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ELECTRONIC EXPERT SYSTEMS FOR BIOLOGY AND MEDICINE

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The purpose of the present work was to carry out a deep investigations of prototypes of information expert systems, their structure, functions and practical application, and to develop a new one for solving practical problems in biotechnology, laboratory practice and environmental protection. The observed prototypes were developed for the use in genetic studies, agricultural production, nature protection from pests and environmental pollutants, for works in medicine, and etc. During the work, following methods were used such as methods of comparative research of the samples of technical devices, imitation and program modeling, which were based on numerical results obtained in experiments with the recording of chemosensitive transmembrane electrical currents in neurons in voltage clamp mode. As a result, an original expert system was developed. It was coupled with a detector group, databases and interface. The developed expert system was able to distinguish automatically the certain types of chemicals at the input, to display their identification data and, if necessary, the reports about their harmfulness. Conclusions were done about the practical value of these data for the elaboration of new electronic expert systems for monitoring the presence of harmful substances in the environment. It was also discussed the possibility of developed expert system application for new methods of qualitative and quantitative analysis of some organic compounds.

Key words: biological and medical expert systems, electronic informational systems, bioinformatics, databases.

Electronic biomedical expert systems are powerful tools in contemporary biotechnology. In computer sciences expert systems were studied usually together with knowledge bases as models of experts' behavior using the procedures of logical conclusion and decision making in a certain field of knowledge [1]. Knowledge bases, consequently, were seen as a set of facts and rules of logical conclusion in the chosen subject area of any activity. In our previous publications we had written aready about contemporary computer information systems with expert subsystems [1–10], as well as about mathematic tools used for expert systems' construction [2–5]: methods of artificial neural networks [2, 3], methods of cluster analysis [2, 4], methods of images processing [2, 5]. Present article is dedicated to different aspects of modern expert systems constructions and functions because of great importance of expert systems' role for biotechnology as well as for contemporary biology and medicine [1].

An expert system is a computer system capable to replace (or to replace partially) professional-expert (human) in the problem solution according to classic definition. Modern expert systems started to be developed by researchers of artificial intelligence in 1970s, and in 1980s expert systems received commercial groundings. There are some evidences exist that early prototypes of biomedical expert systems were proposed by S. N. Korsakov on 1832. He invented mechanical devices, so-called "intellectual machines" that allowed to find task solutions under some given conditions, for example, to determine the most appropriate drugs in accordance with observed patient's symptoms of disease. The similar actions today were performed by such software tool as "search or reference (encyclopedic) system". According to user request, it provided the most suitable (relevant) chapters from the article bases (knowledge about objects from the field of knowledge, their virtual model).

While expert systems technology has now existed for more than 30 years, environmental expert systems are 15 years "younger" [11]. Nonetheless, the development has been rapid with over 68 systems in existence today [11]. All of the early systems and the bulk of the current systems are PC-based, but as the limitations of the delivery capability are reached, more and more systems are moving toward larger delivery environments such as minicomputers and dedicated workstations.

From other side, the "classic" concept of expert systems developed in the 1970-th — 1980-th years, is in deep crisis today. For example, the "classic" approach to the construction of expert systems is co-excided difficultly wth the relational data model, which makes it impossible to use effectively modern industrial databases to organize knowledge bases for such systems.

Electronic expert systems as one of the important types of modern electronic information systems. In our previous publications, we have already done a large-scale review of modern electronic information systems (IS) with databases (DB) [1–10]. There was suggested our invented classification of ISs main types for biology, medicine and neurophysiology (neurophysiology is at the junction of the first two spheres). It has been shown that electronic expert systems occupy the leading positions in the list of ISs' types for each of studied spheres [1, 7, 8]. They attract attention of scientists and engineers-developers by variety of their types and technical implementations, as well as by importance of solved tasks [1]. For example, in case of medical ISs, the expert systems were placed to the second place in the list of the most important ISs types (1-st place — "Medical ISs of general purpose", 2-d place — Expert systems, 3-d place — "Electronic systems for the works with images", and so on). Placing ISs' types in the hierarchy, we adhered to the principle: the more publications contain modern scientific and technical literature on a certain type of ISs, the higher the name of this ISs' type is in our list.

Regarding to classification of ISs used in biology, biotechnology, environmental research, the most of these ISs have been designed as 1- ISs with databases for science. Than they were followed by 2 — electronic library systems in biology, 3 — electronic databases in biology, 4 — electronic systems for the work with images. And only the next type in this classification hierarchy — 5-th place occupied expert biological systems (for example, to estimate the pests presence in the fields, to detect bees diseases and etc. Determining the position of ISs' type we placed them in decreasing order — ISs that had better representation in scientific and technical publications were placed highly in this hierarchical list [1].

We would like to overlook various examples of modern biomedical expert systems that can be successfully used in biotechnology. In addition, the experience of such systems development could be used successfully for expert systems construction specifically for biotechnology, for example, to perform specific biotechnological or research tasks. The principles of such systems structure, as well as their functioning as part of biomedical electronic network information systems (IS), will also be considered. And, finally, an example of expert system developed by the author for an IS with databases (DB) for eco-monitoring of environment polluded with harmful and/or toxic substance will be described.

Mathematic methods as well as models that we described in our previous articles and published by other authors also may be used for ISs functioning or to be simulated in result of their functioning [1–5, 10–81]. A spectrum of mathematic methods were used for the newest biomedical ISs elaboration one can find in [1–6, 11, 75, 77–80, 82–159]. Content for described in this article databases was obtained usually from the results of biological and medical observations and experiments [12–17, 24–44, 47–49, 61, 68, 71–74, 82–90, 94, 104, 106, 109, 111–113, 125–191]. All such technical information systems (tIS) are electronic databases (DB) distributed in networks today [1–11, 25–69, 90–109, 112–120, 159]. The newest parts of authors work were inventions supported by patents [162–172].

Expert systems in biotechnology. Some examples of electronic expert systems, developed for task solutions in biotechnology had been supported by patents; their descriptions are suggested in this sub-chapter.

1. *Expert system "Artificial intelligence system for genetic analysis"*. In the patent of Glenn F. Osborne, Simon S. M. Chin, Paul

McDonald, Scott Schneider their expert system "Artificial intelligence system for genetic analysis" is described in [12]. They published that their invention provides a complete artificial intelligence system for the acquisition and analysis of nucleic acid array hybridization information. The system includes a central data processing facility and one or more user facilities, linked by encrypted connections. Each user facility may include an optical scanning system to collect hybridization signals from a nucleic acid array, an image processing system to convert the optical data into a set of hybridization parameters, a connection to a data network, and a user interface to display, manipulate, search, and analyze hybridization information. This system reads the data from a nucleic acid microarray, analyzes test results, evaluates patient risk for various ailments, and recommends methods of treatment. The automated artificial intelligence system is a real time, dynamic decision making tool that can be used in conjunction with a clinical analysis system, and with the information obtained in a research and development environment.

2. *Expert system for classification and prediction of genetic analysis.* Other example of expert system for biotechnology we would like to observe Roland Eils patent "Expert system for classification and prediction of genetic analysis" [13]. It was directed to methods, devices and systems for classifying genetic conditions, diseases, tumors, etc., and/or for predicting genetic diseases, and/or for associating molecular genetic parameters with clinical parameters and/or for identifying tumors by gene expression profiles etc. The invention specifies such methods, devices and systems with the steps of providing molecular genetic data and/or clinical data, automatically classification, prediction, association and/or identification data by means of a supervising machine learning system. There were further described methods making use of these steps and respective means. This invention related to the method and system for classifying genetic conditions, diseases, tumors etc., and/or for predicting genetic diseases, and/or for associating molecular genetic parameters with clinical parameters and/or for identifying tumors by gene expression profiles etc., with the following features: providing molecular genetic data and/or clinical data, optionally automatically generating classification, prediction, association and/or identification data by means of machine learning, and automatically generating (further) classification, prediction, association and/or identification data by means of supervised machine learning.

