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SELECTED PAPERS *from*
THE EUROREGIONAL CONFERENCE
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Building Information Society in the Healthcare in Euroregion Niemen

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MEDICAL UNIVERSITY *of* BIAŁYSTOK
DEPARTMENT *of* PATHOPHYSIOLOGY *of* PREGNANCY

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FACULTY *of* COMPUTER SCIENCES

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Contents

Recording of biosignals from the human uterus, a basis for the development of new therapies in preterm labour and primary dysmenorrhoea

Åkerlund M

Department of Obstetrics and Gynecology, University Hospital of Lund, Sweden

Extended abstract of presentation at the Euroniemen Conference in Bialystok, Poland, February 18, 2005

The uterine contractility of labour preterm and at term pregnancy can be monitored by external recording by a pressure sensor and quantified as frequency of uterine contractions. After rupture of the fetal membranes intrauterine pressure can be studied and various parameters analysed, e.g. frequency and amplitude of contractions and the basal tone. The area under the curve (AUC) constitutes a summary of these parameters. The activity of the pregnant human uterus on a cellular level can be investigated *in vitro* by recording of isometric contractions of myometrial strips obtained at caesarean section. These methods have been a basis for the development of antagonists to the hormones oxytocin and vasopressin, which via an action over oxytocin and vasopressin V_{1a} receptors play a central role in the onset of preterm labour (see Åkerlund, Roczniki Akademii Medycznej w Białymstoku 2004; 49: 18-21).

Oxytocin and vasopressin are synthesised in the hypothalamus and released to the blood via the posterior pituitary lobe. During the stress of labour the uterus also produces oxytocin and vasopressin in substantial amounts. Recently, immunoreactive oxytocin and vasopressin have been demonstrated in the myometrium of pregnant women. The uterine oxytocin and vasopressin receptors vary to some extent during pregnancy and seem to be somewhat up-regulated at the onset of labour preterm and at term. After infusion of oxytocin and at advanced labour the receptor concentrations decrease.

Irrespective of the source of origin, antagonists of the oxytocin and vasopressin V_{1a} receptors may have a therapeutical effect in preterm labour and a project to develop receptor antagonists was commenced more than 20 years ago by our group in Lund together with the pharmaceutical company Ferring in Malmoe, Sweden. During the development phase different compounds were first investigated *in vitro* as to potency and duration of effect as well as regarding intrinsic agonistic action. They were later studied *in vivo* in non-pregnant, healthy volunteers by recording of intrauterine pressure and in patients with preterm labour in pregnancy weeks 33-35. The lead compound, atosiban, was also studied in women with very early preterm labour and then extensively in huge multi-centre trials. This substance was found to be at least as potent as previous therapies but to have a much higher specificity in action, leading to markedly reduced side effects. Atosiban is now marketed word-wide.

In non-pregnant condition uterine contractility *in vivo* can be measured by recording of intrauterine pressure by microtransducer catheters with one or several pressure sensors. Uterine blood flow in women is usually measured by thermodilution techniques or Doppler ultrasound. *In vitro*, the most common method of studying contractility for the non-pregnant uterus is by recording isometric contractions of myometrial strips obtained at hysterectomy.

The myometrial activity and uterine blood flow in women vary in a characteristic way during the menstrual cycle with well-coordinated contractions of high amplitude at the onset of menstruation and lower, localised contractile activity with higher basal tone at midcycle. In women with primary dysmenorrhoea the myometrial activity is increased and uterine blood flow reduced, which to a large extent causes the pain of the condition. Prostaglandins have a well-established role in the aetiology of the increased uterine contractility of primary dysmenorrhoea. An even more forceful uterine stimulant, which has to be shown of importance in the condition is vasopressin. The circulating level of this hormone in women with primary dysmenorrhoea is elevated 2-4 times, which can induce endometrial synthesis of contractile prostaglandins. Furthermore, in dysmenorrhoea the uterine sensitivity of vasopressin as well as the concentration of vasopressin V_{1a} receptors is increased. Oxytocin is a five times

ADDRESS FOR CORRESPONDENCE:
Mats Åkerlund
Department of Obstetrics and Gynecology
University Hospital of Lund
SE-221 85 Lund, Sweden
Tel: +46 46 17 25 53 Fax: +46 46 15 78 68
e-mail: mats.akerlund@gyn.lu.se

weaker uterine stimulant than vasopressin in non-pregnant condition. However, our group recently demonstrated oxytocin mRNA in the endometrium of non-pregnant women by in-situ hybridisation and real time PCR. The amount seems to vary during the menstrual cycle reaching the highest level around the time of ovulation. The importance of oxytocin as an aetiological agent of primary dysmenorrhoea is not clear.

A new therapeutic approach for primary dysmenorrhoea is to develop orally active antagonists of uterine vasopressin V_{1a} receptors. In the process of developing vasopressin V_{1a} and oxytocin antagonists for using non-pregnant condition, recording of contractile activity of human myometrial strips and uterine arteries of different diameters is a useful approach. Studies on such tissues from other species give little guidance. *In vivo*, initial testings in healthy, sterilised women with recordings of intrauterine pressure, experienced pain and plasma levels of biomarkers of uterine ischemia during administration of vasopressin and antagonists are a suitable option. Such recording can then be performed in dysmenorrheic subjects before commencing larger clinical trials. A therapeutic effect of vasopressin V_{1a} and oxytocin receptor blocking agents have been demonstrated by our group in dysmenorrhoea both for the peptide analogue atosiban and for the orally active compound SR 49059.

Prepared mind and the innovative process. A personal account of drug discovery

Batra S

Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden

It is now recognised that there is considerable, even unlimited potential for innovative research in all academic research establishments – be it a university, a hospital or a research institute.

Most of the major discoveries leading to the benefit of public at large have come from university research. Some notable examples are: Lasers, Semiconductors, Superconductors, Computers, Biotechnology and a variety of therapeutic agents, one of the recent one being Viagra for which the ground was laid by the academic scientists in the eighties.

The author illustrated by describing his personal account of how an unexpected finding when logically followed can lead to the discovery of novel compounds with potential for use in oncology.

The novel compounds which have been patented are steroid carbonates and were shown to markedly potentiate the cytotoxic effect of cancer therapeutics in multidrug resistant (MDR) tumor cells (US patent no 604182)

In contrast to USA, the intellectual property (IP) management at the European universities, unfortunately, has received little attention and in some cases it is still non-existent, which has resulted in the loss of opportunities to commercialise the discoveries and the innovative findings. The reasons for this in the authors view are, partly tradition, partly individual attitudes, lack of information and the lack of risk/venture capital.

It is in the interest to each country to capitalise on the knowledge, which is created within the university and hospital communities.

For this to happen researchers and administrators (or managers) must be aware of not only importance of protection of the IP but of the responsibility of creating a research environment in which the individual researcher is prepared to utilise the full innovative potential of his (her) research.

ADDRESS FOR CORRESPONDENCE:
Satish Batra
Department of Obstetrics and Gynecology,
University Hospital, SE-221 85 Lund, Sweden

Discoveries are made by individuals whose minds are prepared to see and interpret events and observations that have made no or little impressions on others. This is nicely put up by Louis Pasteur some 150 years ago when he said "Chance favours only the prepared mind".

There are numerous examples of discoveries made through serendipity. The simple definition of serendipity is the gift of finding valuable or agreeable things not sought for or, the faculty of making fortunate and unexpected discoveries by accident (dictionary definitions).

Only very few individuals have the gift of genius (born genius). However, it is possible to train oneself to a considerable extent. Two important measures to be taken are:

Spark of genius: Unless the mind is thoroughly charged, it does not ignite.

Can train:

- Making & recording observations – both expected & unexpected. Observation of things one is not looking for flexible thinking and interpretation.
- Should not strive to fit new info/knowledge into the dogma of the day. Which means, thinking not circulatory, but tangentially, differently

A brief description of how to protect IP was given along with the process of patent application and prosecution. The role of the university / academic establishment in innovation management was further highlighted.

What is a patent?

