in \mathbb{C}^{1+d}(\mathbb{R}, \mathbb{R}^{n+q}) \) where \( n \) is the amount of states in the system and \( q \) is the amount of parameters. The parameters are thereby considered as state variable where \( \dot{p} = 0 \) since the parameters are constant. By doing this we can extend our nonlinear observability matrix and thereby build the generalised ObsID matrix \( \mathcal{O}_{\tilde{x}}(\tilde{x}) \):
\[
O_T(\tilde{x}) = \begin{pmatrix}
\frac{\partial g(\tilde{x})}{\partial \tilde{x}} \\
\frac{\partial (L_1^j g(\tilde{x}))}{\partial \tilde{x}} \\
\frac{\partial (L_1^2 g(\tilde{x}))}{\partial \tilde{x}} \\
\vdots \\
\frac{\partial (L_{n+q}^j g(\tilde{x}))}{\partial \tilde{x}}
\end{pmatrix}
\tag{2.54}
\]

If this matrix fulfills \(\text{rank}(O_T(\tilde{x})) = n + q\), we say that the corresponding model is locally observable and SI.

**Theorem 2.3.1** (Nonlinear ObsID Condition). If a model \(M\) given by equation 2.1 satisfies \(\text{rank}(O_T(\tilde{x}_0)) = n + q\), with \(O_T(\tilde{x}_0)\) given by equation 2.54, then it is (locally) observable and SI in a neighbourhood \(V(\tilde{x}_0)\) of \(\tilde{x}_0\) (Villaverde, 2019).

Since the generalised ObsID matrix is an extension of the nonlinear observability matrix, it has similar properties. If it has full rank, the states are observable. However, the number of observable states could differ from a stand alone observability test, since the SI of parameters are also tested here. Observability analysis is based on an assumption that the parameters are SI (Di Stefano, 2013), which can lead to wrong conclusions about the states (Villaverde, 2019). This error is always avoided when obsID is used as it tests for both cases simultaneously.

In the case where \(O_T(\tilde{x}_r)\) does not have full rank, we can expand theorem 2.1.5 to include SI of parameters for the case of ObsID.

**Theorem 2.3.2** (Structural Identifiability Condition). Given a model defined by equation (2.1), its \(i\)th state (or parameter) \(x_i\) is locally observable (structurally locally identifiable if it corresponds to a parameter) in a neighbourhood \(V(\tilde{x}_r)\) if \(\text{rank}(O_T^{\ast}(\tilde{x}_r)) < \text{rank}(O_T(\tilde{x}_r))\), where \(O_T(\tilde{x}_r)\) is the observability matrix defined in equation (2.54), generated for the statevector \(x_r\) and \(O_T^{\ast}(\tilde{x}_r)\) is the matrix that results from removing the column corresponding to \(\frac{\partial}{\partial \tilde{x}_i}\) from \(O_T(\tilde{x}_r)\) (Villaverde, 2019).
Example of Structural Identifiability by Extended Observability

We now revisit our old friend, the system of coupled springs, and ask, is this system SI? In this system we have:

$$f(\tilde{x}) = \begin{pmatrix}
\frac{(k_a + k_b)x_1}{m_a} + \frac{x_2}{m_a} \\
\frac{k_b x_3}{m_b} - \frac{k_b x_3}{m_b} \\
\frac{k_b x_1}{m_b} - \frac{x_4}{m_a} \\
0 \\
0 \\
0 \\
0
\end{pmatrix}$$

$$\tilde{x} = (x_1 \quad x_2 \quad x_3 \quad x_4 \quad k_a \quad m_a \quad k_b \quad m_b)\tau$$

$$g(\tilde{x}) = x_3$$

We now want to investigate the ObsID matrix of this model. We follow the same procedure as we did in section 2.1.4. Building the first submatrix:

$$\frac{\partial g(x)}{\partial x} = \begin{pmatrix}
\frac{\partial x_3}{\partial x_1} & \frac{\partial x_3}{\partial x_2} & \frac{\partial x_3}{\partial x_3} & \frac{\partial x_3}{\partial x_4} & \frac{\partial x_3}{\partial k_a} & \frac{\partial x_3}{\partial k_b} & \frac{\partial x_3}{\partial m_b}
\end{pmatrix}
= \begin{pmatrix}
0 & 0 & 1 & 0 & 0 & 0 & 0
\end{pmatrix}$$

Now we can calculate the first Lie derivative.

$$L_1 g(\tilde{x}) = \frac{\partial g(\tilde{x})}{\partial \tilde{x}} \cdot f(\tilde{x}) =$$

$$\begin{pmatrix}
-x_2 \\
\frac{(k_a + k_b)x_1}{m_a} + \frac{x_2}{m_a} \\
\frac{k_b x_3}{m_b} - \frac{x_4}{m_a} \\
0 \\
0 \\
0 \\
0
\end{pmatrix} \cdot \begin{pmatrix}
0 & 0 & 1 & 0 & 0 & 0 & 0
\end{pmatrix} = x_4$$

$$= x_4$$

(2.57)
Again we can build the second submatrix:

\[
\frac{\partial L_f^1 g(\tilde{x})}{\partial \tilde{x}} = \left( \frac{\partial x_4}{\partial x_1} \quad \frac{\partial x_4}{\partial x_2} \quad \frac{\partial x_4}{\partial x_3} \quad \frac{\partial x_4}{\partial k_a} \quad \frac{\partial x_4}{\partial m_a} \quad \frac{\partial x_4}{\partial k_b} \quad \frac{\partial x_4}{\partial m_b} \right) \\
= \left( 0 \quad 0 \quad 0 \quad 1 \quad 0 \quad 0 \quad 0 \quad 0 \right)
\]

(2.58)

Multiplying this by \( f(\tilde{x}) \) we can find the second Lie derivative:

\[
L_f^2 g(\tilde{x}) = \frac{\partial L_f^1 g(\tilde{x})}{\partial \tilde{x}} \cdot f(\tilde{x}) =
\left( \begin{array}{c}
\frac{\partial x_2}{\partial x_1} + \frac{x_2}{m_a} \\
-\frac{(k_a + k_b)x_1}{m_a} + \frac{k_b x_3}{m_a} \\
\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b} \\
0 \\
k_b x_1 - \frac{k_b x_3}{m_b} \\
0 \\
0 \\
0
\end{array} \right)
\]

(2.59)

Now we can build the third submatrix:

\[
\frac{\partial L_f^2 g(\tilde{x})}{\partial \tilde{x}} = \left( \begin{array}{cccc}
\frac{\partial L_f^2 g(\tilde{x})}{\partial x_1} & \frac{\partial L_f^2 g(\tilde{x})}{\partial x_2} & \frac{\partial L_f^2 g(\tilde{x})}{\partial x_3} & \frac{\partial L_f^2 g(\tilde{x})}{\partial x_4} \\
\frac{\partial L_f^2 g(\tilde{x})}{\partial k_a} & \frac{\partial L_f^2 g(\tilde{x})}{\partial m_a} & \frac{\partial L_f^2 g(\tilde{x})}{\partial k_b} & \frac{\partial L_f^2 g(\tilde{x})}{\partial m_b}
\end{array} \right)
\]

(2.60)

\[
\left( \begin{array}{cccc}
\frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0 & 0 & 0 & \left( \frac{x_1}{m_b} - \frac{x_3}{m_b} \right) & \left( -\frac{k_b x_1}{m_b^2} + \frac{k_b x_3}{m_b^2} \right)
\end{array} \right)
\]

As may be seen from the example, calculating the ObsID matrix can become cumbersome to analyse, luckily computers might be of some help to us. The next 3 submatrices are included in appendix A.1. The last two rows are not included as they are quite long. The ObsID matrix was built using the CAS Sage (The Sage Developers, 2017) and the script can be seen in appendix A.2.1. By using the script the interested reader also has an opportunity to see the last two submatrices.

Using Sage to calculate the rank of the full ObsID matrix, we find that \( rank(O_T(\tilde{x})) = 6 \) and since the full ObsID matrix is \( 8 \times 8 \) the system is not SI.
3. **Analysis**

This chapter concerns the application of the ObsID method on several case models of the same system.

For each case model, the structure of the section will be identical. The model is initially presented with a brief description of the biological background. This leads to a presentation of the results from the ObsID analysis, followed by an interpretation of said results.

### 3.1 The Cancitis Model

This section introduces the Cancitis model. The general system is presented, after which the relation between the terms of the model and the theory behind the system is explained.

The Cancitis model seeks to describe the coupling between blood cancer and an inflammatory response. The model tries to explain the interactions between hematopoietic stem cells (HSC), hematopoietic mature cells (HMC), malignant stem cells (MSC) and malignant mature cells (MMC). Furthermore, the model includes dead cells and severity of inflammation (Sajid et al., 2019) and can be seen on figure 3.1.

\footnote{The notation that was used in the theory section, is no longer used. The notation used by the authors of the model is used instead.}
Figure 3.1: The Cancitis model with all of its compartments illustrated by each grey box. The green dotted line represents the competition factor on the renewal rate. The red dotted line represents the effect of the inflammation. Compartment (a) is the dead cells that come from the compartments HSC, HMC, MSC and MMC, where compartment (s) represents the immune systems.

