5.5 A Database System and an Expert System for Realizing Factory Automation in the Bioindustries

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1. Introduction

An industrial microorganism has been thought as an everything which is not only a very small hardware but also a software in a sense that various information is embedded in its DNA. It is the significant meaning of the new biotechnology that we are able to handle with the software part of a microorganism by means of recombinant DNA techniques. Informations in the DNA begin to walk alone parting from the DNA structure now and so that we can design genes as well as enzymes artificially.

But when we look the actual production lines in the bioindustries, we are surprised by the behindness in the technology. Namely, any information of a microorganism, in other words, even the cellular level of functions which are represented by specific rate of substrate consumption, that of oxygen uptake, that of cellular growth, that of metabolic production and so on have not been measured directly yet nor applied to the control of the bioreaction processes. This means that informational studies have not well been fortified in the bioindustries nevertheless they start to use a gene manipulated cell for their production. This situation also tells us the reason why the bioindustry is far behind the other high technology industry in factory automation.

In order to use the information which is inherent in a microorganism to bioprocessings and realize the factory automation in the bioindustries, following problems should be solved first of all:

1) Standardization of bioprocess parameters.
2) Construction of a database system.
3) Codification of expert's knowledge.

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Concerning standardization of bioprocess parameters we explain the parameters in detail in the next chapter, and concerning the other items we discuss the problems and present the concept of our approach in the following chapters.

2. BIOACS (BIO Advanced Control System)

Recently, the authors have developed an automatic monitoring and controlling system for bioprocess (Bio Advanced Control System; BIOACS) in cooperation with Fuji Facom Co. Ltd. and Komatsugawa Chemical Engineering Co. Ltd., that was granted by Research Development Corporation of Japan [1]. During the developmental period, the authors have obtained knowledge of on-line measurement and control of the bioprocesses on the basis of microbial physiological activities.

The characteristics of BIOACS are summarized as follows:

1) On-line measurement of cell mass concentration, one for the substrate and one for the product.
2) On-line monitoring of physiological activities of cells which are represented by various specific rates.
3) Construction of database (Biodatabase), acquiring characteristic properties of bioprocess parameters such as pH-value, temperature, viscosity, etc., and physiological activities of cells.
4) Optimal control of the bioprocesses by using biodatabase.

These characteristics are supported by the following new devices and computer softwares:

1) On-line turbidisensor [2],
2) on-line sampling unit of cell free culture medium [3],
3) accurate estimation of the specific rates via Kalman filter [4, 5], and
4) dynamic responses of the specific rates to fed-batch-operations [6, 7].

Comparison between the automatic monitoring and controlling system developed so far and BIOACS is shown in Table 1.

The concept of BIOACS is shown in Fig. 1 [1]. The biodatabase shown in this figure is a relational database [8], which applies the mathematical concept of a relation to the system. We therefore can cooperate with other database systems via operators as and/or, large/small/equivalent. Another characteristic of the system is the possibility to add or cancel arbitrary data without minding about the program. Furthermore, we can make a necessary report by communicating with a computer. Hereafter we will discuss the expansion of the BIOACS and its biodatabase.

3. BDBS (BioDataBase System)

The term of database was already mentioned without any definition being given. We define this term as follows: A database system is a collection of stored operational data used by the application systems of some particular enterprise [9].

Table 1. Standardization of the bioprocess parameters for monitoring

	Items	Commonly used system	BIOACS
Monitoring	Temperatur	○	○
	Pressure	○	○
	pH-value	○	○
	D.O.	○	○
	Airation rate	○	○
	Agitation speed	○	○
	pO_2 in	○	○
	pO_2 out	○	○
	pCO_2 in	○	○
	pCO_2 out	○	○
	Working volume	○	○
	Torque	○	○
	Turbidity	×	◎ on-line
	Product concentration	×	◎ on-line
	Substrate concentration	×	◎ on-line
	Specific rates	×	◎ on-line
Controlling	Temperature	○	◎ optimal control
	Pressure	○	○ setpoint control
	pH-value	○	◎ optimal control
	pO_2 in	○	○ setpoint control
	Airation rate	○	○ setpoint control
	Agitation speed	○	○ setpoint control
	Feed rate	○	◎ optimal control

This means that a database system provides the enterprise with centralized control of its operational data. Examples of enterprises are:

Pharmaceutical industry,
biochemical industry,

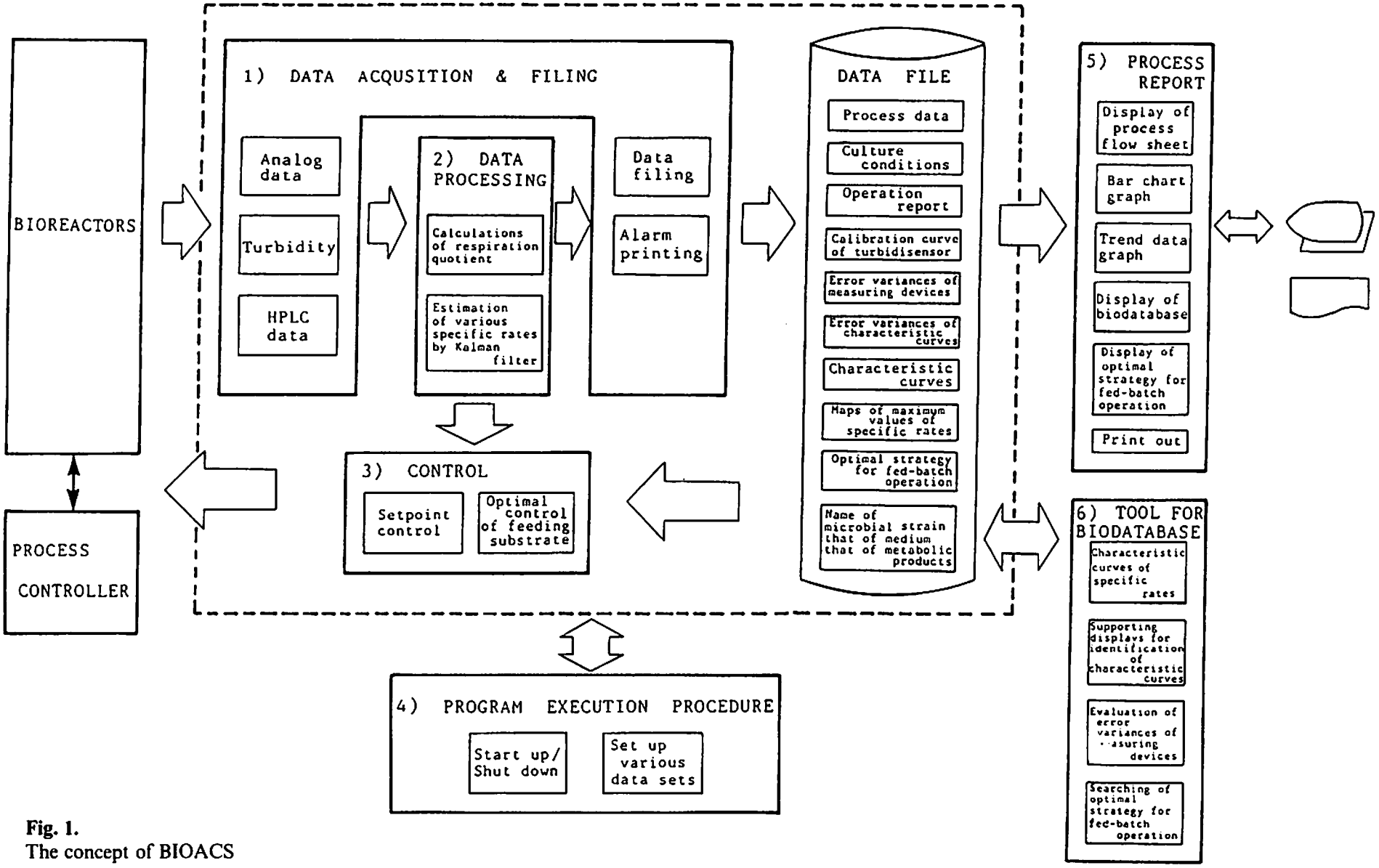

Fig. 1.
The concept of BIOACS

food industry,
universities and
governmental institutes.

The operational data for the enterprise may include

sales data,
product data,
planning data,
process data including down stream processing,
medium composition data,
culture condition data,
characteristic curves concerning various specific rates of cells,
and optimal operational strategies.

The characteristics of these data are rather dynamic than static.

The dynamic data are the fact data. From the viewpoint of a microbiologist, a screened organism is considered to be the most important technical item. But it is of no use to the bioprocess engineer, if the fact data are not accessible from the organism. A database system, which provides the enterprise with the dynamic data, namely, the fact data about bioprocesses, is called the biodatabase system (BDBS). Needless to say that the advantages of the BDBS are the same as those of usual database system. The advantages are:

Redundancy can be reduced,
inconsistency can be avoided,
the data can be shared,
standard can be enforced,
security restrictions can be applied,
integrity can be maintained, and
conflicting requirements can be balanced.