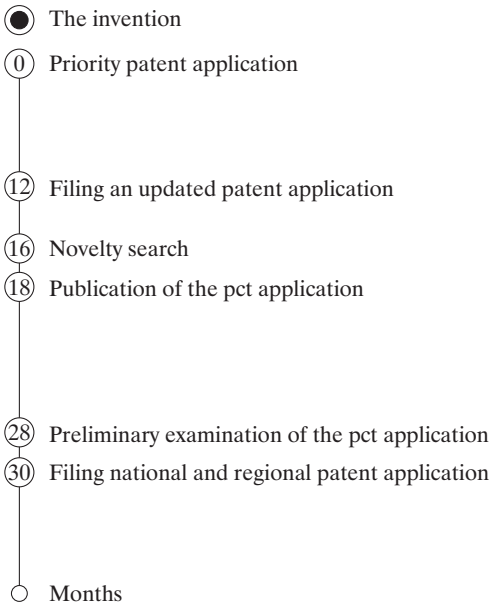
A patent is a mean of protection of intellectual property.

What is patentable?

In order to be patentable an invention (finding) must be novel, and it must have utility. Over the years a third criteria has been added emerged: That the invention is not obvious to a person skilled in the field of the inventions.

Prepared mind in most cases is a prerequisite to grab a passing innovation. One can train to be prepared and university management greatly can help by providing the right envi-

Figure 1. **Patent application drafting and prosecution**



ronment, support, inspiration and research strategy etc. But, although crucial, this in itself is not enough. The university or the academic establishment has a greater role to play in seeing that the innovative research is propelled, harnessed and capitalised by efficient innovation management and IP protection.

At our university in Lund (Sweden), which also was relatively late in starting up Innovation Management (IM), the strategic goals were formulated in 2002, which are IM University of Lund, Faculty of medicine

General objective:

- To increase awareness of innovative potential of ongoing research in the faculty.

Specific objectives:

- To inspire researchers to think in terms of innovative potential of their research project.
- To assist research workers in the evaluation of ideas/method where potential for innovation is considered a possibility.
- To assist researchers in commercialising an innovative finding.

Building eHealth information society in Podlasie region – key strategic factors and struggle for infrastructure and standards

Bobrowski L

Computer Science Faculty, Technical University of Białystok,
Institute of Biocybernetics and Biomedical Engineering PAS, Warsaw, Poland

The Podlasie region is situated in the far north-eastern part of Poland and forms one of the important gates of the European Union to the East. This region with many forests and lakes is known as the green lungs of Poland. Large rural areas with sparse population is characteristic feature of the region. In this context, the demands for the e-health applications are well justified. A variety of the e-health services should be successively planned and implemented in the Podlasie region in the near feature.

The Computer Science Faculty TU Białystok has engaged in building an information society in Podlasie through a variety of educational initiatives and through cooperation with administration units and schools in the region. The Excelence Center in the Technology of Information Society has been appointed recently at our Faculty by The Polish Ministry of Science (KBN). We see the co-operation with the Medical University in Białystok as a real chance for developing e-health services in the region.

One of the fundamental constraints in the developing the information society in the region is the lack of sufficiently efficient telecommunication infrastructure. This situation should be significantly improved by means of development of the broadband network Pionier and the realisation of the grid project Clusterix. These national projects are aimed not only at academic needs but also could be used in the public services within the scope of e-government or e-health.

Our area of expertise is in the methods of knowledge exploration in databases. The techniques of knowledge exploration in databases can be used, among others, in the e-health services aimed at distance consultancy. The basic scheme here is the case based reasoning. Remote e-health consultancy can be based on the search in the referencing databases for the most similar cases to the patient actually analysed. One of the necessary conditions for implementing this scheme is developing standards for patients representation in referencing databases from different medical specializations. The manner of the new patient representation should be the same as the representation of the earlier patients collected in the referencing database. Moreover, the patients representations in the referencing databases should provide the possibility of answering all the basic questions of remote consultancy. The answer to the questions of distance consultancy could be based on the search for precedents in the referencing databases.

The developing of standards and collecting medical information in the referencing databases from variety of complementary medicine specializations is actually the most acute problem in planning and implementing the distance consultancy in e-health applications. Solution to this problem should emerge with strong commitment and good will on the part of medical experts from different areas of medicine and their enduring co-operation with informatitions.

ADDRESS FOR CORRESPONDENCE:
Leon Bobrowski
Computer Science Faculty, Technical University of Białystok
Wiejska 45a, Białystok, Poland

New experimental techniques in genomics: challenges for data processing and analysis

Burzykowski T

Center for Statistics, Limburgs Universitair Centrum, Diepenbeek, Belgium

Abstract

A lot of current research in biology and medicine is aimed at understanding, what is the role of particular fragments of a living's organism genome from a point of view of different biological process taking place in a cell. All cells in an organism contain the same DNA, but despite that, they actually differ. The differences are due to the fact that, stimulated by cell regulatory mechanisms or environmental factors, fragments of DNA (genes) express their code and provide the instructions when and in what quantity to produce specific proteins. This process is called **gene expression**. Differential gene expression implies differential protein abundance, and thus induces different cell functions. Gene expression level is a measure that aims at a quantitative description of the gene expression.

As specified by the **central dogma of molecular biology** (Crick, 1970) [1], in the first step, called **transcription**, the genetic information carried by a gene is transcribed into mRNA (**messenger RNA**). In the second step, called **translation**, an appropriately modified copy of mRNA migrates to the cytoplasm where it serves as a template for protein synthesis. Because the synthesis of the protein associated with a particular gene involves the transcription of DNA into mRNA, one might assume the abundance of mRNA produced during the transcription as a measure of the gene expression.

Analysis of mRNA-based measures of gene expression levels is one of the best practical solution available at this moment. However, due to a variety of reasons, mRNA and protein levels and their alterations often poorly correlate. To study the functional and biochemical features of specific cell types, one should actually investigate both the gene expression levels and the type and abundance of produced proteins. The latter is the aim of **proteomics**. The investigation of **protein expression levels** may be even more important in situations when gene expression analysis is not feasible (e.g. for the complex protein mixtures present in body fluids such as plasma, synovial and cerebrospinal fluid).

Rapid developments in molecular biology technology have led to the development of various experimental methods making possible investigation of gene- or protein-expression levels. These methods include, e.g. microarrays (cDNA, Schena et al. [2]; or oligonucleotide, Lockhart et al. [3]); Serial Analysis of Gene Expression (SAGE; Velculescu et al. [4]); 2-dimensional electrophoresis with mass spectrometric identification; combined fractional diagonal chromatography (COFRADIC; Gevaert and Vandekerckhove, 2004, [5]).

All these techniques share several common features. For instance:

- they use sophisticated instrumentation;
- they are very sensitive, also to systematic effects due to time, place, reagents, personnel, etc.;
- they yield complex data, in terms of correlation, variability, etc.;
- they generate many (10^2-10^5) measurements per biological sample;
- their reproducibility can easily be compromised.

Because of these features, processing and analyzing data produced by these methods is still a challenging task. More specifically, several problems can be listed:

- the need for preliminary preprocessing, aimed at removing of artifacts, normalization, summarizing signals, assessing quality etc.;
- the data require novel methods of analysis, as they do not fit into the classical framework where the number of observations (samples) is greater than the number of variables (measurements);
- taking into account the complexity of data requires advanced methods of analysis;
- the large amount of measurements creates a need for tools allowing automated analyses; on the other hand, it results in computational problems when advanced techniques are used.

ADDRESS FOR CORRESPONDENCE:
Tomasz Burzykowski
Center for Statistics, Limburgs Universitair Centrum,
3590 Diepenbeek, Belgium
e-mail: tomasz.burzykowski@luc.ac.be

In general, one can note that the new experimental technologies are developed at a quicker pace than the methods that can address the problems mentioned above. As a result, sometimes the basic issues regarding repeatability of measurements, susceptibility to systematic effects, generalizability of findings etc., are not well understood and/or resolved before the technology is put into practice. Obviously, this can lead to potentially serious problems.

Potential promises and pitfalls related to the use of the novel genomic technologies are very well illustrated by the following example related to the use of protein mass spectra to discriminate between cancerous and normal samples.