The system is modelled, such that the rate of change for a compartment is equal to the total growth minus total elimination of that compartment. A more visual representation of how the system is perceived (Sajid et al., 2019):

\[
\begin{cases}
\text{Change in amount of a} \\
\text{compartment per time} \\
\{ \text{Rate of production times} \\
\text{the producing source} \} \\
- \{ \text{Rate of elimination times the} \\
\text{amount in the compartment} \}
\end{cases}
\]

(3.1)

The model is given by (Sajid et al., 2019):
\begin{align*}
\dot{x}_0 &= r_x (\phi_x s - \frac{d_{x0} + a_x}{r_x}) x_0 - r_s x_0 \\
\dot{x}_1 &= a_x A_x x_0 - d_{x1} x_1 \\
\dot{y}_0 &= r_y (\phi_y s - \frac{d_{y0} + a_y}{r_y}) y_0 - r_s y_0 \\
\dot{y}_1 &= a_y A_y y_0 - d_{y1} y_1 \\
\dot{a} &= d_{x0} x_0 + d_{y0} y_0 - d_{y1} y_1 - e_a a s \\
\dot{s} &= r_s a - e_s s + I
\end{align*}

where $\phi_x$ and $\phi_y$ represent the competition between HSCs and MSCs in the bone marrow.

\begin{align*}
\phi_x &\equiv \phi_x(x_0, y_0) = \frac{1}{1 + c_{xx} x_0 + c_{xy} y_0} \\
\phi_y &\equiv \phi_y(x_0, y_0) = \frac{1}{1 + c_{yx} x_0 + c_{yy} y_0}
\end{align*}

The model has no inputs, and the terms of the model are expressed in table 3.1.
<table>
<thead>
<tr>
<th>List of terms in the Cancitis model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed states</strong></td>
</tr>
<tr>
<td>(x_1)</td>
</tr>
<tr>
<td>(y_1)</td>
</tr>
<tr>
<td><strong>Unobserved states</strong></td>
</tr>
<tr>
<td>(x_0)</td>
</tr>
<tr>
<td>(y_0)</td>
</tr>
<tr>
<td>(a)</td>
</tr>
<tr>
<td>(s)</td>
</tr>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td>(r_z)</td>
</tr>
<tr>
<td>(c_{xz})</td>
</tr>
<tr>
<td>(c_{xy})</td>
</tr>
<tr>
<td>(a_x)</td>
</tr>
<tr>
<td>(A_x)</td>
</tr>
<tr>
<td>(d_{z1})</td>
</tr>
<tr>
<td>(d_{z0})</td>
</tr>
<tr>
<td>(c_{yz})</td>
</tr>
<tr>
<td>(c_{yz})</td>
</tr>
<tr>
<td>(r_y)</td>
</tr>
<tr>
<td>(a_y)</td>
</tr>
<tr>
<td>(A_y)</td>
</tr>
<tr>
<td>(d_{y0})</td>
</tr>
<tr>
<td>(d_{y1})</td>
</tr>
<tr>
<td>(e_o)</td>
</tr>
<tr>
<td>(r_s)</td>
</tr>
<tr>
<td>(r_m)</td>
</tr>
<tr>
<td>(e_s)</td>
</tr>
<tr>
<td>(I)</td>
</tr>
</tbody>
</table>

**Table 3.1**: A list of the terms in the Cancitis model, and what they represent in the biological system being modelled.

3.2 Structural Identifiability of Case Models

In this section, the method is applied to each case. Correlations between parameters and states are shown, and the results are interpreted.
STRIKE-GOLDD\textsuperscript{2} is a toolbox in MATLAB and is a method of SI analysis developed by Alejandro Villaverde (Villaverde, Barreiro et al., 2016b). The toolbox is based on ObsID, as presented in section 2.3. This toolbox will be used for analysing the SI of different case models in this section. In the cases of models that are not fully SI, the unID combinations of parameters will be analysed. We have used the CPU cluster available at the IMFUFA institute on Roskilde University to run STRIKE-GOLDD.

3.2.1 Simplified Cancitis Model

When applying the STRIKE-GOLDD algorithm to the Cancitis model, it was not possible to determine anything in regards to SI or observability, as the workload required too much memory. Therefore it was necessary to reduce the amount of parameters or states in the system, thus creating a simplified model that is possible to analyse. The chosen simplification of the system, was to consider the functions $\phi_x$ and $\phi_y$ as being constant parameters, despite them being defined as smaller systems representing the competition factors for $x_0$ and $y_0$. We are not making any assumptions on the validity of this model, but rather we simply use this simplified model with the purpose of testing the method of ObsID. It will however be specified under which conditions the simplified model might maintain relevance to the original model.

The function values of $\phi_x$ and $\phi_y$ over time, with default\textsuperscript{3} parameters are shown in figure 3.2:

\textsuperscript{2}STRuctural Identifiability taKen as Extended-Generalized Observability using Lie Derivatives and Decomposition
\textsuperscript{3}The parameter values presented as "default parameter values" in the article (Sajid et al., 2019)
**Figure 3.2:** The function values of $\phi_x$ and $\phi_y$ over time. It is seen that the functions are close to constant during the first and last parts of the graph, and change rapidly between the two. The figure can be created with the scripts in appendix A.3.1.

If the modelling focus is within the initial time period of the course of the disease, it is seen from figure 3.2 that the functions are close to constant near the start of the disease. Thus a possible simplification would be to set the functions constant at their initial value.
**Figure 3.3**: The function values of $\phi_x$ and $\phi_y$ over time, and the term set to constant. It is seen that the functions are close to their constants during the initial time period. The figure can be created with the scripts in appendix A.3.2

With the simplification:

$$\phi_x \equiv \phi_x(x_0, y_0) = \phi_x(x_0(0), y_0(0))$$
$$\phi_y \equiv \phi_y(x_0, y_0) = \phi_y(x_0(0), y_0(0))\quad (3.4)$$

shown on figure 3.3 with regards to default parameters, as replacements for the functions, the model can now be compared to the simplified model.
Figure 3.4: A comparison of the MMC and HMC development in the model and simplified model. It is seen that the MMC’s growth is close to the same within the first 20 years of the course of the disease. The HMC for the simplified model are seen to increase throughout the course of the disease. The figure can be created with the scripts in appendix A.3.3

As can be seen on figure 3.4, the MMC growth is close to the same within the first years of the disease, but the HMC population of the simplified model are seen to increase, which is not what would be expected for the system. This could be addressed by reducing the size of the $\phi_r$ parameter:
Figure 3.5: A comparison of the MMC and HMC development in the model and simplified model, with $\phi_x(x_0, y_0) = \phi_x(x_0(0), y_0(0)) - \epsilon \ (\epsilon = 0.04$ in this figure) and $\phi_y(x_0, y_0) = \phi_y(x_0(0), y_0(0))$. It is seen that the MMC growth is close to the same within the first 18 years of the course of the disease. The figure can be created with the scripts in appendix A.3.4.

As can be seen on figure 3.5, the HMC now decrease over time in the simplified model, while the MMC growth is still quite close within the initial time period. To further compare the development of the MMC in the two models, we will examine them over a shorter period of time:
**Figure 3.6:** A comparison of the MMC development in the model and simplified model, with \( \phi_x(x_0, y_0) = \phi_x(x_0(0), y_0(0)) - \epsilon \) (\( \epsilon = 0.04 \) in this figure) and \( \phi_y(x_0, y_0) = \phi_y(x_0(0), y_0(0)) \). It is seen that the MMC's growth is very close within the years of the disease shown on the figure, being almost indistinguishable from each other. The figure can be created with the scripts in appendix A.3.5

Thereby it can be seen on figure 3.6, that the simplification of considering the competition functions \( \phi_x \) and \( \phi_y \) as being constant, still results in a model that describes the MMC growth in a similar way, if the interest lies within the initial course of the disease. Thus it is possible for the model to express the sought dynamics with a constant \( \phi_x \) and \( \phi_y \).

Furthermore, the simplified model should be able to express the same dynamics as the full model. Studying whether the percentage of mature cells that are MMC, is closely related between the two models, could be a good indicator for this. This is shown on figure 3.7.
Figure 3.7: A comparison of the percentage MMC of the mature cells in the model and simplified model, with $\phi_x(x_0, y_0) = \phi_x(x_0(0), y_0(0)) - \epsilon$ ($\epsilon = 0.04$ in this figure) and $\phi_y(x_0, y_0) = \phi_y(x_0(0), y_0(0))$. It is seen that the development of the percentages are similar even in the later time periods. The figure can be created with the scripts in appendix A.3.6

As is seen on figure 3.7, the percentage of mature cells that are MMC are not as closely related as the developments seen on figure 3.6, but still seems to be a reasonable approximation.

Applying the STRIKE-GOLDD algorithm to this simplified model\(^4\), with $x_1$ and $y_1$ being the outputs, revealed the following:

Observable states: $a$

SI parameters: $d_{x_1}$, $d_{y_1}$ and $e_s$

STRIKE-GOLDD was not able to determine anything in relation to the remaining parameters and states initially. These results were then given as a

\(^4\)If the reader wishes to recreate the STRIKE-GOLDD results presented in this subsection, the relevant matlab file which is not included in the STRIKE-GOLDD package, can be found in appendix A.3.7.
starting point, at which point the workload was reduced to a point, where the rest could be determined to be unID and unobservable definitively.

The relations between the remaining parameters and states in the system, that we determined to be unID and observable, can then be studied. The following unID combinations of parameters, where a single identified parameter leads to the remaining parameters being SI and the state variable being observable, were found:

![Diagram showing unID combinations of parameters]

**Figure 3.8:** UnID combinations of parameters in the simplified Cancitis model, where a single parameter identified makes the remaining SI. For each of the unID combinations, the state variable that becomes observable when these are SI, are shown emboxing the unID combination of parameters. Observability of the state variable also results in all of the parameters they embox becoming SI. State variables are shown in red boxes, while parameters are shown in blue boxes.

From figure 3.8, it can be seen that the parameters $d_{x0}$, $a_x$ and $A_x$ are correlated in such a way, that it is only required to identify a single parameter, for the remaining to be SI. Furthermore, if these parameters are SI, the state $x_0$ is observable. The same can be seen for the parameters $d_{y0}$, $a_y$ and $A_y$ with $y_0$ becoming observable, and the set of parameters $I$, $e_a$ and $r_s$ with $s$ becoming observable. It can thereby be deduced, that all state variables can be observed, if just one parameter of each unID combination is identified.
An unID combination was also found, where a single identified parameter was not sufficient for making the remaining parameters SI, but instead both other parameters had to be identified:

![Diagram showing unID combinations of parameters in the simplified Cancitis model.](image)

**Figure 3.9:** UnID combinations of parameters in the simplified Cancitis model, where identification of two out of the three parts makes the remaining SI. For each of the unID combinations that relate to the observability of a state variable, the state variable is shown emboxing the unID combination of parameters. Observability of the state variable also results in all of the parameters they embo becoming SI. Solid arrows between parameters indicate that a single parameter must be identified for the remaining to be SI, while dotted arrows indicate that all except one, must be identified, for the remaining to be SI. The state variables are shown in red boxes, while parameters are shown in blue boxes.

