

# Monitoring Biological Modes in a Bioreactor Process by Computer Simulation

Samia Semcheddine<sup>1\*</sup>, Abdel Aitouche<sup>2</sup>

<sup>1</sup>Electronic Department, Faculty of Technology  
University of Setif UN1901  
Cit  Maabouda, Route de B jaia 19000, Algeria  
E-mail: [tssamia@yahoo.fr](mailto:tssamia@yahoo.fr)

<sup>2</sup>CRISTAL UMR CNRS 9189, HEI  
13 rue de Toul, 59046 Lille Cedex, France  
E-mail: [abdel.aitouche@hei.fr](mailto:abdel.aitouche@hei.fr)

\*Corresponding author

Received: June 22, 2015

Accepted: November 09, 2015

Published: December 22, 2015

**Abstract:** This paper deals with the general framework of fermentation system modeling and monitoring, focusing on the fermentation of *Escherichia coli*. Our main objective is to develop an algorithm for the online detection of acetate production during the culture of recombinant proteins. The analysis the fermentation process shows that it behaves like a hybrid dynamic system with commutation (since it can be represented by 5 nonlinear models). We present a strategy of fault detection based on residual generation for detecting the different actual biological modes. The residual generation is based on nonlinear analytical redundancy relations. The simulation results show that the several modes that are occulted during the bacteria cultivation can be detected by residuals using a nonlinear dynamic model and a reduced instrumentation.

**Keywords:** Monitoring, Fault detection, Residual generation, Biological modes, *Escherichia coli*.

## Introduction

Genetically modified organisms are increasingly used in the pharmaceutical industry. *Escherichia coli*, or *E. coli*, is still one of the most important host organisms used in the pharmaceutical industry for producing recombinant proteins [2, 4, 12]. This paper aims to explore the possibility of monitoring changes in the metabolism of the *E. coli* during the fed-batch culture process [3]. Roeva and Tzonkov [9] used a heuristic procedure that employed dissolved oxygen probe measurements to distinguish two modes: acetate production or non-production by *E. coli*. This information is used to drive the feeding rate, and the global procedure is called *probing control*. A deeper analysis of the model used by [3] and [12] leads to five different metabolisms, which represent the modes of the *E. coli* cultivation.

One of the objectives of this paper is to identify the actual mode, including the modes related to acetate production, using reduced instrumentation. Our strategy is to reduce the acetate production, dealing with approaches based on Fault Detection (FD). Those methods aim to discover whether or not a fault is occurring in a monitored system (detection). FD consists of comparing a reference behavior with the current behavior, observed via controls and measurement values. Several approaches can be used to perform this comparison. Eliminating internal variables to obtain an input-output representation of the monitored system can be achieved by projections into parity space both in the linear case [6] and in the nonlinear case

[5]. Other approaches can be used, for example, observer-based approaches that reconstruct the process outputs, which are then compared to system measurements [7, 8].

All model-based fault detection methods have to generate residuals between the real behavior and the expected behavior, and some form of redundancy is needed to generate residuals. There are two types of redundancies: hardware redundancy and analytical redundancy. Hardware Redundancy (HR) using redundant sensors, for example has been applied in critical systems. Analytical Redundancy (AR) is obtained through a set of algebraic or differential relationships. The essence of AR in fault detection is to check the consistency of the real system behavior against the expected behavior of the system model. In this study, differential relationships were obtained using different sensor outputs and actuator inputs, and the residuals of these relationships were tested to identify the actual biological mode.

The contributions of this paper are:

- To detect biological modes by using approach of analytical redundancy instead of methods based on active control.
- This approach can be used to reduce the formation of acetate.
- The performances of the proposed approach are shown using the software Matlab – Simulink.

The paper is organized as follows. Section 2 provides a short description of the fed-batch fermentation process, which presents the hybrid structure of the process. Section 3 reports the results of our simulations using a nonlinear process model. Section 4 explains the concept of residual generation used to detect the actual biological mode, and Section 5 deals with the detection process applied to acetate production. Section 6 offers our conclusions and our perspectives for future research.

## Process description

The fed-batch fermentation process considered in this study involves a genetically-modified *E. coli* strain that is cultivated in a bioreactor by using a probing control of fed batch cultivations [3], by modeling *E. coli* using acetate inhibition [9]. The liquid medium contains cells and the substrates that are needed for the cell growth and production. The feed is used to control the substrate concentration. Air is transferred into the liquid in order to supply the culture with oxygen, with a mechanical stirrer agitating the liquid to insure that the air is well mixed with the liquid. A stirrer speed  $N$  is used to control oxygen transfer rate. Temperature and pH are maintained within operating conditions. Cell metabolism is described by the specific rates of growth, glucose uptake, oxygen uptake and net acetate production [4]. The model equations include these rates derived from mass balance in the liquid medium are:

$$\left\{ \begin{array}{l} \frac{dX}{dt} = \mu(G, A)X - \frac{F}{V}X \\ \frac{dG}{dt} = \frac{F}{V}G_{in} - \frac{F}{V}G - q_g(G)X \\ \frac{dC_o}{dt} = K_{La}(N)(C_o^* - C_o) - \frac{F}{V}C_o - q_o(G, A)X \\ \frac{dA}{dt} = q_a(G, A)X - \frac{F}{V}A \end{array} \right. \quad (1)$$

where  $V$ ,  $X$ ,  $G$ ,  $A$ , and  $C_o$  are respectively the liquid volume, the cell concentration, the glucose concentration, the acetate concentration and the dissolved oxygen concentration;  $F$ ,  $G_{in}$  and  $C_o^*$  denote respectively the feed rate, the glucose concentration in the feed, and the dissolved oxygen concentration in equilibrium with the oxygen in gas bubbles; and  $K_{La}$  is the volumetric oxygen transfer coefficient.  $V$  represents the volume variation.

