Structural Identifiability of some Biotechnological Systems

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Abstract: - In this paper we present an algorithm for nonlinear continuous-time model structural identifiability analysis. The method can be included in the *transformation of nonlinear models* framework of structural identifiability analysis and is based on test functions from distribution theory. So, the nonlinear continuous-time models are transformed in linear in parameters models by replacing the state variables and their derivatives with corresponding functionals obtained using distributions. Depending on particular cases, the problem is split in many sub-problems interconnected, the results of one stage of analysis being used to the next stages. The presented method is applied to analyse the structural identifiability of a wastewater biodegradation process, considering that the unknown parameters appear in rational relations with measured variables.

Key-Words: - structural identifiability, wastewater biodegradation process, test functions

1 Introduction

In recent years, a progress has been made in the area of continuous-time system identification. Even if the most physical systems are naturally continuous, a much more attention has been paid to parameter estimation of discrete-time systems, mainly because they are better suited for numerical implementations.

Continuous-time identification makes possible a more direct link to the physical properties and operation of the underlying systems [8, 14], and the direct estimation of physical parameters that have a clear significance [13]. One important direction in continuous-time system identification is to transform the system differential equations to an algebraic system that reveals the unknown parameters. But, the implementation of the estimation algorithms must be preceded by structural identifiability tests [3, 4].

The notion of structural identifiability is related to the possibility to give a unique value to each parameter of a mathematical model. In simple words, given a model structure and a data set of model variables that corresponds perfectly to the model from structural identifiability analysis one may conclude if all the parameters of the model are identifiable. In the biotechnological processes area a very important question is the identifiability study of the dynamical models, prior to any identification, because of the model complexity and the scarcity of on-line sensors.

In this paper, we propose a method for structural identifiability analysis for a class of nonlinear continuous time systems considering that the unknown parameters can appear in rational relations with measured variables. Using techniques utilized in distribution approach the measurable functions and their derivatives are represented by functionals on a fundamental space of testing functions. Such systems are common in biotechnology [1, 11]. It is supposed the system is noise free, described by state equations and all state variables are measurable. Because of the rational dependence, it is not possible to express the unknown parameters by a linear equation in the evaluated functionals. The main idea of this paper is to use a hierarchical configuration for structural identifiability analysis for a wastewater treatment process. First, some state equations are utilized to obtain a set of linear equations in some parameters. The results of this first stage of analysis are utilized for expressing other parameters by linear equations. This process is repeated until all parameters are analysed.

The paper is organized as follows: the structure of a nonlinear continuous time system describing a wastewater biodegradation process is given in Section 2. Section 3 presents some aspects regarding theoretical framework of structural identifiability analysis. The structural identifiability of a wastewater biodegradation process based on distribution approach is presented in Section 4, followed by some conclusions.

2 Mathematical Model of Wastewater Biodegradation Process

Wastewater treatment plants are difficult to control because of nonlinear dynamics and of their unknown parameters whose values can modify in time. We consider a biomethanation process – wastewater biodegradation with production of methane gas that takes place inside a Continuous Stirred Tank Bioreactor whose reduced model is presented in [1, 2]. It is a two phases process. In the first phase, the glucose from the wastewater is decomposed in fat volatile acids (acetates, propionic acid), hydrogen and inorganic carbon under action of the acidogenic bacteria. In the second phase, the ionised hydrogen decomposes the propionic acid CH3CH2COOH in acetates, H2 and carbon dioxide CO2. In the first methanogenic phase, the acetate is transformed into methane and CO2, and finally in the second methanogenic phase, the methane gas CH4 is obtained from H2 and CO2, [2, 9, 10, 11]. The following simplified reaction scheme is considered,

$$\begin{cases} S_1 \xrightarrow{\Phi 1} X_1 + S_2 \\ S_2 \xrightarrow{\Phi 2} X_2 + P_1 \end{cases} \tag{1}$$