From figure 3.9 it is seen, that the unID combination of the parameters $I$, $e_a$ and $r_s$ is linked to the parameters $\phi_y$ and $r_y$ in such a way that if two out of the three parts of the unID combination is identified, the last one will be SI.

For the remaining parameters, $\phi_x$ and $r_x$, it was found that all of the parameters shown in figure 3.8, must be identified, for these to be SI. Furthermore, either $\phi_x$ or $r_x$ must be identified for the other to be SI, but identifying both did not reveal anything about the rest of the system.

**Interpretation of Results**

Due to the many unID parameters, a parameter estimation of the model does not seem meaningful to perform. Through the unID combinations found for the system in the SI analysis, it is however possible to isolate the necessary parameters that must be identified, for the system to be SI. The lowest
amount of parameters that must be identified, for the entire system to become SI, is four.

3.2.2 Full Cancitis Model

It was found for the simplified model, that three parameters were SI and a single state was observable without any dependencies on other parameters or states. By assuming this was true for the full model, it was possible to analyse the model using STRIKE-GOLDD.

Applying the STRIKE-GOLDD algorithm to the full Cancitis model\textsuperscript{5}, showed that no other parameters were SI, excepting the ones that were assumed to be SI. The same was found in relation to states.

For the remaining parameters, the following unID combinations of parameters, where a single identified parameter leads to the remaining parameters being SI and the state variable being observable, were found:

\textsuperscript{5}If the reader wishes to recreate the STRIKE-GOLDD results presented in this subsection, the relevant matlab file which is not included in the STRIKE-GOLDD package, can be found in appendix A.3.8.
Figure 3.10: unID combinations of parameters in the full model, where identification of a single parameter makes the remaining SI. For each of the unID combinations that relate to the observability of a state variable, the state variable is shown embossing the unID combination of parameters. Observability of the state variable also results in the parameters they embox becoming SI. state variables are shown in red boxes, while parameters are shown in blue boxes.

As seen on figure 3.10, the remaining parameters can be divided into three groupings, in which a single identified parameter results in the remaining being identified. This implies that the parameters \( d_y, a_y, A_y, c_{xy} \) and \( c_{yy} \) are linked in such a way, that identifying a single parameter results in the remaining being SI. Furthermore these parameters become SI when the state \( y_0 \) is observable, and the state becomes observable when the parameters are SI. This is seen in the top left of figure 3.10. The same is true for the parameters \( d_x, a_x, A_x, c_{xx} \) which are linked to the state \( x_0 \), seen in the top right of the figure, and the parameters \( I, e_a, r_s, r_x \) and \( r_y \) which are linked to the state \( s \), seen in the bottom of the figure.

Interpretation of results

The first thing to consider, is the validity of the assumptions that allowed the analysis of the model. The assumptions were, that the parameters \( d_{x1}, d_{y1} \) and \( e_s \) were SI and that the state \( a \) was observable.
By instead assuming that one of the three unID combinations, seen on figure 3.10, was identified, it was seen that the parameters $d_{x1}$, $d_{y1}$ and $e_s$ were SI and the state $a$ was observable. This was confirmed to be true regardless of which unID combination was assumed to be identified. This leads to the conclusion of two possible scenarios: either the assumption holds, or the parameters $d_{x1}$, $d_{y1}$ and $e_s$ and the state $a$ form a group, which becomes SI as consequence of identifying one of the three unID combinations. This relation is shown on figure 3.11:

![Diagram showing the relation between SI and unID groupings](image)

**Figure 3.11:** A possible relation between the SI of the unID groupings of parameters, and the group of parameters and state which were assumed to be identifiable and observable. Identifying one of the three grouped parameters depicted in the top, results in the group depicted in the bottom becoming SI. This relation is not bidirectional, as identifying the bottom group, does not reveal anything about the groups in the top. Whether the depicted relation is true, or the assumption holds, is not possible to determine currently.

Figure 3.11 shows the other possible relation with regards to the parameters $d_{x1}$, $d_{y1}$ and $e_s$ and the state $a$, aside from the one which was assumed in the STRIKE-GOLDD analysis. It is however not possible to verify which of the two possibilities that is true, as this would require an analysis without any assumptions.

Disregarding this uncertainty, the full model is seen to be closer to SI, than the simplified model which was previously analysed. The full model only has three groupings of correlated parameters, where one parameter determined is necessary to determine the rest. While the simplified model had the same amount of parameters correlated in the same way, additional correlations were also found. The model is still not SI however, and it is therefore not meaningful to attempt a parameter estimation, before at least one parameter in each unID combination is determined.
3.2.3 Reduced Cancitis Model

A presentation of the next model of interest is given. The model is deduced from an analysis of the dimensions of the full cancitis model, and as such the theory behind the model is not presented again. The simplifications and assumptions for the model which were used by the authors to reduce the model are presented, along with the resulting groupings of parameters from the original model. With the same approach as the previous two sections, the results of an analysis by the STRIKE-GOLD algorithm is presented, followed by an interpretation of the implications for the model.

Making a model dimensionless can reduce the number of free parameters, because the dimensionless parameters are clusters of the original parameters. Furthermore, converting a model to be dimensionless is an opportunity to reduce the model. As such the Cancitis model has both been formulated dimensionlessly, but also reduced with quasi-steady state assumptions afterwards (Ottesen et al., 2019).

The methodology behind converting the model to be dimensionless is that the variables are all scaled by the unit of the variable. The variables are denoted as the same variable with capital notation and a scaling factor carrying the unit of the variable, which is denoted with a bar above. The prime is then the derivative taken with respect to the dimensionless time variable $T$ (Ottesen et al., 2019).

<table>
<thead>
<tr>
<th>Original variable and their dimensionless notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x_0$</td>
</tr>
<tr>
<td>$x_1$</td>
</tr>
<tr>
<td>$y_0$</td>
</tr>
<tr>
<td>$y_1$</td>
</tr>
<tr>
<td>$a$</td>
</tr>
<tr>
<td>$s$</td>
</tr>
<tr>
<td>$t$</td>
</tr>
</tbody>
</table>

Table 3.2: Conversion of variables to dimensionless notation, which was done in the process of creating the reduced Cancitis model.

The Cancitis model with dimensionless variables, derived from equations
(3.2), is given by the equations (Ottesen et al., 2019):

\[
X'_0 = \tilde{t} \left( \frac{S}{1 + c_{yx} \tilde{x}_0 X_0 + c_{zy} \tilde{y}_0 Y_0} - d_{x_0} - a_x \right) X_0
\]

\[
X'_1 = \tilde{t} \left( \frac{\tilde{x}_0}{\tilde{x}_1} a_x A_x X_0 - d_{x_1} X_1 \right)
\]

\[
Y'_0 = \left( \frac{S}{1 + c_{yx} \tilde{x}_0 X_0 + c_{zy} \tilde{y}_0 Y_0} - d_{y_0} (Y) - a_y \right) Y_0
\]

\[
Y'_1 = \tilde{t} \left( \frac{\tilde{y}_0}{\tilde{y}_1} a_y A_y Y_0 - d_{y_1} Y_1 \right)
\]

\[
A' = \tilde{t} \left( d_{x_0} \frac{\tilde{x}_0}{\tilde{a}} X_0 + d_{y_0} (Y_0) \frac{\tilde{y}_0}{\tilde{a}} Y_0 + d_{y_1} \frac{\tilde{y}_1}{\tilde{a}} Y_1 - e_a \delta AS \right)
\]

\[
S' = \tilde{t} \left( \frac{\tilde{r}}{\tilde{s}} A - e_s S + \frac{I}{\tilde{s}} \right)
\]

(3.5)

where the mutation rate \( r_m \) is set to zero and \( d_{y_0}(Y_0) = \tilde{d}_{y_0} + \tilde{d}_{y_0} \tilde{y}_0 \cdot Y_0 \).

This model is then further reduced, by grouping parameters, to the following equations:

\[
X'_0 = \left( \frac{S}{1 + (X_0 + \frac{c_{yx}}{c_{yy}} Y_0)} - 1 \right) X_0
\]

\[
\epsilon_1 X'_1 = (X_0 - X_1)
\]

\[
Y'_0 = \left( \frac{S}{1 + \left( \frac{c_{yx}}{c_{yy}} X_0 + Y_0 \right)} - \frac{d_{y_0}(Y_0) + a_y}{d_{x_0} + a_x} \right) Y_0
\]

\[
\epsilon_1 Y'_1 = \frac{d_{y_1}}{d_{x_1}} (Y_0 - Y_1)
\]

\[
\epsilon_2 \epsilon_3 A' = (b_{x_0} X_0 + b_{y_0}(Y_0) Y_0 + b_{x_1} X_1 + b_{y_1} Y_1 - AS)
\]

\[
\epsilon_2 S' = \left( A - S + \frac{I}{\epsilon_3 \delta} \right)
\]

(3.6)

where \( \epsilon_1 \sim 10^{-5}, \epsilon_2 \sim 10^{-3}, \epsilon_3 \sim 10^{-10}, b_{x_0} \sim 10^{-13}, b_{x_1} \sim 10^{-1}, b_{y_0} \sim 10^{-13} \) and \( b_{y_1} \sim 10^{-1} \). Furthermore, we have \( \frac{d_{y_1}}{d_{x_1}} \sim 1, \frac{c_{yx}}{c_{yy}} \sim 1, \frac{r_x}{r_x} \sim 1, \frac{d_{y_0} + a_y}{d_{x_0} + a_x} \sim 1 \) and \( \frac{1}{\epsilon_3 \delta} \sim 1 \).