In brief, in surface-enhanced laser desorption and ionization time of flight (SELDI-TOF) mass spectrometry a biological sample (such as serum) is apllied to a precoated stainless steel slide, which binds preferentially a particular class of proteins based on their physiochemical properties. The sample is further mixed with an energy absorbing matrix, which causes the entire mixture to crystallize as it dries. The crystal is put into a vacuum chamber and is hit with a laser, what produces ionized protein molecules in the gas phase. A brief electric field is then applied to accelerate the ions down a flight tube, and a detector at the end of the tube records the time of flight, from which the mass-to-charge ratio (m/z value) of the protein can be derived. A typical spectrum consists of the sequentially recorded numbers of ions arriving at the detector (the intensity) coupled with the corresponding m/z value. Peaks (local maxima) in the intensity plot ideally correspond to individual proteins. One can distinguish them from features (the observed intensities at a particular m/z values). A set of spectra will have thousands of features, but only a small fraction of these would correspond to peaks.

Based on a spectrum, one can attempt to build a proteomic pattern, that is, a pattern discriminating between spectra coming from different biological samples. It can be formed by a small key subset of proteins or peptides buried among the entire repertoire of thousands of proteins represented in the sample spectrum. The pattern can be defined by peaks (or features) at key m/z positions.

Petricoin et al. [6] used SELDI-TOF mass spectra to discriminate between ovarian cancer and normal samples. They used samples from 100 ovarian cancer patients, 100 normal controls and 16 pts. with "benign disease" (216 in total). They constructed a proteomic pattern based on 50 cancer and 50 normal spectra ("training set"), and then tested it on the remaining 116 samples ("test set"). As a result, they were able to correctly classified 50 out 50 of the "test" ovarian cancer cases (100% sensitivity) and 63 out of 66 of the "test" non-malignant cases (95% specificity). The estimated values of sensitivity and specificity are impressive and the results deservedly attracted a lot of attention.

In 2004 the same team published results of an additional analysis of the data, using a higher-resolution technique called the hybrid quadrupole time-of-flight (QqTOF) mass spectrometry (Conrads et al. [7]). Using the same biological samples as Petricoin et al. [6], they constructed a proteomic pattern capable of achieving a 100% sensitivity and 100% specificity for identifying cancer from normal.

The paper by Conrads et al. [7] does suggest some issues, though. For instance, the authors acknowledge that their quality assurrance and control (QA/QC) measurements "indicated 32 spectra that were of lesser quality (…). These mass spectra were all generated at the end of the experimental run, suggesting that a deviation in the process had occurred". It appears that these 32 spectra were removed from both the Petricoin et al. [6] and Conrads et al. [7] analyses. More importantly, however, from *Fig. 7* of Conrads et al. [7] one can infer that samples were processed in batches, with normal samples processed first, and control samples next. Thus, a part of the normal samples was processed at the time when the quality of the measurements was deteriorating. This raises a question whether the obtained results are due to confounding of bad quality samples with normal samples.

More insight into the results of Petricoin et al. [6] and Conrads et al. [7] was provided by Baggerly et al. [8]. They reanalyzed the three following datasets:

1. the one described in Petricoin et al. [6] (216 spectra), with spectra obtained using the Ciphergen H4 ProteinChip array;
2. the same 216 samples run on the Ciphergen WCX2 ProteinChip array (corresponding to the paper of Conrads et al. [7]);
3. a new set of 253 spectra (91 normal and 162 cancer samples), run on the WCX2 array.

Based on their analysis, Baggerly et al. [8] reported the following:

- There was an apparent change in protocol in the middle of dataset 1, which might be due to, e.g. a shift between chip types. As the authors comment: "Such technological differences can give rise to real differences in the spectra, but these differences are not biologically interesting".
- There was an offset (a shift along the horizontal m/z scale) between datasets 2 and 3, that was substantially larger than the nominal precision of the procedure. As the authors note: "A shift of this magnitude could cause the same protein to be identified differently in the two different experiments, obscuring the biology".
- They were unable to separate normals from cancers in dataset 3 using the proteomic pattern developed from dataset 2. This questions the generalizability of the discrimination procedure developed by Petricoin et al. [6] and Conrads et al. [7].
- They were able to perfectly classify the samples in dataset 3 using a set of features lying wholly in the noise region (low m/z) of the spectra. However, as there can be no biological reason for the differences between samples in this region, this would suggest a systematic difference in the way the groups of samples were processed. The authors note that "the features supplied for dataset 1 are also in the lower end of the mass range".

The above example clearly illustrates challenges related to the practical use of the novel techniques aimed at quantification of gene- or prtoein-expression levels. Undoubtedly, the techniques offer a great potential for getting more insight into interesting biological processes. However, before implementing them in practice, one should very carefully assess their properties. For instance, one should ensure repeatability of results. To this aim, potential sources of variability should be investigated and methods to control them developed. One should also develop

methods of calibration and normalization of measurements, which would ensure comparability of the results obtained, e.g. in different experiments. Experiments aiming at development of methods of practical application of the techniques should be carefully designed. "Classical" principles of experimental design – e.g. randomizing the order of processing the samples, "blinding" of procedures of sample-processing, balancing the distribution of important experimental factors – might be here more important than ever, given the high susceptibility of the novel techniques to systematic effects. Finally, appropriate methods of data analysis, taking into account potentially complex structure of the data, should be used.

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Evidence-based medicine: new wine in old bottles?

Doroszewski J

Medical Center of Postgraduate Education, Warszawa, Poland

Abstract

The general idea of evidence-based medicine (EBM) and its practical realization are presented and the concept of EBM is discussed from the general methodological point of view. The principal practical merit of this paradigm consists in fostering precision and reliability in the process of solving medical practical problems and its contribution to the general medical knowledge. The emphasis of the EBM approach on direct application of the results of clinical trials should not, however, be introduced into practice to the detriment of the use of theoretical medical knowledge and "classical" methods of reasoning.

Key words: evidence-based medicine, best evidence, observational terms, theoretical terms, clinical problem solving, general survey.

Evidence-based medicine (EBM), a methodological idea, called by its founders "a new paradigm", appeared in 1992 [1]. The main line of development of this concept [2,3] is connected with the direct application in the clinical practice [4,5]; recently, however, the same term is used also in a more basic sense of a type of general clinical methodology [6], in both above varieties, the idea of EBM have strong epidemiological and statistical background. The present work concerns rather the first approach.

The appearance and development of EBM was promoted by the conviction of its authors that medical knowledge the physicians are using in practice, as well as the traditional sources from which it derives, are mostly outdated and that the typical way of doctor's reasoning based mainly on pathophysiological knowledge no more fulfills the needs of modern medicine. Recently, however, the remedies, that may improve this situation have appeared; they consist first of all in a rapid progress and implementation of statistical methodology of clinical research together with the development of the technique of storing huge amounts of data and an easy and fast retrieval of information thanks to the development and practical application of Internet. The joint effect of these factors brings about the possibility of spreading and use of the results of clinical and other studies almost without delay; from the EBM point of view, the most important is an immediate accessibility to the results of multi-center prospective clinical trials embracing thousands of patients, performed according to rigid statistical criteria and generalized by means of meta-analysis. In this situation it may be possible as well as desirable to put into effect the postulate of grounding everyday practice of solving diagnostic, therapeutic, medico-economic and managerial problems on data and general statements deriving either directly from the most recent results of clinical research, either from review articles, websites, guidelines, books etc. prepared especially for this purpose. In order to promote and develop this activity, periodicals and journals, numerous working groups, centers and institutions appear in various countries the ensemble of which may be called EBM system or network (e.g. ACP Journal, The Cochrane Library, BMJ series of evidence-based books devoted to many specialties etc.). Thus, in general terms, EBM is in the same time a postulate based on the assessment of the present state of medicine, a kind of methodology, a suggested direction of the development of medical practice, a set of methods of delivering medical care, and a system aimed at assisting this approach. The most specific general aspect of EBM consists in the fact, that the term "medicine" in this contexts is understood not in the sense of a certain field or discipline, but as medical activity performed in a certain way which may or should be applied to every medical specialty. Hence the belief of the promoters of this movement in its general importance, overall applicability and uniqueness;

ADDRESS FOR CORRESPONDENCE:
Jan Doroszewski,
Medical Center of Postgraduate Education,
ul. Marymoncka 99, 01-813 Warszawa, Poland
e-mail: jan.doroszewski@quicksilver.pl

such an attitude, by the way, rises discussion [7,8], critical studies [9,10], even satirical papers [11].

