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BIOPROCESS MONITORING AND CONTROL USING MOBILE DEVICES

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Abstract. A novel flexible, cross-platform compatible system for monitoring and control of biotechnological processes is proposed. Different architectures of the proposed system are outlined and analyzed. They include bioreactor with digital control unit, computer and application. The application connects to bioreactor's controller, database, web application and cell phones or netbooks as remote clients. Questions of the system's practical implementation are discussed. An example of developed bioprocess monitoring system is presented.

Keywords: remote monitoring and control, mobile devices, biotechnological processes.

1. Introduction

In recent decades modern industrial biotechnology became one of the most rapidly developing sectors of the world economy. The variety of products of the biotechnological processes (hereinafter referred to as bioprocesses) reaches from food additives, amino acids and vitamins (e. g., vitamin B12, lysine) to complex diagnostics and therapeutics based on the molecules that already exist in human or animal bodies (e. g., insulin, interferon, monoclonal antibodies, erythropoietin) [1].

Modern biotechnology is highly multidisciplinary. The production of new pharmaceutics, transgenic organisms and biological fuels on industrial scale was possible due to significant progress in the neighbouring fields of industry and science. Today it involves a series of advanced technologies spanning biology, chemistry, and process engineering [1].

Advances in manufacturing equipment and cultivation methods have also contributed to the development of new applications of industrial biotechnology [2, 3]. Novel indirect state estimation methods and modern monitoring and control techniques have increased the safety and controllability of biotechnological processes [2, 4]. Nevertheless, due to complexity of the bioprocesses their control is still a major issue, especially on the industrial scale. Taking into account high market value of the modern biotechnological products each improvement of process control and, hence, its performance, leads to a significant financial advantage for the biotech-companies. On the other hand, lack of reliable online measurements of those highly complicated products of bioprocesses can lead to certain limitations during the development and production process.

Many technological parameters of a bioprocess, e. g., pH or dissolved oxygen concentration in the cultivation medium, can change rapidly during the cultivation process. They can dramatically influence the important bioprocess state variables, such as specific biomass growth rate and/or specific evolution rate of a target product. The latter variables have direct impact on the bioprocess performance and safety. The dynamics of bioprocess state variables has strongly nonlinear and non-stationary character, and the identification of the mathematical models for control of such processes is problematic and requires special approaches [5]. Under such circumstances, the high quality control of the processes becomes even more complicated and requires application of advanced control techniques [6], e. g., gain scheduling approach [7] that is regarded as a practical method in control of some important technological parameters of bioprocesses [8, 9, 10]. Therefore, it is essential to measure and to analyze these parameters just in time to maintain the optimal cultivation environment, to online monitor and control the growth of biomass and the product formation during the bioprocess, and also in order to prevent deviations from optimal process path because such deviations can have a negative impact on the final amount of a product, its quality or the process safety.

Finally, the development and implementation of suitable and flexible software solutions for monitoring and control of bioprocesses can pay a significant contribution to the progress in the field of modern biotechnology by facilitating the manufacturing processes and increasing their safety. Today, mainly intermediate or high end control systems involving Programmable Logic controllers (PLC) and Human Machine interface (HMI, SCADA) from the well known brand names are used in cultivation processes, also on a laboratory scale, because the stability, reliability and technical service of a control system is very important taking into account the fact that a bioprocess without interruptions must run for prolonged time period, which depending on the cultivated host organism can longs even for weeks. Brand name systems have a relatively wide selection of process control functions. However, if it is necessary to apply an advanced or rather specific process control algorithm, then for user it is of advantage to self-develop PLC or personal computer-based process control programs. Usually this software is not offered as a product. An attempt has been made to develop an enough flexible bioprocess control available for the commercial distribution [11]. This controller gives the possibility to apply customer-defined algorithms using the e-mail and internet-based service of the manufacturer [12].

