

THESIS FOR THE DEGREE OF LICENTIATE OF ENGINEERING

**Nonlinear Observability and Identifiability:
General Theory and a Case Study of a Kinetic Model
for *S. cerevisiae***

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Abstract

Observability is a structural property of a control system defined as the possibility to deduce the state of the system from observing its input-output behaviour.

The first part of this report presents a review of two different methods to test the observability of nonlinear control systems found in literature. The differential geometric and algebraic approaches have been applied to different classes of control systems. Both methods lead to the so-called rank test where the observability of a control system is determined by calculating the dimension of the space spanned by gradients of the Lie-derivatives of its output functions. It has been shown previously that for rational systems with n state-variables, only the first $n - 1$ Lie-derivatives have to be considered in the rank test. In this work, we show that this result applies for a broader class of analytic systems.

The rank test can be used to determine parameter identifiability which is a special case of the observability problem. A case study is presented in which the parameter identifiability of a previously published kinetic model for the metabolism of *S. cerevisiae* (baker's yeast) has been analysed. The results show that some of the model parameters cannot be identified from any set of experimental data. The general features of kinetic models of metabolism are examined and shown to allow a simplified identifiability analysis.

Keywords: Nonlinear observability, identifiability, observability rank condition, nonlinear systems, metabolic model, kinetic model, metabolism, glycolysis, *Saccharomyces cerevisiae*

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Chapter 1

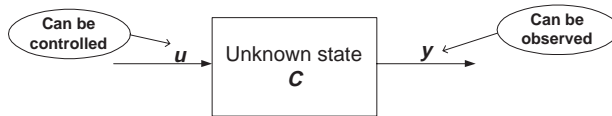
Introduction

1.1 Motivation for studying observability and identifiability

Consider a culture of yeast cells grown in a reactor and the chemical reactions that take place in their metabolism. Thus far, our ability to observe what occurs inside a single cell as far as metabolic fluxes are concerned is very limited. It is therefore not unnatural to consider the cell as a box where we see what goes in (nutrients) and what comes out (secreted products), but not what happens inside.



There is, however, extensive knowledge of the chemistry and biology that takes place within the cell, and based on that, models are made for the transformation that occurs inside the box. In preparation for a mathematical description of the situation, we transform the above picture as follows:



We will now label the part that we can control - for example, the amount of food given to the cells - u and call it “input”, or ”control variable”. The part that can be observed - e.g. the different secreted products the fluxes of which can be measured - is denoted by y and called “output”. What happens inside the cell is accounted for in terms of changes in the concentrations of the different chemical species present with respect to time; these concentrations are referred to as “state-variables” and denoted by c . We also have a number of parameters that come with the model used for cellular metabolism, denoted by p . The following “state-space” model can now be formulated:

$$\begin{cases} \dot{p} &= 0 \\ \dot{c} &= f(c, p, u) \\ y &= g(c, p) \end{cases} .$$

We assume a hypothetical setting where we start feeding an input u to the cell at time zero when the system is at an unknown state c and we observe the cell’s behaviour in terms of the outputs produced. It is assumed that u is a function of time that we can choose, and that the values of y and all its time-derivatives at the starting point (time zero) can be measured. \dot{c} denotes the time-derivative of the state-variables.

It is often the case that the model parameters, besides being numerous, have, many of them, unknown values. The only means of estimating them is from observing the input-output behaviour of the system. The property of identifiability is the possibility to define the values of the model parameters uniquely in terms of known quantities, that is, inputs, outputs and their time-derivatives.

1.2 Problem statement

A generalisation of identifiability is the property of observability. Consider the following ”control system” which generalises the example above:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) \\ y &= g(x, u) \end{cases} .$$

In this system, x are the state-variables, the inputs are denoted by u and the outputs by y . Note that parameters can be considered state-variables with time-derivative zero. We have no knowledge of the initial conditions for

the state-variables (or, respectively, of the parameter values). It is assumed that we have a perfect measurement of the outputs so that they are known as functions of time in some interval and all their time-derivatives at time zero can be calculated. The observability problem consists of investigating whether there exist relations binding the state-variables to the inputs, outputs and their time-derivatives and thus locally defining them uniquely in terms of controllable/measurable quantities without the need for knowing the initial conditions. If no such relations exist, the initial state of the system cannot be deduced from observing its input-output behaviour. In the biological setting above, for instance, this can mean that there are infinitely many parameter sets that produce exactly the same output for every input and thus the model parameters cannot be estimated from any experimental measurements.

Before we define the problem of observability, consider the following example of a control system taken from [20]:

$$\begin{aligned} \dot{x}_1 &= \frac{x_2}{x_1} \\ \dot{x}_2 &= \frac{x_3}{x_2} \\ \dot{x}_3 &= x_1\theta - u \\ y &= x_1 \quad . \end{aligned}$$

In this system, x_1, x_2 and x_3 are state-variables, θ is a parameter, there is a single input u and a single output y . In the following we use capital letters to denote initial values of a function and its derivatives, i.e. $u^{(r)}(0) = U^{(r)}$, $y^{(r)}(0) = Y^{(r)}$ for $r \geq 0$. By computing time-derivatives of the output at time zero, we obtain the equations:

$$\begin{aligned} Y^{(1)} &= \dot{x}_1 = \frac{x_2}{x_1} \\ Y^{(2)} &= \ddot{x}_1 = \frac{\dot{x}_2 x_1 - x_1 \dot{x}_2}{x_1^2} = \frac{\frac{x_3}{x_2} x_1 - \frac{x_2}{x_1} x_2}{x_1^2} = \frac{x_3}{x_1 x_2} - \frac{x_2^2}{x_1^3} \\ Y^{(3)} &= x_1^{(3)} = \frac{\dot{x}_3 x_1 x_2 - x_3(x_1 \dot{x}_2 + x_1 \dot{x}_2)}{x_1^2 x_2^2} = \frac{2x_2 \dot{x}_2 x_1^3 - x_2^2 3x_1^2 \dot{x}_1}{x_1^6} = \\ &= \frac{(x_1 \theta - U^{(0)}) x_1 x_2 - x_3 (\frac{x_2}{x_1} x_2 + x_1 \frac{x_3}{x_2})}{x_1^2 x_2^2} = \frac{2x_2 \frac{x_3}{x_2} x_1^3 - x_2^2 3x_1^2 \frac{x_2}{x_1}}{x_1^6} = \\ &= \frac{\theta}{x_2} - \frac{U^{(0)}}{x_1 x_2} - \frac{x_3^2}{x_1 x_2^3} - \frac{3x_3}{x_1^3} + \frac{3x_3^3}{x_1^5} \quad . \end{aligned}$$

For this simple example, it is actually possible to explicitly calculate the initial values of the state-variables and the parameters in terms of the inputs

and outputs and their time-derivatives at time zero as shown in [20]:

$$\begin{aligned}
 x_1 &= Y^{(0)} \\
 x_2 &= Y^{(0)}Y^{(1)} \\
 x_3 &= Y^{(0)}Y^{(1)}((Y^{(1)})^2 + Y^{(0)}Y^{(2)}) \\
 \theta &= \frac{1}{Y^{(0)}}(((Y^{(1)})^2 + Y^{(0)}Y^{(2)})^2 + Y^{(0)}Y^{(1)}(3Y^{(1)}Y^{(2)} + Y^{(0)}Y^{(3)}) - U^{(0)})
 \end{aligned}$$

A given input-output behaviour thus corresponds to a unique state of the system. In general, we are not going to demand a globally unique state. It is enough that the equations have a finite number of solutions each defining a locally unique state. The observability problem concerns the existence of such relations and not the explicit calculation of the state variables from the equations. Depending on the theoretical approach, different definitions of observability can be given, as shown in this report.

1.3 Organisation of the report

In this work, a method for investigating the observability of certain classes of nonlinear control systems is described by using different theoretical points of view, each of which adds to our understanding of the problem.

Chapters 2 and 3 present a survey of the theory on nonlinear observability available in literature. Observability has been dealt with in both a differential geometrical interpretation, and an algebraical one. The two approaches are introduced and the results in terms of obtaining an observability test are described.

Chapter 4 attempts to answer certain questions that arise during the literature surveys. If the derived observability test is to be applied in practice, a bound must be introduced for the number of time-derivatives of the output that have to be considered in obtaining equations for the variables. Such an upper bound is given for rational systems in Chapter 3. In Chapter 4 this bound is shown to apply for analytic systems.

Chapter 5 describes the identifiability problem as a special case of observability.

In Chapter 6 we apply the theory discussed in the preceding chapters to a case study of a kinetic model for the metabolism of *Saccharomyces cerevisiae*, also known as bakers yeast. We use an algorithm by Alexandre Sedoglavic [20] and its implementation in Maple which performs an observability/identifiability test of rational models. We obtain results for the iden-

tifiability of the kinetic model and find the non-identifiable parameters. The results are interpreted in terms of the biological structure of the model.

Chapter 2

Literature survey

Part 1: The differential geometric approach to nonlinear observability

In this chapter we present the basics of the theory of nonlinear observability in a differential-geometric approach that we have gathered from the works of Hermann and Krener [7], Krener [11], Isidori [8], Sontag [24] and Sussmann [26].

2.1 Definitions

Throughout this chapter we will consider control systems affine in the input variables which is a valid description of many real-world systems. They have the form:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) = h^0(x) + h(x)u \\ y &= g(x) \end{cases}, \quad (2.1)$$

where u denotes the input, x the state variables and y the outputs (measurements). We assume that $x \in M$ where M is an open subset of \mathbb{R}^n , $u \in \mathbb{R}^k$, $y \in \mathbb{R}^m$ and h^0 and the k columns of h (denoted by h^i for $i = 1, \dots, k$) are analytic vector fields defined on M . We also have to assume that the system is complete, that is, for every bounded measurable input $u(t)$ and every

$x^0 \in M$ there exists a solution to $\dot{x} = f(x(t), u(t))$ such that $x(0) = x^0$ and $x(t) \in M$ for all $t \in \mathbb{R}$.

Here follow several definitions. Let U denote an open subset of M .

Definition 2.1 A pair of points x^0 and x^1 in M are called ***U-distinguishable*** if there exists a measurable bounded input $u(t)$ defined on the interval $[0, T]$ that generates solutions $x^0(t)$ and $x^1(t)$ of $\dot{x} = f(x, u)$ satisfying $x^i(0) = x^i$ such that $x^i(t) \in U$ for all $t \in [0, T]$ and $g(x^0(t)) \neq g(x^1(t))$ for some $t \in [0, T]$. We denote by $I(x^0, U)$ all points $x^1 \in U$ that are not ***U-distinguishable*** from x^0 .

Definition 2.2 The system Σ is ***observable*** at $x^0 \in M$ if $I(x^0, M) = x^0$.

If a system is observable according to the above definition, it is still possible that there is an arbitrarily large interval of time in which two points of M cannot be distinguished from each other. Therefore a local concept is introduced which guarantees that to distinguish between the points of an open subset U of M , we do not have to go outside of it, which necessarily sets a limit to the time interval as well.

Definition 2.3 The system Σ is ***locally observable*** at $x^0 \in M$ if for every open neighborhood U of x^0 , $I(x^0, U) = x^0$.

Clearly, local observability implies observability as we can set U in Definition 2.3 equal to M . On the other hand, since U can be chosen arbitrarily small, local observability implies that we can distinguish between neighboring points instantaneously (since the trajectory is bound to be within U , setting a limit to the time interval).

Both the definitions above ensure that a point $x^0 \in M$ can be distinguished from every other point in M . For practical purposes though, it is often enough to be able to distinguish between neighbours in M , which leads us to the following two concepts:

Definition 2.4 The system Σ has the ***distinguishability property*** at $x^0 \in M$ if x^0 has an open neighborhood V such that $I(x^0, M) \cap V = x^0$.

In a system having this property, any point x^0 can be distinguished from neighbouring points but there could be arbitrarily large intervals of time $[0, T]$ in which the points cannot be distinguished. In order to set a limit on the time interval, a stronger concept is introduced:

Definition 2.5 *The system Σ has the **local distinguishability property** at $x^0 \in M$ if x^0 has an open neighbourhood V such that for every open neighbourhood U of x^0 , $I(x^0, U) \cap V = x^0$.*

Clearly, local observability implies local distinguishability as we can set V equal to M . Thus, if a system does not have the local distinguishability property at some x^0 , it is not locally observable at that point either.

It is the final property of local distinguishability that lends itself to a test.

2.2 The observability rank condition

This section describes how to determine if a system possesses the local distinguishability property by the so-called "observability rank condition" as introduced by Hermann and Krener [7].

Throughout this section, we will use the following simple example of a control system:

$$\begin{cases} \dot{x}_1 &= 0 \\ \dot{x}_2 &= u - x_1x_2 \\ y &= x_1x_2 \end{cases} .$$

For this system, $h^0(x_1, x_2) = \begin{pmatrix} 0 \\ -x_1x_2 \end{pmatrix}$, $h(x_1, x_2) = \begin{pmatrix} 0 \\ 1 \end{pmatrix}$ and

$g(x_1, x_2) = x_1x_2$ (according to the notation introduced in the previous section) with $m = 1$, $k = 1$, and $n = 2$.

Define the following Lie differentiation of a C^∞ function ϕ on M by a vector field v on M :

$$L_v(\phi)(x) := \langle d\phi, v \rangle .$$

Here $\langle \rangle$ denotes scalar product and $d\phi$ the gradient of ϕ .