In practice, most sensors do not measure the oxygen concentration but the dissolved oxygen tension, which is related to the dissolved oxygen concentration through Henry's law:

$$O = HC_o$$

where  $O$  is the oxygen concentration and  $H$  is Henry's constant and its value is  $14 \times 10^3$  (l%/g),  $O^*$  is the equilibrium dissolved oxygen tension and its value is 100%.

As mentioned in the last paragraph, cell metabolism is described by the specific rates of growth  $\mu$ , glucose uptake  $q_g$ , oxygen uptake  $q_o$  and net acetate production  $q_a$  [3]. The volumetric oxygen transfer coefficient  $K_{La}$  depends on the stirrer speed  $N$  and was approximated using the following linear expression [1].

$$K_{La}(N) = \alpha(N - N_0) \quad (2)$$

For the 3-liter laboratory bioreactor,  $\alpha = 0.95 \text{ h}^{-1} \cdot \text{rpm}$  and  $N_0 = 323 \text{ rpm}$  give a good approximation for stirrer speeds between 400 rpm to 1200 rpm. These values were obtained using the  $K_{La}$  estimation technique suggested by [1].

The model given in System (1) depends on the specific rates mentioned above. The specific rate of growth  $\mu$  is given by:

$$\mu = \begin{cases} (q_g - q_m)Y_{xg}^{ox} + q_a^c Y_{xa} & \text{if } q_g \leq q_g^{crit} \\ (q_g^{crit} - q_m)Y_{xg}^{ox} + (q_g - q_g^{crit})Y_{xg}^{fe} & \text{if } q_g > q_g^{crit} \end{cases} \quad (3)$$

where  $Y_{xg}^{ox}$  is the oxidative biomass/glucose yield and its value is 0.51 g/g,  $Y_{xg}^{fe}$  is the fermentative biomass/glucose yield and its value is 0.15 g/g,  $Y_{xa}$  is the biomass/acetate yield and its value is 0.40 g/g,  $q_g^{crit}$  is the critical specific glucose uptake rate and its value is 0.63 g/(gh).

The glucose consumed by the cells provides energy and raw material for the cell growth. The specific glucose uptake rate  $q_g$  is assumed to be Monod-type:

$$q_g(G) = q_g^{max} \frac{G}{k_s + G} \quad (4)$$

where  $q_g^{max}$  is the maximum specific glucose uptake rate and its value is 1.0 g/(gh),  $k_s$  is the saturation constant for glucose and its value is 0.01 g/l.

A part of the glucose uptake  $q_g$  is assumed to be required for the non-growth associated to maintenance. This is modeled by the flux,  $q_m = \min(q_g, q_{mc})$ , where  $q_{mc}$  is the maintenance coefficient and its value is 0.06 g/(gh).

The oxygen uptake  $q_o$  is given by:

$$q_o = \begin{cases} (q_g - q_m)Y_{og} + q_m Y_{om} + q_a^c Y_{oa} & \text{if } q_g \leq q_g^{crit} \\ q_o^{max} = (q_g^{crit} - q_m)Y_{og} + q_m Y_{om} & \text{if } q_g > q_g^{crit} \end{cases} \quad (5)$$

where  $Y_{og}$  is the oxygen/glucose yield for growth and its value is 0.50 g/g,  $Y_{om}$  is the oxygen/glucose yield for maintenance and its value is 1.07 g/g,  $Y_{oa}$  is the oxygen/acetate yield and its value is 0.55 g/g.

The net acetate production is expressed by  $q_a = q_a^p - q_a^c$ , where  $q_a^p$  and  $q_a^c$  denote respectively acetate production and consumption. The mathematical expression used for  $q_a^c$  is:

$$q_a^c = \begin{cases} \min \left\{ q_a^{c,pot}, \frac{(q_o^{max} - (q_g - q_m)Y_{og} - q_m Y_{om})}{Y_{oa}} \right\} & \text{if } q_g \leq q_g^{crit} \\ 0 & \text{if } q_g > q_g^{crit} \end{cases} \quad (6)$$

where

$$q_a^{c,pot} = \frac{q_a^{c,max} A}{k_a + A} \quad (7)$$

$q_o^{max}$  represents the maximum specific oxygen uptake rate and its value is 0.35 g/(gh),  $q_a^{c,max}$  represents the maximum specific acetate consumption rate and its value is 0.20 g/(gh),  $k_a$  is the saturation constant for acetate uptake and its value is 0.05 g/l.

The mathematical expression used for  $q_a^p$  is:

$$q_a^p = \begin{cases} (q_g - q_g^{crit})Y_{ag} & \text{if } q_g > q_g^{crit} \\ 0 & \text{if } q_g \leq q_g^{crit} \end{cases} \quad (8)$$

$Y_{ag}$  designs acetate/glucose yield and its value is 0.55 g/g.

