Developments in Fuzzy Sets, Intuitionistic Fuzzy Sets, Generalized Nets and Related Topics. Volume I: Foundations

Developments in Fuzzy Sets, Intuitionistic Fuzzy Sets, Generalized Nets and Related Topics Volume II: Applications

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Systems Research Institute
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Generalized net model of an advisory system for on-line control of yeast fed-batch cultivation

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Abstract

The apparatus of Generalized Nets (GN) is here applied to a description of an advisory system for on-line control of yeast fed-batch cultivation. The advisory system has been built over the preliminary developed system for functional state recognition, both elaborated using EpiData – free software for entering and documenting data. Developed here GN model could advise the user which new functional state can be reached and what kind of control actions have to be taken. The advisory system and its GN model appear as an expert system, comprising knowledge of well-trained operators of cultivation processes. Developed GN model of the advisory system is here applied to a fed-batch cultivation of *Saccharomyces cerevisiae*.

Keywords: generalized nets, fed-batch process, functional states, advisory system, on-line control.

1 Introduction

In contemporary biotechnology there is an obvious need of improved process control and optimization. An important step for process optimization and high-quality control is the development of adequate models. Fermentation processes are characterized by a complicated structure of organization and interdependent characteristics, which determine their non-linearity and non-stationary properties. These processes are known to be very complex and their modelling may be a rather time consuming task. Many mathematical models of fermentation processes have been proposed [5, 10, 21] but just a few have been

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used to optimize industrial plants. The common modelling approach is the development of an overall nonlinear model of fermentation process that performs satisfactorily through the entire operating range. Unfortunately, this approach has a lot of disadvantages. Complex global models are characterized with a big number of parameters, which complicate the model identification and simulation. Moreover, the global model is not able to describe the metabolic changes during the entire operating range and the parameter non-stationary. As an alternative, an increasingly popular multiple-model approach, and in particular – functional state modelling approach can be applied to cope with strongly nonlinear and time-varying systems [4÷6, 9, 12, 14, 20, 22, 23]. Using this approach complicated problems are decomposed into subproblems that can be solved independently. Then the individual solutions of the decomposed problems lead to the global solution of the complex problem. Functional state modelling approach is an appropriate tool for monitoring and control of complex processes such as fermentation processes [5, 6, 12, 14, 20, 22, 23]. The process is decomposed into different stages giving a simplified and transparent nonlinear model. When using functional state modelling approach, the step of the recognition of current functional state is an important task for development of an adequate model. Next, based on the current recognized functional state, advices for the further process control could be disposed to the users. Up to now GN have been used as a tool for the modeling of parallel processes in several areas [1÷3] – economics, transport, medicine, computer technologies, and so on. The apparatus of GN has been successfully applied to modeling and control of fermentation processes [15÷19, 21]. The theory of GN permits on-line tracking of all process variables, included in the GN model, which cannot be done when the process is described with differential equations [21]. The use of the GN for the description of cultivation processes affords the opportunities for on-line control, for searching optimal conditions for the fermentation, for process of learning on the basis of experimental data and for control on the basis of expert systems. An advisory (expert) system for on-line control of a fed-batch cultivation of *S. cerevisiae* has been developed [13]. The present work is devoted to the description of this advisory system using the apparatus of GN.

2 Functional states modelling approach to S. cerevisiae fed-batch cultivation

The main idea of the functional state modelling approach is that the process is divided into macrostates, called *functional states* (FS), according to behavioural equivalence. In each FS the yeast metabolism is dominated by certain metabolic pathways. Based on a lot of investigations, Zhang et al. [22, 23] have supposed that the whole yeast growth process can be divided into at least five functional states in batch and fed-batch cultures (Table 1).

Table 1

Functional state	**Rules for recognition**
first ethanol production state (FS I)	$S > S_{crit}$ and $O_2 > O_{2crit}$
mixed oxidative state (FS II)	$S \leq S_{crit}$, $O_2 \geq O_{2crit}$ and $E > 0$
complete sugar oxidative state (FS III)	$S \leq S_{crit}$, $O_2 \geq O_{2crit}$ and $E = 0$
ethanol consumption state (FS IV)	$S = 0$ and $O_2 \geq O_{2crit}$
second ethanol production state (FS V)	$S \leq S_{crit}$, $O_2 < O_{2crit}$ and $E > 0$

In Table 1 S denotes substrate concentration [g/l], E – ethanol concentration [g/l], and O_2 –dissolved oxygen concentration [%]. Subscript *crit* is used for their critical levels.