Definition and role

According to Sackett [7] "evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research"; a similar definition is given in his seminal book [1] and by other authors. As concerns the practical use of EBM methodology in the process of solving problems related to individual patients, the following steps or phases are recommended: formulation of a clear clinical question, search of the literature for relevant clinical articles, evaluation of the evidence for its validity and usefulness, implementation of useful findings in clinical practice [4].

The practical application of EBM resembles – in a more diversified and flexible form – the systems supporting clinical problem solving based on the use of statistical data, other mathematical methods and/or artificial intelligence. The idea of computer support of physician's thinking consists in endowing him or her with relevant external information together with a proposition of application of a certain method of inference making and a suggestion of a probable or possible solution of a given problem. The EBM systems fulfill comparable functions either by means of suggesting problems' solutions based on especially retrieved and prepared results of clinical research, or by providing (collected also directly for a given purpose) a piece of the most recently accepted general knowledge.

As concerns the contents of pieces of evidence in the EBM meaning which may be used in the process of medical problem solving, three main categories may be distinguished: a) up-dated fragments of knowledge presented as reviews containing epidemiological, pathophysiological and clinical information, b) the results of the most recent and reliable research (mostly clinical trials) published as papers in the form of research reports, c) schemes and models of diagnostic or therapeutic action, guidelines and suggested solutions of particular problems.

Pragmatic and theoretical aspects

From the methodological point of view, the manner of understanding and application of the notion of "best evidence" ("current best evidence") is of crucial importance. According to Sackett [1] "by the best research evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient-centered clinical research…". In general terminology "evidence" means "something that makes another thing evident, indication, sign, something that tends to prove, ground for belief" [12]. In empirical sciences the ultimate criterion of truth is observation, the majority of statements, however, are accepted on the grounds of indirect, usually long and complex, relations with the external facts, and the scientific knowledge is composed of observational statements as well as theoretical ones. In the context of EBM methodology, the "best evidence" means first of all the evidence based directly on clinical studies (i.e. a kind of systematic observation), while the majority of "textbook laws" belong to the class of theoretical statements. The problem solving reasoning, including decision-making inference, consists in mental operations performed on complex sets of propositions, the majority of which (theoretical ones) are based on the observational ones only in an indirect way. In order, however, to accept or reject these judgments, it is necessary to refer to the observation (experiment), the validity of which requires application of statistical methods. The statistical methods, therefore, are related in the first place to the process of verification of hypotheses, while that of their formation (with the exception of the starting phase) is based mainly on theoretical statements. In other words, for some purposes the observational statements (i.e. close to the experiment) may serve as the best evidence, for other ends – the pieces of theoretical (i.e. abstractly enriched) knowledge, whereas always the best evidence is composed of both types of statements in various proportions.

Some suggestions

In the light of the above considerations, a full realization of the postulate (stated, e.g. in 1) of integration of statistical "best evidence" with the medical general knowledge and expertise appears especially important; a broader theoretical analysis of this link, however, could make its application more effective. It seems, moreover, that special emphasis should be put on the process of problem (clinical question) formulation (see, e.g. 1, 4) in the initial phase of clinical reasoning. Special attention should be given to the individual patients' features (somatic as well as psychic) and the sphere of values which cannot be effectively integrated into the problem solving framework without the use of theoretical knowledge. Other fundamental questions are connected with the applicability of overall results of clinical trials to individual patients [13,14] and with the relation of the notions of quantitative versus logical probability [15] as well as the subjective uncertainty in medical consultation [16].

To sum up, the development of the EBM "paradigm", methodology and decision support system brings about useful and interesting results and becomes one of significant factors of the progress in medical practice and science. The application of EBM accelerates the incorporation of the results of clinical research into the general bulk of medical knowledge and promotes the use of reliable and precise information in practical medical problem solving. These effects, however, could be made more valuable, if the spreading of the EBM approach were accompanied by a more refined theoretical analysis of relevant methodological problems.

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Multimedia and virtual reality assistance in medical systems

Kącki E[1], Stempczyńska J[2]

[1] Department of Expert System and Artificial Intelligence, Computer Science College of Łódź, Poland
[2] Department of Chemotherapy, Medical University of Łódź, Poland

Abstract

Purpose: The aim of the paper is to present conceptions leading to improvement of communication between medical computer systems and users by multimedia and virtual reality applications based on the authors' experience in constructing and exploitation of medical expert systems.

Material and methods: The examples considered in the paper deal with problems being the subjects of the authors' investigation. They contain the cases of multimedia and virtual reality applications to computer systems destined for assistance of medical education and surgery operations. The systems in experimental version have been tested by physicians and student groups.

Results: The preliminary investigations give ground to confirm that the systems will be easier in use and very helpful as well for the surgeon as in educational processes.

Conclusions: The examples presented in the paper show beyond any doubt that contemporary medicine is inseparably connected with the latest information techniques, among which the system making use of the multimedia and virtual reality occupy a firmly established position.

Key words: computer medical system, multimedia, virtual reality.

ADDRESS FOR CORRESPONDENCE:
Edward Kącki
Department of Expert System and Artificial Intelligence,
Computer Science College of Łódź,
ul. Rzgowska 17A, 93-008 Łódź, Poland,
e-mail: e25kacki@cosmosnet.pl
or Joanna Stempczyńska
Department of Chemotherapy, Medical University of Łódź,
ul. Paderewskiego 4, 93-548 Łódź, Poland,
e-mail: Joasia53@poczta.onet.pl

Introduction

The paper presents the main ideas of multimedia [1] and virtual reality [2] applications to medical computer systems or internet medical systems and shows how they can contribute to the improvement of its activity efficiency and of man-system communication. The work describes first of all the results of own authors investigations relating: 1) to patient simulator [3] assisting training in diagnosing; 2) to simulator of the radiotherapeutic equipment handling; 3) to surgery-assisting multimedia systems.

The presented patient simulator enables the student to make diagnosis on the basis conversation and it deals with the third multimedia version of training system, subsequently the described simulator of teletherapy based on virtual reality program enables training of teletherapy equipment manipulation for students or nurses and the proposed system for surgery consists of the three blocks: description, communication and expert. The key role of multimedia is to ensure communication comfort between the surgeon and the system as well as a group of physicians and nurses accompanying by the operation.

The paper presents also a concept of an experimental module designed to recognize spoken utterances that cover a limited range of words indispensable dialogs with computer medical systems. Research the recognition of spoken words by module based on artificial neural networks is described. Usefulness of the obtained results for multimedia health care systems and medical educational systems is also discussed.

Material and methods

The third version of the patient simulator program has the software designed with the use of Visual Basic 5.0 and it makes possible to play files WAV and AVI due to which the simulated situations are more authentic. The patient simulator enables the student to make diagnosis on the basis conversation. The way in which a given history is taken, additional examinations

suggested by the student, qualification of given examination results, and the final diagnosis are all evaluated with points by the system. The conversation with the simulator consists in selecting appropriate questions and medical examinations from a list presented by the system and answers to these questions provided by the simulator which chooses them randomly from the set of admissible answers for the unrevealed disease unit. The system traces the kind of questions asked by the student, their order, the choice of additional examinations suggested by the student as well as his qualification of given examination results, and assigns a suitable number of points to each decision of the student. Consequently, the system evaluates the quality of the history taking and the final diagnosis concerning both the general condition of the patient and identification of the disease unit. At the end of the procedure the students learns total score as well as the number of points for particular steps.

The virtual teletherapy simulator of the therapeutic equipment handling has been build according to the author's idea. Its software enables training in operating the equipment, i.e. enables making necessary adjustments before irradiation of the patient, entire visualisation of an operation, treatment planning and collecting data referring to give operations. The simulator works in the Windows environment and therefore it is operated by the system of dialog windows, menu and buttons of the toolbar. The exploitation of virtual reality in the software makes it possible to watch the devices and the patient during the operation in the 3D space with the possibility of easy change of viewpoint performed with the use of the mouse.