The reduced Cancitis model is derived from the dimensionless Cancitis model through quasi-steady state assumptions, by setting the terms \( \epsilon_1 = 0, \epsilon_2 = 0 \) and \( \epsilon_3 = 0 \) from model (3.6). This leads to four of the models six differential equations becoming the algebraic equations:
\[\epsilon_1 X'_1 = 0 = (X_0 - X_1)\]
\[\epsilon_1 Y'_1 = 0 = \frac{d_y}{d_x_1}(Y_0 - Y_1)\]
\[\epsilon_2 \epsilon_3 A' = 0 = (b_{x0} X_0 + b_{y0} (Y_0) Y_0 + b_{x1} X_1 + b_{y1} Y_1 - AS')\]  \hspace{1cm} (3.7)
\[\epsilon_2 S' = 0 = (A - S + \frac{I}{e_3 S})\]

Using these algebraic equations, it is possible to group parameters into clusters, such that the amount of parameters is greatly reduced. Using equations (3.7) in this way, the system is reduced to the following:

\[X'_0 = \left(\frac{J + \sqrt{J^2 + 2B_x X_0 + 2B_y Y_0}}{1 + X_0 + C_y Y_0} - 1\right) X_0\]  \hspace{1cm} (3.8)
\[Y'_0 = \left(R \frac{J + \sqrt{J^2 + 2B_x X_0 + 2B_y Y_0}}{1 + C_x X_0 + Y_0} - D_0 - D_1 Y_0\right) Y_0\]

With the grouped parameters being:

<table>
<thead>
<tr>
<th>Combinations and terms in the reduced Cancitis model</th>
</tr>
</thead>
<tbody>
<tr>
<td>(d_{y_0})</td>
</tr>
<tr>
<td>(X_0)</td>
</tr>
<tr>
<td>(Y_0)</td>
</tr>
<tr>
<td>(J)</td>
</tr>
<tr>
<td>(R)</td>
</tr>
<tr>
<td>(D_0)</td>
</tr>
<tr>
<td>(D_1)</td>
</tr>
<tr>
<td>(C_x)</td>
</tr>
<tr>
<td>(C_y)</td>
</tr>
<tr>
<td>(2B_x)</td>
</tr>
<tr>
<td>(2B_y)</td>
</tr>
</tbody>
</table>

**Table 3.3:** List of terms in the reduced Cancitis model, and how they relate to the parameters in the full Cancitis model.

The system is reduced from a system of six coupled differential equations and nineteen parameters, to a system of two coupled differential equations.
and eight parameters. This simplifies the system greatly, and reduces possible interactions that could lead to the system being unID.

Applying the STRIKE-GOLDD algorithm to the reduced cancitis model\(^6\), showed that the system was SI, and that all state variables were observable. This is not unexpected, due to the greatly reduced amount of parameters, and differential equations in the system.

**Interpretation of Results**

The reduced model was seen to be SI and both states were observable (a given, as both were outputs). For this model, it is then possible to perform a meaningful parameter estimation, to fit the model to data, and thereby compare the model to data.

### 3.3 Comparison of Results

*The correlated parameters are cross-referenced between the simplified Cancitis model and the full Cancitis model. These correlations are also compared to the parameter groupings made for the reduced Cancitis model.*

#### 3.3.1 Simplified Model and Full Model

This subsection will concern the differences between the parameter correlations found for the simplified Cancitis model, presented is subsection 3.2.1, and the full Cancitis model, presented in subsection 3.2.2.

For the full model, it was presented that there exists three groups of correlated parameters, in which a single identified parameter resulted in the rest of the group becoming SI. Each of these groups can be seen as expansions of the three parameter groupings for the simplified model, where a single identified parameter likewise resulted in the remaining becoming SI. These different groupings are shown on figure 3.12.

\(^6\)If the reader wishes to recreate the STRIKE-GOLDD results presented in this subsection, the relevant matlab file which is not included in the STRIKE-GOLDD package, can be found in appendix A.3.9.
As can be seen on figure 3.12, the groupings in the full model all encompass the groupings for the simplified model, but are expanded to include two extra parameters each. The grouping related to the state $x_0$ is expanded to include the parameters $c_{yx}$ and $c_{xx}$, seen as the top rightmost grouping in each of the subfigures in figure 3.12. With regards to the state $y_0$, it is expanded to include $c_{xy}$ and $c_{yy}$, seen in the top right groupings. Lastly for the bottom groupings, which regard the state $s$, it is expanded to include $r_x$ and $r_y$. 

Figure 3.12: Comparison between the unID combinations, where a single identified parameter makes the remaining SI, for the simplified Cancitis model and the full Cancitis model.
The remaining parameters of the simplified model, which are not shown in figure 3.12a, are $\phi_x$, $\phi_y$, $r_y$, and $r_x$. $\phi_x$ and $\phi_y$ had the original form:

$$
\phi_x \equiv \phi_x(x_0, y_0) = \frac{1}{1 + c_{xx}x_0 + c_{xy}y_0}
$$

$$
\phi_y \equiv \phi_y(x_0, y_0) = \frac{1}{1 + c_{yx}x_0 + c_{yy}y_0}
$$

From figure 3.12, it can be seen, that the parameters in $\phi_x$ and $\phi_y$, which are multiplied by the state $x_0$, are now included in the combination concerning the state $x_0$. Likewise, the same can be seen to be true for $y_0$. Their relation to the combination that they can be found in, in the full cancitis model, thereby seems meaningful. There is no clear cause for the remaining two parameters $r_x$ and $r_y$ to be related to the last combination.

If the assumption holds, that the parameters $d_{x1}, d_{y1}$ and $e_a$ are SI and the state $a$ is observable unconditionally in the full model, this would be another point at which the two models draw the same conclusions. The converse could be said, if the assumption doesn’t hold.

### 3.3.2 Simplified Model and Reduced Model

This subsection will concern the relation between the correlated parameters found for the simplified Cancitis model and the grouped parameters in the reduced model, listed in table 3.3.

The unID combination of $A_x$, $a_x$ and $d_{x0}$ are all grouped into the parameter $B_x$. Likewise, the combination of $A_y$, $a_y$ and $d_{y0}$ are all grouped into the parameter $B_y$.

The combination of $r_s$, $e_a$ and $I$ is split into multiple groupings of parameters. $r_s$ and $e_a$ are grouped into both the $B_x$ and $B_y$ parameters, while the parameter $I$ is present in the $J$ and $D_1$ parameters.

Following these unID combinations through the groupings, it can be seen that the three groups of parameters, which only require a single identified parameter for full identification of the entire group, are grouped into only one or two parameters. Thereby the unID combinations should become SI, which is also seen in the reduced model. In the case where they are grouped into a single parameter, it is true by default. In the case where only two of the parameters are grouped, it could be theorised, that the reduction to two
terms, is sufficient to remove the unID of the group.

The parameters $I$, $e_a$ and $r_a$ were also involved in an unID combination with the parameters $\phi_y$ and $r_y$, in which two out of the three parts must be identified, for the remaining to be SI. The parameter $r_y$ is grouped into the parameter $R$, while $\phi_y$, was a simplified term covering the parameters $c_{yy}$ and $c_{yz}$, which are present in the groupings $D_1$, $B_y$, $C_y$ and $C_x$.

As this unID combination is split across such a multitude of groupings, the SI of the combination could be a result of the other reductions in the system. In the case of this unID combination, there is no clear similarity between the groupings of parameters and the unID groupings found through the STRIKE-GOLDD analysis. Furthermore it is hard to draw similarities, due to the term $\phi_y$, which was reduced in the simplified model.

The remaining parameters to study from the full system, is $\phi_x$ and $r_x$. $\phi_x$ and $r_x$ were related to the parameters present on figure 3.8 in such a way, that if all the parameters on the figure were SI, as well as one of these parameters, the other became SI. $\phi_x$ covers the parameters $c_{xx}$ and $c_{xy}$, and as such is present in the groupings $C_x$, $C_y$ and $B_x$. The parameter $r_x$ is present in even more groupings; $J$, $R$, $B_x$ and $B_y$.

Again there is no clear way to see how the groupings break up the unID structures. The relation is also muddled again, as the term $\phi_x$ is present.

### 3.3.3 Full Model and Reduced Model

Lastly the unID combinations for the full Cancitis model, presented in subsection 3.2.2, can now be related to the grouped terms in the reduced Cancitis model, shown in table 3.3 in subsection 3.2.3.

It is hard to draw parallels from the full models unID combinations, to the grouped terms used in the reduced model. This is due to the combinations being so large, that they are spread across nearly all of the grouped terms in the reduced model. The combination related to the state $x_0$ is for example present in all terms excepting $R$. Thereby it is hard to see the intricacies that lead to the unID combination being removed in this case.

The combination concerning the state $y_0$ is present in the terms $D_0$, $D_1$, $C_y$ and $B_y$. Since it was originally a combination of five parameters, where a single identified parameter made the remaining SI, the reduction to four
terms, could be seen as the cause of the unID combination becoming SI.

For the last combination concerning $s$, the parameters are present in the terms $J, R, B_x$ and $B_y$, and as such is reduced to four terms. By the same logic as before, this could be seen as the reasoning for the combination becoming SI.
4. Discussion

The first subject of the discussion, will be SI evaluated on its own. Secondly the usefulness of the ObsID method is discussed. Finally the method is evaluated through the case study.

4.1 Structural Identifiability

4.1.1 Identifiability: Structural and Numerical

It is an important distinction that the quality which ObsID is able to investigate is not identifiability but specifically SI. Data is rarely perfectly noise-free, in which case it may not be possible to estimate parameter values, even if they are SI. For real applications of models, SI is thus a condition for identifiability but is not sufficient on its own, numerical identifiability is required as well (DiStefano, 2013). NI analysis is strongly related to sensitivity and covariance. Sensitivity is a measure of how much a change in the value of a parameter affects the output of the model, whilst covariance is a measure of how close parameters are to be linearly independent. As such, covariance is then conceptually linked to SI, in the sense that SI can roughly be interpreted as a structural investigation of covariance with the assumption of perfect data and with a binary result of the form, "are the parameters 100% linearly dependent or not?".

Identifiability analysis is often performed solely as an investigation of the NI of the model, yet there does not exist a perfectly efficient and robust methodology for doing so and thus the methods used in practice vary a lot (DiStefano, 2013). Since SI and NI are not interchangeable, ObsID does not serve as a replacement suggestion for these kinds of analyses but rather as complementary. First of all a parameter that is not SI can never be NI, so a priori SI analysis might help identifying potential reductions to the model and thus the workload of the algorithms to test for NI. Secondly, for a parameter that is determined as not NI, but is found to be SI, the parameter can potentially be determined through improved datasets with less noise. Whether this is realistic is a judgment call on a case by case basis, where
the potential for obtaining better data is weighed against the sensitivity and covariance of the given parameters.