A yeast growth process switches from one functional state to another when the metabolic conditions are changed. The functional state diagram of the process can be illustrated as it is shown in Fig. 1 [22, 23].

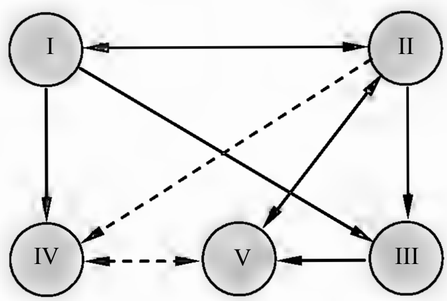

Figure 1: Functional state diagram

In principle FS I can appear in all batch, fed-batch and continuous yeast growth processes. FS IV normally appears only in batch culture. The functional states FS II, FS III and FS V are normally found in fed-batch and continuous cultures [22, 23]. The solid arrows in Fig. 1 indicate the necessary or normal transition between various functional states of the process. The dotted arrows indicate that the transitions take place when the mode of culture changes between batch and fed-batch cultures. It should be noted that the fermentation process could be only in one functional state at any time. However, a certain functional state can appear in the process more than once during one run.

3 GN model of an advisory system for on-line control of S. cerevisiae fed-batch cultivation

The design of the advisory system for on-line control of a fed-batch cultivation of *S. cerevisiae* [13] is based on the preliminary developed system for recognition of functional states during a fermentation process [11]. As a test set a fed-batch cultivation of *S. cerevisiae* as considered in [11] and performed in the *Institute of Technical Chemistry, University of Hannover, Germany* has been used. The functional states recognition system is built on the rules for recognition, described in Table 1, and it is learned in such way to recognize all five FS, although not all of them appear during the test data set. Further, all five functional states, with some explanations and possible control actions, are consequently presented.

If the recognition system identifies that the process is in *first ethanol production state* (FS I), the advisory system responds as shown in Fig. 2. Additionally, a part of GN model, described the possibilities for switching from this FS to another, is presented for each of recognized FS (Figs. 2 to 6). Dotted lines present "a whole picture" of the possible transitions. Further, when the whole GN model of the advisory system is presented, all "parts of GN model" from Figs. 2 to 6 are combined for a common description.

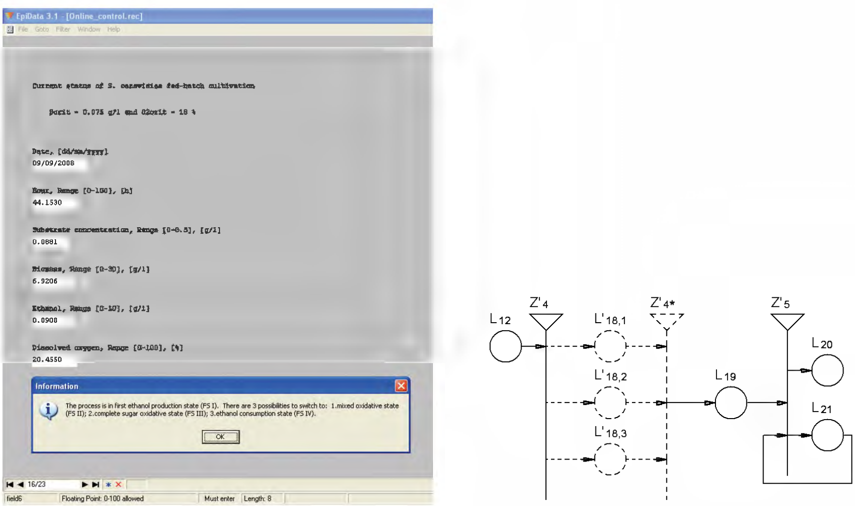

Figure 2: Advisory system and a part of GN model at *first ethanol production state* (FS I)

If the user likes to switch the process to another functional state, dissolved oxygen has to be kept to be sufficient and substrate concentration has to be decreased to be equal to or below the critical level. Then:

- If there is ethanol in the broth, the process can be switched to *mixed oxidative state* (FS II).
- If there is no ethanol in the broth, the process can be switched to *complete sugar oxidative state* (FS III).
- If there is no substrate in the broth, the process can be switched to *ethanol consumption state* (FS IV).