The system consists of three main blocks named: description, communication, and expert. The first block covers patient's personal data, records of patient's condition before operation (e.g. description, scanned roentgenogram, microphotogram, tomogram, electrocardiogram, etc.), brief description of the operation and of convalescence. The communication block includes a collection of statements and dialogues necessary for the operating surgeon's communication with the group assisting him in the operation as well as graphic signs and sounds needed in this communication. The third block is an expert system in the area of the surgeon's specialisation. The software of the mentioned blocks is immersed in a multimedia environment.

Experimental module of spoken language recognition, based on neural networks and applied to the described medical systems, was composed of the following two blocks [4]: a) classifying block; b) approximating block.

Speech recognition requires a variety of speech signal analyses and extraction of suitable parameters. What makes the process more difficult is the fact that each utterance can be pronounced differently, i.e. with different speed, sound intensity, accent or intonation.

The way an utterance is pronounced is partly an individual characteristic of a speaker, but it is also subject to a temporary emotional, psychological or physical condition of the speaker.

There are numerous external parameters on which an utterance depends. Thus it is clear that the choice of a suitable set of parameters that would describe speech is of essential importance.

In the investigations that have been carried out the following stages can be distinguished: experimental selection of structural model parameters close to optimal; creation of sets of one- or multi-word expressions; classification of the elements of the expression sets; analysis of the neural network learning and an expression recognition procedure; selection of parameters for recognition criteria.

Discussion

Assessment of usefulness of the experimental module of spoken language recognition for the multimedia surgery-assisting system involved operations were preceded by numerous discussions with surgeons and the presented education system have been tested in student groups of Medical University of Łodź. The investigations and discussions give ground to confirm will be very helpful as well for surgeons as in education processes.

The patient simulator not only helps the student revise the acquired knowledge or catch up with the material but creates situations in which the student must take decisions by himself. This trains him in logical thinking and drawing conclusions, the skills whose value cannot be overestimated.

At present, the virtual reality technology is frequently used to assist many sorts of medical work. Due to special programming tools it is not very difficult to construct virtual reality computer systems or multimedia system carrying out educational tasks or assisting diagnosing, therapy or hospital management.

Acknowledgments

The described applications of the presented module of spoken language recognition have been discussed on seminaries of Polish Society of Medical Informatics in Łódź.

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Medical informatics ethics and its subject

Trzęsicki K

University of Białystok, Institute of Informatics, Białystok, Poland

Abstract

Application of information and communication technology (ICT) in medicine and health care is a source of ethical questions of practical importance. We argue that medical informatics ethics (MIE) is not a new branch of applied ethics. It is rather a name under which some problems of medical (ME) and computer ethics (CE) are gathered. Some questions of application of ICT in medicine belong to CE and others to ME. In MIE medical ethics meets computer ethics. The borderline between them is neither clear no easy to draw.

Key words: computer ethics, medical ethics, medical informatics ethics, code of ethics.

Beginnings of medical informatics ethics

Computer ethics (CE) has its beginnings in works of Norbert Wiener, the father of cybernetics. Around 1948 he started considering the impacts of information and communication technology (ICT) upon human values like peace, knowledge, health, education, justice. Published in 1950, his book "The Human Use of Human Beings" [1] established his position as the creator of CE. Since the middle of the sixties when Don Parker started an investigation of unethical and illegitimate use of computers, CE is still under development. Creation of the natural-language processing system ELIZA by Weizenbaum was the next important event for CE. ELIZA imitated a psychologist. Weizenbaum was appalled when psychiatrists suggested that the program might be an acceptable substitute for human therapy. Horrified, Weizenbaum began work on the philosophical problem presented by the mechanization of human characteristics and talents. His book [2] "Computer Power and Human Reason" published in 1976, is Weizenbaum's exploration of his own misgivings about technology and Artificial Intelligence (AI).

Health care is a very important area of application of ICT since the technology has been developed. ICT has many advantages and can deliver great hopes for better health care. Advances in ICT provide users with new capabilities without ethical policies having been formulated to guide those users in their conduct. The concern about ethical implications of the use of ICT in medicine/health care is ongoing. Today it is the subject of conference papers (e.g. ETHICOMP), publications (e.g. Kenneth Goodman [ed.], Ethics, Computing, and Medicine: "Informatics and the Transformation of Health Care" [3]), teaching (the course "Ethical, Legal and Social Issues in Medical Informatics" MINF 515 – 2 credits – is offered by Department of Medical Informatics & Clinical Epidemiology, Oregon Health Sciences University[1]; Medical College of Wisconsin[2] offers the course in "Ethics in Medical Informatics" MI-13201[3]). There are established organizations with the aim of setting and observing ethical standards of using ICT in medicine, e.g. The Health On the Net Foundation (HON)[4]. This non-governmental

ADDRESS FOR CORRESPONDENCE:
Kazimierz Trzęsicki
University of Białystok, Institute of Informatics,
ul. Sosnowa 64, 15-887 Białystok, Poland
e-mail: Kasimir@ii.pb.bialystok.pl

[1] See http://www.ohsu.edu/dmice/courses/offering.shtml The course comprises the following topics: The protection of confidentiality and privacy in an electronic environment; Implications of the use of telemedicine and decision-support tools in diagnosis and treatment; The implications of electronic communication for the physician-patient relationship; Principles for design and functionality of consumer-oriented Web sites.

[2] See http://www.mcw.edu/display/Home.asp

[3] See http://www.journeyofhearts.org/jofh/jofh_old/minf_528/intro.htm The following topics are included in the course: privacy, security, confidentiality, encryption, coding, reimbursement, conflicts of interests, reporting, protecting information.

[4] HON's mission is to guide lay persons or non-medical users and medical practitioners to useful and reliable online medical and health information. HON provides leadership in setting ethical standards for Web site developers. More on the site: http://www.hon.ch/ The Code of Conduct for Medication and Health Web Sites is translated in Polish by Piotr Kasztelowicz (http://www.hon.ch/HONcode/Polish) and presented at the II Conference of Medical Internet in 1997.

organization was created in 1995 under the aegis of the Direction générale de la santé Département de l'Action Sociale et de Santé: République et canton de Genève, Switzerland). Porfirio Barroso Asenjo at the conference ETHICOMP 95 presented which had been already accepted in Greece "Health Informaticians' Deontology Code" (HIDEC). In 2000 the eHealth Ethics Initiative introduced an international code of ethics for health care sites and services on the Internet[5]. There are working groups dedicated to investigations of ethical, and legal issues of medical informatics, e.g. the Working Group "Ethical, Legal, and Social Issues" (ELSI-WG) of American Medical Informatics Association[6]. In 2002 at Taipei the International Medical Informatics Association (IMIA)[7] endorsed "The Ethical Code of Practice"[8]. A working group "Ethical, Legal, and Social Issues" of IMIA is represented by Peter Winkelstein (AMIA)[9].

In this paper the methodological status and major questions of medical informatics (computer) ethics (MIE) will be discussed.

There are at least two sets of issues. One set concerns existing problems of medical ethics (ME) which are exacerbated by the employment of ICT in medicine, e.g. the problem of privacy and anonymity. The second set concerns potentially new problems, problems which as yet have not arisen, at least not in any significant way, e.g. the existence of cyborg.

MIE comprises problems of CE that are related to health and health care and questions of ME that arise from applications of ICT. It means that MIE is not a separate scientific discipline. It is rather a conglomerate of CE and ME. For example, the question of sale of drugs via the Web belongs to CE, but the questions concerning treatment supported by an expert program belong to ME. We will try to establish a demarcation line between problems of MIE that are considered by CE and problems of MIE that are subject of ME. As we will see the borderline is neither clear nor easy to observe. The frontiers are fuzzy. Our coverage of the main themes is by no means intended to be exhaustive, and several of the issues raised here need further consideration.

Subject of medical informatics ethics

We will try to determine the scope of MIE. We will argue that it comprises several subjects of study.

In order to achieve our aim first of all we have to distinguish between ethical problems of impact of ICT on health and ethical problems of application of ICT in health care and medicine.