The BDBS consists of four main parts. The first part is called a BIOTRON in which hundreds of mini jar fermentors are operated under various conditions by a single robot. The second part is a supervisory computer for the BIOTRON. The third part is an analysis room for the culture media and product concentrations. The fourth part is the DB machine for acquiring and assembling the fact data.

The reason why we need the help of a robot is that the fact data are so varied and abundant that they exceed the limit of manpower. Many apparatuses, such as the refrigerator for the preservation of the microorganisms, the clean bench for inoculations and the incubator for precultivations, etc., should be improved so that they can assist the work of the robot effectively.

4. Expert Systems for Bioprocess

There are several stages in bioprocesses from upstream processing to downstream processing, and specific problems exist in the individual processes. It leads that knowledge is necessary to solve the problems, and implementation of the knowledge

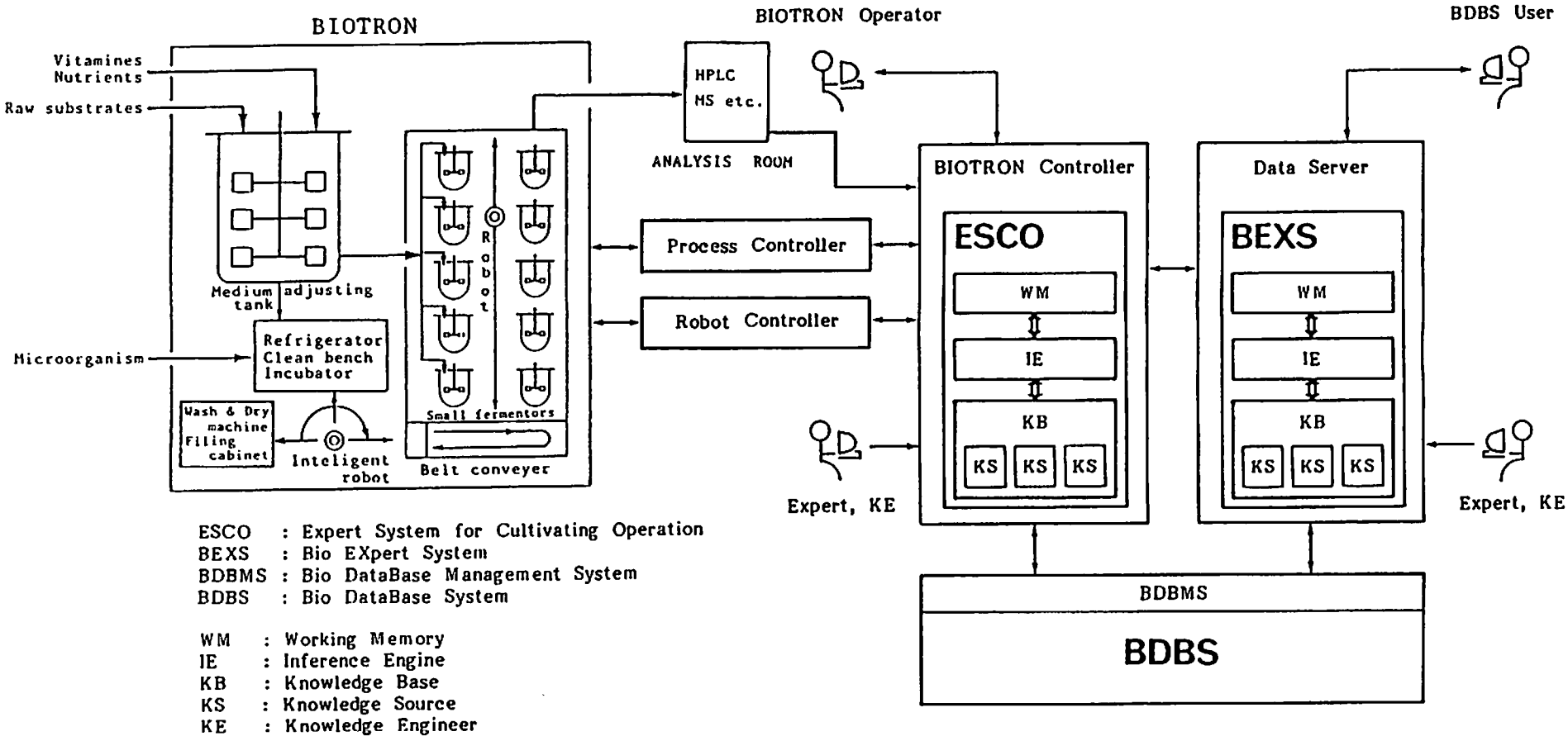

Fig. 2. The concept of biodatabase system (BDBS) and expert systems (ESCO & BEXS)