In general, today's process automation systems are capturing large volumes of bioprocess data and storing them in databases. Further, computer control utilities are available and are relatively easy to use so that data, in terms of trend plots, is easy to visualize. In addition, software tools are available to help to mine the information and knowledge content in the stored data. These tools include model building software (e. g., artificial neural networks, *ANN*), statistical analysis (e.g., *JMP*), principle component analysis, decision tree generation, three dimensional graphics, rule-based systems to analyze incoming data in real-time, etc. [13].

In modern industrial biotechnological cultivations, process control and almost all cultivation activities are automated. Due to this reason the processes are often carried out without the presence of laboratory personal. Therefore, often it appears necessary to remotely monitor such processes in order to take additional actions if the control strategy needs to be changed during the process or an urgent action should be taken in order to solve unexpected problems. One option is to monitor the process from a remote computer over the wired Internet connection. Practically, in some cases this can restrict the monitoring possibilities if a person in charge at a specific time has no possibility to use a desktop computer. This problem can be solved if one has an opportunity to monitor and influence a cultivation process using mobile devices, e. g., mobile phones.

There are several software solutions of bioreactor remote monitoring systems on the market. Most of them are developed as *Microsoft Windows* applications for personal computer (PC). For instance, commercial remote monitoring solutions *Iris V5* (*Infors AG*, [14]), *BioCommand Software* (*New Brunswick Scientific*, [15]), *Dasgip Control 4.0* (*Dasgip AG*, [16]) and *MFCS/DA, MFCS/WIN* (*Sartorius BBI Systems*, [17]) are offered on the market. These solutions provide flexible options for data-logging, visualization, remote monitoring and control. So far, only *Dasgip AG* offers bioreactor remote monitoring system for mobile phone which is compatible only with *Apple iPhone* and *iPod touch*. Web monitoring makes use of *Microsoft Silverlight*. Therefore it is compatible only with *Microsoft Windows*.

The proposed bioreactor remote monitoring solution aims to be a cross-platform compatible one. Unlike the solutions discussed before, it is compatible with most mobile phone platforms (*Symbian, Linux, Windows Mobile*) and computer platforms (*Microsoft Windows, Linux, MAC*). The main advantage of developed solution is compatibility with almost every middle-class mobile phone that supports data connectivity protocols (any of *WAP, GPRS, 3G, UMTS, WiFi*) and is connected to the Internet. Actual process data, e. g., dissolved oxygen concentration, pH, temperature and foam level, are displayed on a mobile phone display using web-browser interface.

The proposed bioprocess monitoring and control system is also particularly useful in bioreactor systems where intensive research activities are taking place and process improvement is underway, e. g., research and development departments of biotech-companies or scientific research laboratories of academic institutions. The research group members are communicating intensively during cultivation processes and such features could have positive impact on cooperation within a group and can accelerate development of a new bioprocess.

The concept of such system could become a solution that can be implemented in bioprocess control systems that are currently available on the market. It does not require specific additional equipment or expensive third-party software components.

The aim of the present work was to develop a sufficiently flexible, convenient and advanced process monitoring and control system capable to communicate with mobile devices. At the same time, such a system should eliminate some distinct disadvantages found on the systems that are already available on the market.

2. Structure of the designed system

Components of the designed system are: bioreactor with digital control unit, computer and application. The latter connects to bioreactor's controller, database, web application and cell phones or netbooks as remote clients. Figure 1 presents the symbols of the elements of architecture that will be used in the further illustrations.

Different arrangements of the structural elements lead to different system architectures. In some cases encrypted connection between elements is required in order to avoid possible data leak through an unsecured network. In most cases the connection to bioreactor controller is established through a PC's serial port. Connection between software components, such as application, database and web application is established through *TCP/IP*.