The use of the supervised machine learning according to the present invention leaded to surprisingly better and more reliable results. There was noted that preferably molecular genetic data and clinical data were provided. Used machine learning system was an artificial neural network (ANN) learning system, a decision tree/rule induction system and/or a Bayesian Belief Network. Further preferably for generating the data in the machine learning system at least one decision tree/rule induction algorithm was used. The data automatically generated is tumor identification data making use of gene expression profiles and being generated by a clustering system wherein further the clustering system makes use of one or more of the following clustering methods: Fuzzy Kohonen Networks, Growing cell structures (GCS), K- means clustering and/or Fuzzy c-means clustering. Finally, it was noted that the data automatically generated is tumor classification data being generated by Rough Set Theory and/or Boolean reasoning.

Expert systems in medicine. The Internet provides unprecedented opportunities for invention and elaboration of powerful expert medical systems. In such systems the opportunities for obtaining information (OI) can be realized rather cheaply. This is the best way for large information volumes exchange; to obtain information that is varied, even controversial; to obtain information from medical experts from different fields of medicine and remote geographic regions. Clinical decision support systems (CDSS) have increasingly become used in medical practice in recent years. The first such system, which has been widely used since 1970, has become the medical expert system MYCIN. After it the number of such ISs were elaborated and developed, they provided access to medical information, interpretation of diagnoses, and so on. When these systems were developed, the methods for efficient system construction, decision making, and data usage from databases were searched. So, 2 alternative methods were invented and used: automatic OI and receiving OI in manual mode (manual OI) [1].

1. *Expert system for facilitation the presentation of knowledge and data in database and for knowledge obtaining from the Internet.* Using the above described theoretical approaches, the numbers of medical expert system were elaborated; one of them was

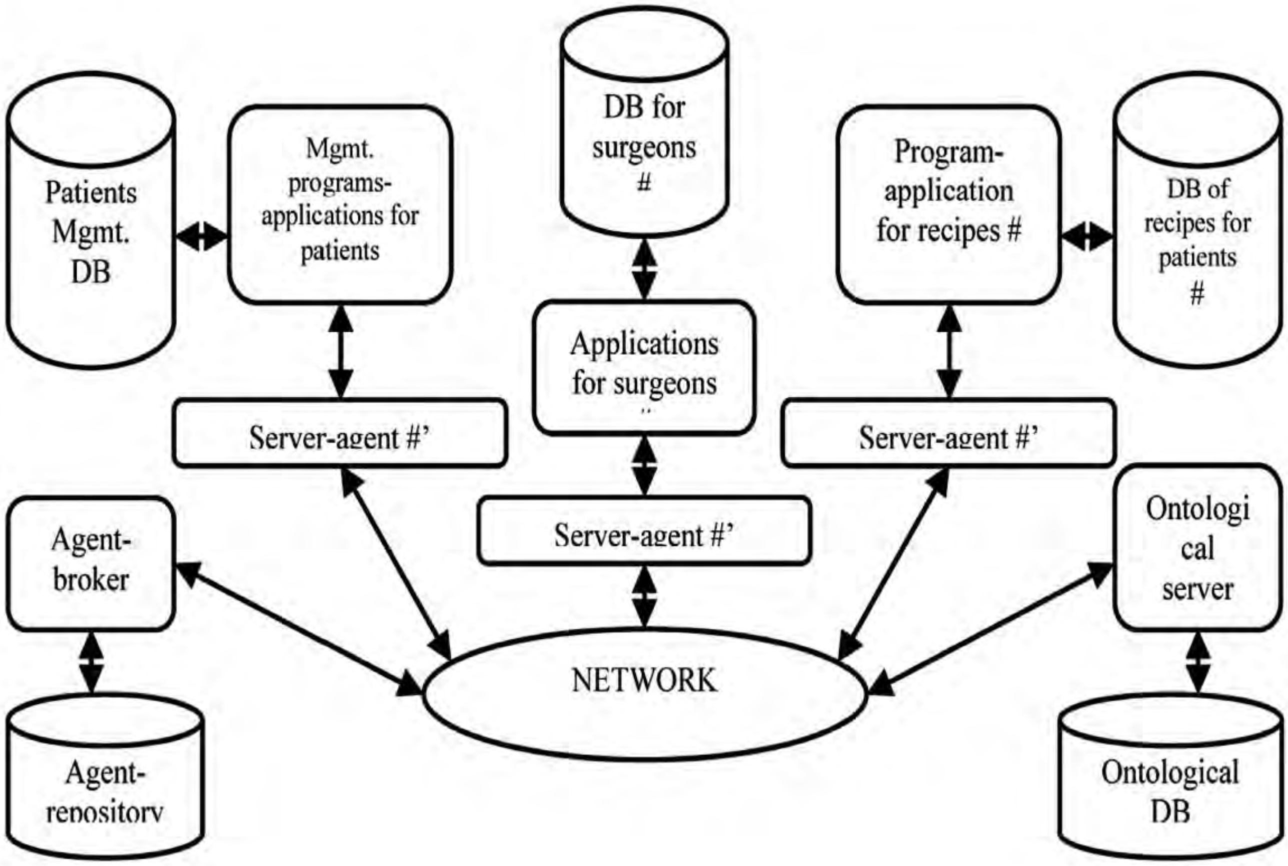
described in [132]. The authors described their system, which was based on three databases of client-server architecture and computer system for its information management (OI), which was the invention of developers. 8-bit encoding scheme and weighting system were proposed to facilitate the presentation of knowledge and data in database and to obtain knowledge from the Internet. The system had been tested already in clinic conditions. The authors set the following goals. 1 — to construct OI medical system and management system for it to facilitate the development and maintenance of medical knowledge bases; 2 — to maximize the distribution of information and its re-use between medical institutions and practical doctors; 3 — to facilitate the decision-making process by medical expert systems. The authors described the method of OI managing from the Internet, which they used to construct the large databases of medical knowledge. The testing system was designed using Delphi 5.0 and Microsoft SQL Server 2000, and it was available online for testing during 1 year. The authors wrote that their method and developed system makes it easy to operate large volumes of medical knowledge.

2. *Expert system for the selection patients for clinical trials in oncology.* Another Internet-based system was developed to select patients for clinical trials in oncology. Large-scale clinical trials are often multicentral in the modern world, which means that they are based on different geographical points of the Earth, often in different countries, for example, with purpose to study the effect of any important drug, which can then be recommended for people treatment. At the same time, for such work it is necessary to provide the highest level of standardization, the record in databases numerous test results and to fulfill a number of other specific requirements. Modern Internet technologies provide the opportunities for such work, although until the last days the selection of patients for tests was carried out manually. Developers of this system from the Moffitt Cancer Center, USA, describe their expert system for patient selection [1]. The data about each patient were recorded to it, and if there are not enough data, the system offers additional tests. The system allows the automating of selection process, the increasing the number of patient that can be selected (previously up to 60% of eligible patients were lost) with a significant reduction in cost of testing procedures. A user-friendly interface has been developed, which allows a healthcare professional to add test data and to make new selection criteria without the help of programmer. This system has been tested in oncological hospitals; and this is extremely important because, according to statistics, only in the United States 550,000 people dies of cancer every year. It is for this sphere of medicine a large number of new medicals are developing and testing constantly. In case of successful results they come to patients immediately — thus for the newly developed medicals the shortest path from the laboratory to the patient is invented.