Applying to our example system, note that $h^0(x_1, x_2)$ and $h(x_1, x_2)$ are vector fields on M and we can calculate the Lie derivative of $g(x_1, x_2)$ along them:

$$L_{h^0}(g)(x_1, x_2) = \langle dg, h^0 \rangle = (x_2 \quad x_1) \begin{pmatrix} 0 \\ -x_1x_2 \end{pmatrix} = -x_1^2x_2$$

and

$$L_h(g)(x_1, x_2) = \langle dg, h \rangle = (x_2 \quad x_1) \begin{pmatrix} 0 \\ 1 \end{pmatrix} = x_1 .$$

The flow $\Phi(t, x)$ of a vector field v on M is by definition the solution of:

$$\begin{cases} \frac{\partial}{\partial t} \Phi(t, x) &= v(\Phi(t, x)) \\ \Phi(0, x) &= x \end{cases} .$$

Observe that we have the following equality:

$$L_v(\phi)(x) = \left. \frac{d}{dt} \right|_{t=0} (\phi(\Phi(t, x))) .$$

The Taylor series of $\phi(\Phi(t, x))$ with respect to t are called Lie series:

$$\phi(\Phi(t, x)) = \sum_{l=0}^{\infty} \frac{t^l}{l!} L_v^l(\phi)(x) .$$

Let us now link the local distinguishability property to these new concepts. First of all, as observed in [26], if two points x^0 and x^1 in M are distinguishable by a bounded measurable input, then they must be distinguishable by a piecewise constant input due to uniform convergence since the outputs depend continuously on the inputs. For a constant input u , $f(x, u)$ defines a vector field on M and we can define the flow $\Phi(t, x)$ and the Lie series expansion of $g_i(\Phi(t, x))$ for $i = 1, \dots, m$. To see how this generalises to piecewise-constant inputs, we follow [8] and consider the input such that for $i = 1, \dots, k$,

$$\begin{cases} u_i(t) &= u_i^1, & t \in [0, t_1) \\ u_i(t) &= u_i^l, & t \in [t_l - 1, t_l), \quad l \geq 2 \end{cases} ,$$

where $u_i^l \in \mathbb{R}$. Define the vector fields

$$\theta_l = h^0 + hu^l$$

and denote their corresponding flows by Φ_t^l . Under this input, the state reached at time t_l starting from x^0 at $t = 0$ can be expressed as

$$x(t_l) = \Phi_{t_l}^l \circ \dots \circ \Phi_{t_1}^1(x^0) .$$

The corresponding output becomes

$$y_i(t_l) = g_i(\Phi_{t_l}^l \circ \dots \circ \Phi_{t_1}^1(x^0)) .$$

The time-derivative at zero of the output g_i can then be calculated and we can define

$$L_f g_i = L_{\theta_1} \dots L_{\theta_l} g_i .$$

We are now able to define the Lie series expansion of $g_i(\Phi(t, x))$ for piecewise-constant inputs. For each such u , the Lie series coefficients define $g_i(\Phi(t, x))$ uniquely due to the system being analytic. Thus, if two neighboring points x^0 and x^1 are U -distinguishable instantaneously (which is the requirement for local distinguishability), then there exists a piecewise-constant input u such that the sets of Lie series coefficients of $g_i(\Phi(t, x^0))$ and $g_i(\Phi(t, x^1))$ differ for some i . Consider now the linear map from M to the space spanned by the functions $L_f^k(g_i)$ at x^0 for $k \geq 0, i = 1 : m$, for all vector fields $f(x, u)$ defined by piecewise-constant inputs u . Intuitively, the system Σ has the local distinguishability property if for every $x^0 \in M$ there exists an open neighborhood V of x^0 such that this map is $1 : 1$. Let us formally describe the "observation" space spanned by the $L_f^k g_i$ which will be denoted by \mathcal{G} . It can be shown ([8], [24]) that

$$\mathcal{G} = \text{span}_{\mathbb{R}}\{L_{h^{i_1}}L_{h^{i_2}}\dots L_{h^{i_r}}(g_i) : r \geq 0, i_j = 0, \dots, k, i = 1, \dots, m\} \quad .$$

Since we are interested in the Jacobian of the $1 : 1$ map mentioned above, the space spanned by the gradients of the elements of \mathcal{G} is introduced and denoted by $d\mathcal{G}$:

$$d\mathcal{G} = \text{span}_{\mathbb{R}_x}\{d\phi : \phi \in \mathcal{G}\} \quad ,$$

where \mathbb{R}_x denotes the field of meromorphic functions on M .

It is the dimension of $d\mathcal{G}$ which determines the local distinguishability property. For each $x \in M$, let $d\mathcal{G}(x)$ be the subspace of the cotangent space at x obtained by evaluating the elements of $d\mathcal{G}$ at x . The rank of $d\mathcal{G}(x)$ is constant in M except at certain singular points, where the rank is smaller (this property is due to the system being analytic, see for example [11] or Chapter 3 in [8]). Then $\dim_{\mathbb{R}_x} d\mathcal{G}$ is the generic or maximal rank of $d\mathcal{G}(x)$, that is, $\dim_{\mathbb{R}_x} d\mathcal{G} = \max_{x \in M} (\dim_{\mathbb{R}} d\mathcal{G}(x))$.

We can now formulate the so-called "observability rank condition" introduced by Hermann and Krener [7]:

Theorem 2.1 *The system Σ has the **local distinguishability property** for all x in an open dense set of M if and only if $\dim_{\mathbb{R}_x} d\mathcal{G} = n$.*

Let us apply this test to the example system. We observe by inspection that the space \mathcal{G} for this system is spanned by functions of the forms x_1^k and $x_1^k x_2$ (the first two Lie derivatives were calculated above). Thus, the space $d\mathcal{G}$ is spanned by one-forms of the type $(kx_1^{k-1} \quad 0)$ and $(kx_1^{k-1}x_2 \quad x_1^k)$.

Therefore we conclude that this example system has the local distinguishability property almost everywhere except on the line $x_1 = 0$.

Consider another example:

$$\begin{cases} \dot{x}_1 &= u - x_1 \\ \dot{x}_2 &= u - x_2 \\ y &= x_1 + x_2 \end{cases} .$$

For this system, $h^0(x_1, x_2) = \begin{pmatrix} -x_1 \\ -x_2 \end{pmatrix}$, $h(x_1, x_2) = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$ and $g(x_1, x_2) = x_1 + x_2$ (according to the previously used notation). The first two Lie derivatives are

$$L_{h^0}(g)(x_1, x_2) = \langle dg, h^0 \rangle = (1 \quad 1) \begin{pmatrix} -x_1 \\ -x_2 \end{pmatrix} = -x_1 - x_2$$

and

$$L_h(g)(x_1, x_2) = \langle dg, h \rangle = (1 \quad 1) \begin{pmatrix} 1 \\ 1 \end{pmatrix} = 2 \quad .$$

As can be deduced by inspection, the space \mathcal{G} is now spanned by constant functions and the function $x_1 + x_2$. Thus, the space $d\mathcal{G}$ is spanned by one-forms of the type $(1 \quad 1)$ and $(0 \quad 0)$. Clearly, this space is of dimension 1, which means that the system does not have the local distinguishability property anywhere.

2.3 From piecewise-constant to differentiable inputs - a different definition of observation space

2.3.1. In the previous section, the observation space was defined in terms of piecewise-constant inputs to be:

$$\mathcal{G} = \text{span}_{\mathbb{R}} \{ L_{h^{i_1}} L_{h^{i_2}} \dots L_{h^{i_r}}(g_i) : r \geq 0, \quad i_j = 0, \dots, k, \quad i = 1, \dots, m \} \quad .$$

In this section it is shown that the observation space can be defined equally well in terms of analytic inputs. We follow the works of Sontag [24] and Krener [11].

A time-dependent vector field $v(t, x)$ defines a time-dependent flow in a similar way as in the previous section:

$$\begin{cases} \frac{\partial}{\partial t} \Phi(t, x) &= v(t, \Phi(t, x)) \\ \Phi(0, x) &= x \end{cases} .$$

Let $\Phi_u(t, x)$ denote the time-dependent flow corresponding to the time-dependent vector field $f(x, u(t))$, where we now assume that we have a single input u which is an analytic function of time (the results in this section can be generalised to apply for vector-valued inputs). Let the initial values of u and its derivatives be $u^{(r)}(0) = U^{(r)}$ for $r \geq 0$ with $U^{(r)} \in \mathbb{R}$. For any non-negative integer l and any $U = (U^{(0)}, \dots, U^{(l-1)}) \in \mathbb{R}^l$, define the functions

$$\psi_{rm+i}(x, U) = \left. \frac{d^r}{dt^r} \right|_{t=0} g_i(\Phi_u(t, x))$$

for $1 \leq i \leq m$, $0 \leq r \leq l-1$. (Observe that the result of this formula is actually the Lie derivation defined earlier, where extra terms appear due to the time dependence of the input. In fact, $\psi_{rm+i}(x, U) = L_f^r g_i$ where we define $L_f = \sum_{j=1}^n f_j \frac{\partial}{\partial x_j} + \sum_l U^{(l+1)} \frac{\partial}{\partial u}$.) Applying repeatedly the chain rule, we see that the functions ψ_i can be expressed as polynomials in $U^{(0)}, \dots, U^{(l-1)}$ with coefficients that are functions of x (Sontag [24]).

As in Section 2.2, we can again define the Taylor series of $g(\Phi_u(t, x))$ with respect to t :

$$g_i(\Phi_u(t, x)) = \sum_{r=0}^{\infty} \psi_{rm+i}(x, U) \frac{t^r}{r!} .$$

Similarly to Section 2.2 where we considered the space spanned by the coefficients of the Lie series for $g_i(\Phi_u(t, x))$, we now construct the space spanned by the ψ_j :

$$\hat{\mathcal{G}} = \text{span}_{\mathbb{R}} \{ \psi_{lm+i}(x, U) : U \in \mathbb{R}^l, l \geq 0, i = 1, \dots, m \} .$$

Wang and Sontag [30] proved that $\mathcal{G} = \hat{\mathcal{G}}$. We can demonstrate this on the observable example from Section 2.2:

$$\begin{cases} \dot{x}_1 &= 0 \\ \dot{x}_2 &= u - x_1 x_2 \\ y &= x_1 x_2 \end{cases} .$$

The time-dependent flow for the time-dependent vector field $f(x, u) = \begin{pmatrix} 0 \\ u - x_1x_2 \end{pmatrix}$ becomes $\Phi_u(t, x) = \begin{pmatrix} \Phi_1(t, x) \\ \Phi_2(t, x) \end{pmatrix}$, where

$$\begin{cases} \frac{\partial}{\partial t}\Phi_1(t, x) &= 0 \\ \frac{\partial}{\partial t}\Phi_2(t, x) &= u - \Phi_1(t, x)\Phi_2(t, x) \\ \Phi_{1,u}(0, x) &= x_1 \\ \Phi_{2,u}(0, x) &= x_2 \end{cases} .$$

The first few ψ_i :s can be calculated as follows:

$$\begin{aligned} \psi_1(x, U) &= g(\Phi_u(t, x))|_{t=0} = (\Phi_1(t, x)\Phi_2(t, x))|_{t=0} = \\ &= \Phi_1(0, x)\Phi_2(0, x) = x_1x_2 \\ \psi_2(x, U) &= \frac{dg(\Phi_u(t, x))}{dt}\Big|_{t=0} = \frac{d(\Phi_1(t, x)\Phi_2(t, x))}{dt}\Big|_{t=0} = \\ &= \left(\Phi_2(t, x)\frac{d\Phi_1(t, x)}{dt} + \Phi_1(t, x)\frac{d\Phi_2(t, x)}{dt}\right)\Big|_{t=0} = \\ &= \left(\Phi_2(t, x) \cdot 0 + \Phi_1(t, x)(u - \Phi_1(t, x)\Phi_2(t, x))\right)\Big|_{t=0} = \\ &= \Phi_1(0, x)(U^{(0)} - \Phi_1(0, x)\Phi_2(0, x)) = x_1(U^{(0)} - x_1x_2) \\ \psi_3(x, U) &= \frac{d^2g(\Phi_u(t, x))}{dt^2}\Big|_{t=0} = \frac{d^2(\Phi_1(t, x)\Phi_2(t, x))}{dt^2}\Big|_{t=0} = \\ &= x_1(U^{(1)} - x_1(U^{(0)} - x_1x_2)) . \end{aligned}$$

We see now that if the $U^{(i)}$:s are free to vary over \mathbb{R} , then the space $\hat{\mathcal{G}}$ for this example is spanned by the functions x_1^k and $x_1^kx_2$ for $k \geq 1$, exactly as the space \mathcal{G} that we calculated in Section 2.2.

2.3.2. Consider now the ψ_j :s as formal polynomials in U^0, U^1, \dots with coefficients that are functions of x . Denote by $\mathcal{K} = \mathbb{R}(U^{(0)}, U^{(1)}, \dots)$ the field obtained by adjoining the indeterminates $U^{(0)}, U^{(1)}, \dots$ to \mathbb{R} . Recall that \mathbb{R}_x is the field of meromorphic functions on M . Define $\mathcal{K}_x = \mathbb{R}_x(U^{(0)}, U^{(1)}, \dots)$ as the field obtained by adjoining the indeterminates $U^{(0)}, U^{(1)}, \dots$ to \mathbb{R}_x . Then \mathcal{K}_x is a vector space over \mathcal{K} . Let $\mathcal{F}^{\mathcal{K}}$ be the subspace of \mathcal{K}_x spanned by the functions ψ_j over \mathcal{K} , that is,

$$\mathcal{F}^{\mathcal{K}} = \text{span}_{\mathcal{K}}\{\psi_j : j \geq 1\} .$$

This is now a different definition of the "observation space". As before, we are also interested in the space spanned by the differentials of the elements of $\mathcal{F}^{\mathcal{K}}$. The latter can be seen as polynomial functions of $U^{(0)}, U^{(1)}, \dots$ with coefficients that are covector fields on M . For the example in 2.3.1, the differentials of the ψ_j :s can be written:

$$\begin{aligned} d\psi_1 &= (x_2 \quad x_1) \\ d\psi_2 &= (U^{(0)} - 2x_1x_2 \quad -x_1^2) = (1 \quad 0)U^{(0)} + (-2x_1x_2 \quad -x_1^2) \\ d\psi_3 &= (U^{(1)} - 2U^{(0)}x_1 + 3x_1^2x_2 \quad x_1^3) = \\ &= (1 \quad 0)U^{(1)} + (-2x_1 \quad 0)U^{(0)} + (3x_1^2x_2 \quad x_1^3) \quad . \end{aligned}$$

Recall from the previous section that the space $d\mathcal{G}$ for this example is spanned by one-forms of the type $(kx_1^{k-1} \quad 0)$ and $(kx_1^{k-1}x_2 \quad x_1^k)$. The covector fields calculated above are clearly of the same form.