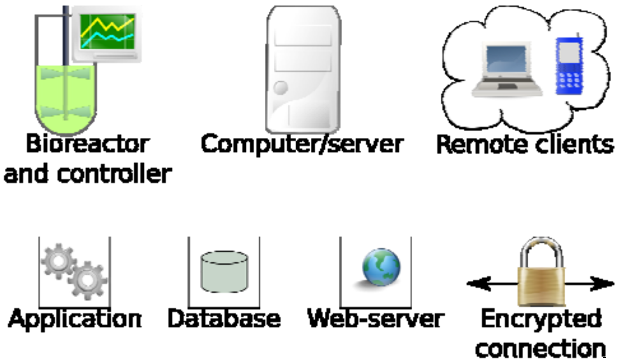

Figure 1. Elements of the architecture

2.1. Client application

Client application is responsible for connection to bioreactor and database. The main task of client application is to read data from bioreactor controller and to store them into a database. In the bioreactor controller the data from sensors is stored in microprocessor's memory. Client application reads the data from microprocessor over *Modbus* communication protocol. Reading is performed continuously each 10 seconds by default or the user can define different reading interval. This time interval is required to read, to process and to store the data into database. As the data is stored in different memory areas of microprocessor and not in turn, during one reading cycle about 100 rows are read from different memory areas. After that, data is processed, and the required measurements are selected and saved in database. Application serves as a bridge from bioreactor controller to database, and therefore it doesn't need a graphical user interface for everyday use. However, it should have a user-friendly wizard for initial set up. The connection to databases as well as computer's serial port, which is connected to bioreactor controller, if computer has many ports, and reading interval are configured during such set up. The application can connect via *TCP/IP* protocol to different geographically separated databases.

2.2. Database

Relational database (see Figure 2) stores data received from the application and web application. This data includes on-line measurement results, information on current process, list of past events, user data, alarm configuration, off-line measurement results and user notes. Furthermore, an additional table for classificators is included which is related to the other database tables for different measurement units and for alarm types. This gives an opportunity to work with different measurement units and to improve the data browsing and selection of specific items.

To prevent data loss, two equal databases on separate physical drives are created. A special mechanism implemented in application and web application writes data into the first database, then closes connection and writes the same data into the second database. Such a mechanism prevents data loss in cases when electricity supply is interrupted and one database file is corrupted. Only the last record would be lost. To decrease possibility of interruption of electricity supply, UPS should be used as well.

Additionally, hard drives that are interconnected using *RAID* technology can be used in order to reduce the possibility of mechanical damage of a hard drive which could lead to a corruption of the information in the database. Also, it is required to frequently make data backups. These are the basic data safety provisions that will be implemented in the system under consideration.

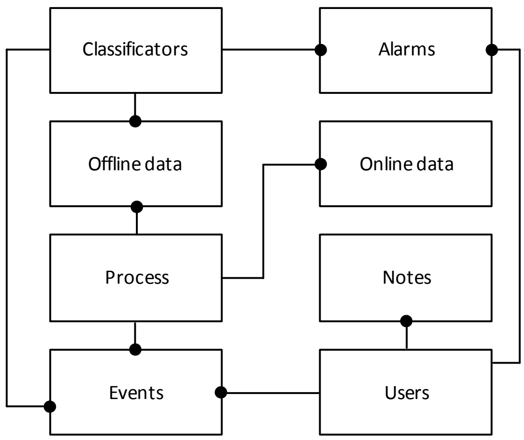

Figure 2. Structure of the database

2.3. Web application

From the user's point of view, web application serves as an interface between bioprocess controller and the user. Practically, the web application communicates with the database. It reads online measurement results from the database and displays them in a web browser.

Web application also provides an interface for entering the off-line measurements data. The stored off-line data include optical density, glucose, lactose, acetate measurements and air flow, oxygen enrichment data. This data is possible to enter in database in different units and an advanced user, using Web application interface, can only select the actual unit from the defined list. Depending on user privileges, the web application allows changing of set points of parameters, e. g., temperature, dissolved oxygen concentration, pH and stirrer. Regardless of the user privileges, web application displays all available on-line measurement data. Web application also displays trend curves of the process. Technically it means that web application puts historical data (on-line and off-line) on a plot. However, all systems have some time-delay. Web application expands time shift even further.