3. *Expert system for patients' selection for clinical trials in oncology.* An electronic expert system with databases for diagnostics of psychosomatic disorders based on the use of fuzzy logic neural models was described [91]. Symptoms and characteristics of diseases were done as text records of patient surveys and collected in the databases. For translation of language samples of patient surveys into electronic form, an artificial domain was elaborated for the linguistic processing of this material; and the values for a fuzzy logic model were determined. These values were input to a multilayer neuronal network with direct feedback. During the work with the network the backpropagation training algorithm was used, and the model after the training was tested using symptoms and signs of disease from new patients. In addition, a comparison of the diagnostic ability of the model with the decisions and diagnoses of the medical expert was realized. The model implementation also was compared with the stochastic model based on the network of Bayesian hopes and statistical model with the use of linear discriminant analysis.

Information system with expert possibilities named "eMAGS" for medicine is suggested on Fig. 1 [141].

Expert systems in biology. This is a special group of information systems (IS) linked with databases in biology are the systems that have both academic and applied value. Intensive industry (including agriculture) requires innovations, and the information of several examples of such systems developed for practical needs, have been published below. There were already some attempts to solve problems of species preservation, environment protection from pests, etc., using electronic expert systems with academic databases as well as attempts to make simulation basing on the data that have been output by expert systems.



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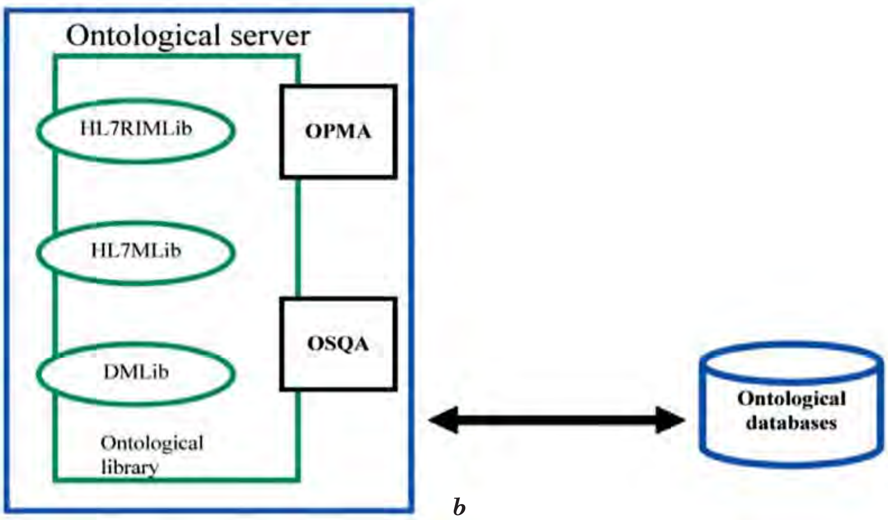

b

Fig. 1. **eMAGS medical system [141]:**
a — Architecture of eMAGS medical system. The essences of "agent" and "ontological" types were components of eMAGS system. Indications: # the greater number of such entities were supposed to be in medical institution; ' the essence of this type had a database and an interface for the user;
b — Ontological server and its components

An "Overview of Environmental Expert Systems" was written by Judith M. Hushon; and this overview accumulates a great volume of information concerning modern expert systems in area of environmental studies [11]. The author wrote that the development of environmental expert systems has been rapid with over 68 systems in existence today [11]. All of the early systems and the bulk of the current systems are PC-based, but as the limitations of the delivery capability were reached, more and more systems are moving toward larger delivery environments such as minicomputers and dedicated workstations. Development was occurred both using Artificial Intelligence languages such as Prolog and LISP as well as expert system "shells". The problems being tackled are also expanding. Whereas a number of the early systems took on very limited areas of expertise, such as the operation of a sewage treatment plant, the systems are now moving out to tackle siting problems and recommendation of complex remedial technology combinations. What is even more important is that expert systems are becoming an accepted vehicle for offering advice for solving environmental problems. Over the next few years more complex systems will be developed that share databases and tackle multiple related environmental problems.

Some other examples of expert systems in different spheres of bioogical practice are given below.

1. *Expert systems in forests protection from the pests*. The concept of integrated protection of forests from the pests has attracted the scientists' attentions for many years. But it could not be realized until present time, when modern monitoring systems appeared with electronic tools: expert systems, decision making, early warning, and etc. [186] Promising electronic decision making tools that include models, database management systems, geographic ISs and expert systems were developed during the last decade, but still it is necessary to carry out the research on user friendly interfaces and artificial intelligence systems for such expert systems. Several projects in North America have made significant progress in the development of monitoring systems and electronic decision-making tools for the elimination of Lepidoptera pests in forests (some species of Noctuidae, and others).

2. *Expert systems for beekeeping*. An electronic expert system was developed for the needs of beekeeping [187]. This system diagnosed the pest presence and determined the species of bees' pests (*Apis mellifera* L.); it offers also appropriate treatment. Developers proposed to use this system not only in beekeeping, but also as a training system for students of corresponding specialties. The diagnosis was performed by scanning of bees' colonies. The databases contain relevant images of normal colonies and pathological ones (with different types of pathology) that were analyzed using modern techniques. This expert system is based on EXSYS for MS Windows.

3. *Expert systems for agriculture: protection of crops from pests.* To solve the problem of crops' protecting from pests, the electronic ISs with databases have been elaborated, and they were used by farmers for contemporary scientifically grounded agriculture management [188]. The system for relational databases' management was described. This electronic management system was elaborated for monitoring and to provide advices to farmers about pests' species *Cydia pomonella* and *Psila rosae*. This system has been used on farms since 1988. This system was developed using INFORMIX-SQL RDBMS Version 2.10.06 and installed on personal computers IBM XT 286 model from PC-DOS Version 3.30. Farmers would be able to monitor insects, and their data of field observations and traps' inspections have been transmitted to research center. There these data were input into the IS, which determined the status of pests. This information was transmitted to agricultural experts. Experts have given the recommendatios to farmers to carry out the certain control procedures concerning the pests on the basis of received data about *Cydia pomonella*. In the case of *Psila rosae*, the individual advices via IS were mailed directly to farmers. Monitoring was carried out only during flight periods; the data were transmitted by post or fax.

4. *Expert system for cotton industry*. Another expert system was invented and designed in Australia for the needs of cotton industry [33]. This is the electronic decision-making system (DSS), and it is widely used today to control pests, to examine the state of feeding of cotton plantations, and to solve other tasks requiring information exchange. The system contained a part of the software called EntomoLOGIC, which is, from other side, the part of larger CottonLOGIC system. In order to use EntomoLOGIC, the farmer went to the area of his interest, and input the information about the condition of this

territory: what pests are present there at this moment, at what stage of development they are, their quantity, and etc. The program forecasted the prospects of these pests development and offered the methods for their elimination or neutralization. Due to these recommendations the farmer made decisions about his work at this territory. Used software includes several databases. Many components of EntomoLOGIC software have been developed on the basis of Palm® OS for IBM.

5. *Expert system for ecological monitoring of fauna for agriculture (registration of Locustae and other flying insects migrations).* Interesting example of modern IS for environmental monitoring and agricultural services was the IS, that had been developed in Australia [1, 10, 189]. This information system consisted on two remotely-spaced radars that were used for insect monitoring; they both were connected to the node computer (NC) of the basic laboratory. PC-NC communications were used to transmit observation data, to perform remote services and to conduct diagnostics. Specially organized automated systems were developed to analyze meteorological information and the data about insects' migrations, recorded by the radar. On the base of this analysis the statistical reports and their graphical representations were prepared daily according to the information received by radars. The reports and graphs provided the data on the intensity, amplitude, velocity and movement of insect migration directions, orientation, size and frequency of migrant wings, as well as weather conditions at the surface of each point of survey. Such reports were transmitted to NCs and inserted automatically into the Internet pages, which users could see since 12.00 p.m. next day. Expert systems were elaborated and used in this system for data analysis as well as for automated answers to users (biologists, ecologists, farmers, others) on their questions and requests. This system was developed to track the number of such insect pests like different *Locustae* and other flying insects-migrants [1, 10, 189].