Now let

$$\mathcal{O}^{\mathcal{K}} = \text{span}_{\mathcal{K}_x} \{d\psi_i : \psi_i \in \mathcal{F}^{\mathcal{K}}\} \quad .$$

Sontag [24] proved the following result:

Theorem 2.2 *For the analytic system (2.1)*

$$\dim_{\mathbb{R}_x} d\mathcal{G} = \dim_{\mathcal{K}_x} \mathcal{O}^{\mathcal{K}} \quad .$$

Thus, the property of local distinguishability can be determined from the dimension of the space $\mathcal{O}^{\mathcal{K}}$. The significance of this result is that u can now be treated symbolically in calculating the rank. This observation is used in Chapter 4 to derive an upper bound for the number of $d\psi_j$ that have to be considered in the rank test.

Chapter 3

Literature survey

Part 2: The algebraic point of view: observability of rational models

This chapter introduces the algebraic point of view in the treatment of the observability problem according to the works of Diop and Fliess ([3],[4],[5]), and Sedoglavic ([20]).

3.1 Example

Before we describe the algebraic setting for our general control problem, consider the following simple example:

$$\begin{cases} \dot{x}_1 &= x_1 x_2^2 + u \\ \dot{x}_2 &= x_1 \\ y &= x_1 \end{cases} .$$

We obtain two equations for the state-variables x_1 and x_2 from the output function and its first Lie derivative where we use the notations $u^{(r)}(0) = U^{(r)}$ and $y^{(r)}(0) = Y^{(r)}$, $r \geq 0$ for the time derivatives at zero of the input and output, respectively:

$$\begin{aligned} Y^{(0)} &= x_1 \\ Y^{(1)} &= L_f x_1 = x_1 x_2^2 + U^{(0)} \end{aligned} ,$$

By simple algebraic manipulation of these equations, we can obtain the following polynomial equations for each of the variables with coefficients in $U = (U^{(0)}, U^{(1)}, \dots)$ and $Y = (Y^{(0)}, Y^{(1)}, \dots)$:

$$\begin{aligned} x_1 &= Y^{(0)} \\ Y^{(0)}x_2^2 + U^{(0)} - Y^{(1)} &= 0 \end{aligned} \quad .$$

There are finitely many (two) solutions of these equations for a given set of inputs and outputs (except on the lines $x_1 = 0$ and $x_2 = 0$). Each one is locally unique and determines the state of the system completely by information on the input and output values without the need for knowing the initial conditions of x . (In the terminology of Chapter 2, this example system has the local distinguishability property for all x except for those on the lines $x_1 = 0$ and $x_2 = 0$).

This was a very simple example where we could derive (and solve) these polynomial equations for the variables explicitly. In general, however, the observability problem concerns the existence of such equations rather than their explicit calculation. For control systems consisting of polynomial or rational expressions, this problem can be formulated algebraically.

3.2 Algebraic setting

3.2.1. Consider now "polynomial" control systems of the form:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) \\ y &= g(x, u) \end{cases} \quad ,$$

where u stands for the k input variables, f and g are for now vectors of n and m polynomial functions, respectively (we will make the transition to rational functions later).

The equations obtained by differentiating the output functions will now contain polynomial expressions only. This allows us to make a new definition of observability based on the following rather intuitive idea - the state-variable x_i , $i = 1, \dots, n$ is observable if there exists an algebraic relation that binds x_i to the inputs, outputs and a finite number of their time-derivatives. If each x_i is the solution of a polynomial equation in U and Y , then we know that a given input-output map corresponds to a locally unique state of the system. We will now prepare for a formal definition of algebraic observability.

Let $\mathbb{R}\langle U, Y \rangle$ denote the field obtained by adjoining the indeterminates $U_i^{(0)}, U_i^{(1)}, \dots$, for $i = 1, \dots, k$ and $Y_j^{(0)}, Y_j^{(1)}, \dots$, for $j = 1, \dots, m$ to \mathbb{R} (or any other field of characteristic zero). Then we can make the following definition of algebraic observability:

Definition 3.1 $x_i, i \in \{1, \dots, n\}$ is algebraically observable if x_i is algebraic over the field $\mathbb{R}\langle U, Y \rangle$. The system Σ is algebraically observable if the field extension $\mathbb{R}\langle U, Y \rangle \hookrightarrow \mathbb{R}\langle U, Y \rangle(x)$ is purely algebraic.

3.2.2. The transcendence degree of the field extension $\mathbb{R}\langle U, Y \rangle \hookrightarrow \mathbb{R}\langle U, Y \rangle(x)$ is now equal to the number of non-observable state-variables which should be assumed known (i.e. should have known initial conditions) in order to obtain an observable system. Our purpose is now to find a way to calculate this transcendence degree. For this we will use the theory of derivations over subfields as described in Jacobson ([9]) and Lang([12]).

Definition 3.2 A derivation D of a ring R is a linear map $d : R \rightarrow R$ such that

$$\begin{aligned} D(a + b) &= D(a) + D(b) \\ D(ab) &= aD(b) + D(a)b \end{aligned}$$

for $a, b \in R$.

For example, the partial derivative $\frac{\partial}{\partial X_i}$, $i = 1, \dots, n$, is a derivation of the polynomial ring $k[X_1, \dots, X_n]$ over a field k .

Consider now a field F of characteristic 0 and a finitely-generated field extension $E = F(x) = F(x_1, \dots, x_k)$. Can D be extended to a derivation D^* on E which coincides with D on F ? Consider the ideal determined by (x) in $F[X]$ and denoted by I , that is, the set of polynomials in $F[X]$ vanishing on (x) . If such a derivation D^* exists and $p(X) \in I$, then the following must hold:

$$0 = D(0) = D^*0 = D^*p(x) = p^D(x) + \sum_{i=1}^n \frac{\partial p}{\partial x_i} D^*x_i \quad ,$$

where p^D denotes the polynomial obtained by applying D to all the coefficients of p (which are elements of F) and $\frac{\partial p}{\partial x_i}$ denotes the polynomial $\frac{\partial p}{\partial X_i}$ evaluated at (x) . If the above is true for a set of generators of the ideal I , then it is satisfied by all polynomials in I . This is now a necessary condition for extending the derivation D to $E = F(x)$. It is also a sufficient condition as shown in [9] and [12]:

Theorem 3.1 *Let D be a derivation of a field F . Let $(x) = (x_1, \dots, x_n)$ be a finite family of elements in an extension of F . Let $p_\alpha(X)$ be a set of generators for the ideal determined by (x) in $F[X]$. Then, if (w) is any set of elements of $F(x)$ satisfying the equations*

$$0 = p^D(x) + \sum_{i=1}^n \frac{\partial p_\alpha}{\partial x_i} w_i \quad ,$$

there is one and only one derivation D^ of $F(x)$ coinciding with D on F and such that $D^*x_i = w_i$.*

Suppose now that the derivation D on F is the trivial derivation, that is, $Dx = 0$ for all $x \in F$. Then, $p^D(x) = 0$ in the equation above and thus, $0 = \sum_{i=1}^n \frac{\partial p_\alpha}{\partial x_i} w_i$. The w_i 's are thus solutions of a homogeneous linear equation system and there exists a non-trivial derivation D^* of $E = F(x)$ only if the matrix formed by the $\frac{\partial p_\alpha}{\partial x_i}$'s is not full-ranked.

Let $Der_F E$ denote the set of derivations of $E = F(x)$ that are trivial on F . $Der_F E$ forms a vector space over E if we define $(bD)(x) = b(D(x))$ for $b \in E$. The dimension of this vector space can be calculated as follows (see [9]):

Theorem 3.2 *Let $E = F(x_1, \dots, x_n)$ and let $X = \{p_1, \dots, p_m\}$ be a finite set of generators for the ideal of polynomials p in $F[X_1, \dots, X_n]$ such that $p(x_1, \dots, x_n) = 0$ (this set exists due to Hilbert's basis theorem). Then:*

$$[Der_F E : E] = n - \text{rank}(J(p_1, \dots, p_m))$$

where $J(p_1, \dots, p_m)$ is the Jacobian matrix

$$\begin{bmatrix} \frac{\partial p_1}{\partial x_1} & \cdots & \frac{\partial p_1}{\partial x_n} \\ \vdots & \cdots & \vdots \\ \frac{\partial p_m}{\partial x_1} & \cdots & \frac{\partial p_m}{\partial x_n} \end{bmatrix} \quad .$$

To see how the space $Der_F E$ is related to the transcendence degree of the field extension $F \hookrightarrow E$ suppose that $E = F(x)$ and x is algebraic over F with minimal polynomial p . If D is a derivation of E which is trivial on F , then $0 = p'(x)Dx$ and thus $Dx = 0$ since $p'(x)$ cannot be zero (the field F has characteristic zero). Therefore D is trivial on E . We have the following general result ([9]):

Theorem 3.3 *If $E = F(x_1, \dots, x_n)$, then $Der_F E = 0$ if and only if E is algebraic over F . Moreover, $[Der_F E : E]$ is equal to the transcendence degree of E over F .*

3.2.3. We now have a way of calculating the transcendence degree of $E = F(x)$ over F by a rank calculation. Suppose that the transcendence degree is equal to $r > 0$ and thus some of the x_i :s are not algebraic over F . We wish to know if element x_j is algebraic over F . Consider the field extensions $F \hookrightarrow F(x_j) \hookrightarrow E$. We can calculate the transcendence degree of the field extension $F(x_j) \hookrightarrow E$ by the method described above. Since $E = F(x_j)(x_1, \dots, x_{j-1}, x_{j+1}, \dots, x_n)$, this will involve a calculation of the rank of the following matrix:

$$\begin{bmatrix} \frac{\partial p_1}{\partial p_1} & \cdots & \frac{\partial p_1}{\partial x_{j-1}} & \frac{\partial p_1}{\partial x_{j+1}} & \cdots & \frac{\partial p_1}{\partial x_n} \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \frac{\partial p_m}{\partial x_1} & \cdots & \frac{\partial p_m}{\partial x_{j-1}} & \frac{\partial p_m}{\partial x_{j+1}} & \cdots & \frac{\partial p_m}{\partial x_n} \end{bmatrix} .$$

If the transcendence degree of the field extension $F(x_j) \hookrightarrow E$ is equal to r (i.e. the above matrix has rank $(n-1) - r$), then the variable x_j is algebraic over F . This is due to the fact that if we have the field extensions $F \hookrightarrow F' \hookrightarrow E$, then ([12]):

$$tr.deg.(E/F) = tr.deg.(E/F') + tr.deg.(F'/F) \quad .$$

We thus have a way of classifying all x_i as either algebraic over F or not by eliminating the i :th column in the Jacobian and observing if there is a change of its rank.

3.3 The observability rank condition for rational systems

3.3.1. Setting $F = \mathbb{R}\langle U, Y \rangle$ and $E = F(x_1, \dots, x_n)$, we can apply this theory to our control problem. We have obtained a method for testing the observability of polynomial control systems by calculating the transcendence degree of the field extension $\mathbb{R}\langle U, Y \rangle \hookrightarrow \mathbb{R}\langle U, Y \rangle(x)$. In order to perform the calculations described above, we need to describe the ideal I of polynomials p in $k\langle U, Y \rangle[X]$ such that $p(x_1, \dots, x_n) = 0$. Clearly, $Y_j^{(0)} - g_j \in I$ for all $j = 1, \dots, m$. Differentiating the j :th output variable with respect to time at zero we obtain (by Lie-derivation where the time-dependence of the inputs is taken into account, as in Section 2.3 of the previous chapter):

$$\begin{aligned} Y_j^{(1)} &= L_f g_j = \sum_{i=1}^n f_i \frac{\partial g_j}{\partial x_i} + \sum_{k=1}^l \sum_{i=1}^m \frac{\partial g_j}{\partial u_i} U^{(k+1)} \\ Y_j^{(2)} &= L_f^2 g_j = \sum_{i=1}^n f_i \frac{\partial(L_f g_j)}{\partial x_i} + \sum_{k=1}^l \sum_{i=1}^m \frac{\partial(L_f g_j)}{\partial u_i} U^{(k+1)} \end{aligned}$$

etc. Clearly $Y_j^{(1)} - L_f g_j$ and $Y_j^{(2)} - L_f^2 g_j$ are elements of $\mathbb{R}\langle U, Y \rangle(x)$ and polynomials in I . In fact, all such polynomials obtained by Lie-derivation belong to I . It can be shown that I is generated by the polynomials $Y_j^{(i)} - L_f^i g_j$ for $j = 1, \dots, m$, $i = 0, \dots, n - 1$ by the following argument of Sedoglavic's [20].

We have

$$\mathbb{R}\langle U \rangle \subset \mathbb{R}\langle U, Y \rangle \subset \mathbb{R}\langle U \rangle(x) \quad ,$$

since each $Y_j^{(i)}$ is a polynomial function of x with coefficients in $\mathbb{R}\langle U \rangle$. Thus, as in 3.2.3,

$$tr.deg.(\mathbb{R}\langle U \rangle(x)/\mathbb{R}\langle U \rangle) = tr.deg.(\mathbb{R}\langle U \rangle(x)/\mathbb{R}\langle U, Y \rangle) + tr.deg.(\mathbb{R}\langle U, Y \rangle/\mathbb{R}\langle U \rangle) \quad ,$$

and the transcendence degree of the field extension $\mathbb{R}\langle U \rangle \hookrightarrow \mathbb{R}\langle U, Y \rangle$ is therefore at most n . Thus, for every $j = 1, \dots, m$, there exist an algebraic relation $q_j(Y_j^{(0)}, \dots, Y_j^{(n)}) = 0$ with coefficients in $\mathbb{R}\langle U \rangle$. Thus the polynomial $Y_j^{(n)} - L_f^n g_j$ belongs to the ideal generated by the polynomials $Y_j^{(i)} - L_f^i g_j$ for $i = 1, \dots, n - 1$. We therefore conclude that we need only consider the equations obtained by the first $n - 1$ Lie-derivatives of the output functions.

Thus, in order to calculate the transcendence degree of the field extension $\mathbb{R}\langle U, Y \rangle \hookrightarrow \mathbb{R}\langle U, Y \rangle(x)$ we have to find the rank of the following matrix:

$$\begin{bmatrix} \frac{\partial L_f g_1}{\partial x_1} & \cdots & \frac{\partial L_f g_1}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial L_f g_m}{\partial x_1} & \cdots & \frac{\partial L_f g_m}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix} \quad .$$

If this Jacobian matrix is full-ranked, then the transcendence degree is zero by theorems 3.2 and 3.3 and we have an algebraically observable system. We have arrived at the observability rank condition that was derived for differentiable inputs in the differential geometric approach in part 2.3.2 of Section 2.3, but this time we have a finite number of Lie derivatives to consider.