The metabolic relations show that the fed-batch fermentation process is a system with autonomous commutation, making it a hybrid dynamic system. According to the metabolic relations cited above, there are two modes. The first mode corresponds to  $q_g > q_g^{crit}$  and is denoted “mode I”; the second mode corresponds to  $q_g \leq q_g^{crit}$  and is denoted “mode II”.

Fig. 1 shows the different situations that can arise in an *E. coli* culture, with one case for mode I and four cases for mode II.

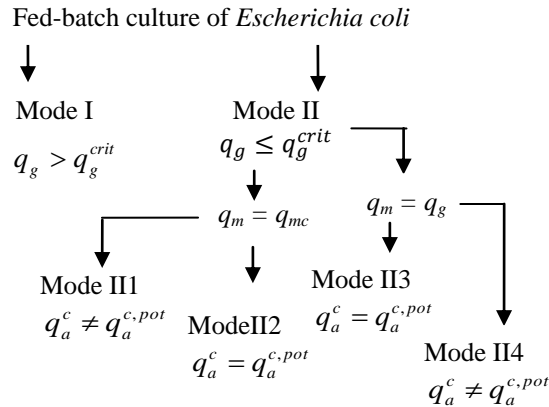


Fig. 1 The different situations those can arise in an *E. coli* culture

### Simulation of the process

We simulated a dynamic model of glucose overflow in fed-batch fermentation of *E. coli* under fully aerobic conditions. The parameter used in this simulation for  $G_{in}$  is 60 g/l. The initial values were:  $V(0) = 2.5$  l,  $G(0) = 10$  g/l,  $X(0) = 10$  g/l,  $A(0) = 0$  g/l and  $O(0) = 30\%$ . The Fig. 2 shows how we have chosen  $F$ . Our simulation results with the proposed model are shown in Fig. 3, Fig. 4 and Fig. 5. Fig. 3 shows that the fermentation process passes through 5 steps. We can interpret the first three phases from Fig. 4 and Fig. 5.