4.1.2 Unidentifiability

If a model is found to be unID, an ObsID analysis can still be valuable by use of theorem 2.3.2. Knowing which parameters are unID might be a starting point for reformulating the model in such a way that it would become SI. The unID parameters could likewise reveal potential dependencies that weren’t clear when formulating the model.

The possibility of making COMBOS out of the unID parameters, might lead to potential connections that the modeller is unaware of and when looking at a real-world problem this would be a great tool in the development of the model. It is however not guaranteed that this COMBO will be NI, because it might be too difficult or impossible to obtain the necessary data. It may also decrease realism and precision of the model to a degree that is unsatisfactory and thus be of little use.

In some situations, it is desirable for a model of a biological system to express mechanisms, which reflect similar dynamics regardless of the values of certain parameters (Villaverde and Banga, 2017). Therefore the dynamics of the model across all combinations of possible parameter values can be studied, to determine whether the model reflects the same type of robust dynamics. This removes the necessity of performing a parameter estimation for evaluating the model, with regards to this specific behavior. Some modellers postulate that this removes the necessity of performing an SI analysis (Gutenkunst et al., 2007), but this is not necessarily true. This removes the necessity of the system to be NI, but not necessarily the need for it to be SI (Villaverde, 2019). This is due to the fact that this behavior could either be a reflection of a correctly modelled system, or a consequence of completely robust parameters (Villaverde and Banga, 2017). Since completely robust parameters result in a structurally unID model, this possibility could be ruled out through an SI analysis. Therefore there are some cases in which it makes sense to perform an SI analysis, even if there is no intention of quantifying the model through a parameter estimation (Villaverde, 2019).
4.2 Structural Identifiability Analysis by Extended Observability

Whilst SI analysis can be performed after data fitting and NI can be predicted beforehand, it is usually most suitable to do SI a priori of parameter estimation and NI a posteriori (DiStefano, 2013). This approach does however put quite a burden on the efficiency of the used algorithm, since the computations can become quite cumbersome for large systems. It is to this end, that ObsID has been introduced as a viable approach to SI analysis, since it is reportedly capable of working effectively for larger systems than alternative methods (Villaverde, Barreiro et al., 2016b). It is however certainly not immune to issues with massive computational requirements for large-scale models. This is partly due to the way the extended observability matrix is built, using higher order Lie derivatives (Villaverde, Barreiro et al., 2016b). This is unfortunate since SI analysis would be extremely beneficial for large-scale systems. It is for instance evident that a systematic approach to reducing a model is increasingly more useful the larger and more complex the model is.

Another aspect of ObsID is that, it does not provide information about whether or not the identifiable parameter is local or global, as stated in theorem 2.3.1. If the parameter is locally identifiable then there may still exist distant parameters in the parameter space that are indistinguishable from the parameter of interest. In almost all cases the locally identifiable parameter will also be globally identifiable, but it is nonetheless impossible to guarantee the existence of globally identifiable parameters (Villaverde, 2019). This adds a degree of uncertainty to the method, since there might be some situations where uniquely determined parameters are a necessary condition. A scenario where the risk can particularly critical, since only a numerical estimate based on a model that is structurally globally identifiable, can characterise a pathological state from a normal state (Saccomani et al., 2010). Since the full Cancitis model is within this domain, analysing it via ObsID could potentially be problematic. There are algorithmic alternatives to ObsID, such as DAISY (Saccomani et al., 2010), that can uniquely determine if identifiable parameters are globally or locally identifiable (DiStefano, 2013) and this trait is explicitly highlighted in comparison to ObsID analysis that STRIKE-GOLDD is an incarnation of. The inability to determine if parameters are globally identifiable, is therefore a restriction that can serve as an argument for using a different method.
When it is infeasible to analyse the entire ObsID matrix for rank, it is still possible to gain information with regards to individual parameters and states, by omitting the highest order Lie derivatives (Villaverde, Barreiro et al., 2016b). We view this as an advantage, as this information can in some cases make it clear how to progress with the model.

4.2.1 Applicability of STRIKE-GOLDD

While we are of the general conviction that STRIKE-GOLDD is a useful tool for analysing the identifiability and observability of a model, it is not perfect. When we tried to run STRIKE-GOLDD for the full Cancitis model, it exhausted all of our available memory. Whether it was due to the optimisation of STRIKE-GOLDD or a property of ObsID as a method that caused this, remains unclear. We suspect that it might, at least in part, be an optimisation issue. This is because it was faster to stop STRIKE-GOLDD when we obtained a result and run STRIKE-GOLDD again, with the preliminary result as a initial condition. All of these problems could also be due to a lack of available memory when using STRIKE-GOLDD. The question then becomes a matter of what "enough memory" entails. If the requirements for using STRIKE-GOLDD are too great, its usefulness could be greatly diminished.

STRIKE-GOLDD is prohibited when models are large, due to the nature of the methodology, since a large amount of manipulations are required to build and evaluate the rank of the ObsID matrix. For large systems, the minimum amount of Lie derivatives that must be computed, which is the ratio of states and parameters to outputs, can be quite large. Thus STRIKE-GOLDD is often inefficient since the process of constructing the ObsID matrix and calculating the rank demands a high memory usage (Villaverde, Barreiro et al., 2016b). The practical potential of ObsID as a method is as much dependent on the algorithm, as of the method itself. This matters, since ObsID is a fairly novel method, especially compared to NI approaches, which means that it is quite plausible that current algorithms could be optimised significantly. Such optimisations would of course not make the method universally applicable but it could widen the range of models for which the method is suitable.

The computational cost in this case, could also be due to the Cancitis model being quite complex, with most of the compartments feeding into each other, causing the parameters to be become interconnected. If the dependency between parameters gets minimised, it would not be unfathomable
that the requirements of STRIKE-GOLDD gets lowered. Therefore it could be, that it would make sense to either reparameterise a model that STRIKE-GOLDD cannot analyse or to try and reduce the model to lower complexity.

4.3 The Cancitis Model

The biological system which the Cancitis models describe, is a system for which it is not completely understood, how it should be represented mathematically which is evident by the sheer amount of models made of the system (Sajid et al., 2019). Therefore it is crucial that the created models are tested for SI, to ensure that the performed parameter estimations are indeed meaningful. Thereby it is possible to use said models to further the understanding of the system and evaluate the models against each other.

In regards to both the simplified and the full Cancitis model, ObsID analysis revealed useful information about the model in addition to determining whether the model was SI. However, it was not possible to analyse the full Cancitis model without making assumptions, and as such the results are not conclusive. In both cases the unID parameters were analysed, to determine which parameters were correlated, and how they could be conditionally SI, based on determining correlated parameters or states. This information is essential if a meaningful parameter estimation is to be performed for the model, as it highlights the parameters which are never uniquely determined. These correlations can then be conveyed along with the results, so that the found parameter values are not taken at face value. These found groupings could also be used to pinpoint measurements that are necessary to perform for the system to become SI. Hereafter unique parameter values for the model can be found, which provides, potentially crucial, new information about the given system. This is not exclusive to the case, but could be said for any unID model.

Aside from this, the unID combinations can also be used to evaluate the structure of the model. This could be done by analysing whether the unID combinations show correlation between parameters or states, which is in direct conflict with known theory, it is an obvious reason for reevaluating the model structure. Furthermore the unID combinations could reveal ways of inferring knowledge in regards to significant parameter values that are hard to measure, through other parameters in the unID combination, which may not necessarily be as hard to pinpoint.
5. Conclusion

An SI analysis is worth performing in almost all cases, as long as the computations are feasible for the model. Furthermore it is an advantage of SI analysis, that it can be performed prior to parameter estimation. Thus it is possible to determine beforehand, whether the estimation is meaningful to perform. SI cannot be seen as a replacement for NI however, and should be performed complementarily to an NI analysis, to assure that the system is identifiable.

ObsID technically only determines local SI, but in almost all of these cases the model will also be globally SI. Furthermore the usefulness of the method relies heavily on the ratio of states and parameters to output, as it is an essential factor for whether the computations turn out to be feasible or not. If they aren’t, it may still be possible to acquire information in regards to some part of the system. If the model is determined to be unID, the method is able to find correlations between unID parameters and unobservable states, as well as pinpoint which parts are SI and observable. These correlations can then be used to specify which parameter values must be determined, to make the model SI.

With regards to the Cancitis model, which was used as a case model, it was not possible to reach any results through STRIKE-GOLDD. Therefore a simplified model was created, for which the computations were feasible. Through some educated guesses, based on these results, the full Cancitis model was analysed with assumptions about SI parameters and observable states. Thereby the correlations between the unID parameters and unobservable states were found. These correlations were however based on this assumption, and are therefore not necessarily true. The reduced Cancitis model was found to be SI.

It is not obvious whether it was a lack of memory, ObsID as a method or STRIKE-GOLDD, which made the calculations for the full Cancitis model infeasible.
6. Perspectives

An obvious avenue of research with regards to the ObsID method, would be through a Big-O analysis, both with regards to the time- and space complexity of the algorithm. This would give a measure of the scaling in the algorithm, so that it could easily be determined whether calculations are feasible. There would probably be some interaction between the two complexities, as the efficiency of the computations would drop drastically when almost no memory is available.

It could also be studied, which traits of the model determine the time it takes to determine whether the system is SI. We found no direct relation between the amount of Lie derivatives and the time it takes to calculate the rank of the ObsID matrix. This suggests that it could be an inherent property of the model which determines whether the computations are infeasible. This could then be used as a precursory test, to determine a priori, whether the method is suitable for a given model.

In the report it was found to be more effective to stop the algorithm, and manually input the preliminary results as a starting condition. It would thereby be beneficial for the algorithm to print the outputs for each time a submatrix is added and the rank is calculated, instead of only creating outputs at when the algorithm terminates. Thereby all progress would not be lost, whenever memory problems occur.
7. References


The Sage Developers. (2017). {S}ageMath, the {S}age {M}athematics {S}oftware {S}ystem ({{V}ersion 8.1}).