If the system is not algebraically observable, we can find the non-observable variables by removing columns in this matrix and calculating the rank of the reduced matrices, as described in 3.2.3.

3.3.2. We will now generalise this theory to apply for rational systems of type:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) \\ y &= g(x, u) \end{cases},$$

where now $f_i = p_i(u, x)/q_i(x)$ for $i = 1, \dots, n$ and $g_j = r_j(x, u)/s_j(x)$ for $j = 1, \dots, m$ with p_i, q_i, r_j and s_j polynomial functions and q_i and s_j have no zeros.

We observe that just as before, $Y_j^{(i)} - L_f^i g_j \in \mathbb{R}\langle U, Y \rangle(x)$ for all $i = 0, \dots, n-1$, $j = 1, \dots, m$, but they are no longer polynomials. However, as shown by Diop ([5]) and Sedoglavic([20]), these rational expressions can be used in the rank test instead of the polynomials that generate the ideal I , allowing us to use the same Jacobian matrix as the one above for polynomial systems.

Remark: Observe that the algebraic interpretation has lead us to the observability rank condition derived for analytic inputs in Section 2.3 of the previous chapter, showing the equivalence of algebraic observability and local distinguishability (see [5]). In fact, the ideal I of polynomials p in $\mathbb{R}\langle U, Y \rangle[X]$ such that $p(x_1, \dots, x_n) = 0$ is generated by the same functions that span the space $\mathcal{F}^{\mathcal{K}}$ defined in Chapter 2. The rank of the Jacobian

$$\begin{bmatrix} \frac{\partial L_f g_1}{\partial x_1} & \cdots & \frac{\partial L_f g_1}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f g_m}{\partial x_1} & \cdots & \frac{\partial L_f g_m}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix}$$

is exactly the dimension of the space $\mathcal{O}^{\mathcal{K}}$ which, as we recall, determines the local distinguishability property according to Theorem 2.2. The result of the algebraic approach of this chapter is that we have been able to show that for rational systems the space $\mathcal{O}^{\mathcal{K}}$ is generated by a finite number of functions. In Chapter 4, we take a different approach to show that this is in fact true for all analytical systems of the form (2.1).

3.4 Symmetry

Suppose now that by applying the rank test above, we find that our control system is not algebraically observable and that the transcendence degree is r . This means that $Der_{\mathbb{R}\langle U, Y \rangle} \mathbb{R}\langle U, Y \rangle(x)$ is not empty and has dimension r . The differential-geometric concept that corresponds to derivations is that of tangent vectors. We can therefore interpret the existence of derivations on $\mathbb{R}\langle U, Y \rangle(x)$ that are trivial on $\mathbb{R}\langle U, Y \rangle$ as the existence of tangent vectors to the space of solutions to our control system, such that if we move in their direction, the output remains the same and we cannot observe that the system is in a different state. In other words, there are infinitely many trajectories for the control system that cannot be distinguished from each other by observing the input-output map.

A derivation therefore generates a family of symmetries for the control system - symmetries in the variables leaving the inputs and outputs invariable. In this section we will show how these can be calculated.

First of all, observe that the partial derivatives $\frac{\partial}{\partial x_i}$ form a basis for the derivations on $\mathbb{R}\langle U \rangle(x)$ that are trivial on $\mathbb{R}\langle U \rangle$ (see Appendix 8.2 for explanation). Of these, we wish to find the ones that are trivial also on $\mathbb{R}\langle U, Y \rangle$. If v is one of them, recall from Theorems 3.1 and 3.2 that we must have:

$$\begin{bmatrix} \frac{\partial L_f g_1}{\partial x_1} & \cdots & \frac{\partial L_f g_1}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f g_m}{\partial x_1} & \cdots & \frac{\partial L_f g_m}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix} \cdot v = 0 \quad .$$

Thus, v belongs to the kernel of the above Jacobian matrix. Suppose that $v = (v_1, \dots, v_n)$, where $v_i \in \mathbb{R}\langle U, Y \rangle(x)$. Then v is the Lie-derivation $v = \sum_{i=1}^n v_i \frac{\partial}{\partial x_i}$ which corresponds to a vector field v and a flow $\Phi(t, x)$ of v given by (see Chapter 2):

$$\begin{cases} \frac{\partial}{\partial t} \Phi(t, x) = v(\Phi(t, x)) \\ \Phi(0, x) = x \end{cases} .$$

The solution of this system of differential equations evaluated at any $t > 0$

corresponds to a new initial state of the system which cannot be distinguished from the original one, (x_1, \dots, x_n) , by observing the input-output it produces.

We now have a strategy for finding the families of symmetries for our control system. First, we have to define a basis for the kernel of the Jacobian matrix. For each of its elements we have to solve the system of differential equations that arises, in order to obtain the family of symmetries associated. To make the calculations simpler, we can use the observations from 3.2.3 to find the non-observable variables. Instead of calculating the kernel of the Jacobian matrix, we can calculate the kernel of its maximal singular minor which is obtained when the columns and rows corresponding to the observable variables are removed. Then, the system of differential equations to be solved will only involve the non-observable variables.

We will now apply this to a non-observable example:

$$\begin{cases} \dot{x}_1 = x_2x_4 + u \\ \dot{x}_2 = x_2x_3 \\ \dot{x}_3 = 0 \\ \dot{x}_4 = 0 \\ y = x_1 \end{cases} .$$

We need to calculate the first three Lie-derivatives of the output function:

$$\begin{aligned} Y^{(1)} &= L_f x_1 = x_2x_4 + U^{(0)} \\ Y^{(2)} &= L_f^2 x_1 = L_f(x_2x_4 + u) = x_4x_2x_3 + U^{(1)} \\ Y^{(3)} &= L_f^3 x_1 = L_f(x_4x_2x_3 + \dot{u}) = x_4x_3x_2x_3 + U^{(2)} . \end{aligned}$$

Thus the Jacobian matrix becomes:

$$\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & x_4 & 0 & x_2 \\ 0 & x_3x_4 & x_2x_4 & x_2x_3 \\ 0 & x_3^2x_4 & 2x_2x_3x_4 & x_2x_3^2 \end{bmatrix} \sim \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & x_4 & 0 & x_2 \\ 0 & 0 & x_2x_4 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} .$$

Clearly, this matrix has rank 3 and the non-observable variables are x_2 and x_4 - removing the second or fourth column does not change the rank of the matrix. We can now eliminate the first and third rows and columns and consider the kernel of the remaining minor, which is the matrix

$$\begin{bmatrix} x_4 & x_2 \\ x_3^2x_4 & x_2x_3^2 \end{bmatrix} .$$

This kernel is generated by the vector $(x_2, -x_4)$. The derivation $x_2 \frac{\partial}{\partial x_2} - x_4 \frac{\partial}{\partial x_4}$ thus corresponds to the system of differential equations:

$$\begin{cases} \dot{\Phi}_2(t, x) = x_2 \\ \dot{\Phi}_4(t, x) = -x_4 \\ \Phi_2(0, x) = x_2 \\ \Phi_4(0, x) = x_4 \end{cases} .$$

The solution is:

$$\begin{cases} \Phi_2(t, x) = x_2 e^t \\ \Phi_4(t, x) = x_4 e^{-t} \end{cases} .$$

If we set $e^t = \lambda$, we find that multiplying x_2 by λ and dividing x_4 by it defines a new state \bar{x} that is indistinguishable from the original one for any λ . Indeed, we see that performing this procedure does not change the output and its Lie-derivatives:

$$\begin{cases} \dot{\bar{x}}_1 = \bar{x}_2 \bar{x}_4 + u = \lambda x_2 x_4 / \lambda + u = x_2 x_4 + u \\ \dot{\bar{x}}_2 = \bar{x}_2 \bar{x}_3 = \bar{x}_2 \bar{x}_3 = \lambda x_2 x_3 \\ \dot{\bar{x}}_3 = 0 \\ \dot{\bar{x}}_4 = 0 \\ \bar{Y}^{(0)} = \bar{x}_1 = x_1 = Y^{(0)} \\ \bar{Y}^{(1)} = L_{\bar{f}} \bar{x}_1 = \bar{x}_2 \bar{x}_4 + U^{(0)} = x_2 x_4 + U^{(0)} = Y^{(1)} \\ \bar{Y}^{(2)} = L_{\bar{f}}^2 \bar{x}_1 = L_{\bar{f}}(\bar{x}_2 \bar{x}_4 + u) = \bar{x}_4 \dot{\bar{x}}_2 + U^{(1)} = \bar{x}_4 \bar{x}_2 \bar{x}_3 + U^{(1)} = \\ = \frac{1}{\lambda} x_4 \lambda x_2 x_3 + U^{(1)} = Y^{(2)} \\ \bar{Y}^{(3)} = L_{\bar{f}}^3 \bar{x}_1 = L_{\bar{f}}(\bar{x}_4 \bar{x}_2 \bar{x}_3 + \dot{u}) = \bar{x}_3 \bar{x}_4 \dot{\bar{x}}_2 + U^{(2)} = \\ = x_3 \frac{1}{\lambda} x_4 \lambda x_2 x_3 + U^{(2)} = Y^{(3)} \end{cases} .$$

We know from 3.3.1 that we need not consider any further Lie derivatives since they depend on the previous ones.

We have now defined a family of symmetries

$$\sigma_\lambda : \{x_1, x_2, x_3, x_4\} \rightarrow \{x_1, \lambda x_2, x_3, x_4 / \lambda\}$$

of the control system which leaves the input and output invariant.

3.5 Sedoglavic's algorithm

There is a published algorithm with Maple implementation by Alexandre Sedoglavic ([20]) which performs an observability test of rational systems

and for non-identifiable systems, predicts the non-identifiable variables with high probability. This is done in polynomial time with respect to system complexity.

The algorithm is mainly based on generic rank computation, for details, see [20]. The symbolic computation of the Jacobian matrix defined in Section 3.3 can be cumbersome for systems with many variables and parameters and it cannot be done in polynomial time. Instead, the parameters are specialised on some random integer values, and the inputs are specialised on a power series of t with integer coefficients. To limit the growth of these integers in the process of rank computation, the calculations are done on a finite field \mathbb{F}_p , see [20]. The probabilistic aspects of the algorithm concern the choice of specialisation of parameters and inputs and also the fact that cancellation of the determinant of the Jacobian modulo p has to be avoided. The calculation of the rank is deterministic for observable systems, that is, when the process states that the system is observable, the answer is correct. For non-observable systems, the probability of a correct answer depends on the complexity of the system and on the prime number p . The predicted non-observable variables can be further analysed to find a family of symmetries which then can confirm the test result.

The Maple implementation takes as an input a rational system of differential equations where parameters, state-variables and inputs have to be stated as such, and also a set of outputs has to be defined. The transcendence degree of the field extension associated to the system (see Section 3.1) is calculated and the non-observable parameters and state-variables are predicted.

We have used this implementation for our case study in Chapter 6.

Chapter 4

The first $n - 1$ derivatives of the output function determine the observability of analytic systems with n state variables

This chapter deals with several questions that arise from the literature surveys. The differential geometric approach from Chapter 2 results in the observability rank test for observability of analytic systems. In this test, the rank of the linear space containing the gradients of all Lie derivatives of the output functions must be calculated. Since no bound is given for the number of Lie derivatives necessary for the calculation, the practical application of the test to other than the simplest examples is difficult. Such an upper bound is derived for the case of rational systems in Chapter 3 using the algebraical approach. The following questions now arise. Can an upper bound be given only for rational systems? How do such requirements for the class of the system arise? In this chapter, we attempt to extend the upper bound for the number of time-derivatives of the output function to apply for the class of analytical systems affine in the input variable that are addressed by the differential-geometric approach in Chapter 2. We are going to use the results by Sontag ([24]) described in Chapter 2, Section 2.3 where the observability rank condition was defined in terms of differentiable inputs.

Consider once again the example from the introduction, taken from [20]:

$$\begin{cases} \dot{x}_1 &= \frac{x_2}{x_1} \\ \dot{x}_2 &= \frac{x_3}{x_2} \\ \dot{x}_3 &= x_1\theta - u \\ y &= x_1 \end{cases} \quad (4.1)$$

Recall that we obtained the following equations for the state-variables and the parameter from calculating the first three time-derivatives at zero of the output (see Chapter 1, Section 1.2):

$$\begin{aligned} r_1(x_1, Y^{(0)}) &= Y^{(0)} - x_1 &&= 0 \\ r_2(x_1, x_2, Y^{(1)}) &= Y^{(1)} - \frac{x_2}{x_1} &&= 0 \\ r_3(x_1, x_2, x_3, Y^{(2)}) &= Y^{(2)} - \left(\frac{x_3}{x_1x_2} - \frac{x_2^2}{x_1^3}\right) &&= 0 \\ r_4(x_1, x_2, x_3, \theta, Y^{(3)}) &= Y^{(3)} - \left(\frac{\theta}{x_2} - \frac{U^{(0)}}{x_1x_2} - \frac{3x_3}{x_1^3} - \frac{x_3^2}{x_1x_2^2} + \frac{3x_2^3}{x_1^5}\right) &&= 0 \quad . \end{aligned}$$

The problem now is to determine whether these equations are enough to ensure that a given input-output behaviour corresponds to a locally unique state of the system. From the Implicit Function theorem it follows that the variables x_1, x_2, x_3 and the parameter θ can be expressed locally (in the neighbourhood of a given point in the space of solutions of the differential equations) as functions of $U^{(0)}$ and $Y^{(0)}, Y^{(1)}, Y^{(2)}, Y^{(3)}$ if the rank of the following Jacobian matrix evaluated at that point is equal to four:

$$\begin{aligned} & \begin{bmatrix} \frac{\partial(r_1)}{\partial x_1} & \frac{\partial(r_1)}{\partial x_2} & \frac{\partial(r_1)}{\partial x_3} & \frac{\partial(r_1)}{\partial \theta} \\ \frac{\partial(r_2)}{\partial x_1} & \frac{\partial(r_2)}{\partial x_2} & \frac{\partial(r_2)}{\partial x_3} & \frac{\partial(r_2)}{\partial \theta} \\ \frac{\partial(r_3)}{\partial x_1} & \frac{\partial(r_3)}{\partial x_2} & \frac{\partial(r_3)}{\partial x_3} & \frac{\partial(r_3)}{\partial \theta} \\ \frac{\partial(r_4)}{\partial x_1} & \frac{\partial(r_4)}{\partial x_2} & \frac{\partial(r_4)}{\partial x_3} & \frac{\partial(r_4)}{\partial \theta} \end{bmatrix} = \\ - & \begin{bmatrix} 1 & 0 & 0 & 0 \\ -\frac{x_2}{x_1^2} & \frac{1}{x_1} & 0 & 0 \\ -\frac{x_3}{x_1^2x_2} + \frac{3x_2^2}{x_1^4} & -\frac{x_3}{x_1x_2^2} + \frac{2x_2}{x_1^3} & \frac{1}{x_1^2x_2} & 0 \\ \frac{u}{x_2x_1^2} + \frac{9x_3}{x_1^4} + \frac{x_3^2}{x_2^2x_1^3} - \frac{15x_2^3}{x_1^6} & -\frac{\theta}{x_2} + \frac{u}{x_1x_2^2} + \frac{3x_3^2}{x_1x_2^4} + \frac{9x_2^2}{x_1^5} & -\frac{3}{x_1^3} - \frac{2x_3}{x_1x_2^3} & \frac{1}{x_2} \end{bmatrix} \quad . \end{aligned}$$

Clearly, this matrix has full rank for all values of x_1, x_2, x_3 and θ and thus the system has a locally unique state for a given input-output behaviour.