where: S_1 represents the glucose substrate, S_2 the acetate substrate, X_1 is the acidogenic bacteria, X_2 the acetoclastic methanogenic bacteria and P_1 represents the product, i.e. the methane gas. The reaction rates are denoted by Φ_1, Φ_2. The corresponding dynamical model is

$$\frac{d}{dt}\begin{bmatrix} X_1 \\ S_1 \\ X_2 \\ S_2 \\ P_1 \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ -k_1 & 0 \\ 0 & 1 \\ k_2 & -k_3 \\ 0 & k_4 \end{bmatrix} \begin{bmatrix} \Phi_1 \\ \Phi_2 \end{bmatrix} - D \begin{bmatrix} X_1 \\ S_1 \\ X_2 \\ S_2 \\ P_1 \end{bmatrix} + \begin{bmatrix} 0 \\ DS_{in} \\ 0 \\ 0 \\ -Q_1 \end{bmatrix} \tag{2}$$

where the state vector of the model is:

$$\xi = \begin{bmatrix} X_1 \\ S_1 \\ X_2 \\ S_2 \\ P_1 \end{bmatrix} = \begin{bmatrix} \xi_1 \\ \xi_2 \\ \xi_3 \\ \xi_4 \\ \xi_5 \end{bmatrix} \tag{3}$$

whose components are concentrations in (g/l). The reaction rates are nonlinear functions of the state components, expressed as

$$\Phi = \Phi(\xi) = \begin{bmatrix} \Phi_1(\xi) \\ \Phi_2(\xi) \end{bmatrix} \tag{4}$$

The reaction rates for this process are given by the Monod law

$$\Phi_1(\xi) = \mu_1 \frac{S_1 \cdot X_1}{K_{M_1} + S_1} \tag{5}$$

and the Haldane kinetic model

$$\Phi_2(\xi) = \mu_2 \frac{S_2 \cdot X_2}{K_{M_2} + S_2 + S_2^2 / K_i} \tag{6}$$

where K_{M_1}, K_{M_2} are Michaelis-Menten constants, μ_1, μ_2 represent specific growth rates coefficients and K_i is the inhibition constant.

For simplicity, shall we denote the plant parameters by the vector:

$$\theta = [\theta_1 \quad \theta_2 \quad \theta_3 \quad \theta_4 \quad \theta_5 \quad \theta_6 \quad \theta_7 \quad \theta_8 \quad \theta_9]^T \tag{7}$$

where:

$$\begin{aligned} &\theta_1 = k_1; \quad \theta_2 = k_2; \quad \theta_3 = k_3; \quad \theta_4 = k_4; \\ &\theta_5 = \mu_1; \ \theta_6 = \mu_2; \\ &\theta_7 = K_{M_1}; \ \theta_8 = K_{M_2}; \ \theta_9 = K_i; \end{aligned} \tag{8}$$

Because the dilution rate D can be externally modified, it will be considered the third component of the input vector

$$u = [u_1 \quad u_2 \quad u_3]^T \tag{9}$$

The other two components of u are the concentration S_{in} and the methane gas outflow rate Q_1 so,

$$u_1 = S_{in}; \ u_2 = Q_1; \ u_3 = D \tag{10}$$

Usually Q_1 depends on state variables, $Q_1 = \psi(\xi)$, determining a feedback to the input u_2. Written explicitly by components, the state equation (2), within the above notations, takes the form,

$$\dot{\xi}_1 = \Phi_1 - u_3 \cdot \xi_1 \tag{11}$$

$$\Phi_1 = \theta_5 \cdot \frac{\xi_1 \cdot \xi_2}{\theta_7 + \xi_2} \tag{12}$$

$$\dot{\xi}_2 = -\theta_1 \cdot \Phi_1 - u_3 \cdot \xi_2 + u_1 \cdot u_3 \tag{13}$$

$$\dot{\xi}_3 = \Phi_2 - u_3 \cdot \xi_3 \tag{14}$$

$$\Phi_2 = \theta_6 \cdot \frac{\xi_3 \cdot \xi_4}{\theta_8 + \xi_4 + \theta_9^{'} \cdot \xi_4^2}, \ \theta_9^{'} = \frac{1}{\theta_9} \tag{15}$$