Development of electronic workplaces for electronic information systems with expert capabilities. Development of electronic expert system within the IS requires the development of a user-friendly interface. The author developed several types of electronic workplaces (EWP) for scientists and other professionals, which de facto fulfilled the functions of the interface. Let's describe original version of EWP named "EWP-Z" — "electronic workplace for zoologist", which can be used by zoologists, environmentalists and professionals of other specialties; EWP-Z can serve as interface to IS with expert capabilities (like other versions of EWP). In stationary laboratory conditions electronic ISs are usually networked and realized on the base of devices and equipments specialized for this research direction. We decided to develop "electronic work places" (EWP) for such ISs for some biological specialties on early 2000-th. EWP-Z was originally developed for insects' adaptation studies in mountain conditions of Elbrus region (Caucasus, Russia), at Elbrus Medical and Biological Station (EMBS, National Academy of Sciences of Ukraine), where the author was in staff at that time. Hence, this system could be used also by researchers who study the influence of extreme conditions on bioorganisms. Since, basing on such data, the databases for monitoring, observations are subsequently formed for environmental problems solution; the EWP-Z might be also a desirable tool for ecologists who use insects' observations for ecological analysis of the environment state. EWP-Z can be used locally and autonomously, as well as a segment of electronic monitoring system, for monitoring of bioorganisms' population state, ecological monitoring in nature preserves, in neighborhood of industrialized polluted regions, etc. Block diagram of EWP-Z is shown on Fig. 2.

The images of biological objects (insects, other bioindicators) form a necessary part of databases for EWP-Z. During this system development, in the author's version, there were images of moths *Noctuidae (Lepidoptera);* they were necessary for appropriate databases development. Such databases further may be used for electronic identifiers of insects, expert systems that should determine pests' species, and etc.

Newly developed biotechnical monitoring system with expert subsystem. To solve the set of tasks during the monitoring of dangerous chemical substances influence on organisms in polluted environment, Dr. Klyuchko O.M. suggested the simplest version of biotechnical monitoring system supplemented with A) sensor group ("biotechnical sub-system" — "BTS") and B) expert subsystem. The main task of sensor group was "data generation" or "data mining" for the B) expert system. As input data to expert system we suggest using the data of well-known electrophysiological experiments with registration of transmembrane chemosensitive electric

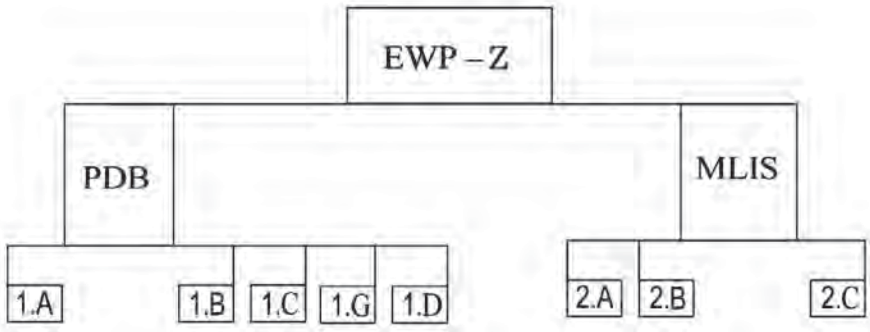

Fig. 2. **The scheme of electronic work place for ecologists and zoologists (EWP-Z) as interface in IS with expert system**

PDB-Z — own databases of zoologist: 1.A — electronic versions of publications selected by the scientist (printed versions of his own articles, prepared for publication, electronic versions of necessary articles of other authors); 1.B — database with information about substances and reagents; 1.C — DB with his own experimental, working data, monitoring data; 1.G — database with images; 1.D — DB with films of observations. MLIS is a mini-library Internet system for zoologists

currents that depended on applied chemical substances; so, we tried to demonstrate direct links between chemical structure of applied chemicals (input information) and characteristics of electric responses (output information). Expert system had to do: 1 — to distinguish the approximate types of acting chemical substances by the characteristics of electrical currents' records at BTS output; 2 — to "decide" whether this substance was dangerous or no; and 3 — to output necessary information on PC screen (whether the situation is "dangerous" or "not dangerous"). This sensor group A) that in our investigations was called "biotechnical subsystem" (or unit) — "BTS" is shown on Fig. 3.

BTS output electric signals further were transmitted to B) expert subsystem as input signals to it. The purpose of the work done was to develop computer biotechnical monitoring system for monitoring and profound study of different chemical substances influence on organism in different time intervals, from the time when the substance started to influence on organism. BTS might be a complex of electrophysiological devices for the registration of transmembrane electric currents and influences of different chemical substances on them with relative methodics — patch-clamp, votage-clamp, different microelectrode methods, and/or other methods from this spectrum. Influences of chemical substances were studied on mammal nervous cells (Wistar rats) as a result of changes in the characteristics of transmembrane electrical chemosensitive currents. Generally BTS contained three parts: mechanical-hydraulic part with biological fragment (BF — neuronal membrane, or other objects like this), electric part (electric cirquit), and computer part (Fig. 3).

BTS allowed the registration of new received data, their recording in computer memory (in local and network databases). BTS also allowed visualizing obtained results, their processing performance, data output and their analysis, and their transmission with the use of network technologies. The registration process was realized as following algorithm: the chemicals were applied to neuronal membrane in the BTS; after the applying of agonist the electrical signal could be registered; the changes of electrical ion transmembrane currents were measured. The actions of substances were measured in quantitative units. Some examples of BTS output electric currents registered by the author with collaborators in Bogomoletz Institute of Physiology NASU are shown on Fig. 4. There are some recordings of glutamate- (Glu) and kainat- (KK) transmembrane electric currents and influences on them by *Araneidae* toxins (like JSTX-3 (*Nemphila clavata*) and AR (argiopine from *Argiope lobata*, also newly synthetized substances were used) [163–182]). Other phenol- and indol-derivatives might be studied also (including some organic environmental pollutants). Examples of BTS output electrical signals might be taken to expert system input for their further processing [178].

Biological fragments (BF) in our experiments undergo preliminary processing according to specially developed procedures, including enzyme treatment; in experiments