Technology enhances productivity, expands functionality and improves quality of life. This statement is especially true about ICT. But it is only one side of technology. Technology has also another side. It is potentially harmful to the natural environment and in particular to health, physiologically and psychologically[10]. Long hours spent at the computer can cause problems with sight, spine, wrist. Health may be threatened by radiation emanating from computer monitors. It is possible, for example, that users will feel stressed trying to keep up with high-speed computerized devices. Addiction to computers and Internet is already a social issue. For example, in 2004 a centre to help addicted young people was established in Ełk, a Polish town of 60 000 inhabitants. Problems of ICT effects on individual and on public health are subjects of work safety. Their ethical aspects are being considered by CE.

Medicine in the broadest sense comprises organization and administration of health services, prophylaxis, treatment and rehabilitation, manufacturing and distribution of medical equipment and drugs, study and education. Ethical problems both in medicine and in application of ICT are common to all these domains. It seems that as in ME as well as in MIE the problems should be divided according to human values. If so the MIE has to be focused on human and his/her health or – quite generally speaking – on human life.

The Hippocratic Oath expresses the principal precepts of ME. It is not only the oldest professional code but a pattern of professional codes at all. In 1976 one of the creators of CE, Walter Maner, "while teaching a medical ethics course, noticed that, often, when computers are involved in medical ethics cases, new ethically important considerations arise. Further examination of this phenomenon convinced Maner that there is a need for a separate branch of applied ethics, which he dubbed 'computer ethics' (Wiener had not used this term, nor was it in common use before Maner). By the early 1980s, the name 'computer ethics' had caught on, and other scholars began to develop this 'new' field of applied ethics [4]. Maner noticed that some old ethical problems are made worse by computers, while others are wholly new because of information technology. He[11] defined CE as a branch of applied ethics which studies ethical problems "aggravated, transformed or created by computer technology". For Deborah Johnson, CE studies the way in which computers "pose new versions of standard moral problems and moral dilemmas, exacerbating the old problems, and forcing us to apply ordinary moral norms in uncharted realms"[12]. James Moor taking into account that ICT provides us new capabili-

[5] http://www.ihealthcoalition.org/ethics/ehcode.html

[6] The mission of the Group is:

To draw attention to and raise awareness of ethical, legal, and social issues (ELSI-WG) in health informatics.

To serve as a resource to help AMIA members and others address ethical, legal and social issues in professional and academic endeavors.

To identify additional resources and develop educational programs and curricular materials for AMIA members and others.

To conduct and support scholarly research aimed at identifying ethical, legal, and social issues in health informatics and at expanding discussions and analyses of these issues.

See http://www.amia.org/working/elsi/main.html

[7] http://www.imia.org

[8] IMIA Code of Ethics for Health Information Professionals: http://www.imia.org/English_code_of_ethics.html

[9] See http://www.imia.org/2002_scientific_map.html

[10] The same is true about medicine. The famous Hippocratic aphorism *primum non nocere* (first do no harm) reminds a physician that he or she must consider the possible harm that any intervention might do. It is most often mentioned when debating use of an intervention with an obvious chance of harm but a less certain chance of benefit.

[11] Maner contributed not only to the theory of CE. Traveling around America gave speeches and conducted workshops at conferences. He self-published A Starter Kit for Teaching Computer Ethics [5]. Computer Ethics [6], the first textbook – and for more than a decade, the defining textbook – in the field was published by Deborah Johnson of Rensselaer Polytechnic Institute.

[12] See [6], p. 1.

ties and these in turn give us new choices for action, maintains that a "typical problem in computer ethics arises because there is a policy vacuum about how computer technology should be used"[13]. For Terrell Ward Bynum it is the best available definition of the field[14]. Krystyna Górniak-Kocikowska predicts that due to globalization of ICT, computer ethics will disappear. "Local" ethical theories will eventually be superceded by a global ethics evolving from today's CE. "Computer" ethics, then, will become the "ordinary" ethics of the information age[15] Deborah Johnson maintains that in information age CE will become ordinary ethics and ordinary ethics will become CE[16]. On Johnson's view, in information age ICT will permeate all aspects of our everyday life. Its presence will no longer be noticed. Thus there will be no special CE problems. In all the ethical issues the questions of CE will be involved.

For the discussed concepts of CE, MIE is a part of CE that concerns ethical questions raised by application of ICT in medicine. ME is not proper to examine ethical problems of medicine implied by ICT technology. Moreover, in the future ME will be only a branch of applied CE (albeit – according to Górniak-Kocikowska and Johnson – the name CE may not be in usage).

Different approach to defining the field of CE is advocated by Donald Gotterbarn. For him CE is a branch of professional ethics. It concerns "the values that guide the day-to-day activities of computing professionals in their role as professionals. By computing professional I mean anyone involved in the design and development of computer artefacts. The ethical decisions made during the development of these artefacts have a direct relationship to many of the issues discussed under the broader concept of computer ethics" [10]. For this concept of CE we may maintain that as ICT engineers and medical doctors are different professions as CE and ME are different ethics. As long as there is no such a profession as ICT medical doctor or medical ICT engineer, there is no MIE branch of professional ethics.

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[16] Cf. [9].

Computer systems of histology image analysis in Belarus

Nedzved A, Belotserkovsky A, Ablameyko S

United Institute of Informatics Problems of The National Academy of Sciences of Belarus

Abstract

The most interesting Belarussian medical systems which deal with histological images to carry out an analysis of histological and cell structures of different tissues are presented here. In this paper basic properties of system "Bioscan-IW", "AutoScan", "Contour" and "Cytron" are described. These systems are the most interesting among Belarussian histological image applications.

Key words: histology, automated system, morphometry, image processing.

Introduction

Medical morphology is the most reliable method in the diagnostic process. It is realized in the form of the biopsy, cytological and histological investigation where histological and cell structures of different tissues of the human body are the prime object of analysis. In particular, this method is vital in diagnosing various human diseases.

Computer application improves arithmetic precision for investigation in morphology. Automated systems exclude mistake of human factor and decrease expended time for process of verification diagnosis. There are not enough specialists, who can execute correct morphology analysis yet. What is more they are amassed only in big medical centers. At the same time clinicians are trying to identify complex forms of disease and reduces to mistaken diagnostics. Therefore there are a lot of cases, when incorrect untimely treatment results to disablement or death. Therefore the task of automation for morphology diagnostics is very important in medicine. The computer system for morphological diagnostics improves accuracy of diagnostics and compensates deficit of morphologist-specialists.

The objective analysis of cytological and histological images has been the subject of research for many years. Most difficult fields in histological image analysis are automated extraction and classification of cells and analysis tissue. However, due to a complex nature of histological images, it is difficult to select or develop automatic segmentation methods that can be applied for any type of these images. Therefore the system for automation morphology investigation in histology include complex unique algorithms and techniques.

There are some international global developers of automated system: Leica Microsystems (www.leica-microsystems.com), Applied Imaging (www.aicorp.com), Hamiltone Thorne (www.hamiltonthorne.com), Laboratory Imaging (www.lucia-cytogenetics.com), IMSTAR (www.imstar.fr), Media Cybernetics (www.mediacy.com), etc. These companies introduce one or more computer complexes for using in histological investigation [1,2]. The main goal of development in such direction is universal computer system for morphometry.

There are some automated computer system developed in Republic of Belarus. The "Bioscan-IW", "AutoScan", "Contour", "Cytron" are most interesting.

Systems of histology image analysis

"AutoScan"

(http://www.bsuproduct.by/index.php/.20.212...0.0.0.html)

This system is developed in Belarussian State University. The main application of this system is metallography. But "AutoScan" consist of visual and threshold allocation of objects in a picture, qualifying editing of objects, splitting of objects into arbitrarily adjusted classes, 40 measured characteristics of objects, arbitrarily formed reports (tables, histograms). The systems have specialized part of calculation of statistical infor-

ADDRESS FOR CORRESPONDENCE:
Alexander Nedzved
United Institute of Informatics Problems
of The National Academy of Sciences of Belarus
6, Surganov Str., 220012, Minsk, Belarus
e-mail: NedzvedA@newman.bas-net.by

Figure 1. **Screenshots of "Contour" for measurement of separate cell**

Figure 2. **Screenshots of "Contour" for measurement of conglomerate of cells**

mation over the all characteristics, report generation (tables, histograms). This features permit to solve some task of histology. For example geometric cells measurement, cells counting.