The on-screen data can be updated with regular html-auto-refreshes. Without advanced *Modbus* tweaks in client application, the time delay cannot be minimized to less than approximately 15 seconds. The whole delay is the sum of sensor reaction time, data transfer over *Modbus* protocol, data transfer to and from database, and data transfer to web browser. Since data transfer to browser must be initiated from the browser itself, user experience can be enhanced with *AJAX* technology.

Additional challenge for developers is to make the user interface adaptable to different screen sizes. For example, parameters and data plots should occupy all the space available on the screen. It does not make sense to render data plot smaller than a screen and, at the same time, it is not acceptable that cell phone user has to scroll web application's interface to see important data.

2.4. User roles

The designed system provides four user roles: advanced user, basic user, guest and administrator. Advanced user is the person who carries out cultivation, so there can be only one advanced user logged into the system at the same time.

Advanced user can change set points, switch devices on and off, cancel alarms, change process parameters and edit profiles of the other users.

Basic user can only see the process parameters and enter off-line measurement results. Basic user could be a person who is involved in biotechnological cultivation process, but is not responsible for the entire process. It can be a person who works in another room, analyzes samples and processes off-line measurements data.

Guest can only see the process parameters and submit suggestions.

Administrator's profile is not the combination of the privileges of the other roles. Administrator's task is to set up the system, configure connections and create the first profile of an advanced user. System administrator is not directly involved into a bioprocess, and an advanced user is not solving tasks directly related to IT problems.

All the users regardless of the privileges can leave notes in a common list on notes.

3. Different architecture implementations of the system

System architecture is dependent on a particular situation and user requirements. In the designed system, it doesn't matter if software components are geographically separated or not – client application, database and web application communicate through *TCP/IP*. The designed system aims to be cross-platform compatible. It means that there should be no restrictions regarding operating system, programming language, database management, web server and remote client (browser) software.

3.1. Single-bioreactor/single-database architecture

Architecture with one bioreactor is the simplest solution possible. There is one bioreactor and one computer in this case, also all software components are installed on that single computer (see Figure 3). The only link that must be encrypted is connection between web application and browser. If web server accepts connections only from *localhost*, even this link may remain unencrypted.

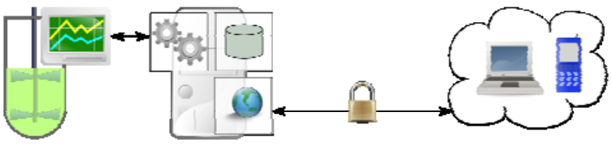

Figure 3. Single-bioreactor/single-database architecture

3.2. Multiple-bioreactors/single-database architecture

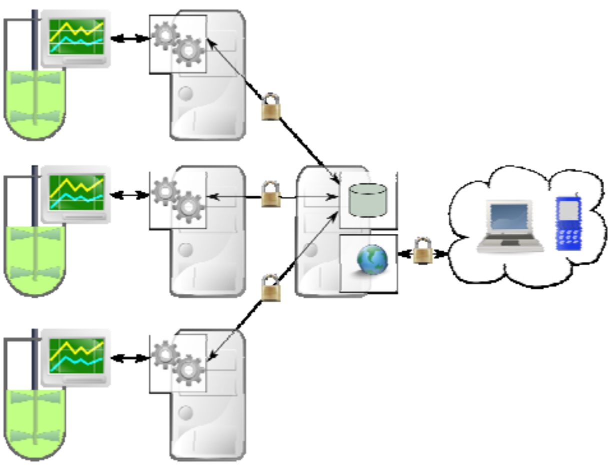

Figure 4. Multiple-bioreactors/single-database architecture

There are multiple architectures with more than one bioreactor possible. In case of multiple bioreactors one computer per bioreactor is needed. In multiple-bioreactors/single-database architecture (see Figure 4) computer runs only client application which retrieves information from bioreactor controller and sends it to geographically separated database. The benefit of this architecture is that data from all bioprocesses is stored in one place. It means that there is only one server and one data storage that requires regular backups. The disadvantage is that this architecture is sensitive to network delays and failures.