If the recognition system identifies that the process is in *mixed oxidative state* (FS II), the advisory system responds as shown in Fig. 3.

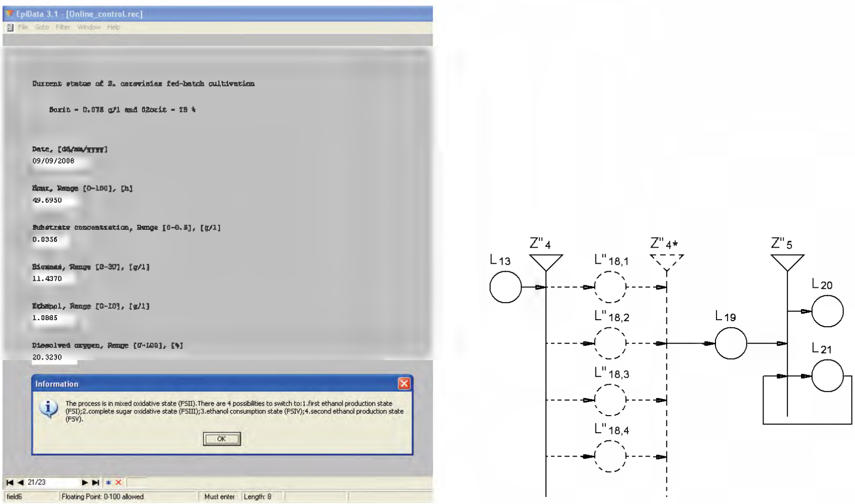

Figure 3: Advisory system and a part of GN model
at *mixed oxidative state* (FS II)

Following control actions have to be taken:

- If the user likes to switch the process to *complete sugar oxidative state* (FS III), substrate concentration has to be kept to be equal to or below the critical level, sufficient dissolved oxygen has to be kept and ethanol should not be available in the broth.
- If the user likes to switch the process to *first ethanol production state* (FS I), sufficient dissolved oxygen has to be kept and the culture has to be fed so substrate concentration to be increased above the critical level.
- If the user likes to switch the process to *second ethanol production state* (FS V), substrate concentration has to be kept to be equal to or below the

critical level, but dissolved oxygen has to be decreased below the critical level.

- If the process accidentally switches from fed-batch to batch mode – to *ethanol consumption state* (FS IV, shown with dotted arrows in Fig. 1), sufficient dissolved oxygen has to be kept, but substrate should not be available in the broth.

If the recognition system identifies that the process is in *complete sugar oxidative state* (FS III), the advisory system responds as shown in Fig. 4. There is only one possibility the process to be switched to another functional state, namely to *second ethanol production state* (FS V). Aiming that substrate concentration has to be kept to be equal to or below the critical level, but dissolved oxygen has to be decreased below the critical level. Also, ethanol should be available in the broth.