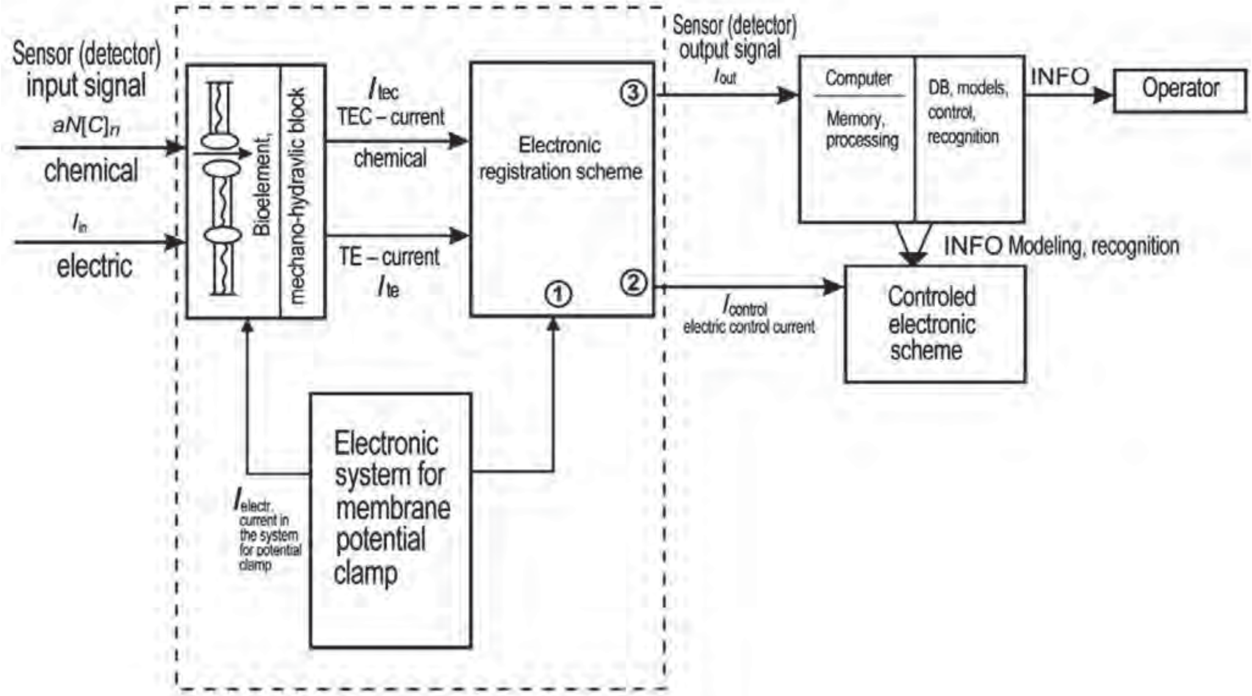

Fig. 3. **General technical scheme of BTS for the registration of transmembrane electric currents and influence of different chemical substances on them**

with pyramidal neurons of rat hippocampus we used proteases from *A.oryzae* and/or other substances in solutions with specially developed compositions and gas environments, temperature and time modes of treatment.

Substances (antagonists) were either taken from the nature, or artificially synthetized — they could be obtained using various chemical and biochemical methods. BF could be replaced depending on processing of their molecules, the type of chemicals that were analyzed; and the BF acted as the primary link in all developed biotechnical systems — as biodetector and/or bioanalyzer of active substances (including environmental pollutants). For different versions of our developed monitoring system the names BTSM-3, BTSM-4 were given; the general name of all family of such ISs is "Ecological Information System" (abbreviation in English is "EcoIS") [176]. Expert subsystem coupled with BTS was a system linked with DBs with direct and/or remote access that contains a number of subsystems for analyzing the information coming from BTS subsystem about the chemicals' influence on organisms.

Recordings on Fig. 4 were done during electrophysiological BTS experiments where BF was influenced by various chemicals (including toxins JSTX-3 and argiopin AR). The following electrical signals were obtained by the registration of transmembrane electrical currents using voltage-clamp method; object — rat hippocampal membranes (similar experiments were carried out on numerous objects of other types: motoneurons, rat brain neurons, and other diverse living objects).

Development of analytical expert system as a part of technical system for monitoring of different chemical pollutants in environment (with recognition of different molecular structures). Physical and program model of new technical system for environment monitoring with expert subsystem was elaborated [163–178]. The system was able to detect the presence of different chemicals — pollutants, to collect and to accumulate the data about such pollutants with recognition of different molecular structures, to transfer this information to local and networked databases (with open access or with restricted access), and to show corresponding output information on PC interface.

*Algorithm and its description. A*n algorithm of the work of developed technical analytical system with incorporated the simplest version of expert subsystem is represented on Fig. 5. It wass supposed that units described on Fig. 3 are included into the beginning unit on Fig. 5.

Obtained BTS results were processed (their mathematical processing was carried out by a number of methods, including methods of statistical processing, etc.), and they

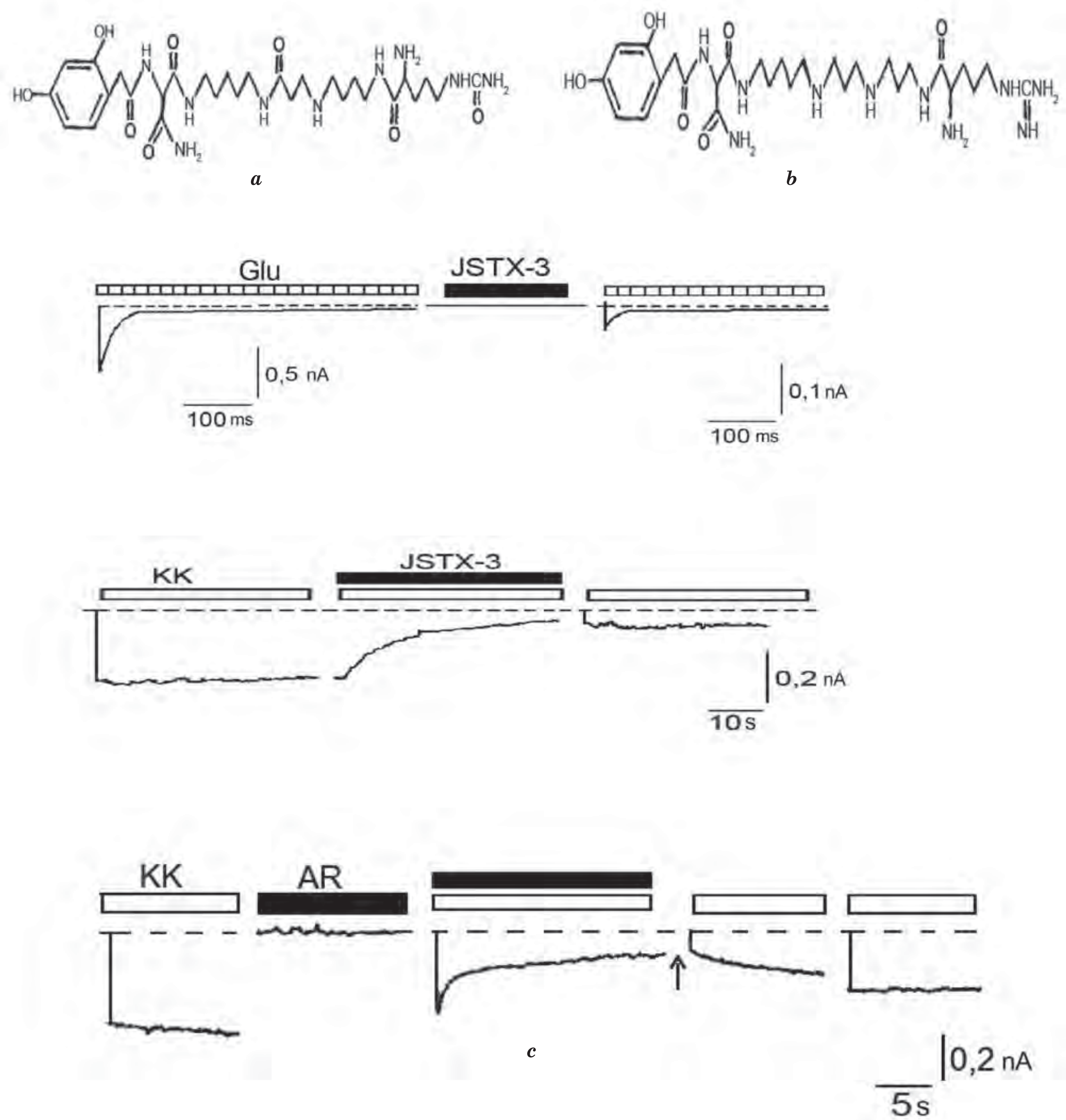

Fig. 4. **Electrical signals at the output of the BTS:**
toxins: *a* — JSTX-3 (from Nemphila clavata); *b* — AR (from Argiope lobata); *c* — their influences on transmembrane electric currents.
Toxin JSTX-3 blocked glutamate-activated (Glu, above) and kainat-activated (KK, middle) transmembrane ionic currents. After receiving the control response to KK, toxin JSTX-3 was applied by the background of the KK-activated current. Concentrations of Glu and KK were 1 mmol/l, JSTX-3 was 10^{-4} mol/l. V_{hold}= −50 mV [163–178].
Toxin argiopine (AR, below) blocked the open state of KK-activated ion channels. After receiving the control response to KK, the neuron was maintained in AR during 3 min., then on the background of AR the KK-solution was added. Concentrations: KK 1 mmol/l, AR $1{,}6\cdot10^{-2}$ mol/l, V_{hold} = −100 mV. Toxin was removed from the membrane through 15 s [163–178].
All records were done on different neurons

were analyzed by comparing them with the corresponding values from the databases, which are linked with expert system (the DB are located in the memory of local or remote servers). During processing of input electrical signals, the sets of characteristics like the times of electric currents' amplitude decline after the action of chemical antagonists, the binding and dissociation constants of complex receptor-antagonist, etc., were calculated.