Now the following question arises - if the rank of the above matrix is not full, can we then conclude that the system is not locally observable without

considering further derivatives of the output function which would produce new equations? In other words, is the rank of the Jacobian determined by the first n equations, where n is the total number of state-variables and parameters? We will now show that this is true for the analytic systems affine in the input variable that were discussed in Chapter 2.

Consider again the analytic control system of the form (equation (2.1)):

$$\Sigma \begin{cases} \dot{x} &= f(x, u) = h^0(x) + h(x)u \\ y &= g(x) \end{cases} .$$

As previously (see Chapter 2), the elements of the n -dimensional vectors h^0 and h are analytic functions and we assume for the moment that we have a single analytic output $g(x)$ and also a single analytic input u . The n state-variables x are assumed to occupy an open subset M of \mathbb{R}^n .

The first two equations obtained by differentiating the output function with respect to time at zero are:

$$\begin{aligned} Y^{(1)} &= L_f g(x) = dg \cdot f|_{t=0} = dg \cdot (h^0 + hU^{(0)}) = dg \cdot h^0 + U^{(0)}(dg \cdot h) \\ Y^{(2)} &= L_f^2 g(x) = L_f(dg \cdot f) = (d(dg \cdot f) \cdot f)|_{t=0} + \frac{\partial(dg \cdot f)}{\partial u} U^{(1)} = \\ &= d(dg \cdot h^0 + U^{(0)}(dg \cdot h)) \cdot (h^0 + hU^{(0)}) + \frac{\partial(dg \cdot h^0 + u(dg \cdot h))}{\partial u} U^{(1)} = \\ &= d(dg \cdot h^0 + U^{(0)}(dg \cdot h)) \cdot h^0 + U^{(0)}d(dg \cdot h^0 + U^{(0)}(dg \cdot h)) \cdot h + \\ &\quad + U^{(1)}(dg \cdot h) = \\ &= d(dg \cdot h^0) \cdot h^0 + U^{(0)}(d(dg \cdot h) \cdot h^0 + d(dg \cdot h^0) \cdot h) + \\ &\quad + (U^{(0)})^2(d(dg \cdot h)) \cdot h + U^{(1)}(dg \cdot h) \quad . \end{aligned}$$

These calculations demonstrate the result by Sontag ([24]) (used in Chapter 2, Section 2.3) that the first $n - 1$ Lie derivatives of the output function $g(x)$ for the system (2.1) are polynomial functions of $U^{(0)}, U^{(1)}, \dots, U^{(n-2)}$ with coefficients that are analytic functions on M .

Thus we have that $L_f^{(i)} g \in \mathcal{K}_x$ for $i = 0, \dots, n - 1$ (recall from Chapter 2, Section 2.3 that $\mathcal{K}_x = \mathbb{R}_x(U^{(0)}, U^{(1)}, \dots)$ is the field of meromorphic functions on M to which we add the indeterminates $U^{(0)}, U^{(1)}, \dots$ and obtain rational functions of $U^{(0)}, U^{(1)}, \dots$ with coefficients that are meromorphic functions on M , see also [24]).

Following the notation from example (4.1) above, the first n equations for the state-variables can now be formulated:

$$\begin{aligned} r_1(x, Y^{(0)}) &= Y^{(0)} - g = 0 \\ r_2(x, u, Y^{(1)}) &= Y^{(1)} - L_f g = 0 \\ \dots & \dots \dots \\ r_n(x, u, \dots, u^{(n-2)}, Y^{(n-1)}) &= Y^{(n-1)} - L_f^{n-1} g = 0 \end{aligned}$$

Therefore, the Jacobian that we are interested in is:

$$- \begin{bmatrix} \frac{\partial g}{\partial x_1} & \dots & \frac{\partial g}{\partial x_n} \\ \dots & \dots & \dots \\ \frac{\partial L_f^{n-1} g}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g}{\partial x_n} \end{bmatrix}$$

Since $L_f^{(i)}g \in \mathcal{K}_x$ for $i = 0, \dots, n - 1$, the elements of this Jacobian also belong to \mathcal{K}_x . We will now show that if this Jacobian is not full-ranked, that is, the first n gradients of the output function and its Lie derivatives are linearly dependent over the field \mathcal{K}_x , then any further Lie derivative produces a gradient which is linearly dependent of the first n and we can thus conclude that the system is not locally observable. Furthermore, if the first m gradients, where $m \leq n$, are linearly-dependent, then no further gradients are necessary for the calculation of the rank, which becomes $\leq m - 1$. In fact, we can stop Lie differentiating the output function at the first instance of linear dependence.

Remark: To be able to discuss linear dependence, we have to know that the gradients of the Lie derivatives produce a linear space over a field (or a free module over a commutative ring). This was the case for the rational systems in Chapter 3 and this is also the case here for analytic systems of the above type, as the elements of the Jacobian belong to the field \mathcal{K}_x .

Theorem 4.1 *Let Σ be the system:*

$$\begin{cases} \dot{x} = f(x, u) = h^0(x) + h(x)u \\ y = g(x) \end{cases},$$

where x is a vector of n state-variables occupying an open subset M of \mathbb{R}^n , h^0 and h are n -dimensional vectors of analytic functions on M , the output $g(x)$ is an analytic function on M and the control variable u is an analytic function of time.

If m is an integer such that $dL_f^{(i)}g$, $i = 0, \dots, m$ are linearly dependent over the field \mathcal{K}_x , then the dimension of the space $\mathcal{O}^{\mathcal{K}} = \text{span}_{\mathcal{K}_x}\{dL_f^{(i)}g, \quad i \geq 0\}$ (see Chapter 2, Section 2.3) is less than or equal to $m - 1$. If $m < n$, the system Σ is not locally observable.

Proof: Suppose that the first m gradients are linearly dependent and m is the least such number (it certainly exists as the rank is $\leq n$ and a single non-zero vector is linearly independent of itself). Then, there exist coefficients $k_i \in \mathcal{K}_x$, $i = 0, \dots, m - 1$, not all of them zero, such that

$$\sum_{i=0}^{m-1} k_i dL_f^i g = \mathbf{0} \quad .$$

We can take the Lie derivative of both sides (which are co-vector fields) to obtain:

$$\mathbf{0} = L_f \left(\sum_{i=0}^{m-1} k_i dL_f^i g \right) = \sum_{i=0}^{m-1} L_f (k_i dL_f^i g) = \sum_{i=0}^{m-1} ((L_f k_i) dL_f^i g + k_i L_f (dL_f^i g)) \quad .$$

We now observe the following fact (which is simply saying that the d and L_f operators commute even when f depends on a control variable $u(t)$, see Appendix 8.1 for derivation):

$$L_f (dL_f^i g) = dL_f^{i+1} g \quad ,$$

for $i \geq 0$.

We thus obtain:

$$\mathbf{0} = \sum_{i=0}^{m-1} ((L_f k_i) dL_f^i g + k_i dL_f^{i+1} g) \quad .$$

Recalling the structure of the field \mathcal{K}_x , we know that $L_f k_i \in \mathcal{K}_x$ since:

$$L_f k_i = dk_i \cdot f + \frac{\partial k_i}{\partial u} U^{(1)} = dk_i \cdot (h^0 + hU^{(0)}) + \frac{\partial k_i}{\partial u} U^{(1)} \quad ,$$

which is clearly a rational function of $U^{(0)}, U^{(1)}, \dots$ with coefficients that are meromorphic functions of x . Since we know that k_{m-1} is not zero (we assumed that m was the least number such that the first m gradients are

linearly dependent), we conclude that $dL_f^m g$ is linearly dependent on the preceding gradients.

Using the same calculations we can prove by induction that any further gradient is linearly dependent on the previous ones which then means that $dL_f^0 g, \dots, dL_f^{m-1} g$ form a basis for the space $\mathcal{O}^{\mathcal{K}}$ which determines local distinguishability (by Theorems 2.1 and 2.2) and thus local observability. If $m < n$, this space has rank less than n and thus the system is not locally observable. \square

Thus it is enough to consider the first $n - 1$ Lie derivatives of the output function in the rank test and also, we can stop calculating further derivatives of the output function at the first instance of linear dependence among their gradients.

Remark: We note that in the case of multiple output functions one needs to calculate n time-derivatives of each.

Chapter 5

Parameter identifiability

In this relatively short chapter we will present the problem of the parameter identifiability of nonlinear control systems as a special case of the observability problem.

Identifiability is the possibility to identify the parameters of a control system from its input-output behaviour. By considering parameters as state-variables with time derivative zero, one can use the observability rank test to determine identifiability. The property of local observability is then interpreted as the existence of only finitely many parameter sets that fit the observed data, each of them locally unique. The use of the rank test for determining the identifiability of nonlinear systems dates back to at least 1978 when Pohjanpalo [17] used the coefficients of the Taylor series expansion of the output to determine the parameter identifiability of a class of nonlinear systems applied in the analysis of saturation phenomena in pharmacokinetic studies. A more recent example is the work by Xia and Moog ([31]) where different concepts of nonlinear identifiability are studied in an algebraic framework and the theory is applied to a four dimensional HIV/AIDS model showing that the theorems developed by the authors lend themselves to characterisations of whether all the parameters in the model are determinable from the measurement of CD4+ T cells and virus load, and if not, what else has to be measured. The minimal number of measurements of the variables for the complete determination of all parameters and the best period of time to make such measurements are calculated. Another example with biological application is the work by Margaria et al ([15]) where the identifiability of some highly structured biological models of infectious disease dynamics is analysed both using the rank method and Sedoglavic's

algorithm ([20]) and also by the constructive method of characteristic set computation described by Ollivier ([16]), Ljung and Glad ([14]) and others. The latter method can only be applied to relatively small control systems as its complexity is exponential in the number of parameters.

We will now describe how the observability rank test can be used to determine parameter identifiability. Consider a physical/chemical/biological model:

$$\Sigma \begin{cases} \dot{x} &= f(x, p, u) \\ y &= g(x, p) \end{cases} ,$$

where as before, x denote the n state-variables, u the l inputs and y the m observed quantities. The k model parameters are denoted by p and $f(x, p, u)$ and $g(x, p)$ are vectors of analytical functions. We may or may not be given a set of initial conditions for the state-variables:

$$x(0) = x^0 \quad .$$

In order to be able to use the theory from the previous chapters, we observe that the above model can be represented by the following control system:

$$\Sigma \begin{cases} \dot{p} &= 0 \\ \dot{x} &= f(x, p, u) \\ y &= g(x, p) \end{cases} ,$$

where x and p can now be considered as the same type of variables. We can apply the rank test to this system in exactly the same way as discussed in the previous chapters.

Without initial conditions for x , the non-observable variables can be both in x and in p . Suppose now that we are given a full set of initial conditions on x :

$$x(0) = x^0 \quad .$$

The problem of the observability of the x variables now disappears as the initial state is already uniquely defined. What is left, is exactly the problem of identifiability for the parameters - is the set of parameters that realises a given input-output map unique, at least locally?

This can be determined by the rank test described in the previous chapters. For analytical systems (see Chapter 4) the rank test amounts to calcu-

lating the rank of the following Jacobian matrix:

$$\begin{bmatrix} \frac{\partial L_f g_1}{\partial p_1} & \cdots & \frac{\partial L_f g_1}{\partial p_k} \\ \cdots & & \\ \frac{\partial L_f g_m}{\partial p_1} & \cdots & \frac{\partial L_f g_m}{\partial p_k} \\ \cdots & & \\ \frac{\partial L_f^{n-1} g_1}{\partial p_1} & \cdots & \frac{\partial L_f^{n-1} g_1}{\partial p_k} \\ \cdots & & \\ \frac{\partial L_f^{n-1} g_m}{\partial p_1} & \cdots & \frac{\partial L_f^{n-1} g_m}{\partial p_k} \end{bmatrix} .$$

If the rank of this matrix is k , then the model is identifiable. If not, the non-identifiable parameters can be found using the same procedure we used earlier for finding non-observable variables, see Chapter 3, Section 3.2., part 3.2.3.