"Bioscan-IW"
(http://itlab.anitex.by/bioscan/)

This system was developed in Belarussian State Medical University. This is a universal computer system with powerful software for image processing and measuring. The build-in script-interpretator allows to create macros for various investigation and diagnostic medical task [1].

This system is successfully used for diagnostic in clinical oncology and pathology anatomy, for analysis of cells evolution, for investigation to influence of new pharmacology medication, for fixation to control points in neurosurgery [4]. Unlike any other image analysis software, "Bioscan-IW" incorporates graphic editing tools and functions that work with a wide variety of image types including 16-bit, 32-bit and 64-bit (complex) images. In this connection this system promises to quality densitometry measurements. A multiple window interface allows for simultaneous display of static and live images, charts, and measurements for the rapid creation of custom applications and development of new imaging techniques. Automatic and interactive measurement functions support more than 100 built-in and user-defined geometrical, optical and topological parameters. A number of proprietary processing algorithms and interface innovations make "Bioscan-IW" one of a kind.

"Contour"
(http://uiip.bas-net.by/eng/l_ipr_projects_3.html)

This system is an expert system for thyroid carcinoma diagnosis based on a set of karyometric parameters of follicular cells and developed computer analyzer of color images is described here (*Fig. 1,2*). Main tasks of automated color images processing and binarization by applying of several developed segmentation algorithms, automatic raster-to-vector transformation and biological objects formation, morphometric assessment of biological objects by quantitative parameters characterizing the changes of cell nuclei and diagnostic rules formulating with further diagnosis of thyroid cancer were done. "Contour" was developed by specialists from United Institute of Informatics Problems of The National Academy of Sciences of Belarus and Research and Clinical Institute of Radiation Medicine and Endocrinology [3,5].

"Cytron"

This system is morphological application of diseases diagnostic of human organs morphometrical investigations of tissue, cells and cell's accumulation in human organs. This system is in developing in United Institute of Informatics Problems of The National Academy of Sciences of Belarus now [6].

On the base of form, size, color and morphologic structure of tissue and cells, the algorithms of cell segmentation and cell morphology structure extraction from histological images identify histology patterns. The system consist of software packages of image processing including filtering, binarization, segmentation, contouring, extraction and morphometric estimation of objects based on geometrical and densitometry features. The software of diagnostic approaches allow to detect indication of pathology in human organs and lesion degree or to confirm the absence of diseases automatically based on analysis of some sets of morphometric features through a database. Unique algorithms of tissue analysis allow to define more exactly diagnose by morphometry investigation on different optical magnification. The software package will be used for estimation of changes of cell morphological structures of different extent of lesion.

Conclusions

Among systems of general purpose «Bioscan-IW» is the most adapted system to carry out a histological investigations since it has specialized script for morphometry and larger number of measurement parameters than «Autoscan».

System "Contour" is specialized expert system which is only for thyroid carcinoma diagnostics purpose. "Cytron" is more universal system for oncology diagnostic, but now it is developed.

These systems meet the international specification and are used in medical organizations in Belarus.

This brief overview shows that among a wide spectrum of systems and technologies for image processing and interpretation created in Belarus there are four interesting examples of developments applied to histological investigations, which are differ in their functionality. The comparison of these systems by it functional properties are presented in the table below.

Properties	**Bioscan-IW**	**AutoScan**	**Contour**	**Cytron**
Number of measure parameters	111	40	20	80
Advanced measure statistic	Excel-like	Special report	Special report	Special report
Specialized scripts	yes	no	no	no
Expert analysis	no	no	thyroid carcinoma	Basic oncology properties
Advanced image processing	yes	no	no	Lite
Video input	VFW, Twain, Matrox. IEEE-1394, BitFlow	VFW, Twain	Twain	VFW, Twain

Automation of morphology investigation in histology is one of interesting and complex problem. The several Belarusian teams are working in this field. United Institute of Informatics Problems of The National Academy of Sciences of Belarus, Belarussian State Medical University, and Belarussian State University are leader of histology automation. These organizations have not only developed computer system for histology investigation. They have many scientific achievements in such fields as cells extraction, tissue separation, morphomery automation, histology expert system and teleconsultation.

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Measurements of the working time of doctors, physiotherapists and the use of specialized equipment at the Rehabilitation Ward of Specialist Hospital in Zamość

Sapuła R[1], Wdowiak L[1], Mataczyński K[2], Sitko SJ[3]

[1] Department of Management and Health Protection Economics Department, Medical University of Lublin, Poland
[2] Rehabilitation Ward of Specialist Hospital in Zamość, Poland
[3] Institute of Public Health, Faculty of Healthcare, Jagiellonian University, Poland

Abstract

The aim of this article is to examine the workload of the doctors and physiotherapists during the fitness process of patients with different disorders and in different clinical condition. The survey regarded the workload of doctors, physiotherapists and the measurement of the use of specialised equipment in the process of rehabilitation of 361 patients, hospitalized from October 2002 till September 2004. In the research some elements of activity sampling method and elements of self-photography of the working day were used. The authors divided doctors' work into two categories: indirect activities and direct activities, the criterion being the contact with patients. The most demanding in terms of the doctors' involvement, were the patients in the most serious clinical condition: patients with hemiparesis (0-55 on Barthel scale), with multiple sclerosis in severe phase, with tetraplegia and tetraparesis. Indirect activities account for only about 40% of the doctor's working time, while the indirect activities are close to 60%. The working time of physiotherapists was divided into three categories: preparation, organizational activities, and main activities. The main activities take up most time with patients in the most severe clinical condition. Preparatory and organizational activities occupied comparative amounts of time. The authors also observed that the use of specialized equipment is lowest in rehabilitation of patients in the most severe clinical condition. The reason is that those patients first of all need in-bed treatment.

Key words: rehabilitation, management, economics.

ADDRESS FOR CORRESPONDENCE:
Rafał Sapuła
Department of Management and Health Protection Economics Department, Medical University of Lublin
ul. Chodźki 1, 20-950 Lublin, Poland

Introduction

Measurements of the working time are chiefly serving the purpose of establishing time standards and the results of the measurements may be used for organizational research. The measurements are a significant source of information about the current state of the organization, about its efficiency and productivity. The purpose of measuring work is also detection of the lost time, its amount, character and reasons. The measurements create foundations for finding methods of eliminating the losses [1,3-5].

The present rehabilitation facilities and limitations introduced by the contracts with the payer of medical services do not allow to satisfy rehabilitation needs of Polish society. Long queues of patients expecting hospitalization and limited chances of urgent receptions are the result of this state of affairs [2]. At the same time the problem of planning the treatment in the ward taking into account human and equipment resources is rising. Each patient requires different kind of commitment from doctors, physiotherapists and nurses, depending on his or her clinical state and specific illness. In cases requiring particularly big amounts of labour, exceeding the capability of an institution, the quality of treatment decreases drastically.

The aim of the article

The aim of this article is to examine the workload of the doctors and physiotherapists during the improvement process of patients with different disorders and in different clinical condition and the use of specialized equipment at the Rehabilitation Ward of Specialist Hospital in Zamość. The knowledge resulting from this analysis may help to utilise the potential of the ward more effectively, protect the organization against losses and raise the quality of provided services.

Material and methods

The survey regarded the workload of doctors, physiotherapists and the measurement of the use of specialized equipment in the process of rehabilitation of 361 patients, hospitalized from October 2002 till September 2004. The authors divided doctors' work into two categories: indirect activities and direct activities, the criterion being the contact with patients. The working time of physiotherapists was divided into three categories: preparation, organizational activities, and main activities:

- preparation – acquainting oneself with the plan for improving of the patient prepared by doctors, the preparation of the patient and equipment, tidying;
- organizational activities – preparing medical documentation (written observations from the course of rehabilitation of patients) and preparing administrative documentation;
- main activities – executing physical therapy treatment, the presentation of exercises, control of correctness of exercises executed by the patient, patients' education.