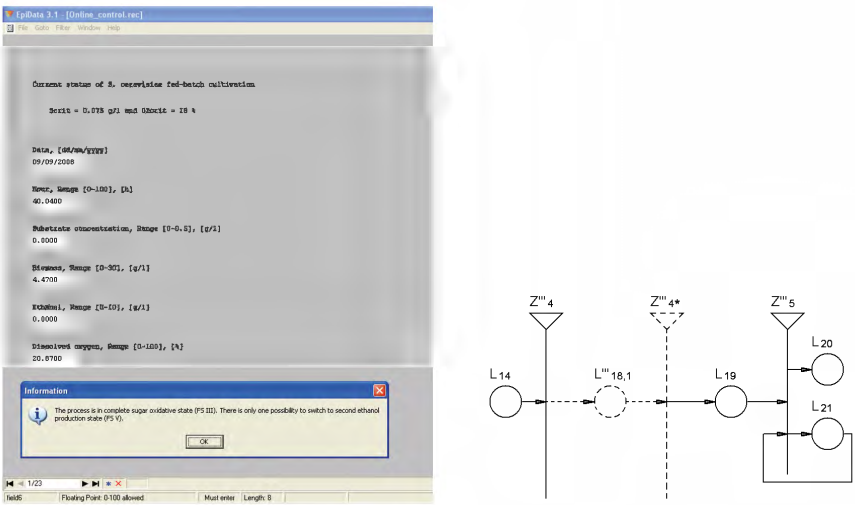

Figure 4: Advisory system and a part of GN model at *complete sugar oxidative state* (FS III)

If the recognition system identifies that the process is in *ethanol consumption state* (FS IV), the advisory system responds as shown in Fig. 5. FS IV normally appears only in batch culture. But if the process accidentally switches from fed-batch to batch mode (FS IV), there is only one possibility the process to be switched to another functional state, namely to *second ethanol production state* (FS V). Aiming that substrate concentration has to be increased, but to be equal to or below the critical level, and dissolved oxygen has to be decreased below the critical level. Also, ethanol should be available in the broth.

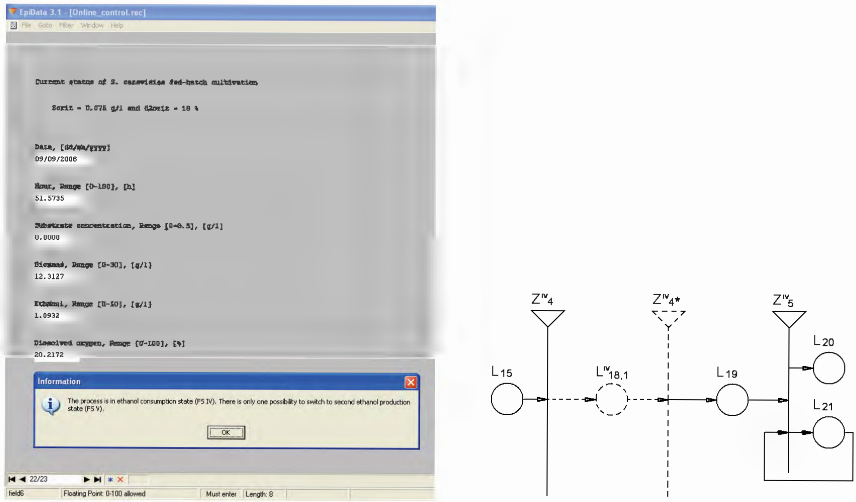

Figure 5: Advisory system and a part of GN model
at *ethanol consumption state* (FS IV)

If the recognition system identifies that the process is in *second ethanol production state* (FS V), the advisory system responds as shown in Fig. 6.

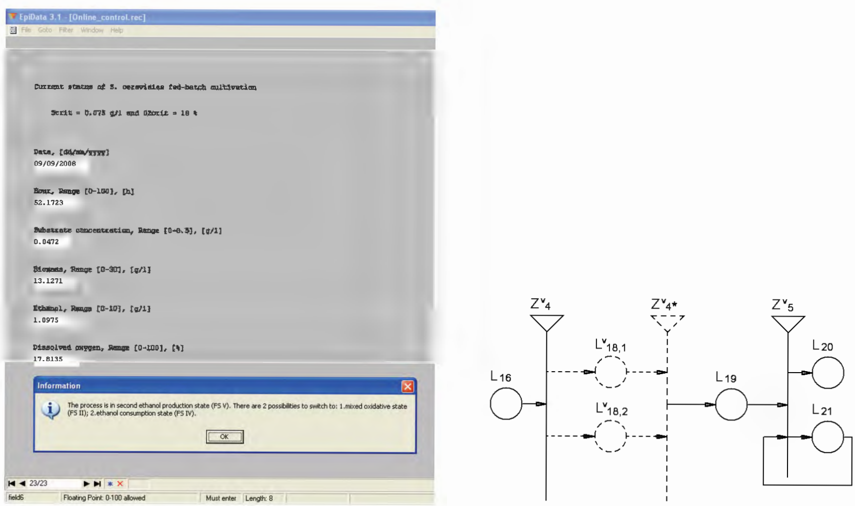

Figure 6: Advisory system and a part of GN model
if the process is in *second ethanol production state* (FS V)