The results of obtained recordings analysis were displayed on the output monitors of the expert system (Fig. 6, 7). If such expert system is incorporated into the biotechnical system for monitoring BTSM-4, the results of analysis were displayed on the output

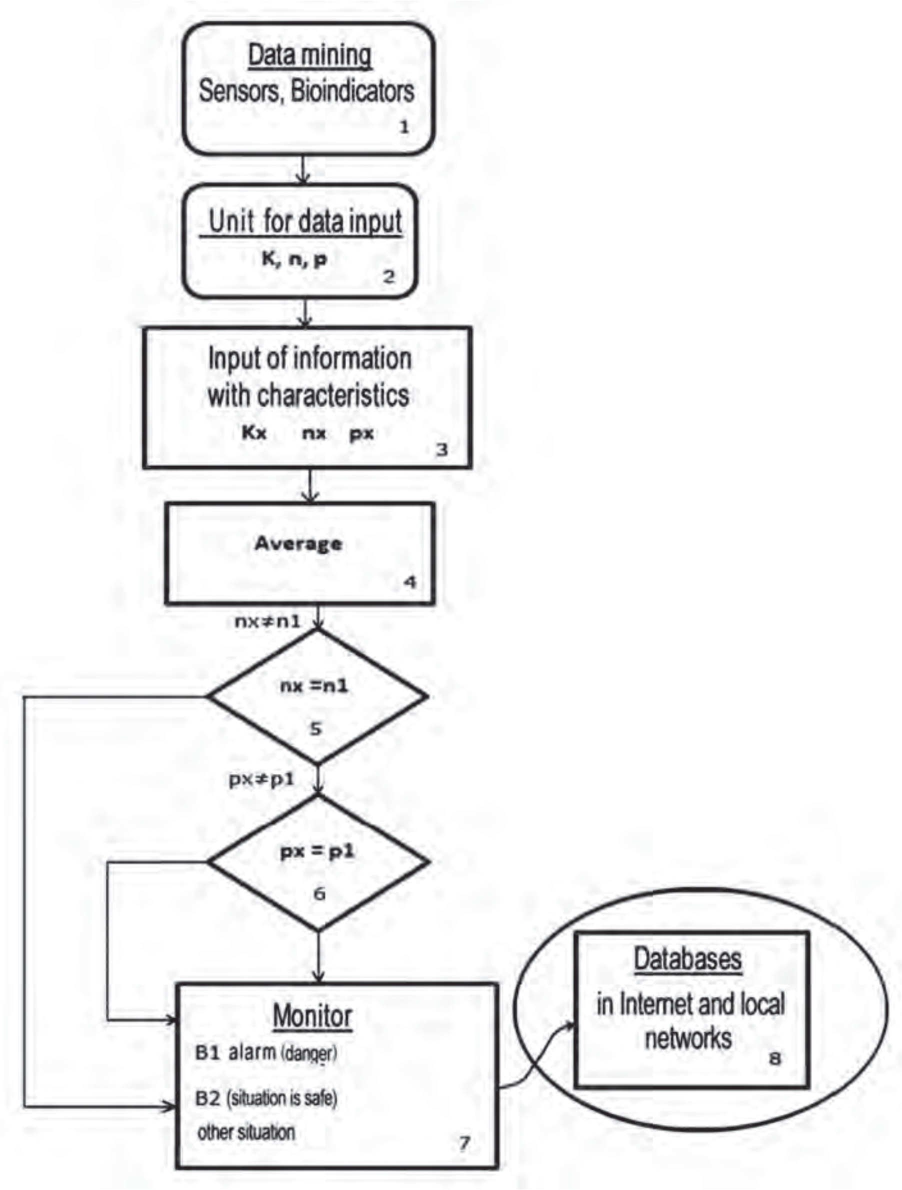

Fig. 5. **An algorithm of expert system functioning with the output data recording and the work of linked alarm subsystem:**

Comments to the algorithmof expert system functioning

Unit 1) Input data mining and/or obtaining. The data were input from sensors (like described ones, or registered by bioindicators).

Unit 2) Data input.

Unit 3) Input of the data with certain characteristics (information supply).

Unit 4) Calculation of average values.

Units 5; 6) The heart of analytical — expert system: expertise providing. Formation of output messages depending on characteristics of revealed and studied chemical substances.

Unit 7) Display of information on the monitor with corresponding comments (alarm or no).

Unit 8) Information was transmitted and recorded in local and Internet databases monitor of BTSM-4. In case when the result of comparison by expert system determined the nature of the substance (the substance is dangerous to organism, or it is safe, or its effect is other), then an appropriate message is displayed on output interface of the expert system (BTSM-4 monitor). The presence of BTS in the network of WEB-based system BTSM-4 created the possibilities for data transfer, data spreading over the network with the further use of all opportunities and benefits of network technologies.

In such a way a number of effects might be registered. For example, let's imagine that on BF influenced the substances JSTX-3 or AR — antagonists of glutamate- and kainat-activated electrical sodium transmembrane currents — and corresponding current registrations were done (recording on Fig. 4). Before there were demonstrated that both JSTX-3 and AR stops activity of glutamatergic synapses in mammals' brains in organism; in some cases, a paralysis or a fatal end is possible. The expert system [Fig. 5] processed this information and it is displayed on monitor screen [Fig. 6, 7]. If necessary, a signal of danger (sound, flash, other signal) appeared. For the implementation of the method, both software from standard packages and specially designed original samples were used (internal databases of the expert system were not shown on Fig. 5).

Program code and its description. Corresponding original software was developed. Program code was written in Java language fot interfase in Ukraine. The program code was written for the work of technical analytical expert system that is able to distinguish environmental hazard according to a number of input variables (in); the fragment of program code is presented below.

```
import java.util.Arrays;
import java.util.List;
import java.util.Scanner;
import java.sql.*;
import java.util.Properties;

public class Detector{

    public static void main( String[] args ) {

        List<String> a = Arrays.asList(
"1", "2" );
        List<String> t = Arrays.asList( "3",
"4" );
        List<String> A = Arrays.asList( "A",
"A" );

        Scanner sc = new Scanner( System.in );

        System.out.println( "Введіть вхідні
дані  у такому вигляді \"Ах Тх Х\" ( напри-
клад 1 3 А ):" );

        String inputLine = sc.nextLine();
        String[] input = inputLine.split(" ");
        String result = "";
        Boolean detected = false;

        for ( int i = 0; i < 2; i++ ) {

            if ( input[ 0 ].equals( a.get( i ) )
&& input[ 1 ].equals( t.get( i ) ) && input[ 2
].equals( A.get( i ) ) ) {

                result = "B" + ( i + 1 );
                System.out.println( "Знайдено
речовину:" + result );
                saveToDB( result );
                detected = true;
                break;

            }

        }

        if( detected == false ) {

            System.out.println( "Знайдено
іншу речовину" );

        }

    }

    public static void saveToDB( String
result ) {

        String dbURL = "jdbc:mysql://
localhost:3306/detector";
        String username ="root";
        String password = "password";

        Connection dbCon = null;
        ResultSet rs = null;

        try {

            dbCon = DriverManager.
getConnection( dbURL, username, password );

            String query = "INSERT INTO
substance ( substance_code ) VALUES ( ? )";

            PreparedStatement stmt
= dbCon.prepareStatement( query );
```

```
                        stmt.setString( 1, result );

                        stmt.executeUpdate();

                        dbCon.close();

                } catch ( SQLException ex ) {

                System.out.println(
"SQLException: " + ex.getMessage() );
                System.out.println( "SQLState:
" + ex.getSQLState() );
                System.out.println(
"VendorError: " + ex.getErrorCode() );
                }

        }

    }
```