A. Appendix
A.1 ObsID matrix for spring system

Here we see the rows 4-6 of the ObsID matrix corresponding to the spring system example:

\[ \mathcal{O}_I(\ddot{x})_{4,*} = \begin{pmatrix} 0 \\ k_a/m_b \\ 0 \\ -k_a/m_b \\ 0 \\ -k_a x_3/m_b \end{pmatrix}^T \]  
\[ (A.1) \]

\[ \mathcal{O}_I(\ddot{x})_{5,*} = \begin{pmatrix} -k^2/m_b^2 - (k_a+k_b)/m_a m_b \\ 0 \\ k^2/m_b^2 + k^2/m_a m_b \\ 0 \\ k_b/k_a + k_b/m_a m_b \end{pmatrix}^T \]  
\[ \left( \begin{array}{c} \frac{k_b}{m_b} \left( \frac{x_1}{m_a^2} + \frac{x_3}{m_b} \right) - \frac{k_b}{m_b} \left( \frac{x_1}{m_a^2} - \frac{x_3}{m_b} \right) - \frac{m_b}{m_a} \left( \frac{x_1}{m_a^2} - \frac{x_3}{m_b} \right) + \frac{m_b}{m_b} \left( \frac{x_1}{m_a^2} + \frac{x_3}{m_b} \right) \end{array} \right) \]  
\[ (A.2) \]

\[ \mathcal{O}_I(\ddot{x})_{6,*} = \begin{pmatrix} 0 \\ -k^2/m_b^2 - (k_a+k_b)/m_a m_b \\ 0 \\ k^2/m_b^2 + k^2/m_a m_b \\ 0 \\ k_b/k_a + k_b/m_a m_b \end{pmatrix}^T \]  
\[ \left( \begin{array}{c} -x_2 \left( \frac{2 k_a}{m_b} + \frac{k_a+k_b}{m_a m_b} + \frac{k_b}{m_a m_b} \right) + 2 x_3 \left( \frac{k_a}{m_b^2} + \frac{k_b}{m_a m_b} \right) \end{array} \right) \]  
\[ (A.3) \]
A.2 Sagemath scripts

A.2.1 Spring example script

```
1 # coding: utf-8
2
3 # In[1]:
4
5 var('k_a k_b m_a m_b y')
6 A=matrix(SR, 4)
7 A[0,1]=1; A[2,3]=1
8 A[1,0]=-(k_a+k_b)/m_a; A[1,2]=k_b/m_a
9 A[3,0]=k_b/m_b; A[3,2]=-k_b/m_b
10
11 # In[2]:
12
13 show(A)
14
15
16 # In[3]:
17
18 #Controllability
19 #B=transpose(matrix(SR, [0, 0 ,0, 1]))
20 #show(B)
21 #R=transpose(matrix([vector(B), vector(A*B), vector(A^2*B),
22 vector(A^3*B)]))
23 #show(R)
24
25 # In[4]:
26
27 C=matrix([[0, 0, 1, 0]])
28
29 # In[5]:
30
31 Observability=matrix(SR, [vector(C), vector(C*A), vector(C*A^2),
32 vector(C*A^3)])
33```
40
41
42 # In[6]:
43
44 #Uncomment next line to see Observability matrix
45 show(Observability)
46
47
48 # In[7]:
49
50 #Uncomment next line to see rank of Observability matrix
51 rank(Observability)
52
53
54 # In[8]:
55
56 #Lav x vektor
57 X=[]
58 for j in range(1,5):
59     X.append(var('x_' + str(j)))
60 X=matrix(X)
61 X=transpose(X)
62
63 #Definer f som giver x'
64 f=A*X
65
66 #Definer g som giver y
67 C=matrix(SR, [0, 0, 1, 0])
68 g=C*X
69
70 # In[9]:
71
72 def Lie_deriv(f, g, x):
73     nn=x.nrows()
74     mm=g.ncols()
75     LD=matrix(SR, mm, nn)
76     for n in range(nn):
77         # print n, m, diff(g[0, m], X[n, 0]), show(LD)
78         for m in range(mm):
79             LD[n, m]= diff(g[0, m], x[n, 0])
80     # print LD.nrows(), LD.ncols()
81     return LD
```python
# In[10]:

def Lie_derivs_recs(f, g, x, k):
    if k==0:
        return g
    elif k==1:
        return Lie_deriv(f, g, x)
    else:
        return Lie_deriv(f, Lie_derivs_recs(f, g, x, k-1), x)

#Bemærke at vi indeksere fra 0, men maadden vi har defineret Lie
#afledte paa stemmer overens med dette.
def Lie_derivs_submatr_recs(f, g, x, k):
    #print show(f, g, x)
    gg=Lie_derivs_recs(f, g, x, k)
    nn=x.nrows()
    mm=gg.ncols()
    LD=matrix(SR, mm, nn)
    for n in range(nn):
        for m in range(mm):
            LD[n, m]=diff(gg[0, m], x[n, 0])
    #print LD.nrows(), LD.ncols()
    return LD

# In[11]:

non_linear_observability_matrix=[]
for i in range(X.nrows()):
    non_linear_observability_matrix.append(vector(
        Lie_derivs_submatr_recs(f, g, X, i)))
non_linear_observability_matrix=matrix(SR,
    non_linear_observability_matrix)

#Uncomment next line to see Observability matrix, calculated by
#nonlinear method
#show(non_linear_observability_matrix)

# In[12]:

V
# Uncomment next line to see the rank of the Observability matrix, calculated by nonlinear method
# rank(non_linear_observability_matrix)

# In[13]:

#definer state plus parameters
p=transpose(matrix(SR, [k.a, m.a, k.b, m.b]))
Xp=transpose(matrix(SR, list(vector(X))+ list(vector(p))))

#definer f som udtrykt ved variable og parameire
fp=A*X
fp=transpose(matrix(SR, list(vector(f))+ list(vector([0,0,0,0])))

# In[14]:

non_linear_observability_matrix=[]
for i in range(Xp.nrows()):
    non_linear_observability_matrix.append(vector(Lie_deriv_submatr_recurc(fp, g, Xp, i)))
non_linear_observability_matrix=matrix(SR, non_linear_observability_matrix)

# uncomment next line to see full matrix, it is rather large though
show(non_linear_observability_matrix)

# uncomment next 2 lines to see each row separately of the ObsID matrix of the spring system
# for i in range(7):
#    show(non_linear_observability_matrix[i, :])

# uncomment next line to see rank og ObsID matrix of spring system
# rank(non_linear_observability_matrix)

A.2.2 Unobservable example script

# coding: utf-8
# In[11]:

VI
A.3 Matlab Scripts

The MATLAB scripts that were used for this report can be accessed in a separate zip file. The folders where the relevant files can be found, are named the same as the section in the appendix which describes how to use it.

A.3.1 $\phi$ Function Values

Download all files, and run the "phi.m" file.

A.3.2 $\phi$ as a Function and $\phi$ as a Constant

Download all files, and run the "phi_constant.m" file.
A.3.3 First Comparison of Models
Download all files, and run the "Comparison1.m" file.

A.3.4 Second Comparison of Models
Download all files, and run the "Comparison2.m" file.

A.3.5 Third Comparison of Models
Download all files, and run the "Comparison3.m" file.

A.3.6 Fourth Comparison of Models
Download all files, and run the "Comparison4.m" file.

A.3.7 Creating the Simplified Cancitis Model
Download and run the file "a_create_cancitis1.m". This file defines the model that was analysed by STRIKE-GOLDD for identifiability of the simplified Cancitis model.

A.3.8 Creating the Full Cancitis Model
Download and run the file "a_create_cancitis2.m". This file defines the model that was analysed by STRIKE-GOLDD for identifiability of the full Cancitis model.

A.3.9 Creating the Reduced Cancitis Model
Download and run the file "a_create_cancitis3.m". This file defines the model that was analysed by STRIKE-GOLDD for identifiability of the reduced Cancitis model.
A.4 Indices

A.4.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ObsID</td>
<td>Structural identifiability analysis by extended observability</td>
</tr>
<tr>
<td>LTI</td>
<td>Linear time-invariant</td>
</tr>
<tr>
<td>SI</td>
<td>Structural identifiability</td>
</tr>
<tr>
<td>COMBOS</td>
<td>Reparameterisation in terms of structurally identifiable combinations</td>
</tr>
<tr>
<td>STRIKE-GOLDD</td>
<td>Structural identifiability taken as extended-generalised observability using lie derivatives and decomposition</td>
</tr>
<tr>
<td>HSC</td>
<td>Hematopoietic stem cells</td>
</tr>
<tr>
<td>HMC</td>
<td>Hematopoietic mature cells</td>
</tr>
<tr>
<td>MSC</td>
<td>Malignant stem cells</td>
</tr>
<tr>
<td>MMC</td>
<td>Malignant mature cells</td>
</tr>
<tr>
<td>NI</td>
<td>Numerical identifiability</td>
</tr>
<tr>
<td>unID</td>
<td>Unidentifiable</td>
</tr>
</tbody>
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A.4.2 Equations

\[
\begin{align*}
\dot{x} &= f(x, u, p, t) \\
y &= g(x, u, p, t) \\
x_0 &= x(t_0)
\end{align*}
\]  
(2.1)

\[
\begin{align*}
\dot{x} &= Ax + Bu \\
y &= Cx \\
t_0 &= 0
\end{align*}
\]  
(2.2)

\[
y(t) = e^{H(t)} \int_{t_0}^{t_1} e^{-A(x)} g(x) \, dx + ce^{H(t)}
\]  
(2.3)
\[ x(t) = e^{At} \int_{t_0}^{t_1} e^{-A(u)} Bu \, du + ce^{At} \quad (2.4) \]

\[ \dot{x} = Ax \]
\[ y = Cx \]
\[ t_0 = 0 \quad (2.5) \]

\[ x(t) = e^{At} \int_{t_0}^{t} e^{-A(u)} \, du + ce^{At} = ce^{At} \quad (2.6) \]

\[ x(t_0) = ce^{A0} = c \equiv x_0 \quad (2.7) \]

\[ y_0 = Cx_0 \quad (2.8) \]

\[ y_0 = Cx_0 \]
\[ \dot{y}_0 = C \dot{x}_0 = CAx_0 \]
\[ \ddot{y}_0 = C \ddot{x}_0 = CA^2x_0 \]
\[ \vdots \]
\[ y_0^{(i)} = Cx_0^{(i)} = CA^i x_0 \quad (2.9) \]

\[ X \]
\[ y = Cx \]
\[ \dot{y} = C\dot{x} = CAx \]
\[ \ddot{y} = C\ddot{x} = CA^2x \]
\[ \vdots \]
\[ y^{(i)} = Cx^{(i)} = CA^ix \]  