- There is only one possibility the process to be switched to another functional state, namely to *mixed oxidative state* (FS II). Substrate concentration has to be kept to be equal to or below the critical level, but sufficient dissolved oxygen has to be supplied in order the concentration to become above the critical level. Also, ethanol should be available in the broth.

- There is a possibility the process accidentally to switch to batch mode – namely to *ethanol consumption state* (FS IV). For that purpose substrate should not be available in the broth but sufficient dissolved oxygen has to be supplied in order the concentration to become above the critical level.

A GN model described the presented above advisory system for on-line control of yeast fed-batch cultivation is developed here (Fig. 7). This model is based on the GN model for functional state recognition, developed for *E. coli* fed-batch cultivation [16] and on the proved analogies between the yeast and *E. coli* metabolisms [14]. Presented GN model describes one more FS compared to [16], as well as it has been designed as an expert system which to be able to advise the user which new functional state can be reached and what kind of control actions have to be taken.

The token α enters GN in place L_1 with a characteristic "initial concentration of biomass, substrate, ethanol, dissolved oxygen and volume". The token β enters GN in place L_2 with an initial characteristic "flow rate (feeding of the process)". This token obtains characteristics "concentration of substrate added to the bioreactor" in place L_3 and "amount of the feeding solution in storage" in place L_4. The form of the first transition of the GN model is as follows:

$$Z_1 = <\{L_2, L_4\}, \{L_3, L_4\}, r_1, \vee(L_2, L_4)>$$

$$r_1 = \begin{array}{c|cc} & L_3 & L_4 \\ \hline L_2 & false & true \\ L_4 & W_{4,3} & true \end{array}$$

where $W_{4,3}$ is "need of substrate concentration change, dependent on the value in place L_5".

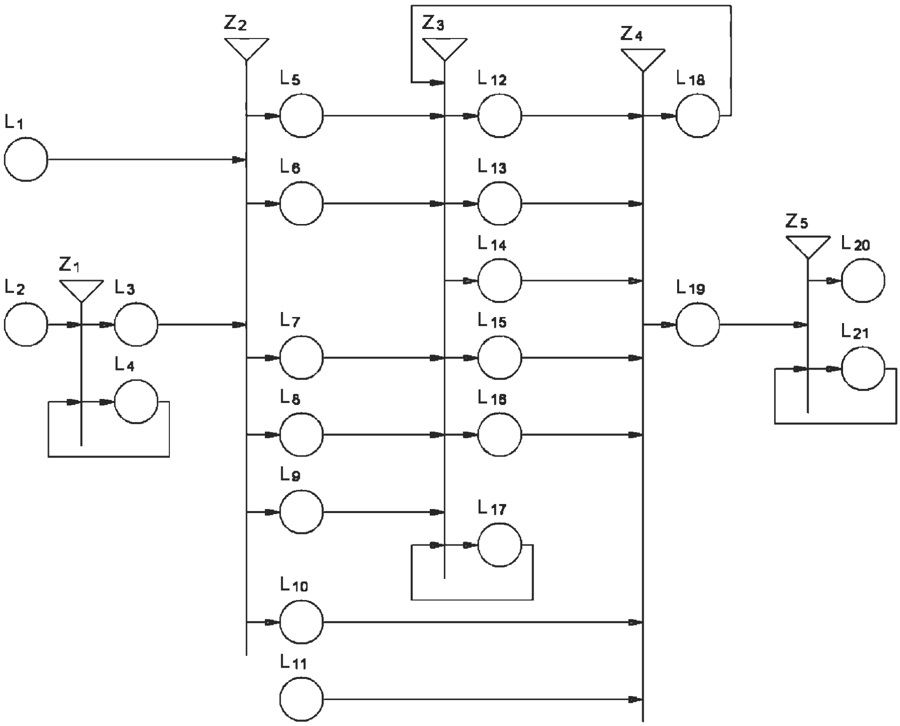

Figure 7: GN model of an advisory system for on-line control of yeast fed-batch process