Technical results of developed expert system examination were as following. 1. An original expert analytical system was developed, which determines the quantitative and qualitative components of the presence of toxic pollutants (phenol- and indol- derivatives) in environment (industrial regions, other). 2. The use of developed electronic expert system permits to determine the presence of harmful and toxic substances in the environment and to send the signal-notification about their availability and quality. 3. It gives the possibility to monitor the effects of a large number of different chemicals much better, more efficiently, with higher accuracy than prototypes did. 4. BTS linked with the expert system allows analysing the impact of a large number of substances of natural and artificial origin. 5. Results recordings in the form of digitized electrical signals (in local and network databases) in memory of network computers permits to visualize them, to process, to analyse, to output the data, and to transfer them using all advantages of network technologies. 6. The algorithm of expert system functioning, and corresponding software code were developed for this original expert analytical system.

Development of new methods of qualitative and quantitative analysis. Using described expert systems it became possible to develop new methods of qualitative and quantitative analysis of chemicals according to their physiological influence on registered electric currents in neurons of biological organisms. Necessary requirements for this were to make links between the expert system and enough numbers of chemicals and recordings (electrical responces of cell membrane) in the databases; and such databases had to have as more as possible experimental recordings like ones on Fig. 4. Some numbers of such recordings have to be declared as “standard” and to be recorded into separated database for comparison with newly obtained data. The

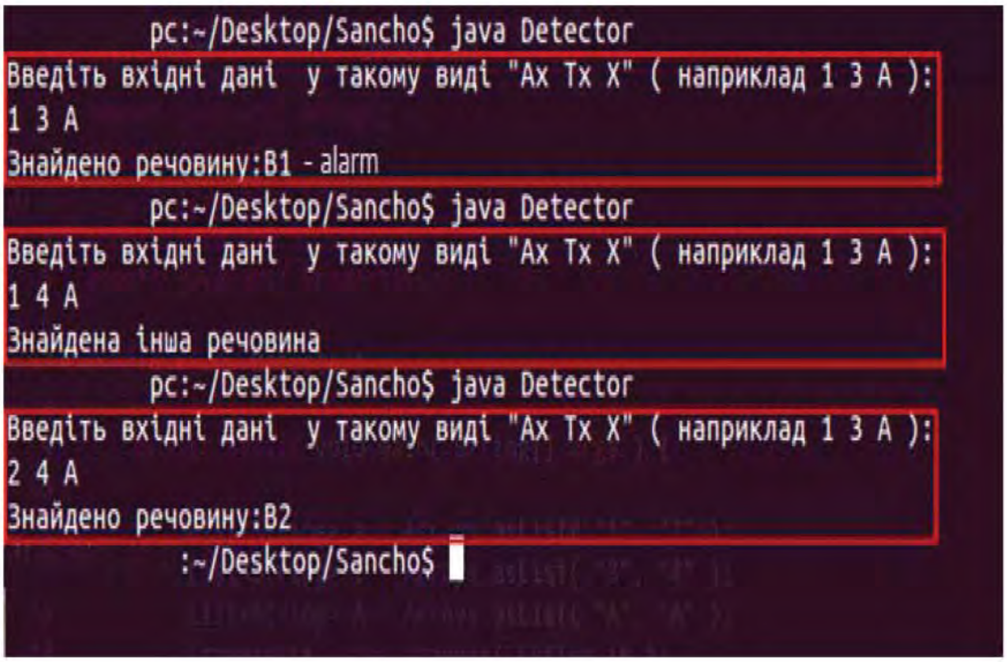

Fig. 6. **Interface for operator communication with expert analytic system; view of monitor screen:** comments and instructions were written in Ukrainian for domestic use of device

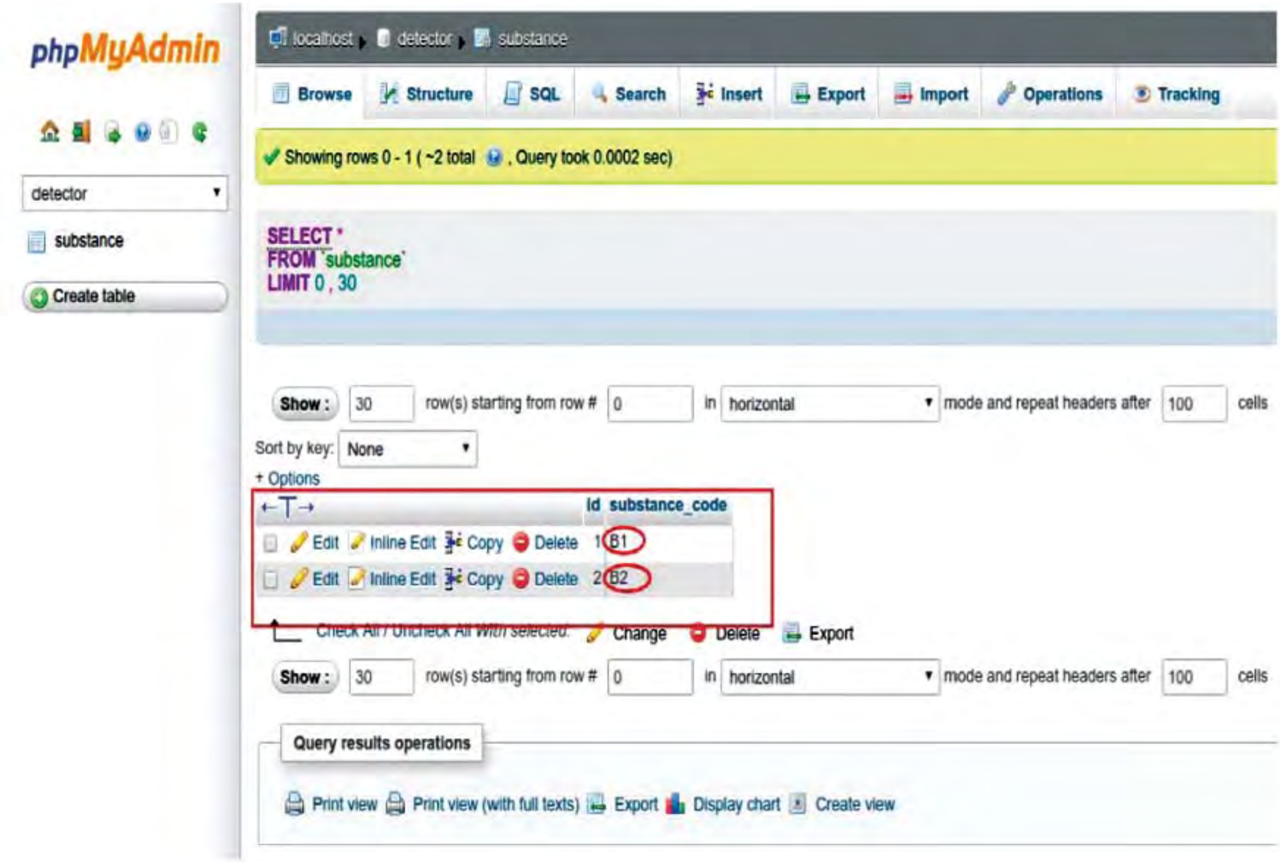

Fig. 7. **Data output from expert analytical system to operator and to databases in the Internet**