$$\dot{\xi}_4 = \theta_2 \cdot \Phi_1 - \theta_3 \cdot \Phi_2 - u_3 \cdot \xi_4 \tag{16}$$

$$\dot{\xi}_5 = -u_3 \cdot \xi_5 + \theta_4 \cdot \Phi_2 - u_2 \tag{17}$$

3 Structural Identifiability of Nonlinear Systems

3.1 Problem statement

The notion of structural identifiability is related to the possibility to give a unique value to each parameter of a mathematical model. From the structural identifiability analysis one may conclude that, in some cases, only combinations of the model parameters are identifiable. If the number of resulting combinations is lower than the original model parameters, or if there is not a one-to-one relationship between both parameter sets, then a priori knowledge about some parameters is required to achieve identifiability of each individual parameter. A simple example may illustrate this: in the model $y = ax_1 + bx_2 + c(x_1 + x_2)$, only the parameter combinations $a+c$ and $b+c$ are structurally identifiable. The parameters a and b will be identifiable if the value of c is known a priori.

For linear systems, the structural identifiability is rather well understood, and besides classical identifiable models (like dynamical models in canonical form), there exists a number of tests for identifiability: Laplace transform method, Taylor series expansion of the observations, Markov parameter matrix approach, modal matrix approach, etc. For models that are nonlinear in the parameters, like the model studied in this paper, the problem is much more complex. The most largely used methods for structural identifiability are [3, 4]:

a) *Taylor series expansion*
b) *Generating series*
c) *Local state isomorphism*
d) *Transformation of nonlinear models*
e) *Lyapunov based observer analysis*

One way to analyse the structural identifiability is to transform the nonlinear model into a model linear in parameters, and then look at the identifiability of the linear model. In the following we propose the utilisation of the test functions from distribution theory to transform the nonlinear models from biotechnology into linear in parameters models.

3.2 Distributions based method for structural identifiability analysis

In this approach the set of nonlinear differential equations describing the state evolution is mapped into a set of linear algebraic equations respect to the model parameters. Using techniques utilized in distribution approach, the measurable functions and their derivatives are represented by functionals on a fundamental space of testing functions. The main advantages of this method are that a set of algebraic equation with real coefficients results and the formulations are free from boundary conditions.

If Φ_n is the fundamental space from the distribution theory [16], of the real functions $\varphi : R \to R,\ t \to \varphi(t)$. Let $q : R \to R, t \to q(t)$ be a function which admits a Riemann integral on any compact interval T from **R**. Using this function, a unique distribution

$$F_q : \Phi_n \to R, \varphi \to F_q(\varphi) \in R \tag{18}$$

can be build by the relation:

$$F_q(\varphi) = \int_R q(t)\varphi(t)dt, \forall \varphi \in \Phi_n \tag{19}$$

In distribution theory, the notion of k-order derivative is introduced. If $F_q \in \Phi_n$, then its k-order derivative is a new distribution $F_q^{(k)} \in \Phi_n$ uniquely defined by the relations:

$$F_q^{(k)}(\varphi) = (-1)^k F_q(\varphi^{(k)}),\ \forall \varphi \in \Phi_n \tag{20}$$

$$\varphi \to F_q^{(k)}(\varphi) = (-1)^k \int_R q(t)\varphi^{(k)}(t)dt \in R \tag{21}$$

where

$$\varphi^{(k)} : R \to R,\ t \to \varphi^{(k)}(t) = \frac{d^k\varphi(t)}{dt^k} \tag{22}$$

is the k-order time derivative of the testing function.

When $q \in C^k(R)$, then

$$F_q^{(k)}(\varphi) = \int_R q^{(k)}(t)\varphi(t)dt = (-1)^k \int_R q(t)\varphi^{(k)}(t)dt, \tag{23}$$

that means the k-order derivative of a distribution generated by a function $q \in C^k(R)$ equals to the distribution generated by the k-order time derivative of the function q.