The tokens α and β are combined into a new token γ, which is immediately split into five tokens $\gamma_1 \div \gamma_5$, obtaining the following characteristics:

- γ_1 in place L_5 – "substrate concentration in the bioreactor";
- γ_2 in place L_6 – "dissolved oxygen concentration in the bioreactor";
- γ_3 in place L_7 – "ethanol concentration in the bioreactor";
- γ_4 in place L_8 – "biomass concentration in the bioreactor";
- γ_5 in place L_9 – "bioreactor volume".

The token β obtains a new characteristic in place L_{10}, namely "current value of the flow rate". A new token δ enters GN in place L_{11} with a characteristic "aeration of the medium".

The form of the second transition of the GN model is as follows:

$$Z_2 = <\{L_1, L_3\},\ \{L_5, L_6, L_7, L_8, L_9, L_{10}\}, r_2, \wedge(L_1, L_3) >,$$

		L_5	L_6	L_7	L_8	L_9	L_{10}
$r_2 =$	L_1	*true*	*true*	*true*	*true*	*true*	*true*
	L_3	*true*	*true*	*true*	*true*	*true*	*true*

The form of the third transition of the GN model is as follows:

$$Z_3 = <\{L_5, L_6, L_7, L_8, L_9\}, \{L_{12}, L_{13}, L_{14}, L_{15}, L_{16}, L_{17}\}, r_3, \wedge(L_5, L_6, L_7, L_8, L_9) >$$

		L_{12}	L_{13}	L_{14}	L_{15}	L_{16}	L_{17}
$r_3 =$	L_5	$W_{5,12}$	$W_{5,13}$	$W_{5,14}$	$W_{5,15}$	$W_{5,16}$	*true*
	L_6	$W_{6,12}$	$W_{6,13}$	$W_{6,14}$	$W_{6,15}$	$W_{6,16}$	*true*
	L_7	*true*	$W_{7,13}$	$W_{7,14}$	*true*	$W_{7,16}$	*true*
	L_8	*false*	*false*	*false*	*false*	*false*	*true*
	L_9	*false*	*false*	*false*	*false*	*false*	*true*

where $W_{5,12}$ is "$S > S_{crit}$"; $W_{5,13}$, $W_{5,14}$ and $W_{5,16}$ are "$S \leq S_{crit}$"; $W_{5,15}$ is "$S = 0$"; $W_{6,12}$ is "$O_2 > O_{2crit}$"; $W_{6,13}$, $W_{6,14}$ and $W_{6,15}$ are "$O_2 \geq O_{2crit}$"; $W_{6,16}$ is "$O_2 < O_{2crit}$"; $W_{7,13}$ and $W_{7,16}$ are "$E > 0$" and $W_{7,14}$ is "$E = 0$".

The tokens γ_1, γ_2 and γ_3 are combined in a new token σ, which obtains the following characteristics:

- in place L_{12} – "*first ethanol production state* (FS I)";
- in place L_{13} – "*mixed oxidative state* (FS II)";
- in place L_{14} – "*complete sugar oxidative state* (FS III)";
- in place L_{15} – "*ethanol consumption state* (FS IV)";
- in place L_{16} – "*second ethanol production state* (FS V)";
- in place L_{17} – "concentration of biomass, substrate, ethanol, dissolved oxygen and volume".

The form of the fourth transition of the GN model is as follows:

$$Z_4 = <\{L_{10}, L_{11}, L_{12}, L_{13}, L_{14}, L_{15}, L_{16}, L_{17}\}, \{L_{18}, L_{19}\}, r_4, \wedge(L_{11}, L_{17}), \vee(L_{12}, L_{13}, L_{14}, L_{15}, L_{16})>$$

	L_{18}	L_{19}
$r_4 =$ L_{10}	*true*	*false*
L_{11}	*true*	*false*
L_{12}	$W_{12,18}$	$W_{12,19}$
L_{13}	$W_{13,18}$	$W_{13,19}$
L_{14}	$W_{14,18}$	$W_{14,19}$
L_{15}	$W_{15,18}$	$W_{15,19}$
L_{16}	$W_{16,18}$	$W_{16,19}$
L_{17}	$W_{17,18}$	$W_{17,19}$

where $W_{1i,18}$, (i = 2÷7) is "there is still feeding solution in place L_4", and $W_{1i,19}$, (i = 2÷7) = $\neg$ $W_{1i,18}$.