essence of these methods of qualitative and quantitative analysis was in the discovered regularities between the structures of chemical substances and physiological effects they occur, for example, between chemical structures of JSTX-3 and AR and differences in their blocking activity (Fig. 4). After the obtaining of output transmembrane electric currents records (for example, KK-activated) under the influences of different chemical substances (Fig. 4) it was possible to compare them with standard recordings in databases and then to identify them with defined chemical structures. With enough good and complete databases the expert system can do these procedures with good result. According to the simpliest algorithm we suggested in logical units on Fig. 5 the functions of comparison were realized. There were compared two main characteristics of activity of examined substances JSTX-3 and AR: 1) (nx) — whether antagonist decreased the amplitude of transmembrane electric current: “yes” (1) or “no”(0); 2) (px) — whether it was possible to remove of antagonist from membrane by “washing” with consequent restoring of electrical currents’ amplitudes: “yes” (1) or “no”(0). Sure, more logical subunits it is possible to use also for each individual task solution depending on processed input information. More details about such methods of qualitative and quantitative analysis of chemicals we hope to write in our following publications. Described methods of BTS using with the expert system and nowel methods of qualitative and quantitative analysis were defended by our patents [179–182].

Thus, in present publication were demonstrated that electronic biomedical expert systems might be powerful tools in contemporary biotechnology as well as in biology and medicine in general. The purpose of present article was to make profound review of such information expert systems, their structure, functions and practical applications to give ones a possibility to develop new system types for specific biotechnological or research tasks solution. We discussed the abilities of electronic expert systems, their use as one of important type of modern electronic information systems. Further the information about different prototypes of expert systems in biotechnology as well as in other biomedical spheres was suggested (possibilities of these systems application for production in agriculture, nature protection from pests and ecological pollutants, for medical systems, and etc.). The principles of expert systems' structure, electronic workplaces, as well as their functioning in biomedical electronic network information systems were demonstrated. Actual information about bioorganisms populations monitoring using electronic information systems with databases and expert capabilities was given. Biotechnical system with expert subsystem for monitoring of substances, harmful for living objects was described.

Developed original electronic information system for ecological monitoring was called "EcoIS" ("Ecological information system"), and one of its versions described in present article was called "BTSM-4". In framework of developed electronic information system the design of user interfaces ("Electronic work places — EWP") were done. The structure and function of one of such versions "EWP-Z" was described in details in present article. All abovementioned numerous electronic systems have been described already in publications in technical scientific literature and defended by patents [173–178].

The developed the simplest version of the expert system for monitoring and profound studying of different chemical substances' influences on organism (chemical environmental pollutants) also was described in details [178]. The advantages of proposed expert system and method were achieved due to co-work of two in-built into "EcoIS" subsystems: subsystem 1 (expert) and subsystem 2 (specially developed BTS with variable BF). Due to the functional capabilities of both subsystems, it was possible to register changes in electrical transmembrane currents in neuronal membranes after the influence of chemicals on them, which may indicate a possible danger to living organism; the output monitor of electronic system then receives corresponding signal. The analysis of the data obtained from BTS was carried out by comparing the data from the corresponding inner databases connected with the expert system. After such analysis by expert system the resulting report about the presence (or absence or otherwise) of danger to organism in zone with chemical substances were displayed on the monitor at the output of electronic information system BTSM-4; if necessary, an alarm signal (sound, flash-signal, others) is output also. The use of BF as a detector and/or bioanalyser allows a significant increase of chemicals number in the list of substances, and among them it is possible to register such harmful and dangerous substances for humans, as some derivatives of phenols and/or indoles. BTSM-4 can be used also as an express system.

Using described expert systems it became possible to develop new methods of qualitative and quantitative analysis. The essence of these methods was in registered regularities between the structure of chemical substances and physiological effects they occur. After the obtaining of output transmembrane electric currents records under the influences of different chemical substances (Fig. 4) it was possible to compare them with standard recordings in databases and then to identify them with defined chemical structures. With enough good and complete databases the expert system can do this procedure with satisfactory result. The described methods of BTS using with the expert system and nowel methods of qualitative and quantitative analysis were defended and supported by patents [162–182]. The work done might be implemented in such branches as biotechnology, biophysics, ecology, ecological safety, pharmacology.

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ЕЛЕКТРОННІ ЕКСПЕРТНІ СИСТЕМИ ДЛЯ БІОЛОГІЇ ТА МЕДИЦИНИ

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Метою роботи було дослідження прототипів інформаційних експертних систем, їхньої структури, функцій, практичного використання та розроблення нової системи для вирішення завдань у галузі біотехнології, в лабораторній практиці й захисті довкілля. Розглянуті прототипи розроблено для застосування в генетичних дослідженнях, у сільському господарстві, охороні природи від шкідників та екологічних забруднювачів, у медицині тощо. Під час виконання роботи використовували методи компаративних досліджень зразків технічних пристроїв, імітаційного та програмного моделювання, які базувалися на числових результатах, отриманих у експериментах з реєстрацією хемочутливих трансмембранних електричних струмів у нейронах у режимі фіксації потенціалу. У результаті було розроблено оригінальну експертну систему, поєднану з детекторною групою, базами даних та інтерфейсом. Розроблена експертна система здатна автоматично розрізняти деякі типи хімічних речовин на вході й виводити дані їх ідентифікації та за потребою — повідомлення щодо їхньої шкідливості. Зроблено висновки про практичну цінність наведених даних для створення нових електронних експертних систем для моніторингу наявності шкідливих речовин у довкіллі. У заключній частині також обговорюється можливість застосування розробленої експертної системи для нових методів якісного та кількісного аналізу деяких органічних сполук.

Ключові слова: біологічні та медичні експертні системи, електронні інформаційні системи, біоінформатика, бази даних.

ЭЛЕКТРОННЫЕ ЭКСПЕРТНЫЕ СИСТЕМЫ ДЛЯ БИОЛОГИИ И МЕДИЦИНЫ

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Целью работы было исследование прототипов информационных экспертных систем, их структуры, функций и практического применения, а также разработка новой системы для решения задач в области биотехнологии, в лабораторной практике и защите окружающей среды. Рассмотренные прототипы разработаны для применения в генетических исследованиях, в сельском хозяйстве, охране природы от вредителей и экологических загрязнителей, в медицине и т. д. При выполнении работы использовали методы компаративных исследований образцов технических устройств, имитационного и программного моделирования, базирующиеся на численных результатах, полученных в экспериментах с регистрацией хемочувствительных трансмембранных электрических токов в нейронах в режиме фиксации потенциала. В результате была разработана оригинальная экспертная система, соединенная с детекторной группой, базами данных и интерфейсом. Разработанная экспертная система способна автоматически различать некоторые типы химических веществ на входе, выводить данные их идентификации и при необходимости — сообщения об их вредности. Сделаны выводы о практической ценности приведенных данных для создания новых электронных экспертных систем для мониторинга наличия вредных веществ в окружающей среде. В заключении также обсуждается и возможность применения разработанной экспертной системы для новых методов качественного и количественного анализа некоторых органических соединений.

Ключевые слова: биологические и медицинские экспертные системы, электронные информационные системы, биоинформатика, базы данных.