3.3. Multiple-bioreactors/multiple-databases architecture

The disadvantage of multiple-bioreactors/single-database architecture can be overcome if data from bioreactor is stored on the same computer that is connected to it. In this case no bioprocess data is lost when network fails (see Figure 5). This is the only architecture with multiple databases discussed in this article, so, if web application once has been working with one database, it has to be adapted to work with multiple databases now. A peculiarity of such architecture is that web application gathers data from multiple resources, formats them and passes further to browser. If there are several guest users observing each cultivation, an overload risk becomes an issue. Each guest requests new data every few seconds. However, web application has no bioprocess data and it requests this data from database. One request from browser means several requests from web application to the database. This rises the risk of computer overload, and depending on operating system can even hang the computer. This can be solved in two complementary ways. The first one is to increase adjustable time interval after which the data is represented on the screen. If browser requests new data every 10 seconds, the interval would be 60 seconds. The second way is to introduce data caching for web application. If browser requests new data too often, web application responds with the most recent data available in cache.

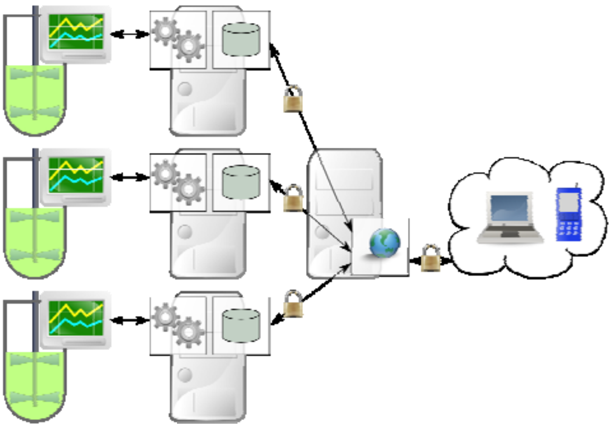

Figure 5. Multiple-bioreactors/multiple-databases architecture

3.4. Multiple-bioreactors/single-database architecture with a separate web server

Multiple-bioreactors/single-database architecture with a separate web server (see Figure 6) is sensitive to the same interferences as multiple-bioreactors/single-database architecture, but overload risk is evaded by physically separating all software components. Although this architecture is sensitive to intranet network delays, security in case of external cyber attack is increased. If web server has been compromised, attacker still has no direct access to database.

Vulnerability of this architecture is mostly dependent on encryption strength and security holes in web application.

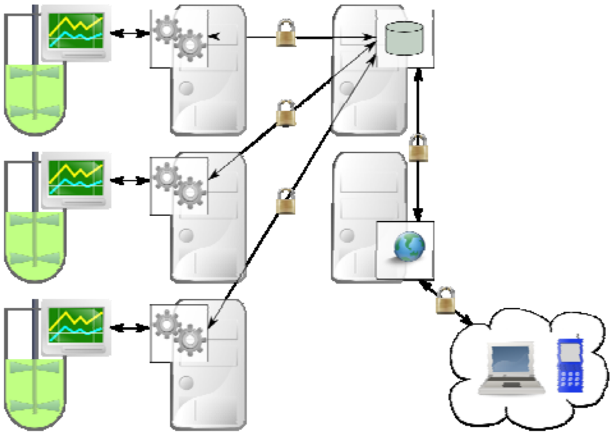

Figure 6. Multiple-bioreactors/single-database architecture with a separate web server

3.5. Single-bioreactor/single-database architecture with Modbus connection

This may be the weirdest solution (see Figure 7). Since *Modbus* can operate via *TCP/IP* too, one has to discuss it. In this case it doesn't matter on how many computers the software components have been distributed. It is theoretically possible to communicate straight from web application to bioreactor controller and to use database only as a data storage (not as a middle layer as discussed before). However, bioreactor controller may have no data encryption options, therefore single shielded Ethernet cable should be used for communications with bioreactor controller. Any networking equipment, such as router between bioreactor controller and computer would increase data leakage threat.