(2.10)

\[ \mathcal{O}_L = \begin{pmatrix} 
C \\
CA \\
CA^2 \\
\vdots \\
CA^{n-1} 
\end{pmatrix} \]  

(2.11)

\[ \lambda^n + a_{n-1}\lambda^{n-1} + \ldots + a_2\lambda^2 + a_1\lambda + a_0 = 0 \]  

(2.12)

\[ A^n + a_{n-1}A^{n-1} + \ldots + a_2A^2 + a_1A + a_0 = 0 \]  

(2.13)

\[ A^n = -a_{n-1}A^{n-1} - \ldots - a_2A^2 - a_1A - a_0I \]  

(2.14)

\[ A^n = \sum_{j=0}^{n-1} -a_jA^j \]  

(2.15)
\[ A^{n+1} = -a_{n-1}A^n - \ldots - a_2A^3 - a_1A^2 - a_0A \] (2.16)

\[
\begin{align*}
\dot{x}_1 &= x_2 \\
\dot{x}_2 &= -\frac{k_a}{m_a} x_1 - \frac{k_b}{m_a} (x_1 - x_3) \\
\dot{x}_3 &= x_4 \\
\dot{x}_4 &= -\frac{k_b}{m_b} (x_3 - x_1)
\end{align*}
\] (2.17)

\[
\dot{x} = Ax = \begin{pmatrix}
0 & 1 & 0 & 0 \\
-\frac{k_a + k_b}{m_a} & 0 & \frac{k_b}{m_a} & 0 \\
0 & 0 & \frac{k_b}{m_b} & 0 \\
\frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0
\end{pmatrix}
\begin{pmatrix}
x_1 \\
x_2 \\
x_3 \\
x_4
\end{pmatrix}
\] (2.18)

\[ C = (0 \ 0 \ 1 \ 0) \] (2.19)

\[ \mathcal{O}_L = \begin{pmatrix}
C \\
CA \\
CA^2 \\
CA^3
\end{pmatrix} \] (2.20)

XII
\[ CA^3 = (CA^2) A = \begin{pmatrix} \frac{k_a}{m_b} & 0 & -\frac{k_b}{m_b} & 0 \end{pmatrix} \begin{pmatrix} 0 & 1 & 0 & 0 \\ -\frac{k_a + k_b}{m_a} & 0 & \frac{k_b}{m_a} & 0 \\ 0 & 0 & 0 & 1 \\ \frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0 \end{pmatrix} \] (2.21)

\[ CA^3 = \begin{pmatrix} 0 & \frac{k_a}{m_b} & 0 & -\frac{k_b}{m_b} \end{pmatrix} \]

\[ O_L = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ \frac{k_a}{m_b} & 0 & -\frac{k_b}{m_b} & 0 \\ 0 & \frac{k_a}{m_b} & 0 & -\frac{k_b}{m_b} \end{pmatrix} \] (2.22)

\[ L_j g(x) = \frac{\partial g(x)}{\partial x} f(x) \] (2.23)

\[ L_j^1 g(x) = \frac{\partial g(x)}{\partial x} f(x) \] (2.24)

\[ L_j^2 g(x) = \frac{\partial L_j^1 g(x)}{\partial x} f(x) \] (2.25)

\[ L_j^k g(x) = \frac{\partial L_j^{k-1} g(x)}{\partial x} f(x) \text{ with } L_j^0 g(x) = g(x) \] (2.26)

XIII
\[ O_{NL}(x) = \begin{pmatrix} \frac{\partial g(x)}{\partial x} \\ \frac{\partial}{\partial \xi} (L^1 f g(x)) \\ \frac{\partial}{\partial x} (L^2 f g(x)) \\ \vdots \\ \frac{\partial}{\partial x} (L^{n-1} f g(x)) \end{pmatrix} \] (2.27)

\[ f(x) = \begin{pmatrix} \frac{(k_a + k_b)x_1}{m_a} + \frac{x_2}{m_a} \\ \frac{k_b x_3}{m_a} \frac{x_4}{m_b} - \frac{k_b x_3}{m_b} \end{pmatrix} \] (2.28)

\[ g(x) = x_3 \]

\[ \frac{\partial g(x)}{\partial x} = \begin{pmatrix} \frac{\partial x_3}{\partial x_1} & \frac{\partial x_3}{\partial x_2} & \frac{\partial x_3}{\partial x_3} & \frac{\partial x_3}{\partial x_4} \end{pmatrix} = \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix} \] (2.29)

\[ L^1 f g(x) = \frac{\partial g(x)}{\partial x} \cdot f(x) \]

\[ = \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} \frac{(k_a + k_b)x_1}{m_a} - \frac{k_b x_3}{m_a} \\ \frac{k_b x_3}{m_a} \frac{x_4}{m_b} - \frac{k_b x_3}{m_b} \end{pmatrix} = x_4 \] (2.30)
\[ \frac{\partial}{\partial x} (L^1_j g(x)) = \left( \frac{\partial x_4}{\partial x_1}, \frac{\partial x_4}{\partial x_2}, \frac{\partial x_4}{\partial x_3}, \frac{\partial x_4}{\partial x_4} \right) = (0, 0, 0, 1) \quad (2.31) \]

\[ L^2_j g(x) = (0, 0, 0, 1) \begin{pmatrix} -\frac{(k_a + k_b)x_1}{m_a} + \frac{x_2}{m_a} \\ \frac{x_4}{m_b} - \frac{k_b x_3}{m_b} \end{pmatrix} = \frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b} \quad (2.32) \]

\[ \mathcal{O}_{3,*} = \begin{pmatrix} \frac{\partial}{\partial (\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b})} \\ \frac{\partial}{\partial (\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b})} \\ \frac{\partial}{\partial (\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b})} \\ \frac{\partial}{\partial (\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b})} \end{pmatrix} \left( \begin{pmatrix} k_b \\ x_2 \\ m_b \\ m_b \end{pmatrix} \right) = (0, 0, 0, 1) \quad (2.33) \]

\[ L^3_j g(x) = \begin{pmatrix} k_b \\ 0 \end{pmatrix} \begin{pmatrix} \frac{k_b}{m_b} \\ 0 \end{pmatrix} \left( \begin{pmatrix} -\frac{(k_a + k_b)x_1}{m_a} + \frac{x_2}{m_a} \\ \frac{x_4}{m_b} - \frac{k_b x_3}{m_b} \end{pmatrix} \right) \quad (2.34) \]
\[ O_{4,*} = \begin{pmatrix} \frac{\partial}{\partial x_1} \left( \frac{k_b x_2 - k_b x_4}{m_b} \right) \\ \frac{\partial}{\partial x_2} \left( \frac{k_b x_2 - k_b x_4}{m_b} \right) \\ \frac{\partial}{\partial x_3} \left( \frac{k_b x_2 - k_b x_4}{m_b} \right) \\ \frac{\partial}{\partial x_4} \left( \frac{k_b x_2 - k_b x_4}{m_b} \right) \end{pmatrix} \]  

(2.35)  

\[ O = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ \frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} & 0 \\ 0 & \frac{k_b}{m_b} & 0 & -\frac{k_b}{m_b} \end{pmatrix} \]  

(2.36)  

\[ L_1^g(x) = \frac{\partial g(x)}{\partial x_1} \cdot f(x)_1 + \frac{\partial g(x)}{\partial x_2} \cdot f(x)_2 \]  

(2.37)  

\[ \frac{\partial g(x)}{\partial x_1} \cdot f(x)_1 + \frac{\partial g(x)}{\partial x_2} \cdot f(x)_2 = 0 \]  

(2.38)
\[ f(x_1) = -\left( \frac{\partial g(x)}{\partial x_2} \right) \cdot f(x_2) \quad (2.39) \]

\[ f(x) = \begin{pmatrix} (\cos(x_1) + \sin(x_2)) \cos(x_2) \\ \sin(x_1) \\ \cos(x_1) + \sin(x_2) \end{pmatrix} \quad (2.40) \]

\[ L^1 g = \left( \frac{\partial g(x)}{\partial x_1} \right) \cdot \left( \frac{\partial g(x)}{\partial x_2} \right) \cdot \begin{pmatrix} (\cos(x_1) + \sin(x_2)) \cos(x_2) \\ \sin(x_1) \\ \cos(x_1) + \sin(x_2) \end{pmatrix} \quad (2.41) \]

\[ = (-\sin(x_1) \cos(x_2)) \cdot \begin{pmatrix} (\cos(x_1) + \sin(x_2)) \cos(x_2) \\ \sin(x_1) \\ \cos(x_1) + \sin(x_2) \end{pmatrix} \]

\[ = (\cos(x_1) + \sin(x_2)) \cos(x_2) - \cos(x_2)(\cos(x_1) + \sin(x_2)) = 0 \]

\[ \mathcal{O} = \begin{pmatrix} -\sin(x_1) & \cos(x_2) \\ 0 & 0 \end{pmatrix} \quad (2.42) \]

\[ p_{\text{guess}} \in V(p^*) \text{ and } y(t, p_{\text{guess}}) = y(t, p^*) \implies p_{\text{guess}} = p^* \quad (2.43) \]

\[ \dot{x} = x + k \quad (2.44) \]

\[ k = \dot{x} - x \quad (2.45) \]
\[ \dot{x} = x + k_1 + k_2 \quad (2.46) \]

\[ \dot{x} - x = k_1 + k_2 \quad (2.47) \]

\[ p^* = \begin{pmatrix} a \\ b \end{pmatrix} \quad (2.48) \]

\[ x = \dot{x} - a - b \quad (2.49) \]

\[ p_{\text{guess}} = \begin{pmatrix} c \\ d \end{pmatrix} \quad (2.50) \]

\[ x = \dot{x} - c - d \quad (2.51) \]

\[ \dot{x} - c - d = \dot{x} - (a + \epsilon) - (b - \epsilon) = \dot{x} - a - b \quad (2.52) \]
\[ y = g(x, u, t, p) = \sum_{i=0}^{n} \frac{d^i g(x(0), u(0), 0, p)}{dt^i} \frac{t^i}{i!} \]  