Chapter 6

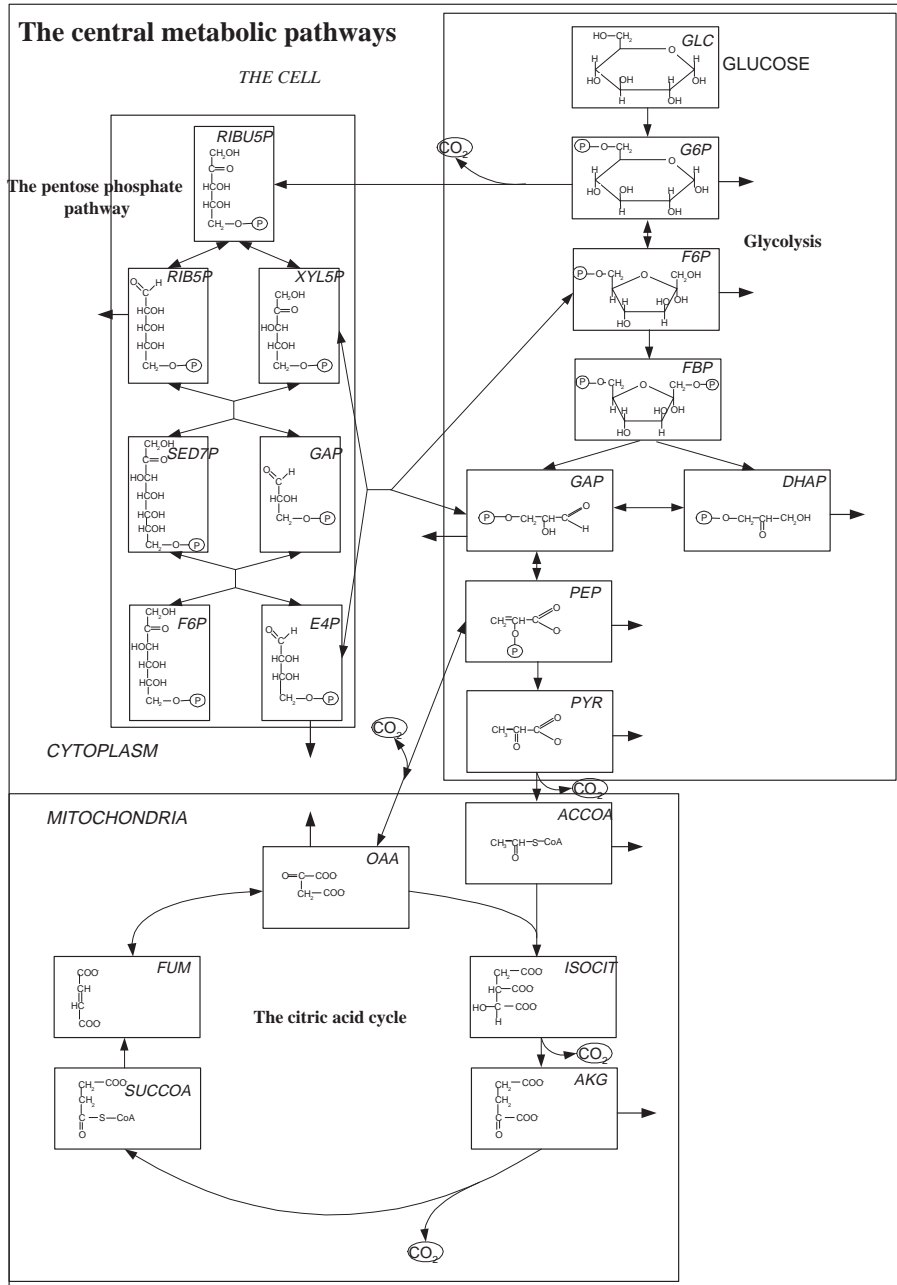
Case study: Identifiability analysis of a kinetic model for *S. Cerevisiae*

In this case study, we have investigated the identifiability of a published model of the metabolic dynamics in *S. Cerevisiae* by Rizzi et al [18]. We begin by a short description of the biochemistry of the central metabolic pathways.

6.1 The central metabolic pathways

Metabolism is the overall network of enzyme-catalysed reactions in a cell. Its degradative, or energy-releasing phase is called catabolism. The central catabolic pathways which are more or less universal among organisms consist of glycolysis, the pentose phosphate pathway and the citric acid cycle. In glycolysis sugars are degraded to a three-carbon compound called pyruvate. In the absence of oxygen pyruvate is then reduced to lactate, ethanol or other fermentation products. In aerobic conditions, it is instead oxidised via the citric acid cycle in the process of cellular respiration. A simplified scheme of some of the most important reactions in the central metabolic pathways is shown in the figure on the next page.

The different species in the boxes are called metabolites. The reactions marked by arrows are catalysed by enzymes which determine their “reaction rate” or “flux”, that is, the speed with which the reaction occurs.



Reaction rates are often modelled by using the so-called Michaelis-Menten or Hill kinetics where an equation is derived for the reaction rate based on

a biochemical description of the general way in which enzymatic reactions occur. For example, a reaction in which a single substrate (reactant) A is transformed to a single product B under the catalysis of a single enzyme E has the following rate equation [13]:

$$r = \frac{r^{max} A}{K_m + A} \quad ,$$

where the constants r^{max} and K_m are specific for this reaction. r^{max} is the maximal rate of the reaction and K_m is the substrate concentration at which the reaction rate is half r^{max} .

An enzyme can have several binding sites for the substrate in which case a so-called Hill equation is used. For the above reaction where we allow n binding sites for the enzyme, the equation becomes (see for example Chapter 5 in [25]):

$$r = \frac{r^{max} A^n}{K_m + A^n} \quad .$$

These equations can take much more complicated forms depending on the number of substrates and products and other factors such as reversibility of the reaction, inhibition and cooperation effects on the enzymes, etc (see [13], [21] and [18] for details).

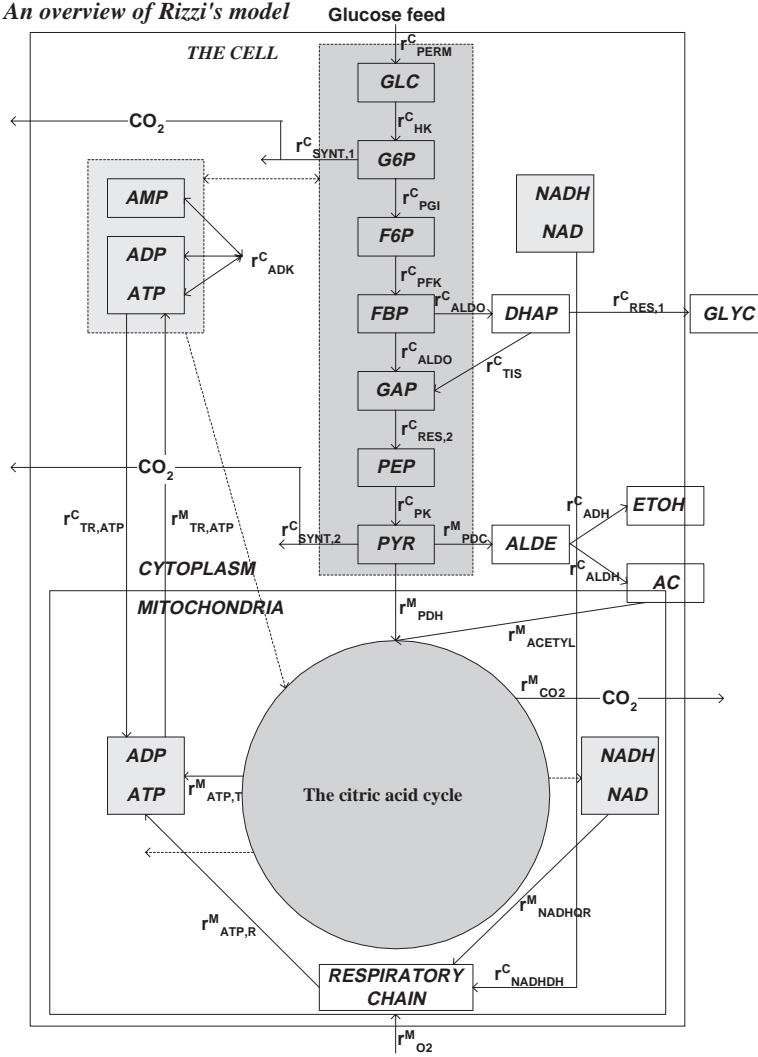
6.2 The model of metabolic dynamics by Rizzi et al

We will now proceed to describe a mathematical model of the dynamics of the chemical reactions in the central metabolic pathways formulated by Rizzi et al [18].

The authors proposed a kinetic model for the reactions of glycolysis, the citric acid cycle, the glyoxylate cycle and the respiratory chain in growing cells of *S. cerevisiae*. The model aims to predict the short-term changes in the metabolic states of the cells under *in vivo* conditions after a change in the glucose feed rate. A schematic picture adapted from [18] describing the metabolites and fluxes included in the model (for details, see [18]) is shown on the next page.

For each metabolite in the scheme, a mass balance is written where the change of its concentration in time is expressed accounting for the incoming

An overview of Rizzi's model



and outgoing fluxes as well as the effect of dilution. The following system of differential equations is obtained for the concentrations of the different species (see Appendix 8.3 for nomenclature and parameter description):

$$\frac{dC_{GLC}^e}{dt} = D(C_{GLC}^0 - C_{GLC}^e) - \frac{C_X}{\rho} r_{PERM}^C \quad (6.1)$$

$$\frac{dC_{GLYC}^e}{dt} = \frac{C_X}{\rho} r_{RES,1}^C - DC_{GLYC}^e \quad (6.2)$$

$$\frac{dC_{AC}^e}{dt} = \frac{C_X}{\rho} r_{ALDH}^C - DC_{AC}^e \quad (6.3)$$

$$\frac{dC_{ETOH}^e}{dt} = \frac{C_X}{\rho} r_{ADH}^C - DC_{ETOH}^e \quad (6.4)$$

$$\frac{dC_{CO_2}^e}{dt} = \frac{C_X}{\rho} \left(\frac{V_M}{V_C} r_{CO_2}^M + r_{PDC}^C + a_{CO_2,1} r_{SYNT,1}^C + a_{CO_2,2} r_{SYNT,2}^C \right) + S_{CO_2} \quad (6.5)$$

$$\frac{dC_{O_2}^e}{dt} = -\frac{V_M}{V_C} \frac{C_X}{\rho} r_{O_2}^M + S_{O_2} \quad (6.6)$$

$$\frac{dC_{GLC}^C}{dt} = r_{PERM}^C - r_{HK}^C - \mu C_{GLC}^C \quad (6.7)$$

$$\frac{dC_{G6P}^C}{dt} = r_{HK}^C - r_{PGI}^C - r_{SYNT,1}^C - \mu C_{G6P}^C \quad (6.8)$$

$$\frac{dC_{F6P}^C}{dt} = r_{PGI}^C - r_{PFK}^C - \mu C_{F6P}^C \quad (6.9)$$

$$\frac{dC_{FBP}^C}{dt} = r_{PFK}^C - r_{ALDO}^C - \mu C_{FBP}^C \quad (6.10)$$

$$\frac{dC_{DHAP}^C}{dt} = r_{ALDO}^C - r_{TIS}^C - r_{RES,1}^C - \mu C_{DHAP}^C \quad (6.11)$$

$$\frac{dC_{GAP}^C}{dt} = r_{ALDO}^C + r_{TIS}^C - r_{RES,2}^C - \mu C_{GAP}^C \quad (6.12)$$

$$\frac{dC_{PEP}^C}{dt} = r_{RES,2}^C - r_{PK}^C - \mu C_{PEP}^C \quad (6.13)$$

$$\frac{dC_{PYR}^C}{dt} = r_{PK}^C - \frac{V_M}{V_C} r_{PDH}^M - r_{PDC}^C - r_{SYNT,2}^C - \mu C_{PYR}^C \quad (6.14)$$

$$\frac{dC_{ALDE}^C}{dt} = r_{PDC}^C - r_{ADH}^C - r_{ALDH}^C - \frac{V_M}{V_C} r_{ACETYL}^M - \mu C_{ALDE}^C \quad (6.15)$$

$$\begin{aligned} \frac{dC_{ADP}^C}{dt} = & r_{HK}^C + r_{PFK}^C + a_{ATP,1} r_{SYNT,1}^C + a_{ATP,2} r_{SYNT,2}^C + m_{ATP} - \\ & - 2r_{ADK}^C - r_{RES,2}^C - r_{PK}^C - r_{TR,ADP}^C - \mu C_{ADP}^C \end{aligned} \quad (6.16)$$

$$\begin{aligned} \frac{dC_{ATP}^C}{dt} = & r_{RES,2}^C + r_{PK}^C + \frac{V_M}{V_C} r_{TR,ATP}^M + r_{ADK}^C - r_{HK}^C - r_{PFK}^C - \\ & - a_{ATP,1} r_{SYNT,1}^C - m_{ATP} - a_{ATP,2} r_{SYNT,2}^C - \mu C_{ATP}^C \end{aligned} \quad (6.17)$$

$$\frac{dC_{AMP}^C}{dt} = r_{ADK}^C - \mu C_{AMP}^C \quad (6.18)$$

$$\begin{aligned} \frac{dC_{NADH}^C}{dt} = & r_{RES,2}^C + a_{NADH,2} r_{SYNT,2}^C - r_{RES,1}^C - r_{ADH}^C - r_{ALDH}^C - \\ & - r_{NADHDH}^C - \mu C_{NADH}^C \end{aligned} \quad (6.19)$$

$$\frac{dC_{ATP}^M}{dt} = r_{ATP,R}^M + r_{ATP,T}^M - r_{TR,ATP}^M - \mu C_{ATP}^M \quad (6.20)$$

$$\frac{dC_{NADH}^M}{dt} = r_{NADH,T}^M - r_{NADHQR}^M - \mu C_{NADH}^M \quad (6.21)$$

Remark: After comparison with the original version of the model (see [1]), some minor modifications have been made to the model description in Rizzi, et al. ([18]) due to what appears to be typing errors in the latter, see [2].

The fluxes r have rate equations based on Michaelis-Menten, Hill or other types of enzyme kinetics gathered from the literature or proposed by the authors. For example:

$$r_{TIS}^C = r_{TIS}^{max} \frac{C_{DHAP}^C - \frac{C_{GAP}^C}{K_{eq,6}}}{K_{DHAP,6} \left(1 + \frac{C_{GAP}^C}{K_{GAP,6}}\right) + C_{DHAP}^C} .$$

Most of the fluxes in the model are rational expressions with the exception of those fluxes where the Hill coefficients are not integers. This fact is important for the identifiability analysis and will be discussed later.