So, in place of the states and their time derivatives of a system one utilize the corresponding distributions and, in some particular cases, it is possible to obtain a system of equations linear in parameters. If the system is compatible then all the model parameters are structurally identifiable.

This method can be used also for testing the structural identifiability of linear systems described by differential equations.

4 Structural Identifiability Analysis of a Wastewater Biodegradation Process

Consider all state variable accessible for measurements. The dynamical system (11)-17 contains rational dependences between parameters and measured variables. To obtain linear equations in unknown parameters, the identifiability analysis problem is split in several simpler problems.

Based on the specific structure of this system, it is possible to group the state equations, in such way to determine five interconnected relations [15]. They are organized in a hierarchical structure. In the first stage some state equations are utilized to obtain a set of linear equations in some parameters. If this parameters are identifiable then they can be used as known parameters in the following stages. This process is repeated in the other stages until all the parameters are verified.

Stage 1. *Identifiability analysis of* θ_1

Substituting expression Φ_1 from (11) into (13) we obtain:

$$\left(-\dot{\xi}_2 - u_3\xi_2 + u_1 \cdot u_3\right) = \left(\dot{\xi}_1 + u_3\xi_1\right)\cdot \theta_1 \tag{24}$$

that is linear in parameter θ_1. Multiplying both sides of relation (24) with test functions $\varphi_i(t) \in \Phi_n$ and integrating over R one get a system of linear equations in respect with parameter θ_1:

$$F_v(\varphi) = \theta_1 F_{w_1}(\varphi) \tag{25}$$

$$F_{w_1}(\varphi) = \int_R [\xi_1(t)]\cdot\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_1(t)]\varphi^{(0)}(t)dt \tag{26}$$

$$F_v = \int_R [\xi_2(t)]\varphi^{(1)}(t)dt + \int_R [-u_3(t)\cdot\xi_2(t)]\varphi^{(0)}(t)dt + \int_R [u_1(t)\cdot u_3(t)]\varphi^{(0)}(t)dt \tag{27}$$

Hence, the parameter θ_1 is identifiable.

Stage 2. *Identifiability analysis of* θ_5 *and* θ_7

Considering known $\theta_1 = \hat{\theta}_1$ from *Stage 1*, and substituting (12), equation (13) becomes,

$$F_v(\varphi) = \theta_5 F_{w_1}(\varphi) + \theta_7 F_{w_2}(\varphi) \tag{28}$$

$$\dot{\xi}_2 = -\hat{\theta}_1 \cdot \theta_5 \cdot \frac{\xi_1 \cdot \xi_2}{\theta_7 + \xi_2} - u_3 \cdot \xi_2 + u_1 \cdot u_3 \tag{29}$$

or

$$\begin{aligned}&(-\dot{\xi}_2 \cdot \xi_2 - u_3 \cdot \xi_2^2 + u_1 \cdot u_3 \cdot \xi_2) = \\ &(\xi_1 \cdot \xi_2 \cdot \hat{\theta}_1)\cdot\theta_5 + (\dot{\xi}_2 + u_3\cdot\xi_2 - u_1\cdot u_3)\cdot\theta_7\end{aligned} \tag{30}$$

that is linear in parameters θ_5 and θ_7. Multiplying both sides of relation (30) with test functions $\varphi_i(t) \in \Phi_n$ and integrating over R one get a system of linear equations in respect with parameters θ_5 and θ_7:

$$F_{w1}(\varphi) = \int_R [\xi_1(t)\cdot\xi_2(t)\cdot\hat{\theta}_1]\varphi^{(0)}(t)dt \tag{31}$$

$$F_{w_2}(\varphi) = \int_R [-\xi_2(t)]\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_2(t)]\varphi^{(0)}(t)dt - \int_R [u_1(t)\cdot u_3(t)]\varphi^{(0)}(t)dt \tag{32}$$

$$F_v(\varphi) = \int_R [-\frac{1}{2}\xi_2^2(t)]\varphi^{(1)}(t)dt + \int_R [-u_3(t)\cdot\xi_2^2(t)]\varphi^{(0)}(t)dt + \int_R [u_1(t)\cdot u_3(t)\cdot\xi_2]\varphi^{(0)}(t)dt \tag{33}$$

Consequently, parameters θ_5 and θ_7 are identifiable.