is indispensable to realize an automated system, though the knowledge is quite spread over various processes. Moreover, as factory automation can never accomplish the efficiency unless the whole processes are integrated and automated, the functions of the automated system should be extensible easily. From these points of view, we discuss the application of knowledge engineering and construction of a bio-expert system which supports the factory automation in bioengineering.

Our concept of the BDBS and two expert systems is illustrated in Fig. 2. One is an expert system for cultivating process, and the other is an expert system for providing adequate data and designing downstream processes in actual industrial operations.

4.1 ESCO (Expert System for Cultivating Operations)

We are developing ESCO aiming at automation of operations in BIOTRON, or supporting operators of BIOTRON in designing and preparing experiments, operating bioreactors in cultivation, diagnosing troubles, measuring, analyzing the obtained data, and storing the data in BDBS. This system is applicable to the factories in product development.

Figure 3 shows a flow of operations in our BIOACS as a typical example of cultivating operations of bioprocess. Some operations are procedural (but rather complicated), and can be described easily in a computer. Others, however, are non-procedural, and quite dependent on knowledge that operators of bioreactors own and apply, which should be called knowhows and heuristics. Knowledge engineering can be considered to give a solution for problems with non-procedural operations.

Experimental design is one of the typical problem which requires expert knowledge. The process of experimental design can be divided in two steps. First step of inference is optimal conditions for the best productivity, which makes cultivating parameters assumed, and second step of inference is measurability of medium components including microorganism, substrates products and by-products. The system should design all the conditions for cultivation and its measurement, e.g., medium composition, pH, temperature, agitation speed for cultivation, and concentration and flow rate of buffer proper column, measuring wave length of spectrometer of liquid chromatograph for measurement.

But when we design experiments, we usually have only such a part of information concerning cultivation as the kind of microorganism and its main products, but not detail information of by-products or composition of natural medium. Therefore experimental design system should cover the function of re-designing after acquiring sample data of past experiments to find better solutions.

Concerning the trouble diagnosing system, cultivating system consists of several devices and pipes. For example in the case of BIOACS, it consists of a reactor, heaters, coolers, pH control agent pots, pumps, air filters, various sensors (pH-sensor, thermometer, dissolved oxygen sensor, high performance liquid chromatograph, turbidisensor, form sensor), various valves, and pipes. Pipes are provided with water line, steam line, and air line. Devices are not always so reliable that we should take account of possible troubles, the method for diagnosing and recovering them.