(2.53)

\[ O_{\tilde{x}}(\tilde{x}) = \begin{pmatrix} \frac{\partial g(\tilde{x})}{\partial \tilde{x}} \\ \frac{\partial}{\partial \tilde{x}} (L_1 g(\tilde{x})) \\ \frac{\partial}{\partial \tilde{x}} (L_2 g(\tilde{x})) \\ \vdots \\ \frac{\partial}{\partial \tilde{x}} (L_n g(\tilde{x})) \end{pmatrix} \]  

(2.54)

\[ \dot{x} = f(\tilde{x}) = \begin{pmatrix} -\frac{(k_a + k_b)x_1}{m_a} + \frac{k_b x_3}{m_a} \\ \frac{1}{m_a} x_4 \\ \frac{1}{m_b} k_b x_3 - \frac{1}{m_a} k_b x_3 \\ 0 \\ 0 \\ 0 \end{pmatrix} \]  

(2.56)

\[ \dot{x} = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 & k_a & m_a & k_b & m_b \end{pmatrix}^T \]

\[ y = x_3 \]

\[ \frac{\partial g(x)}{\partial x} = \begin{pmatrix} \frac{\partial x_3}{\partial x_1} & \frac{\partial x_3}{\partial x_2} & \frac{\partial x_3}{\partial x_3} & \frac{\partial x_3}{\partial x_4} & \frac{\partial x_3}{\partial k_a} & \frac{\partial x_3}{\partial m_a} & \frac{\partial x_3}{\partial k_b} & \frac{\partial x_3}{\partial m_b} \end{pmatrix} \]

(2.55)

\[ = \begin{pmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \]
\[ L_1^1 g(\ddot{x}) = \frac{\partial g(\ddot{x})}{\partial \ddot{x}} \cdot f(\ddot{x}) = \]
\[
\begin{pmatrix}
\frac{(k_a + k_b)x_1}{m_a} + \frac{k_b x_3}{m_b} \\
\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b} \\
0 \\
0 \\
0 \\
0
\end{pmatrix}
\]
\[
= \begin{pmatrix} x_2 \\
x_4 \\
0 \\
0 \\
0 \\
0
\end{pmatrix} = x_4 
\] (2.57)

\[
\frac{\partial L_1^1 g(\ddot{x})}{\partial \dddot{x}} = \begin{pmatrix}
\frac{\partial x_4}{\partial x_1} & \frac{\partial x_4}{\partial x_2} & \frac{\partial x_4}{\partial x_3} & \frac{\partial x_4}{\partial k_a} & \frac{\partial x_4}{\partial m_a} & \frac{\partial x_4}{\partial k_b} & \frac{\partial x_4}{\partial m_b}
\end{pmatrix}
\]
\[
= \begin{pmatrix} 0 & 0 & 0 & 1 & 0 & 0 & 0
\end{pmatrix} 
\] (2.58)

\[ L_1^2 g(\ddot{x}) = \frac{\partial L_1^1 g(\ddot{x})}{\partial \ddot{x}} \cdot f(\ddot{x}) = \]
\[
\begin{pmatrix}
\frac{(k_a + k_b)x_1}{m_a} + \frac{k_b x_3}{m_b} \\
\frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b} \\
0 \\
0 \\
0 \\
0
\end{pmatrix}
\]
\[
= \begin{pmatrix} x_2 \\
x_4 \\
0 \\
0 \\
0 \\
0
\end{pmatrix} = \begin{pmatrix} \frac{k_b x_1}{m_b} - \frac{k_b x_3}{m_b}
\end{pmatrix} 
\] (2.59)
\[
\frac{\partial L^2 g(\bar{x})}{\partial \bar{x}} = \left( \begin{array}{cccc}
\frac{\partial L^2 g(\bar{x})}{\partial x_1} & \frac{\partial L^2 g(\bar{x})}{\partial x_2} & \frac{\partial L^2 g(\bar{x})}{\partial x_3} & \frac{\partial L^2 g(\bar{x})}{\partial x_4} \\
\frac{\partial L^2 g(\bar{x})}{\partial k_1} & \frac{\partial L^2 g(\bar{x})}{\partial m_a} & \frac{\partial L^2 g(\bar{x})}{\partial k_5} & \frac{\partial L^2 g(\bar{x})}{\partial m_b}
\end{array} \right)
\]
\[
\left( \frac{k_b}{m_b} \ 0 \ -\frac{k_b}{m_b} \ 0 \ 0 \ \frac{x_1}{m_b} - \frac{x_3}{m_b} \ \left( -\frac{k_b x_1}{m_b^2} + \frac{k_b x_3}{m_b^2} \right) \right) (2.60)
\]

\[
\left\{ \begin{array}{l}
\text{Change in amount of a} \\
\text{compartment per time}
\end{array} \right\} = 
\left\{ \begin{array}{l}
\text{Rate of production times} \\
\text{the producing source}
\end{array} \right\} - 
\left\{ \begin{array}{l}
\text{Rate of elimination times the} \\
\text{amount in the compartment}
\end{array} \right\} (3.1)
\]

\[
\dot{x}_0 = r_x (\phi_x s - \frac{(d_x + a_x)}{r_x}) x_0 - r_m s x_0
\]
\[
\dot{x}_1 = a_x A_x x_0 - d_x x_1
\]
\[
\dot{y}_0 = r_y (\phi_y s - \frac{(d_y + a_y)}{r_y}) y_0 - r_m s y_0
\]
\[
\dot{y}_1 = a_y A_y y_0 - d_y y_1
\]
\[
\dot{a} = d_{a0} x_0 + d_{a1} y_0 - d_{a1} y_1 - e_a a s
\]
\[
\dot{s} = r_a a - e_s s + I
\]

\[
\phi_x \equiv \phi_x(x_0, y_0) = \frac{1}{1 + c_{xx} x_0 + c_{xy} y_0}
\]
\[
\phi_y \equiv \phi_y(x_0, y_0) = \frac{1}{1 + c_{yx} x_0 + c_{yy} y_0}
\] (3.3)
\[
\phi_x(x_0, y_0) = \phi_x(x_0(0), y_0(0)) \\
\phi_y(x_0, y_0) = \phi_y(x_0(0), y_0(0)) \tag{3.4}
\]

\[
X_0' = \bar{t} \left( \frac{S}{\bar{x}_x} - d_{x_0} - a_x \right) X_0
\]

\[
X_1' = \bar{t} \left( \bar{x}_o a_y A_x X_0 - d_{x_1} X_1 \right)
\]

\[
Y_0' = \left( \frac{S}{\bar{y}_y} + c_{xy} \bar{x}_0 X_0 + c_{yy} \bar{y}_0 Y_0 - d_{y_0} (Y) - a_y \right) Y_0
\]

\[
Y_1' = \bar{t} \left( \bar{y}_1 a_y A_y Y_0 - d_{y_1} Y_1 \right)
\]

\[
A' = \bar{t} \left( d_{x_0} \bar{x}_0 X_0 + d_{y_0} (Y_0) \bar{y}_0 \frac{a}{a} Y_0 + d_{y_1} \bar{y}_1 Y_1 - e_{a} \bar{s} A S \right)
\]

\[
S' = \bar{t} \left( \frac{a}{\bar{s}} (A - e_{a} S + \frac{I}{\bar{s}}) \right)
\]

\[
X_0' = \left( \frac{S}{1 + (X_0 + \frac{c_{xx} Y_0}{c_{yy}})} - 1 \right) X_0
\]

\[
\epsilon_1 X_1' = (X_0 - X_1)
\]

\[
Y_0' = \left( \frac{r_y}{r_x} \left( \frac{S}{1 + (\frac{c_{xx} X_0 + Y_0}{c_{yy}})} - \frac{d_{y_0} (Y_0) + a_y}{d_{x_0} + a_x} \right) \right) Y_0 \tag{3.6}
\]

\[
\epsilon_1 Y_1' = \frac{d_{y_1}}{d_{x_1}} (Y_0 - Y_1)
\]

\[
\epsilon_2 \epsilon_3 A' = (b_{x_0} X_0 + b_{y_0} (Y_0) Y_0 + b_{x_1} X_1 + b_{y_1} Y_1 - A S)
\]

\[
\epsilon_2 S' = \left( A - S + \frac{I}{\epsilon_i s} \right)
\]
\[ X_0' = 0 = (X_0 - X_1) \]
\[ Y_1' = 0 = \frac{d_{y_1}}{d_{x_1}} (Y_0 - Y_1) \]
\[ A' = 0 = (b_{x_0} X_0 + b_{y_0} Y_0 + b_{x_1} X_1 + b_{y_1} Y_1 - AS') \]
\[ S' = 0 = \left( A - S + \frac{I}{\varepsilon_3 \varepsilon_5} \right) \tag{3.7} \]

\[ X_0' = \left( J + \sqrt{J^2 + 2B_x X_0 + 2B_y Y_0} \right) \frac{1}{1 + C_x X_0 + C_y Y_0} - 1 \] \( X_0 \)
\[ Y_0' = \left( R J + \sqrt{J^2 + 2B_x X_0 + 2B_y Y_0} \right) \frac{1}{1 + C_x X_0 + Y_0} - D_0 - D_1 Y_0 \] \( Y_0 \) \tag{3.8}

\[ \phi_x \equiv \phi_x(x_0, y_0) = \frac{1}{1 + c_{xx} x_0 + c_{xy} y_0} \]
\[ \phi_y \equiv \phi_y(x_0, y_0) = \frac{1}{1 + c_{yx} x_0 + c_{yy} y_0} \] \tag{3.9}