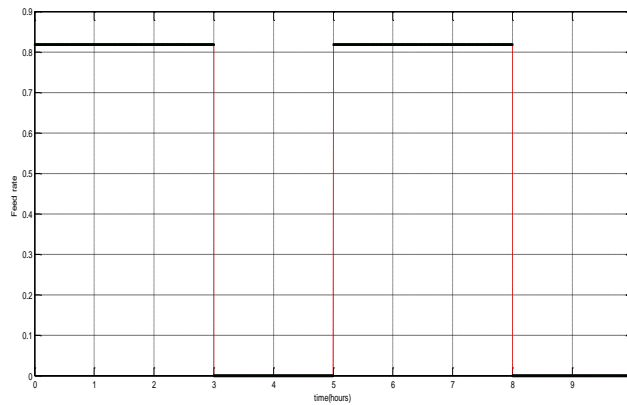


Fig. 2 Feed rate

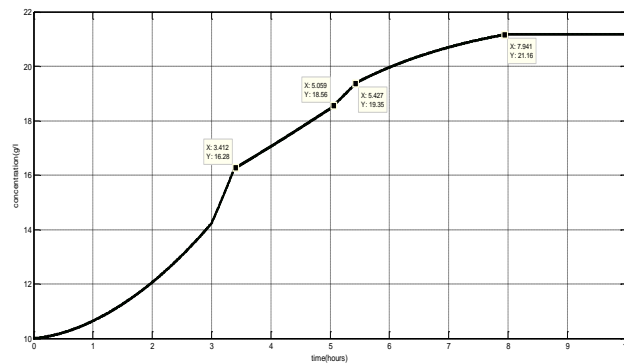


Fig. 3 Biomass concentration

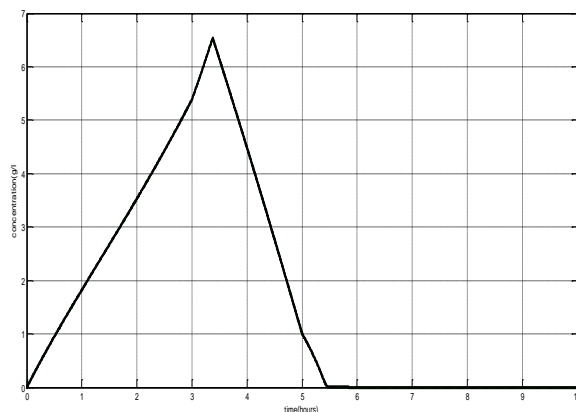


Fig. 4 Acetate concentration

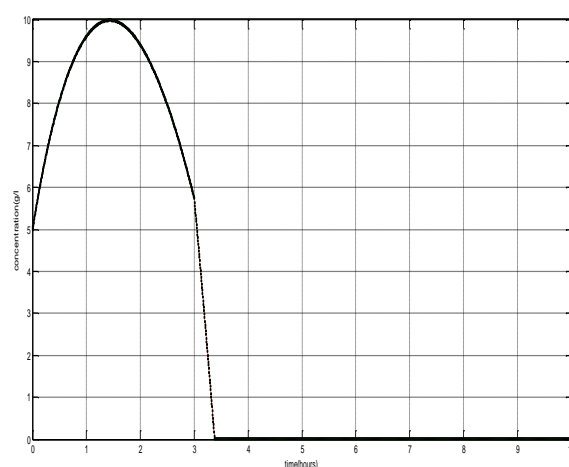


Fig. 5 Glucose concentration

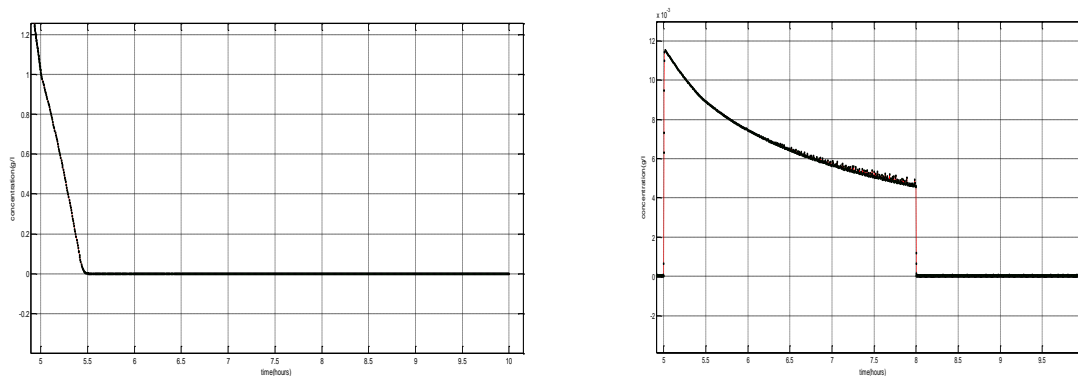


Fig. 6 Acetate and glucose concentration after 5 h

The supplied glucose leads to acetate production and good cell development (i.e., the biomass increases exponentially); when the glucose has been completely consumed, the biomass consumes the acetate to remain living, which leads to poor cell development. At about 5 h,  $F$  is different of zero (Fig. 2) and therefore, the cell consumes glucose. The Fig. 4 also shows that at this moment, the slope of the acetate concentration curve increases slightly what proves that the presence of glucose leads to the production of acetate. But the curve remains decreasing what proves that the cell consumes acetate.

To interpret the last two phases, we must show Fig. 6 that describes acetate and glucose concentration after 5 h.

When acetate is completely consumed, the biomass consumes glucose only; when acetate and glucose are completely consumed, the biomass stops developing.

The question that could be asked is at what mode is the process as was noted in the description of the hybrid dynamic system? The answer to this question is given in the following section, which presents residual generation as a method for detecting the modes of a biological system.

### Residual generation

The method of residual generation is often used to detect the failure in automated systems. From a system model, it is possible to generate signals, called residuals, which are theoretically close to zero under normal operating conditions and not equal to zero when a failure occurs. Residuals can be also used in the context of a dynamic process whose evolution passes through several modes.

The evaluation procedure for redundancy relations given by the system model is based on elimination theory [10]. Two sensors are used to measure the glucose concentration ( $G$ ) and the acetate concentration ( $A$ ). In this case, the biomass  $X$  is deduced by using the second equation in the System (1), yielding:

$$\hat{X} = \frac{k_s + G}{q_g^{max} G} \left( \frac{F}{V} G_{in} - \frac{F}{V} G - \frac{dG}{dt} \right) \quad (9)$$

Then, the biomass  $X$  can be estimated by measuring the glucose concentration  $G$ .

The redundancy relations can also be obtained using the system model, by eliminating the unknown variables in the model equations. Without losing the generality of this paper, we will show how the biomass residual can be obtained using the first equation of the System (1):

$$rX = \frac{d\hat{X}}{dt} - \mu(G, A)\hat{X} + \frac{F}{V}\hat{X} \quad (10)$$

In Fig. 1, the metabolic relation is replaced by its different expressions, or modes. There are 5 modes, thus 5 residuals related to the estimated biomass, for example:  $rIX$  denotes a residual of mode I (acetate production) related to the biomass:  $r$  related to residual,  $I$  related to mode I and  $X$  related to biomass.

$$\left\{ \begin{array}{l}
 rIX = \frac{d\hat{X}}{dt} - (q_g^{crit} - q_{mc}) Y_{xg}^{ox} \hat{X} - \left( q_g^{max} \frac{G}{k_s + G} - q_g^{crit} \right) Y_{xg}^{fe} \hat{X} \\
 rII1X = \frac{d\hat{X}}{dt} + \frac{F}{V} \hat{X} - \left( q_g^{max} \frac{G}{k_s + G} - q_{mc} \right) Y_{xg}^{ox} \hat{X} \\
 rII2X = \frac{d\hat{X}}{dt} + \frac{F}{V} \hat{X} - \left( q_g^{max} \frac{G}{k_s + G} - q_{mc} \right) Y_{xg}^{ox} \hat{X} - \frac{q_a^{c,max} A}{k_a + A} Y_{xa} \hat{X} \\
 rII3X = \frac{d\hat{X}}{dt} - \left( q_a^{c,max} \frac{A}{k_a + A} - \frac{F}{V} \right) \hat{X} \\
 rII4X = \frac{d\hat{X}}{dt} + \frac{F}{V} \hat{X} - \left( q_o^{max} - q_g^{max} \frac{G}{k_s + G} \right) Y_{oa}^{xa} \hat{X}
 \end{array} \right. \quad (11)$$