The token σ obtains the following characteristics in place L_{18}:

- if the token has been in place L_{12} with a characteristic "*first ethanol production state* (FS I)" and:
  - the user likes to switch the process to *mixed oxidative state* (FS II), the $W_{12,18}^{II}$ is "the feeding in place L_{10} has to be decreased in such way to reach $S \leq S_{crit}$, dissolved oxygen has to be kept $O_2 \geq O_{2crit}$ and ethanol should be available in place L_7"; the token will obtain a new characteristic "*mixed oxidative state* (FS II)" and will appear in place L_{13} in the next cycle;
  - the user likes to switch the process to *complete sugar oxidative state* (FS III), the $W_{12,18}^{III}$ is "the feeding in place L_{10} has to be decreased in such way to reach $S \leq S_{crit}$, dissolved oxygen has to be kept $O_2 \geq O_{2crit}$ and ethanol should not be available in place L_7"; the token will obtain a new characteristic "*complete sugar oxidative state* (FS III)" and will appear in place L_{14} in the next cycle;
  - the user likes to switch the process to *ethanol consumption state* (FS IV), the $W_{12,18}^{IV}$ is "substrate should not be available in place L_5 (caused by lack of feeding solution in place L_4 or very fast growth of the yeast), and dissolved oxygen has to be kept $O_2 \geq O_{2crit}$"; the token will obtain a new characteristic "*ethanol consumption state* (FS IV)" and will appear in place L_{15} in the next cycle. The process switches to batch mode.

- if the token has been in place L_{13} with a characteristic "*mixed oxidative state* (FS II)" and:
  - the user likes to switch the process to *first ethanol production state* (FS I), the $W^{I}_{13,18}$ is "the feeding in place L_{10} has to be increased in such way to reach $S > S_{crit}$ and dissolved oxygen has to be kept $O_2 > O_{2crit}$"; the token will obtain a new characteristic "*first ethanol production state* (FS I)" and will appear in place L_{12} in the next cycle;
  - the user likes to switch the process to *complete sugar oxidative state* (FS III), the $W^{III}_{13,18}$ is "ethanol should not be available in place L_7, substrate has to be kept $S \leq S_{crit}$ and dissolved oxygen has to be kept $O_2 \geq O_{2crit}$"; the token will obtain a new characteristic "*complete sugar oxidative state* (FS III)" and will appear in place L_{14} in the next cycle;
  - the user likes to switch the process to *ethanol consumption state* (FS IV), the $W^{IV}_{13,18}$ is "substrate should not be available in place L_5 (caused by lack of feeding solution in place L_4 or very fast growth of the yeast), and dissolved oxygen has to be kept $O_2 \geq O_{2crit}$"; the token will obtain a new characteristic "*ethanol consumption state* (FS IV)" and will appear in place L_{15} in the next cycle; the process switches to batch mode;
  - the user likes to switch the process to *second ethanol production state* (FS V), the $W^{V}_{13,18}$ is "substrate has to be kept $S \leq S_{crit}$, the aeration in place L_{11} has to be decreased in such way to reach $O_2 < O_{2crit}$ and ethanol should be available in place L_7"; the token will obtain a new characteristic "*second ethanol production state* (FS V)" and will appear in place L_{16} in the next cycle.
- if the token has been in place L_{14} with a characteristic "*complete sugar oxidative state* (FS III)" and:
  - the user likes to switch the process to *second ethanol production state* (FS V), the $W^{V}_{14,18}$ is "substrate has to be kept $S \leq S_{crit}$, ethanol should be available in place L_7 and the aeration in place L_{11} has to be decreased in such way to reach $O_2 < O_{2crit}$"; the token will obtain a new characteristic "*second ethanol production state* (FS V)" and will appear in place L_{16} in the next cycle.
- if the token has been in place L_{15} with a characteristic "*ethanol consumption state* (FS IV)" and:
  - the user likes to switch the process to *second ethanol production state* (FS V), the $W^{V}_{15,18}$ is "the feeding in place L_{10} has to be increased, but to be kept $S \leq S_{crit}$, the aeration in place L_{11} has to be decreased in such