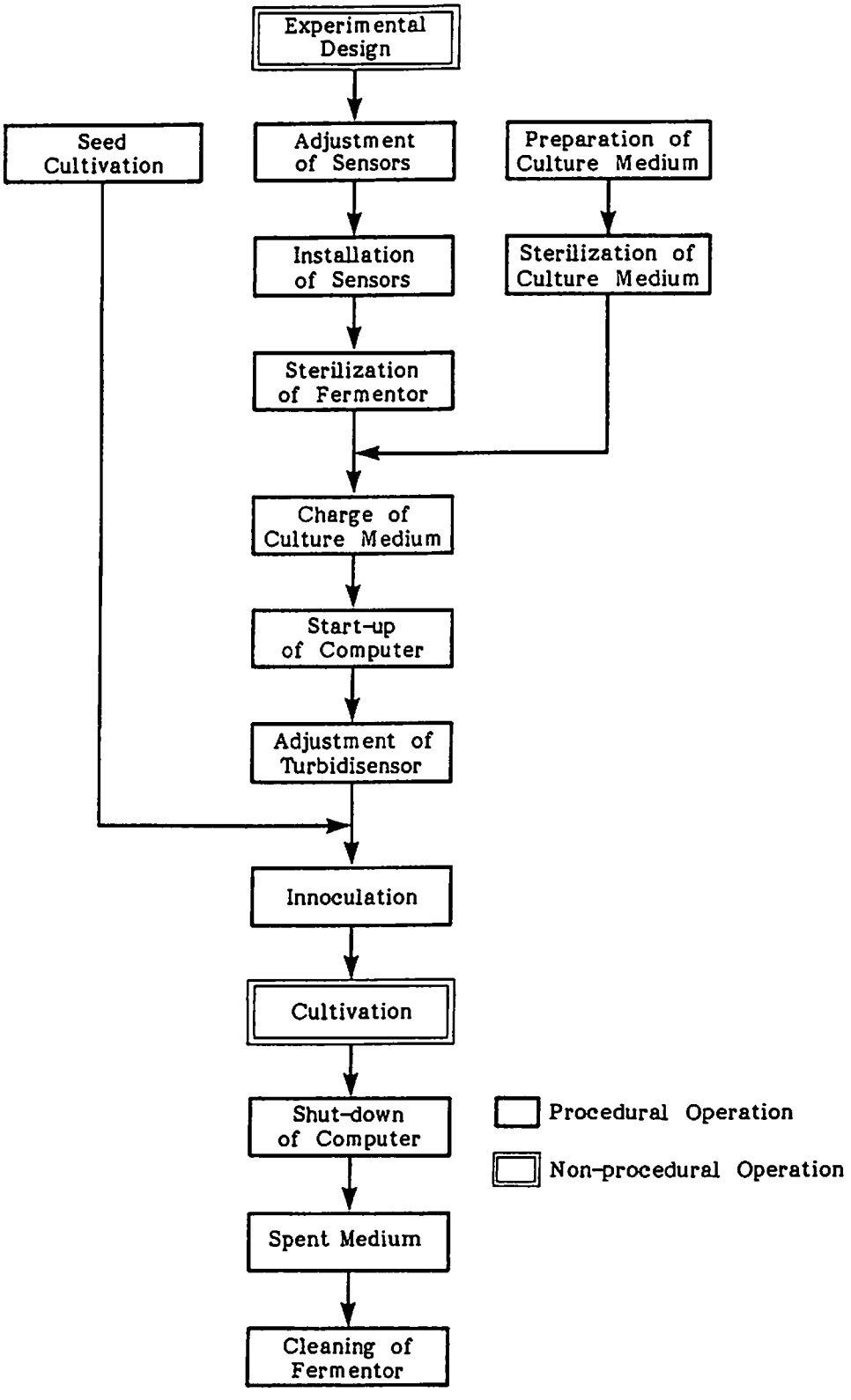

Fig. 3. A flow of cultivating operations in BIOACS

Troubles are usually recognized by monitoring measured values from sensors. In the development stage, however, it can be often the case that microorganisms behave contrary to the primary estimation. Namely we can not always know the behavior when we design the cultivating experiments as mentioned above. These cases should not be dealt with as troubles or errors, but the new data acquired in the

process which introduce the new solutions with regard to cultivating conditions. Therefore expert knowledge is also required for the judgement of troubles occurrence.

4.2 BEXS (Bio EXpert System)

The fact data are of no use, if we do not know how to use them for actual industrial operations. For this reason we have planned to build an expert system by which users of the BDBS can ask for the desired data or acquire knowledge of solving emergency. This system is called BEXS.

This system searches data in BDBS and delivers adequate data to end-user, or generates commands to data generator BIOTRON to acquire insufficient data.

The data stored in BDBS should be utilized not only for the purpose of planning of cultivating conditions, but also for the purpose of industrial production. On the stage of industrial production, downstream operations with separating and purifying technologies, are desired to design. We can combine such operations to introduce a sequence for producing products, as liquid chromatography, liquid-liquid extraction, membrane separation, electrophoresis, etc. taking account of conditions of property of microorganism, its products and by-products, components of culture medium, and other parameters in cultivation.

Namely BEXS should have not only a function of searching and presenting required data in the past records, but also a function of introducing optimal procedures to synthesize the operations for production. Therefore the system should be an advanced knowledge based system with expert knowledge with regard to downstream.

5. Conclusion

Firstly, we have proposed a standardization of bioprocess parameters for monitoring and controlling and introduced our advanced control system (BIOACS), which we developed.

Secondly, a model of a database system for bioindustry (BDBS) has been presented.

Thirdly, as a tool for processing information about the effective use of the BDBS, the indispensability of expert systems (ESCO and BEXS) was discussed.

We are just at the starting point of the worldwide development of database systems and expert systems. Substantial development of these systems will realize the FMS in bioindustry.

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