Similarly, using the last equation in the System (1), the acetate residual can be obtained:

$$rA = \frac{dA}{dt} - q_a(G, A) \hat{X} + \frac{F}{V} A \quad (12)$$

The acetate residual can thus be obtained for each mode. The expressions of these 5 residuals are given by the following equations:

$$\left\{ \begin{array}{l}
 rIA = \frac{dA}{dt} - \left( q_g^{max} \frac{G}{k_s + G} - q_g^{crit} \right) \hat{X} + \frac{F}{V} A \\
 rII1A = \frac{dA}{dt} - \frac{q_o^{max} - \left( q_g^{max} \frac{G}{k_s + G} - q_{mc} \right) Y_{og}}{Y_{oa}} \hat{X} + \frac{q_{mc} \hat{Y}_{om}}{Y_{oa}} \hat{X} + \frac{F}{V} A \\
 rII2A = \frac{dA}{dt} + q_a^{c,max} \frac{A}{k_a + A} \hat{X} + \frac{F}{V} A \\
 rII3A = \frac{dA}{dt} + q_a^{c,max} \frac{A}{k_a + A} \hat{X} + \frac{F}{V} A \\
 rII4A = \frac{dA}{dt} - \frac{q_o^{max} - \left( q_g^{max} \frac{G}{k_s + G} Y_{om} \right)}{Y_{oa}} \hat{X} + \frac{F}{V} A
 \end{array} \right. \quad (13)$$

The Fig. 7 to Fig. 11 show the evolution of each mode's residuals. The left-hand side of these figures shows the evolution of residuals related to the estimated biomass concentration and the right-hand side of these figures shows the evolution of residuals related to the acetate concentration. Fig. 7 shows that the 2 mode I residuals are null until 3.4 hours. This mode corresponds to acetate production (see Fig. 4).



Fig. 8 shows that, after 3.4 hours, the 2 mode II3 residuals are null for a period which lasts until 5 hours, which corresponds to the acetate consumption. This consumption can be correlated with the decrease of acetate concentration (see Fig. 4).

Fig. 9 shows that, after 5 hours, the 2 mode II1 residuals are null for a period of less than half hour, which corresponds to the acetate consumption. This consumption can be correlated with the decrease of acetate concentration (see Fig. 4). In this mode, the acetate consumption related to goes to zero due to the lack of acetate. At the end of the fermentation process, mode II2 is active; the 2 residuals are null from 5.4 hours until 7.9 hours.