way to reach $O_2 < O_{2crit}$ and ethanol should be available in place L_7"; the token will obtain a new characteristic "*second ethanol production state* (FS V)" and will appear in place L_{16} in the next cycle.

- if the token has been in place L_{16} with a characteristic "*second ethanol production state* (FS V)" and:
  - the user likes to switch the process to *mixed oxidative state* (FS II), the $W^{II}_{16,18}$ is "substrate has to be kept $S \le S_{crit}$, the aeration in place L_{11} has to be increased in such way to reach $O_2 \ge O_{2crit}$ and ethanol should be available in place L_7"; the token will obtain a new characteristic "*mixed oxidative state* (FS II)" and will appear in place L_{13} in the next cycle;
  - the user likes to switch the process to *ethanol consumption state* (FS IV), the $W^{IV}_{16,18}$ is "substrate should not be available in place L_5 (caused by lack of feeding solution in place L_4 or very fast growth of the yeast) and the aeration in place L_{11} has to be increased in such way to reach $O_2 \ge O_{2crit}$"; the token will obtain a new characteristic "*ethanol consumption state* (FS IV)" and will appear in place L_{15} in the next cycle. The process switches to batch mode.

Developed and presented here GN model advises the user for the possibilities which new functional state can be reached and what kind of control actions have to be taken in each of all possible five functional states.

4 Conclusion

GN model of an advisory system for on-line control of yeast fed-batch cultivation is here developed based on preliminary designed system for recognition of functional states during the cultivation and the advisory system for the process on-line control. The advisory system and its GN description appear as an expert system, comprising knowledge for metabolic changes during the cultivation processes. GN model of the advisory system is further demonstrated for a fed-batch cultivation of *S. cerevisiae*. In all reported five functional states the user is advised for the possibilities which new functional state can be reached and what kind of control actions have to be taken. Such advisory system could be exceptionally useful if it is implemented in the automated control equipment of bioreactor. In the same time the applied controllers have to permit implementation of process knowledge [8, 22] or to be a controller with variable structure allowing taking into account the model changes during the process [7]. Thus designed advisory system and its GN model could be of a high efficiency for on-line control and optimal carrying out of cultivation processes.

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The papers presented in this Volume 2 constitute a collection of contributions, both of a foundational and applied type, by both well-known experts and young researchers in various fields of broadly perceived intelligent systems.
It may be viewed as a result of fruitful discussions held during the Eighth International Workshop on Intuitionistic Fuzzy Sets and Generalized Nets (IWIFSGN-2009) organized in Warsaw on October 16, 2009 by the Systems Research Institute, Polish Academy of Sciences, in Warsaw, Poland, Centre for Biomedical Engineering, Bulgarian Academy of Sciences in Sofia, Bulgaria, and WIT – Warsaw School of Information Technology in Warsaw, Poland, and co-organized by: the Matej Bel University, Banska Bistrica, Slovakia, Universidad Publica de Navarra, Pamplona, Spain, Universidade de Tras-Os-Montes e Alto Douro, Vila Real, Portugal, and the University of Westminster, Harrow, UK:

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The Eighth International Workshop on Intuitionistic Fuzzy Sets and Generalized Nets (IWIFSGN-2009) has been meant to commence a new series of scientific events primarily focused on new developments in foundations and applications of intuitionistic fuzzy sets and generalized nets pioneered by Professor Krassimir T. Atanassov. Moreover, other topics related to broadly perceived representation and processing of uncertain and imprecise information and intelligent systems are discussed.

We hope that a collection of main contributions presented at the Workshop, completed with many papers by leading experts who have not been able to participate, will provide a source of much needed information on recent trends in the topics considered.

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