Stage 3. *Identifiability analysis of* θ_2 *and* θ_3

Considering known $\theta_5 = \hat{\theta}_5$ and $\theta_7 = \hat{\theta}_7$ from *Stage 2,* the estimated expression $\hat{\Phi}_1$ of the rational Φ_1 is

$$\hat{\Phi}_1(t) = \hat{\theta}_5 \cdot \frac{\xi_1(t)\cdot\xi_2(t)}{\hat{\theta}_7 + \xi_2(t)} \tag{34}$$

Substituting expression Φ_2 from (14) and (32) instead of Φ_1 into (16) one obtain,

$$\dot{\xi}_4 + u_3\cdot\xi_4 = \theta_2\cdot\hat{\Phi}_1 - \theta_3\cdot[\dot{\xi}_3 + u_3\cdot\xi_3] \tag{35}$$

that is linear in parameters θ_2 and θ_3. Multiplying both sides of relation (33) with test functions

$\varphi_i(t) \in \Phi_n$ and integrating over R one get a system of linear equations in respect with parameters θ_2 and θ_3:

$$F_v(\varphi) = \theta_2 F_{w_1}(\varphi) + \theta_3 F_{w_2}(\varphi) \quad (36)$$

$$F_{w_1}(\varphi) = \int_R [\hat{\Phi}_1(t)]\varphi^{(0)}(t)dt$$

$$F_{w_2}(\varphi) = \int_R [-\xi_3(t)]\varphi^{(1)}(t)dt + \int_R [-u_3(t)\cdot\xi_3(t)]\varphi^{(0)}(t)dt$$

$$F_v(\varphi) = \int_R [-\xi_4(t)]\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_4(t)]\varphi^{(0)}(t)dt$$

Consequently, parameters θ_2 and θ_3 are identifiable.

Stage 4. *Identifiability analysis of* θ_6, θ_8 *and* θ_9'

Considering known $\theta_2 = \hat{\theta}_2$ and $\theta_3 = \hat{\theta}_3$ from *Stage 3,* and substituting (15) in (16) where Φ_1 is replaced by $\hat{\Phi}_1$ one obtain,

$$\dot{\xi}_4 = \theta_2 \cdot \hat{\Phi}_1 - \hat{\theta}_3 \cdot \theta_6 \cdot \frac{\xi_3 \cdot \xi_4}{\theta_8 + \xi_4 + \theta_9' \cdot \xi_4^2} - u_3 \cdot \xi_4 \quad (37)$$

or

$$(\xi_4 \cdot \dot{\xi}_4 + u_3 \cdot \xi_4^2 - \hat{\theta}_2 \cdot \hat{\Phi}_1 \cdot \xi_4) = (\xi_3 \cdot \xi_4 \cdot \hat{\theta}_3) \cdot \theta_6 + (\dot{\xi}_4 + u_3 \cdot \xi_4 - \hat{\theta}_2 \cdot \hat{\Phi}_1) \cdot \theta_8 + (\xi_4^2 \cdot \dot{\xi}_4 + u_3 \cdot \xi_4^3 - \hat{\theta}_2 \cdot \hat{\Phi}_1 \cdot \xi_4^2) \cdot \theta_9' \quad (38)$$

that is linear in parameters θ_6, θ_8 and θ_9'.