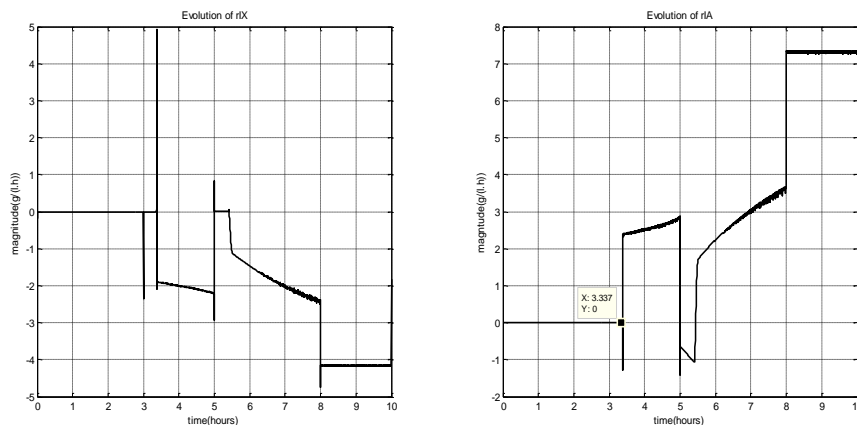


Fig. 7 Mode I residuals

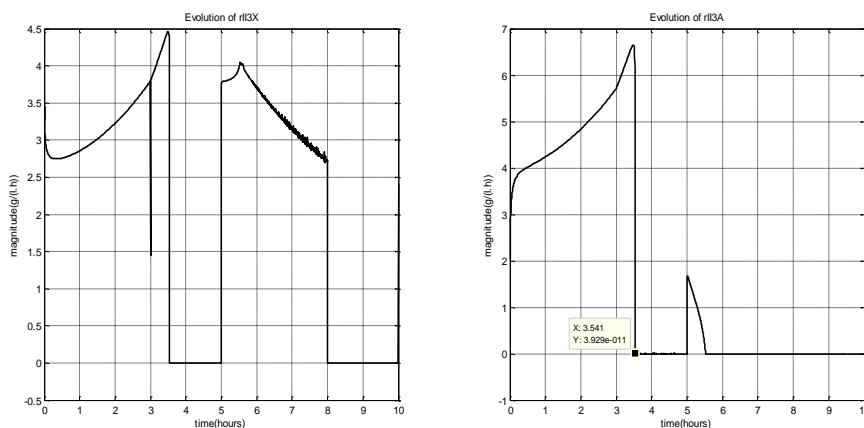


Fig. 8 Mode II3 residuals

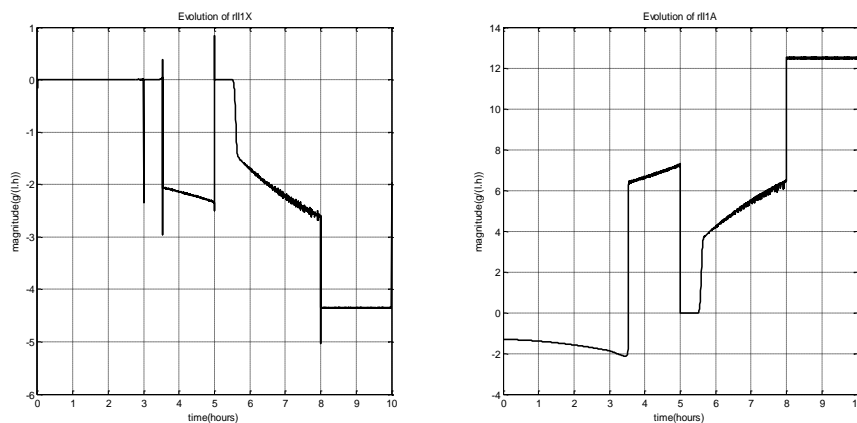


Fig. 9 Mode II1 residuals

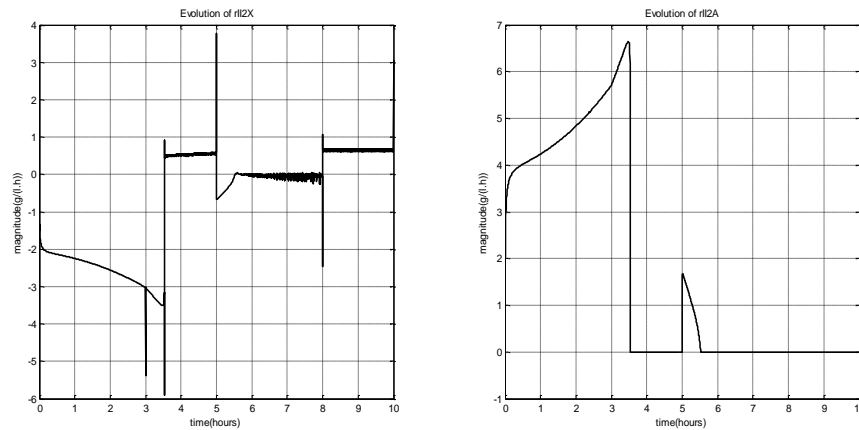


Fig. 10 Mode II2 residuals

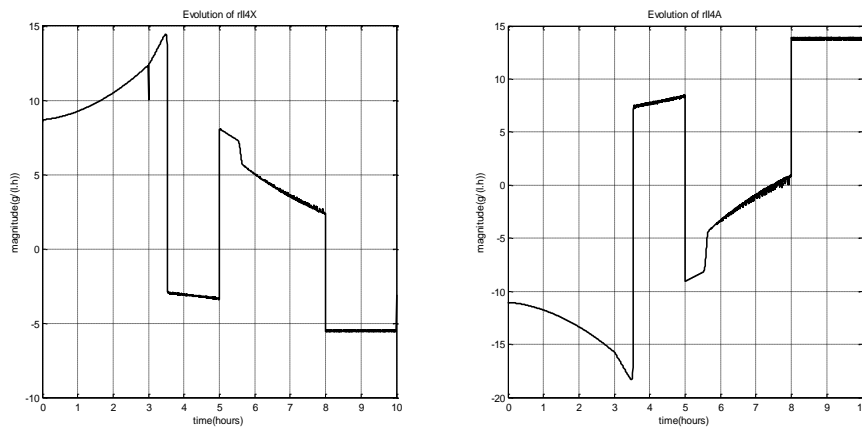


Fig. 11 Mode II4 residuals

The 2 residuals are null from 5.4 hours until 8 hours (Fig. 8), mode II2 is active. In this mode, the glucose is limited, and acetate is no longer available.

Thus, the evolution of the mode II4 residuals (Fig. 11) is never close to zero. Thus, we can conclude that this mode is not reached by the process. We can also conclude that the simulation results shown in Fig. 7, Fig. 8, Fig. 9, Fig. 10, and Fig. 11 do not correspond to the results summarized in Fig. 1. To understand these phenomena, we must analyze the evolution of the specific glucose uptake and the acetate consumption, shown in Fig. 12.