The above model was evaluated in [18] on the basis of experimental observations previously described in [27]. The model predictions were compared to the experimental results and the parameters were estimated from the data [18]. We will now attempt to use the theory of identifiability to find out whether the kinetic parameters of this model can be uniquely determined from the perfect set of experimental data. We must first formulate a control system for the model. For this the appropriate set of inputs and outputs must be chosen from the description of the experimental setting in [27]. In the latter, a methodology was developed where the changes in metabolite concentrations after a glucose feed pulse (a fast injection of a certain volume of glucose in the medium [27]) were measured over time. The initial conditions were the priorly-known values of the metabolite concentrations under so-called "steady-state growth" - a condition when biomass concentration (and other factors) has stabilised to a constant value for the culture, see [27] for details.

In order to translate the information in the above paragraph into mathematical language, we include a perfect measurement of all metabolite concentrations c (thus including the given initial conditions) in the outputs of the control system:

$$\begin{cases} \dot{p} & = 0 \\ \dot{c} & = f(c, p, u) \\ y & = c \\ (c(0) & = c^0) \end{cases} ,$$

where c is the vector of metabolite concentrations, f is the right-hand side of the equation arrays (6.1)-(6.21) and we denote all the model parameters by

p . The initial conditions are in parenthesis as the information they provide is included in the output set. The input u is assumed to be the glucose feed.

6.3 Identifiability analysis

We performed an identifiability analysis of the above control system. For this, Sedoglavic's implementation (see the last section of Chapter 3) was used as the model has around a hundred parameters which makes calculations by hand very difficult. As the algorithm works only for rational control systems, we approximated any non-integer values of the Hill coefficients by integers. Of course, in general, such approximations can have an important effect on the identifiability of the system. This turns out not to be the case for Rizzi's model, as shown in the next section.

Sedoglavic's algorithm produced the following results - the control system was not identifiable with transcendence degree 2 and the non-identifiable parameters were the kinetic parameters of two of the rate equations - the equation for the flux $r_{RES,2}^C$ and the one for r_{PDH}^M which have the following form:

$$r_{RES,2}^C = r_{RES,2}^{max} \frac{\frac{C_{NAD}^C}{K_{NAD,7}} A^{n_1,7-1} + L_{0,7} \frac{C_{NAD}^C}{K'_{NAD,7}} B^{n_1,7-1}}{A^{n_1,7-1} + L_{0,7} B^{n_1,7-1}} \frac{C_{GAP}^C{}^{n_2,7}}{K_{GAP,7} + C_{GAP}^C{}^{n_2,7}} \quad ,$$

where

$$\begin{aligned} A &= 1 + \frac{C_{NAD}^C}{K_{NAD,7}} + \frac{C_{NADH}^C}{K_{NADH,7}} \\ B &= 1 + \frac{C_{NAD}^C}{K'_{NAD,7}} + \frac{C_{NADH}^C}{K'_{NADH,7}} \end{aligned}$$

and

$$\begin{aligned} r_{PDH}^M &= r_{PDH}^{max} C_{PYR}^C C_{NAD}^M / (K_{NAD,13} C_{PYR}^C + K_{PYR,13} C_{NAD}^M + \\ &+ \frac{K_{I-PYR,13} K_{NAD,13}}{K_{I-NADH,13}} C_{NADH}^M + C_{PYR}^C C_{NAD}^M + \frac{K_{NAD,13} K_{I-NADH,13}}{K_{I-NADH,13}} C_{PYR}^C C_{NADH}^M) \quad . \end{aligned}$$

Observe that the concentrations C_{NAD}^C and C_{NAD}^M are used in the rate equations although no differential equations are formulated for them in Rizzi's model. Instead, these are defined in [18] as:

$$C_{NAD}^C = k_1 - C_{NADH}^C \quad (6.22)$$

$$C_{NAD}^M = k_1 - C_{NADH}^M \quad , \quad (6.23)$$

where k_1 and k_2 are known constants.

More results from the identifiability analysis are shown in Appendix 8.4.

6.4 Symmetry

The results obtained from the Sedoglavic implementation are probabilistic (see [20]) - their validity must be ascertained by the actual finding of symmetries in the model. From the theory described in Chapter 3 we know that we have to find two derivations that each of them give rise to a symmetry in the model. The fact that the non-identifiable parameters can be separated into two groups, each belonging to a rate equation, suggests the possibility that the symmetries may be found within each rate expression (since the kinetic parameters of the fluxes $r_{RES,2}^c$ and r_{PDH}^m are not used anywhere else in the model). If this is true, the calculation of the symmetries may be greatly simplified - following the formal procedure from Section 3.4. for the 11 non-identifiable parameters can be rather cumbersome. In order to verify this hypothesis, we first used Sedoglavic's algorithm on our control system where we added measurements of the fluxes $r_{RES,2}^C$ and r_{PDH}^M to the set of outputs:

$$\begin{cases} \dot{p} = 0 \\ \dot{c} = f(c, p, u) \\ y = \begin{pmatrix} c \\ r_{RES,2}^C \\ r_{PDH}^M \end{pmatrix} \end{cases} .$$

The idea behind this test is that if this system turns out to result in a transcendence degree of 2 and the same non-identifiable parameters as before, then there exist two families of symmetries in these parameters that leave both c and $r_{RES,2}^C$ and r_{PDH}^M invariant (see Section 3.4). This means that the expressions $r_{RES,2}^C$ and r_{PDH}^M themselves have symmetries in their kinetic parameters.

We tested the above system in the Sedoglavic implementation and found our hypothesis to be true. The rate expressions $r_{RES,2}^C$ and r_{PDH}^M were then analysed further to find the symmetries in the parameters by inspection. The strategy was to look for a transformation of the parameters that would multiply the numerator and the denominator of each expression by the same number which would then cancel out. We found the following families of

symmetries (see Chapter 3, Section 3.4.) for $r_{RES,2}^C$:

$$\sigma_\lambda : \left\{ \begin{array}{l} r_{RES,2}^{max} \\ K_{NAD,7} \\ K'_{NAD,7} \\ K_{NADH,7} \\ K'_{NADH,7} \\ L_{0,7} \end{array} \right\} \rightarrow \left\{ \begin{array}{l} \frac{r_{RES,2}^{max} k_1}{K_{NAD,7}(1-\lambda^{-1/n_1,7})+k_1} \\ \frac{K_{NAD,7} \lambda^{-1/n_1,7} k_1}{K_{NAD,7}(1-\lambda^{-1/n_1,7})+k_1} \\ \frac{(K'_{NAD,7}-K_{NAD,7}(1-\lambda^{-1/n_1,7}))k_1}{K_{NAD,7}(1-\lambda^{-1/n_1,7})+k_1} \\ \frac{K_{NADH,7} \lambda^{-1/n_1,7} k_1}{K_{NADH,7}(1-\lambda^{-1/n_1,7})+k_1} \\ \frac{(K'_{NAD,7}-K_{NAD,7}(1-\lambda^{-1/n_1,7}))k_1}{K_{NAD,7}(1-\lambda^{-1/n_1,7})+\frac{K'_{NAD,7}}{K'_{NADH,7}}k_1} \\ \frac{\lambda L_{0,7}(K'_{NAD,7}-K_{NAD,7}(1-\lambda^{-1/n_1,7}))^{n_1,7}}{K_{NAD,7}^{n_1,7}} \end{array} \right\}$$

and for r_{PDH}^M :

$$\sigma_\lambda : \left\{ \begin{array}{l} r_{PDH}^{max} \\ K_{NAD,13} \\ K_{PYR,13} \\ K_{I-PYR,13} \\ K_{I-NADH,13} \end{array} \right\} \rightarrow \left\{ \begin{array}{l} \lambda r_{PDH}^{max} \\ \lambda K_{NAD,13} + k_2(\lambda - 1) \\ \lambda K_{PYR,13} \\ \frac{\lambda K_{NAD,13} K_{I-PYR,13}}{(1-\lambda)K_{I-NADH,13} + \lambda K_{NAD,13}} \\ \frac{K_{I-NADH,13}(\lambda K_{NAD,13} + k_2(\lambda - 1))}{(1-\lambda)K_{I-NADH,13} + \lambda K_{NAD,13}} \end{array} \right\}.$$

We see that the constants k_1 and k_2 appear in the symmetries. In fact, it is exactly the definitions 6.17 and 6.18 that cause the system to be non-identifiable.

We can now certify that the kinetic parameters $r_{RES,2}^{max}$, $K_{NAD,7}$, $K'_{NAD,7}$, $K_{NADH,7}$, $K'_{NADH,7}$, $L_{0,7}$, r_{PDH}^{max} , $K_{NAD,13}$, $K_{PYR,13}$, $K_{I-PYR,13}$, $K_{I-NADH,13}$ cannot be identified from any experimental data. If parameter estimation is to be performed on Rizzi's model, for example by a numerical procedure where the error between model predictions and experimental results is minimised, then one of the parameters in each of the groups $r_{RES,2}^{max}$, $K_{NAD,7}$, $K'_{NAD,7}$, $K_{NADH,7}$, $K'_{NADH,7}$, $L_{0,7}$ and r_{PDH}^{max} , $K_{NAD,13}$, $K_{PYR,13}$, $K_{I-PYR,13}$, $K_{I-NADH,13}$ must be fixed to a value, while varying the rest of the parameters.

Remark: Using Sedoglavic's algorithm, we investigated the identifiability of this model with other sets of outputs than the ones discussed above (some of the results are shown in Appendix 8.4). As well as including all possible outputs - all concentrations c_j and all fluxes r_j , we also tried to limit the number of measurements by finding a single output which produced the same transcendence degree for the system. One such example is the rate $r_{RES,1}^C$.

Measuring this flux should in theory (with perfect error-free measurements) produce the same information on the parameter values as measuring all concentrations and all fluxes. Sedoglavic’s algorithm can thus be used in the practical planning of an experiment to validate a given model.

6.5 General features of kinetic models and identifiability

The control systems associated to kinetic models of metabolism can often be described by the following structure, as shown in Chapter 8 of the book on metabolic engineering by Stephanopoulos et al, [25]:

$$\begin{cases} \dot{c}_j &= u_j + \sum_i \nu_{ij} \cdot r_i(c, p_i) - \mu c_j \quad \forall j \\ y &= c \end{cases}, \quad (6.24)$$

for each metabolite j . The coefficients ν_{ij} are the stoichiometric coefficients associated to each reaction.

In Rizzi’s model, the non-identifiable parameters could be separated into two groups each associated to one rate equation. The question is whether this is true for all non-identifiable kinetic models of the above form.

The first step in the construction of a kinetic model for cellular metabolism is usually formulating a network of fluxes which, at steady-state, obey Kirchhoff’s law at every node. This underlying steady-state model must be such that the stationary values of all fluxes r_i can be calculated uniquely from the set of linear equations for r obtained at steady-state. Mathematically, this means that the stoichiometric matrix $[\nu_{ij}]$ is of full rank.

If we rewrite the first equation in (6.24), we have:

$$\dot{c}_j - u_j + \mu c_j = \sum_i \nu_{ij} \cdot r_i(c, p_i) \quad .$$

Since $y = c$, all the quantities on the left-hand side are known, if we assume that we know the value of the specific growth rate μ . The matrix $[\nu_{ij}]$ is assumed to be of full rank and we thus have unique values of $r_i(c, p_i)$ completely determined by a given set of inputs and outputs. This means that if the system is not identifiable and there exist non-identifiable parameters such that there is a symmetry in them leaving the inputs and outputs invariant, then this symmetry will also leave the r_i :s invariant. Since each flux r_i only involves the parameters in the subset p_i of p , then any symmetry in p leaving

r_i invariant must involve only the parameters in p_i . In result, a kinetic model of metabolism of the form (6.24) is not identifiable only if some of the rate expressions are symmetric in their respective kinetic parameters.

Chapter 7

Discussion

The subject of this report was the problem of investigating the observability of nonlinear control systems, a special case of which is the identifiability problem. We presented a review of two rather different theoretical approaches to the problem used in literature - the differential-geometric approach and the algebraic one. Each of the two approaches lead to a test for the observability of a class of control systems. The differential-geometric approach covered analytical control systems of the form

$$\Sigma \begin{cases} \dot{x} &= f(x, u) = h^0(x) + h(x)u \\ y &= g(x) \end{cases}, \quad (7.1)$$

while the algebraic one treated rational systems:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) \\ y &= g(x, u) \end{cases}.$$

Both approaches lead to the so-called observability rank test where the rank of the space spanned by gradients of the Lie-derivatives of the output functions is calculated. In the algebraic approach there is an upper bound derived for the number of Lie-derivatives that have to be considered in the test for rational systems. We were not able to find an equivalent in the literature for the class of analytical control systems treated in the differential-geometric approach, meaning that the rank test could be applied in practice to only the simplest examples where one could see by inspection what form the infinitely many Lie-derivatives of the output functions would take and could thus conclude on the rank of the space spanned by their gradients.

We addressed this problem in Chapter 4 where we derived the same upper bound for the number of Lie-derivatives of the output functions for the class of analytical systems affine in the input variables that were considered in the differential-geometric approach. It remains as future work to investigate the validity of such an upper bound for other classes of control systems.

The identifiability problem is a special case of observability and we could thus use the previously derived rank test in the investigation of identifiability. This was done in a case study of a dynamic model of the metabolism of *S. cerevisiae*. By finding symmetries in the model, we showed that certain model parameters could not be identified from any set of experimental data. The results from the treatment of this model were generalised to show how the special structure of kinetic models of metabolism considerably simplified the analysis of their identifiability and especially the derivation of symmetries.

Chapter 8

Appendix

8.1 Why do d and L_f commute when f depends on a control variable u ?

This appendix is used in the calculations of Chapter 4.