Multiplying both sides of relation (38) with test functions $\varphi_i(t) \in \Phi_n$ and integrating over R one get a system of linear equations in respect with parameters θ_6, θ_8 and θ_9':

$$F_v(\varphi) = \theta_6 F_{w_1}(\varphi) + \theta_8 F_{w_2}(\varphi) + \theta_9' F_{w_2}(\varphi) \quad (39)$$

$$F_{w_1}(\varphi) = \int_R [\xi_3(t)\cdot\xi_4(t)\cdot\hat{\theta}_3(t)]\varphi^{(0)}(t)dt \quad (40)$$

$$F_{w_2}(\varphi) = \int_R [\xi_4(t)]\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_4(t)]\varphi^{(0)}(t)dt + \int_R [-\hat{\theta}_2(t)\cdot\hat{\Phi}_1(t)]\varphi^{(0)}(t)dt \quad (41)$$

$$F_{w_3}(\varphi) = \int_R [\frac{1}{3}\xi_4^3(t)]\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_4^3(t)]\varphi^{(0)}(t)dt + \int_R [-\hat{\theta}_2(t)\cdot\hat{\Phi}_1(t)\cdot\xi_4^2(t)]\varphi^{(0)}(t)dt \quad (42)$$

$$F_v(\varphi) = \int_R [-\frac{1}{2}\xi_4^2(t)]\varphi^{(1)}(t)dt + \int_R [-u_3(t)\cdot\xi_4^2(t)]\varphi^{(0)}(t)dt + \int_R [\hat{\theta}_2(t)\cdot\hat{\Phi}_1(t)\cdot\xi_4(t)]\varphi^{(0)}(t)dt \quad (43)$$

Consequently, parameters θ_6, θ_8 and θ_9' are identifiable.

Stage 5. *Identifiability analysis of* θ_4

Considering known $\theta_6 = \hat{\theta}_6$, $\theta_8 = \hat{\theta}_8$ and $\theta_9' = \hat{\theta}_9'$ from *Stage 4,* the estimated expression $\hat{\Phi}_2$ of the rational Φ_2 is

$$\hat{\Phi}_2 = \hat{\theta}_6 \cdot \frac{\xi_3 \cdot \xi_4}{\hat{\theta}_8 + \xi_4 + \hat{\theta}_9' \cdot \xi_4^2} \quad (44)$$

Substituting expression (40) instead of Φ_2 into (17), one get,

$$\dot{\xi}_5 = -u_3 \cdot \xi_5 + \theta_4 \cdot \hat{\Phi}_2 - u_2 \quad (45)$$

or

$$(\dot{\xi}_5 + u_3 \cdot \xi_5 + u_2) = (\hat{\Phi}_2) \cdot \theta_4 \quad (46)$$

that is linear in parameter θ_4. Multiplying both sides of relation (46) with test functions $\varphi_i(t) \in \Phi_n$ and integrating over R one get a system of linear equations in respect with parameter θ_4:

$$F_v(\varphi) = \theta_4 F_{w_1}(\varphi) \quad (47)$$

$$F_{w_1}(\varphi) = \int_R [\hat{\Phi}_2(t)]\varphi^{(0)}(t)dt \quad (48)$$

$$F_v(\varphi) = \int_R [\xi_5(t)]\varphi^{(1)}(t)dt + \int_R [u_3(t)\cdot\xi_5(t)]\varphi^{(0)}(t)dt + \int_R [u_2(t)]\varphi^{(0)}(t)dt \quad (49)$$

Hence, the parameter θ_4 is identifiable.

6 Conclusions

In this paper we presented a novel approach for nonlinear continuous-time model structural identifiability analysis. The method can be included in the *transformation of nonlinear models* framework of structural identifiability analysis and is based on test functions from distribution theory.

So, the nonlinear continuous-time models are transformed in linear in parameters models by replacing the state variables and their derivatives with corresponding functionals obtained using distributions. Depending on particular cases, the problem is split in many sub-problems interconnected, the results of one stage of analysis being used to the next stages. The presented method is applied to analyse the structural identifiability of a wastewater biodegradation process, considering that the unknown parameters appear in rational relations with measured variables. The structural identifiability analysis is performed in five stages. In every stage the nonlinear differential equation is transformed into an algebraic equation linear in model parameters. Using the functionals defined by distribution theory, one obtains a system of linear equations in model parameters. If one parameter is structural identifiable then it is used as a known parameter for analysis to the next stages.

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