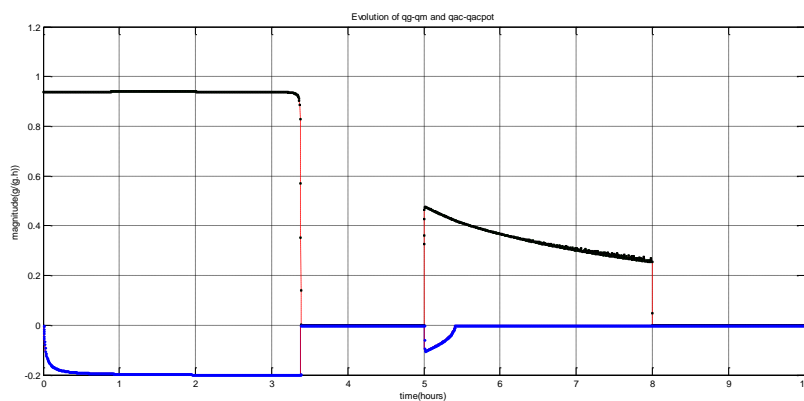


Fig. 12 Evolution of  $q_g - q_m$  and  $q_a^c - q_a^{c,pot}$  over time

Fig. 12 shows the temporal evolution of  $q_g - q_m$  and  $q_a^c - q_a^{c,pot}$ . In Fig. 1, the mode II4 is reached when  $q_g - q_m$  is equal to zero and  $q_a^c - q_a^{c,pot}$  is different to zero. But Fig. 12 shows that when temporal evolution of  $q_g - q_m$  is nul then  $q_a^c - q_a^{c,pot}$  is also null. The metabolic reaction does not fire modeII4. Thus, the residuals relating to this case is never null, as can be seen in Fig. 11. We deduced that the process does not really reach mode II4. We can thus conclude that the residual generation method can detect all the operating modes of the process, but only the modes represented in the Fig. 13 can be used.

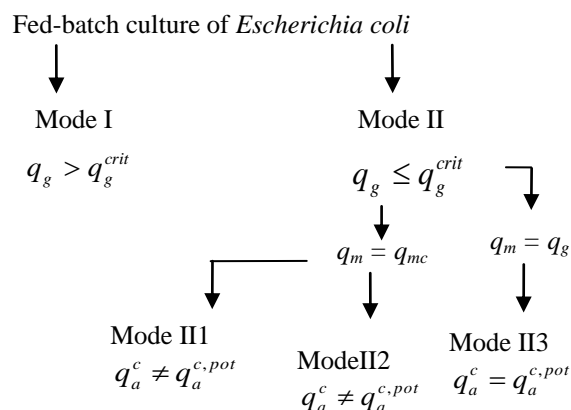


Fig. 13 Various modes by which really the process passes

### Detection of the acetate production mode

Acetate accumulation has been reported to inhibit growth and to reduce recombinant protein production. Thus, the interest of detecting this mode is quite obvious. In this section, we report the results of our experiments for detecting acetate production in a fed-batch culture of *E. coli*.

According to the metabolic relations described above, there are two modes: the first mode corresponds to  $q_g > q_g^{crit}$  and is denoted “mode I”; the second mode corresponds to  $q_g \leq q_g^{crit}$  and is denoted “mode II”.

*E. coli* excretes acetate only when the specific glucose uptake rate exceeds the critical rate (see Fig. 14), corresponding to a maximum respiration rate. The specific oxygen uptake rate  $q_o$  was initially fairly constant because  $q_g > q_g^{crit}$  so, according to Eq. (8),  $q_o = q_o^{max}$ , but declined gradually as acetate accumulated.

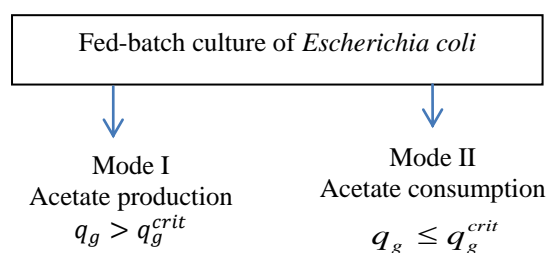


Fig. 14 Modes related to acetate production and acetate production

Two sensors were used to measure  $X$  and  $C_o$ .  $q_o$  was deduced using the last equation in System (1), yielding:

$$q_o(G, A) = \frac{K_{La}(C_o^* - C_o) - \frac{F}{V}C_o - \frac{dC_o}{dt}}{X} \quad (14)$$

Fig. 15 represents the simulation of the residual generation, which can be expressed by the following equation

$$r = q_o^{max} - q_o(G, A) \quad (15)$$

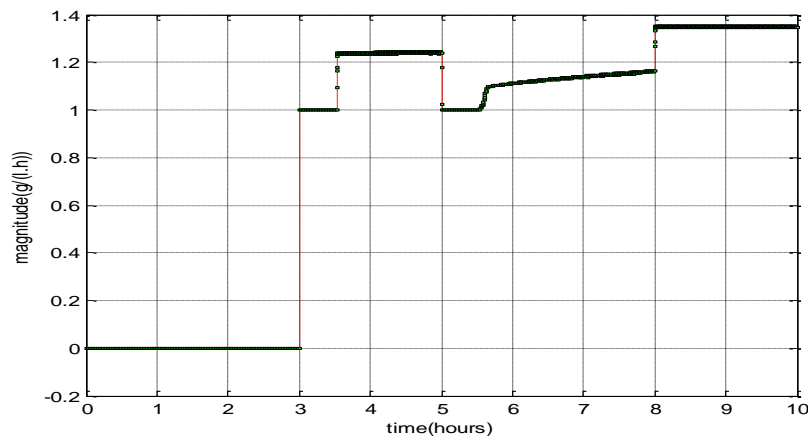


Fig. 15 Residuals related to acetate production detection

Fig. 15 shows that the acetate residual is null before 3 h. This residual was calculated from the available measurements, has to be close to zero when acetate production is detected. Compared to Fig. 15, our simulation results show that we can detect acetate production during the beginning of fermentation of a bacterium.