Consider a control system of the form:

$$\Sigma \begin{cases} \dot{x} &= f(x, u) = h^0(x) + h(x)u \\ y &= g(x) \end{cases}, \quad (8.1)$$

where the elements of the n -dimensional vectors h^0 and h are analytic functions of x and u , where u is the single control variable. Denote, as in Chapter 2, the flow corresponding to the time-dependent vector field $f(x, u)$ by $\Phi_u(t, x)$ which is then an n dimensional vector. Let $\psi(x, u)$ be an analytic function of x, u and u 's time derivatives. We will show that:

$$L_f d\psi = dL_f \psi \quad .$$

Take the i -th element of $dL_f \psi$. It is:

$$\begin{aligned} \frac{\partial}{\partial x_i} L_f \psi &= \frac{\partial}{\partial x_i} \left(\sum_{j=1}^n f_j \frac{\partial \psi}{\partial x_j} + \sum_{l=0} \frac{\partial \psi}{\partial u^{(l)}} U^{(l+1)} \right) = \sum_{j=1}^n \frac{\partial}{\partial x_i} \left(f_j \frac{\partial \psi}{\partial x_j} \right) + \sum_{l=0} \frac{\partial}{\partial x_i} \left(\frac{\partial \psi}{\partial u^{(l)}} U^{(l+1)} \right) = \\ &= \sum_{j=1}^n \frac{\partial f_j}{\partial x_i} \frac{\partial \psi}{\partial x_j} + \sum_{j=1}^n \frac{\partial^2 \psi}{\partial x_i \partial x_j} f_j + \sum_{l=0} \frac{\partial}{\partial x_i} \left(\frac{\partial \psi}{\partial u^{(l)}} \right) U^{(l+1)} \quad . \end{aligned}$$

Now consider the i -th element of the covector $L_f d\psi$. Following the definition

again,

$$\begin{aligned}
\left. \frac{d}{dt} \left(\frac{\partial \psi(\Phi_u(t, x), u(t))}{\partial x_i} \right) \right|_{t=0} &= \left. \frac{d}{dt} \left(\sum_{j=1}^n \frac{\partial \psi}{\partial \Phi_{u,j}} \frac{\partial \Phi_{u,j}}{\partial x_i} \right) \right|_{t=0} = \sum_{j=1}^n \left. \frac{d}{dt} \left(\frac{\partial \psi}{\partial \Phi_{u,j}} \frac{\partial \Phi_{u,j}}{\partial x_i} \right) \right|_{t=0} = \\
&= \sum_{j=1}^n \left(\left. \frac{d}{dt} \left(\frac{\partial \psi}{\partial \Phi_{u,j}} \right) \right|_{t=0} \frac{\partial \Phi_{u,j}}{\partial x_i} \right|_{t=0} + \left. \frac{d}{dt} \left(\frac{\partial \Phi_{u,j}}{\partial x_i} \right) \right|_{t=0} \frac{\partial \psi}{\partial \Phi_{u,j}} \Big|_{t=0} \right) = \\
&= \sum_{j=1}^n \left(\left(\sum_{k=1}^n \frac{\partial}{\partial \Phi_{u,k}} \left(\frac{\partial \psi}{\partial \Phi_{u,j}} \right) \right) \Big|_{t=0} \frac{d\Phi_{u,k}}{dt} \Big|_{t=0} + \sum_{l=0} \frac{\partial}{\partial u^{(l)}} \left(\frac{\partial \psi}{\partial \Phi_{u,j}} \right) \Big|_{t=0} U^{(l+1)} \right) \delta_{ij} + \frac{\partial \psi}{\partial x_j} \frac{\partial f_j}{\partial x_i} = \\
&= \sum_{j=1}^n \left(\left(\sum_{k=1}^n \frac{\partial^2 \psi}{\partial x_k \partial x_j} f_k + \sum_{l=0} \frac{\partial}{\partial u^{(l)}} \left(\frac{\partial \psi}{\partial x_j} \right) U^{(l+1)} \right) \delta_{ij} + \frac{\partial \psi}{\partial x_j} \frac{\partial f_j}{\partial x_i} \right) = \\
&= \sum_{k=1}^n \frac{\partial^2 \psi}{\partial x_k \partial x_i} f_k + \sum_{l=0} \frac{\partial}{\partial u^{(l)}} \left(\frac{\partial \psi}{\partial x_i} \right) U^{(l+1)} + \sum_{j=1}^n \frac{\partial \psi}{\partial x_j} \frac{\partial f_j}{\partial x_i} .
\end{aligned}$$

One can now see that the i -th elements of the covectors $L_f d\psi$ and $dL_f \psi$ are the same, which shows the above equality.

8.2 A basis for derivations on $\mathbb{R}\langle U \rangle(x)$ that are trivial on $\mathbb{R}\langle U \rangle$

This appendix refers to Section 3.4 and is based on p.371-372 in [12].

First of all, observe that the x_i form a transcendence basis for $\mathbb{R}\langle U \rangle(x)$ over $\mathbb{R}\langle U \rangle$. The transcendence degree of the field extension is thus n which is also the dimension of $Der_{\mathbb{R}\langle U \rangle} \mathbb{R}\langle U \rangle(x)$. Consider the n derivations $D_i = \frac{\partial}{\partial x_i}$. Clearly, $D_i x_j = \delta_{ij}$. Let D be a derivation in $Der_{\mathbb{R}\langle U \rangle} \mathbb{R}\langle U \rangle(x)$ and let $D x_i = w_i$ (a derivation is defined by its action on a set of generators of the transcendence basis). Then $D = \sum_i w_i D_i$ and thus the D_i :s form a basis for $Der_{\mathbb{R}\langle U \rangle} \mathbb{R}\langle U \rangle(x)$. Therefore the partial derivatives $\frac{\partial}{\partial x_i}$ form a basis for the derivations on $\mathbb{R}\langle U \rangle(x)$ that are trivial on $\mathbb{R}\langle U \rangle$.

8.3 Nomenclature for Rizzi's model

This appendix refers to Chapter 6.

For the details of the kinetic model by Rizzi et al we refer to [18] but in an attempt to make this report somewhat self-sufficient we here provide nomenclature for the abbreviations and parameters used in Chapter 6.

8.3.1 Superscripts

e	extracellular
C	cytoplasmic
M	mitochondrial

8.3.2 Symbols and abbreviations

a_j	stoichiometric coefficient
S_G	gas supply rate
V_M	volume of mitochondria
V_C	volume of cytoplasm
D	dilution rate
ρ	specific volume
μ	specific growth rate
C_X	biomass concentration
m_{ATP}	maintenance coefficient for ATP

8.3.3 Metabolites

AC	acetic acid
ADP	adenosine diphosphate
ALDE	acetaldehyde
AMP	adenosine monophosphate
ATP	adenosine triphosphate
DHAP	dihydroxyacetone phosphate
ETOH	ethanol
FBP	fructose 1,6-bisphosphate
F6P	fructose 6-phosphate
GAP	glyceraldehyde 3-phosphate
GLC	glucose
GLYC	glycerol
G6P	glucose 6-phosphate
NAD ⁺ /NADH	nicotinamide adenine dinucleotide
PEP	phosphoenol pyruvate
PYR	pyruvate

8.3.4 Enzymes and flux indexes

ACETYL	acetate synthetase
ADH	alcohol dehydrogenase
ADK	adenylate kinase
ALDH	acetaldehyde dehydrogenase
ALDO	fructose bisphosphate aldolase
ATP,R	ATP formation via respiratory chain
ATP,T	ATP formation via the citric acid cycle
HK	hexokinase
NADHDH	NADH-dehydrogenase
NADHQR	NADH-Q-reductase
PDC	pyruvate decarboxylase
PDH	pyruvate dehydrogenase
PERM	hexose transporter
PFK	phosphofructo-1-kinase
PGI	phosphoglucose isomerase
PK	pyruvate kinase
RES,1	combination of glycerol-3-phosphate dehydrogenase and glycerol-3-phosphatase
RES,2	combination of glyceraldehyde 3-phosphate dehydrogenase and other enzymes
SYNT,1;SYNT,2	resulting rates for the formation of monomeric building blocks
TIS	triose phosphate isomerase
TR,ADP and TR,ATP	translocases for ADP and ATP respectively.

8.4 Other results on the identifiability of Rizzi's model

This appendix shows some of the results obtained from the identifiability analysis of Rizzi's model. They can be used in choosing a set of measurements in a hypothetical experiment.

Since the parameters C_X and ρ always appear together as $\frac{C_X}{\rho}$ one of them must be known - otherwise it is clear that they will not be identifiable. We therefore assume that the value of one of them is measured in any hypothetical experiment when we perform the identifiability analysis, although we do

not explicitly write them as outputs. The same applies for the parameters V_M and V_C appearing in $\frac{V_M}{V_C}$.

Outputs	Transcendence degree
$r_{RES,1}^C$	2
$r_{RES,1}^C, r_{RES,2}^{max}, r_{PDH}^{max}$	0
C_{ETOH}^e	8
C_{GLYC}^e	8
all $c_j:s$	2
all $c_j:s, r_{RES,2}^C, r_{PDH}^M$	2
all $c_j:s, \text{all } r_j:s$	2

One conclusion is that measuring $r_{RES,1}^C$ produces as much information for the theoretical identification of parameter values as making all possible measurements altogether.

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**Nonlinear Observability and Identifiability:
General Theory and a Case Study of a Kinetic Model for
*S. cerevisiae***

MILENA ANGUELOVA

Errata

Page, line	Reads	Should read
p.10, line -11	$t_l - 1, t_l$	$t_1 + \dots + t_{l-1}, t_1 + \dots + t_l$
p.13, line 15	$L_f = \sum_{j=1}^n f_j \frac{\partial}{\partial x_j} + \sum_l U^{(l+1)} \frac{\partial}{\partial u}$	$L_f = \sum_{j=1}^n f_j \frac{\partial}{\partial x_j} + \sum_{l=0} U^{(l+1)} \frac{\partial}{\partial u^{(l)}}$
p.19, line 14	a linear map d	a linear map D
p.20, line 5,9	$p^D(x)$	$p_\alpha^D(x)$
p.20, line -13	Hilbert's	Hilbert's
p.21, line -2	$\sum_{k=1} \sum_{i=1}^l \frac{\partial g_j}{\partial u_i} U^{(k+1)}$	$\sum_{k=0} \sum_{i=1}^l \frac{\partial g_j}{\partial u_i^{(k)}} U_i^{(k+1)}$
p.21, line -1	$\sum_{k=1} \sum_{i=1}^l \frac{\partial(L_f g_j)}{\partial u_i} U^{(k+1)}$	$\sum_{k=0} \sum_{i=1}^l \frac{\partial(L_f g_j)}{\partial u_i^{(k)}} U_i^{(k+1)}$
p.22, line 12	exist	exists
p.22,23,24	$\begin{bmatrix} \frac{\partial L_f g_1}{\partial x_1} & \dots & \frac{\partial L_f g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f g_m}{\partial x_1} & \dots & \frac{\partial L_f g_m}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix}$	$\begin{bmatrix} \frac{\partial L_f^0 g_1}{\partial x_1} & \dots & \frac{\partial L_f^0 g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^0 g_m}{\partial x_1} & \dots & \frac{\partial L_f^0 g_m}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix}$
p.26, line 3	$\begin{cases} \dot{\Phi}_2(t, x) = x_2 \\ \dot{\Phi}_4(t, x) = -x_4 \\ \Phi_2(0, x) = x_2 \\ \Phi_4(0, x) = x_4 \end{cases}$	$\begin{cases} \dot{\Phi}_2(t, x) = \Phi_2(t, x) \\ \dot{\Phi}_4(t, x) = -\Phi_4(t, x) \\ \Phi_2(0, x) = x_2 \\ \Phi_4(0, x) = x_4 \end{cases}$
p.36, line 1	algorithm	algorithm
p.37	$\begin{bmatrix} \frac{\partial L_f g_1}{\partial x_1} & \dots & \frac{\partial L_f g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f g_m}{\partial x_1} & \dots & \frac{\partial L_f g_m}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix}$	$\begin{bmatrix} \frac{\partial L_f^0 g_1}{\partial x_1} & \dots & \frac{\partial L_f^0 g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^0 g_m}{\partial x_1} & \dots & \frac{\partial L_f^0 g_m}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_1}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_1}{\partial x_n} \\ \dots & & \dots \\ \frac{\partial L_f^{n-1} g_m}{\partial x_1} & \dots & \frac{\partial L_f^{n-1} g_m}{\partial x_n} \end{bmatrix}$
p.39, title line 3, text line 2	<i>S. Cerevisiae</i>	<i>S. cerevisiae</i>
p.47, line -6	Changes in Remark:	see below
Appendix p.V	Changes in the results table	see below
Appendix p.V, line -3	$r_{RES,1}^C$	$C_{GLYC}^e, C_{AC}^e, C_{ETOH}^e$ and $C_{CO_2}^e$
Bibliography p.VIII, line 1	Johnson J.	Johnson J. 1969.
Bibliography p.VIII, line 9	word congress	world congress

The remark on page 47 reads:

Remark: Using Sedoglavic's algorithm, we investigated the identifiability of this model with other sets of outputs than the ones discussed above (some of the results are shown in Appendix 8.4). As well as including all possible outputs - all concentrations c_j and all fluxes r_j , we also tried to limit the number of measurements by finding a single output which produced the same transcendence degree for the system. One such example is the rate $r_{RES,1}^C$. Measuring this flux should in theory (with perfect error-free measurements) produce the same information on the parameter values as measuring all concentrations and all fluxes. Sedoglavic's algorithm can thus be used in the practical planning of an experiment to validate a given model.

It should read:

Remark: Using Sedoglavic's algorithm, we investigated the identifiability of this model with other sets of outputs than the ones discussed above (some of the results are shown in Appendix 8.4). As well as including all possible outputs - all concentrations c_j and all fluxes r_j , we also tried to limit the number of measurements by finding a smaller set of outputs which produced the same transcendence degree for the system. One such example is the set $C_{GLYC}^e, C_{AC}^e, C_{ETOH}^e$ and $C_{CO_2}^e$. Measuring these concentrations should in theory (with perfect error-free measurements) produce the same information on the parameter values as measuring all concentrations and all fluxes. Sedoglavic's algorithm can thus be used in the practical planning of an experiment to validate a given model.

The table in Appendix page V reads:

Outputs	Transcendence degree
$r_{RES,1}^C$	2
$r_{RES,1}^C, r_{RES,2}^{max}, r_{PDH}^{max}$	0
C_{ETOH}^e	8
C_{GLYC}^e	8
all $c_j:s$	2
all $c_j:s, r_{RES,2}^C, r_{PDH}^M$	2
all $c_j:s, \text{all } r_j:s$	2

It should read:

Outputs	Transcendence degree
$C_{GLYC}^e, C_{AC}^e, C_{ETOH}^e, C_{CO_2}^e$	2
$C_{GLYC}^e, C_{AC}^e, C_{ETOH}^e, C_{CO_2}^e, r_{RES,2}^{max}, r_{PDH}^{max}$	0
all $c_j:s$	2
all $c_j:s, r_{RES,2}^C, r_{PDH}^M$	2
all $c_j:s, \text{all } r_j:s$	2

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