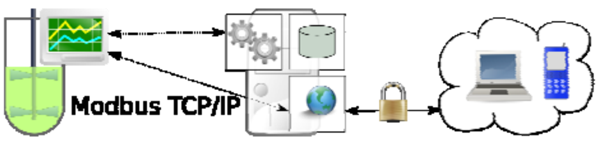

Figure 7. Single-bioreactor/single-database architecture with *Modbus* connection

4. Practical implementation of the proposed architectures

The proposed bioprocess monitoring and control system was implemented at the laboratory of

Biosystems group (Latvia University of Agriculture) where the necessary equipment was installed.

The implemented configuration of the bioreactor monitoring and control system is the following: the bioreactor controller is connected to the computer via serial port. An application that reads data from bioreactor controller, database and web server with web application are installed on this computer. In the analyzed case, the multiple-bioreactors/single-database architecture was chosen.

The bioreactor controller *BIO-3* is developed and produced by *BTC* company (Latvia). It is based on *Tiger* embedded multitasking computer module (*Wilke Technology GmbH*, Germany) that controls the equipment of bioreactor. On the computer, there are installed *PostgreSQL* database, *Apache* web server, on which base web application is working, *PHP* engine and application which is developed in *C#* programming language.

As database, web server and application are installed on the same computer, it is not necessary to encrypt data flow, but in the connection links *SSL* cryptography is used.

When application is switched on, it is possible to choose from a list the database to connect (one basic database, and second is an optional one), where data should be stored. Application reads data from the microcontroller memory with *Modbus* protocol functions. All data is received in an array, then it should be filtered and only required data from specific addresses is selected. Later the connection with database is created and selected data is stored in the database with specific process identification. By default, readings are made each 10 seconds, but the user can change this time interval. It is recommended to use minimum time of 10 seconds, because if it is smaller, data can be lost. In discussed case, in 10 seconds approximately 100 rows are read from microcontroller memory in three steps, because required data are stored in different areas of memory. To decrease data request time, it is easier to read from big areas and then filter data, than to read from a specific memory row. This can increase reading speed. In total, in 10 seconds more than 200 memory rows can be read in one step, but to process this data such a period can be too short.

Web application was developed in *PHP* language. It reads required data from the database and saves changed data. At this moment it can only represent measurements data, which is received from bioreactor controller. To renew data on the web page, *AJAX* technology is used that automatically reads changed data from the database. In web browser, one can edit, add or delete user information, view process data, add offline data and create graphics. It is also possible to send notes to other users. As an example, a view of the developed bioprocess monitoring screen on different mobile phones is presented in Figure 8. Depending on the display size, the interface can be graphical or symbolic. The resolution of the display is detected automatically.

Figure 8. View of the developed bioprocess monitoring interface on different mobile phones

Depending on detected screen size, web application decides whether the remote client is netbook, high-end, middle or budget-class phone. If remote client does not support *JavaScript*, web application generates even simpler HTML. In such case no external *JavaScript* and *CSS* files are loaded.

5. Conclusions and future work

Created and tested system is a suitable alternative to commercially available solutions that eliminates the mentioned limitations; it is more flexible, easy to use and cross-platform compatible. The implemented security and safety solutions provide the necessary preconditions for industrial application of the proposed system. Nevertheless, the additional investigation of more complicated architectures is needed. Until present, only the monitoring subsystem was developed and implemented. The control subsystem is still under development and needs extensive testing.

In future, the developed bioreactor remote monitoring system will be updated by adding a remote real-time control functions. Remote real-time control will not only ensure to follow up online the bioprocess for changes in time of the actual parameters (temperature, dissolved oxygen concentration, pH, foam level, etc.), but also will provide the possibility to a process observer (remote user) to give suggestions, comments, make and edit the set point profiles for feeding rate, temperature, pH and dissolved oxygen concentration during the cultivation process. For safety reasons, during the process in some cases it is necessary to perform a real management command execution in order to prevent a bioprocess running out of control and to avoid significant risks influencing cultivation process. It is planned to implement the modules for the management of users, alarm and events. Also, it is necessary to extend the database in order to enlarge functionality of the system.

6. Acknowledgment

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