## Conclusion

In the process of *E. coli* cultivation, which is a hybrid dynamic system, it is important to detect which kind of mode is active in the process in order to control it. Through our simulation results, this paper shows how the several modes that occur during the fermentation of bacteria can be detected (or not be detected) from the residuals generated from the nonlinear dynamic model of this process and a reduced instrumentation.

We first analyzed the process behavior, which shows that the process is a hybrid dynamic system with autonomous commutation. After this, we detect the different system modes. In order to detect the different modes, we used 2 sensors corresponding to acetate production and glucose uptake, and we showed that biomass, glucose and acetate can be estimated. We also showed that the residuals obtained, using the analytical redundancy approach, are able to detect the different process modes. Our results confirmed that the process reaches only four modes (acetate production, acetate consumption, acetate and glucose consumption and no acetate consumption) instead of all 5 modes. We also determined the exact period of the acetate production mode and the exact time that it takes place, which allows us to control the process.

For future research, we plan to investigate other detection approaches, such as the nonlinear observer approach. In order to reduce the cost of instrumentation, the idea is to use only one sensor, with which we have proved that the system remains observable: oxygen sensor. Indeed, this oxygen sensor is cheap and guarantees the sterility of environment.

## References

1. Aitouche A., B. Ould-Bouamama (2010). Sensor Location with Respect to Fault Tolerance Properties, *International Journal of Automation and Control*, 4(3), 298-316.
2. Akesson M., P. Hagander (1999). A Gain-scheduling Approach for Control of Dissolved Oxygen in Stirred Bioreactors, In: *Preprints 14th world congress of IFAC*, Chen et al. (Eds.), Vol. O, 505-510.
3. Akesson M., P. Hagander, J. P. Axelsson (2001). Probing Control of Fed-batch Cultivations: Analysis and Tuning, *Control Engineering Practice*, 9, 709-723.
4. Bastin G., D. Dochain (1990). *On-line Estimation and Adaptive Control of Bioreactors*, Amsterdam, New York, Elsevier.
5. Bouibed K., A. Aitouche, M. Bayart (2009). Nonlinear Parity Space Applied to an Autonomous Vehicle, *Journal of Energy and Power Engineering*, 3(12), 10-18.
6. Chow E. Y., A. S. Willsky(1984). Analytical Redundancy and the Design of Robust Failure Detection, *IEEE Transactions on Automatic Control*, 29(4), 603-615.
7. Edwards C., S. K. Spurgeon, R. J. Patton (2000). Sliding Mode Observers for Fault Detection and Isolation, *Automatica*, 36, 541-553.
8. Hammouri H., M. Kinnaert, E. H. El-Yaagoubi (1999). Observer-based Approach to Fault Detection and Isolation for Nonlinear Systems, *IEEE Transactions on Automatic Control*, 44(10), 1879-1884.
9. Roeva O., S. Tzonkov (2006). Modelling of *Escherichia coli* Cultivations: Acetate Inhibition in a Fed-batch Culture, *International Journal of Bioautomation*, 4, 1-11.
10. Semcheddine S., A. Aitouche, J. P. Cassar (2006). Detecting Modes in Fed-batch Fermented Process. Application to *Escherichia coli* Cultivations, *IMACS Multiconference on Computational Engineering in Systems Applications*, 1, 858-863.
11. Vant'Riet K. (1979). Review of Measuring Methods and Results in Nonviscous Gas-liquid Mass Transfer in Stirred Vessels, *Industrial and Engineering Chemistry Process Design and Development*, 18(3), 357-364.
12. Xu B., M. Jahic, S. O. Enfors (1999). Modeling of Overflow Metabolism in Batch and Fed-batch Cultures of *Escherichia coli*, *Biotechnology Progress*, 15(1), 81-90.

**Assist. Prof. Samia Semcheddine, Ph.D. Student**E-mail: [tssamia@yahoo.fr](mailto:tssamia@yahoo.fr)

Samia Semcheddine was born on November 26, 1968 in Sétif, Algeria. She graduated from University of Sétif, Algeria in 2007. She became an Assistant Professor in the Department of Electronics at the University of Sétif, Algeria in 1998. She is currently a Ph.D. Student in Department of Electronics where she teaches course “Automatic Materials”. Her research focuses on biotechnology.

**Abdel Aitouche, Ph.D.**E-mail: [abdel.aitouche@hei.fr](mailto:abdel.aitouche@hei.fr)

Abdel Aitouche was born in Algiers and he received his diploma of Engineer in Supelec (France) in 1980 in Electrotechnique. He joined SONELEC in 1980 and the Institute Algerian of Petroleum from 1983 to 1987. He got his Ph.D. Thesis in University of Nancy I in 1990 in the field of Automation. Abdel Aitouche was a lecturer in Hautes Etudes d’Ingenieur de Lille, France (Graduate School of Engineering) since 1991. Since 2009 he is a Professor. Abdel Aitouche is a Searcher at “Center of Research in Informatics, Signal and Automation of Lille”. His scientific interests are in the field of systems nonlinear control, fault tolerant control, model based fault detection and diagnosis. Their application domains are mainly intelligent systems, embedded systems, biotechnology, process engineering, combustion engine, fuel cells and renewable energy (wind, PV).