In the research some elements of activity sampling method and elements of self-photography of the working day were used.

The time of executing exercises by patients and elapsed time of physical treatment was treated as the identical time with using the equipment and was marked with the letter D in the following tables. The time includes preparation of the equipment by the physiotherapist, physiotherapists' main activities, the time of executing exercises by patients and physical treatments without the physiotherapist's participation.

The uniform measuring form was prepared to be filled in for each patient. It provided documentation of the time of each treatment according to the mentioned categories. Times of each treatment were measured and then they were added up at the end of each day. Time of every of treatment, at the given patient, was being measured three times, at the beginning of the hospitalization, in the middle of the hospitalization and a day before leaving the hospital. Distribution of the value of times of these treatments was similar to symmetrical and therefore the arithmetic means were calculated. Moreover, standard deviation was calculated.

The authors divided doctors' work into two categories: indirect activities and direct activities, the criterion being the contact with patients. A measuring sheet was prepared especially for the needs of the examination of direct activities, which "was accompanying" the patient during treatment. Each doctor, once a week, was adding the time he devoted to the patient, i.e. direct activities. Direct activities included the following: collecting information about the patient, the examination, taking some orthopaedic supply, injections, supplying wounds, catheterization, patients' education. Measurements of indirect activities were made similarly. Appropriate sheets were located in the doctors' office. The time was noted down in the appropriate place after every executed activity. Times of each activity were being measured, and then towards the end of every measuring day they were being added up. Times of direct activities for every patient were measured twice: at the beginning of the hospitalization and in the days close to the day of leaving the hospital. Patients with hemiparesis were divided into 5 groups, according to the functional state using the Barthel scale.

Results

Patients with hemiparesis, depending on the functional state, evaluated by means of the Barthel scale, required various amount of labour of physiotherapist — people in the hardest clinical condition on average 121 minutes a day, patients in the best shape on average 52 minutes.

Main activities with patients with tetraplegia took on average 127 minutes, with patients with tetraparesis around 114 minutes, and with persons with paresis of lower limbs on average 85 minutes. Patients with the multiple sclerosis required the workload of around 97 minutes. Main activities with patients after the amputation of a lower limb were occupying on average 56 minutes, with patients with vertebral column pain syndrome 63 minutes, whereas at persons with degenerative changes around 49 minutes.

Preparatory activities and organizational activities were occupying comparable quantities of the time in all cases.

Authors also observed that the usage of the specialized equipment was smallest in case of rehabilitation of patients in the hardest clinical condition. It is resulting from the fact that patients from this group require first of all improving in the bed and next to the bed.

Patients with hemiparesis depending on the functional state, evaluated by means of the Barthel scale, required the various amount of workload of doctors (direct activities), patients in the hardest clinical condition of on average 36 minutes a day, patients in the best shape on average 24 minutes. Direct activities with patients with tetraplegia occupied on average 38 minutes, with patients with tetraparesis of around 32 minutes, and with patients with paraparesis of lower limbs on average 29 minutes. Patients with the multiple sclerosis required direct activities of around 26 minutes. Direct activities with people after the amputation of a lower limb were occupying on average 23 minutes, with patients with spondylalgia 22 minutes, whereas with persons with degenerative joint disease 19 minutes.

Indirect activities were occupying on average from 69 to 52 minutes a day per patient, of what doctors were spending the most time on the general visit, the entry of the observation, the report and the patient's extract from. The least time was consumed for preparing the place of work, the information retrieval about the patient in the hospital computer network and ordering the consultation and extra examinations.

Conclusions

1. The main activities psysiotherapeutist's take up most time with patients in the most severe clinical condition.

2. Preparatory and organizational activities occupied comparative amounts of time.

3. The authors also observed that the use of specialized equipment is lowest in rehabilitation of patients in the most

severe clinical condition. The reason is that those patients first of all need in-bed treatment.

4. The most demanding in terms of the doctors' involvement, were the patients in the most serious clinical condition: patients with hemiparesis (0-55 on index Barthel), with multiple sclerosis , with tetraplegia and tetraparesis. Indirect activities account for only about 40% of the doctor's working time, while the indirect activities are close to 60%.

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Application of the Lempel-Ziv complexity measure to the analysis of biosignals and medical images

Borowska M[1], Oczeretko E[1], Mazurek A[2], Kitlas A[1], Kuć P[2]

[1] Institute of Computer Science, University of Białystok, Poland
[2] Department of Pathophysiology of Pregnancy, Medical University of Białystok, Poland

Abstract

Purpose: **The aim of this study was to apply a Lempel-Ziv complexity measure for quantifying biomedical signals and images.**

Material and methods: **We analyzed angiogenic patterns and the signals (the heart rate, the respiration rate and the blood oxygen concentration). Biomedical signals were obtained by means of Internet. Medical images were from Department of Pathophysiology of Pregnancy Medical University of Białystok.**

Results: **The values of normalized complexity measures for respiratory rate signal are high, what indicates that this time series is close to unstructured randomness. The Lempel-Ziv complexity values for angiogenic patterns were growing with the FIGO stage of disease.**

Conclusions: **Lempel-Ziv complexity may be a very helpful tool in analyzing the signals and images. It can be easily computed from the analysed data.**

Key words: signal and image processing, Lempel-Ziv complexity measure, angiogenic patterns, biomedical time series.

Introduction

Lempel and Ziv proposed a useful complexity measure, which can characterize the degree of order or disorder and development of spatiotemporal patterns [1]. In the first step the signals and images are transformed into binary sequences. Lempel-Ziv algorithm gives the number of distinct patterns contained in the given finite sequence. After normalisation the relative Lempel-Ziv complexity measure (L-Z measure) reflects the rate of new pattern occurrences in the investigated series of the symbols. L-Z values range from near 0 (deterministic equation) to 1 (totally destructured random pattern white noise). That is a new approach for quantifying of medical signals and images [2,3]. The program for Lempel-Ziv complexity analysis was written in C++.

ADDRESS FOR CORRESPONDENCE:
Marta Borowska
Institute of Computer Science, University of Białystok
64 Sosnowa Str., 15-887 Białystok, Poland
Tel/Fax: +48 85 7457662
e-mail: mborowska@ii.uwb.edu.pl

Materials and methods

Biomedical time series

The data were obtained via PhysioNet (http://www.physionet.org/physiobank/santa-fe). PhysioNet offers free Internet access to various kinds of recorded physiological signals and related open-source software [4,5]. PhysioNet is a public service of the Research Resource for Complex Physiological Signals created under the auspices of the National Center for Research Resources of the National Institutes of Health (USA).

These multivariate data were obtained from a sleeping patient and contain three simultaneously recorded signals: heart rate (signal s1), which is defined through the number of heartbeats per minute, respiration rate (or chest volume) – signal s2 and blood oxygen concentration (measured by ear oximetry) – signal s3. The respiration rate and the blood oxygen concentration are given in uncalibrated analog-to-digital converted units. For these three time series the sampling frequency was 2 Hz. The studied patient shows sleep apnea. Sleep apnea is a disorder in which a person stops breathing during the night (sometimes a hundreds of times). He stops breathing for up to 45 seconds.

These signals were divided into 8 segments. Each segment contained 2000 elements.

Angiogenic images

Quantification of angiogenesis is a valuable prognostic tool for tumor progression and metastasis [6,7]. Angiogenic images were from Department of Pathophysiology of Pregnancy Medical University of Białystok. We analyzed 42 angiogenic patterns which were divided into three groups: group A I FIGO stage of disease (n = 19), group B II FIGO stage of disease (n = 13) and group C III FIGO stage of disease (n = 10).

The images were binarized by means of Otsu method [8].

The Lempel-Ziv Complexity Measure – algorithm

The signal to be analyzed is transformed into sequence whose elements are a few symbols. The binary sequence is simple to construct: the data values below or equal the mean have the symbol "1" and the values above the mean have the symbol "0". This algorithm gives the number of distinct patterns contained in the given finite sequence S=s1, s2, …, sn [9]. The calculation of c(n) (Lempel-Ziv complexity) proceeds on diagram (*Fig. 1*).

This method uses comparison and accumulation so the computation of c(n) is easy to calculate.

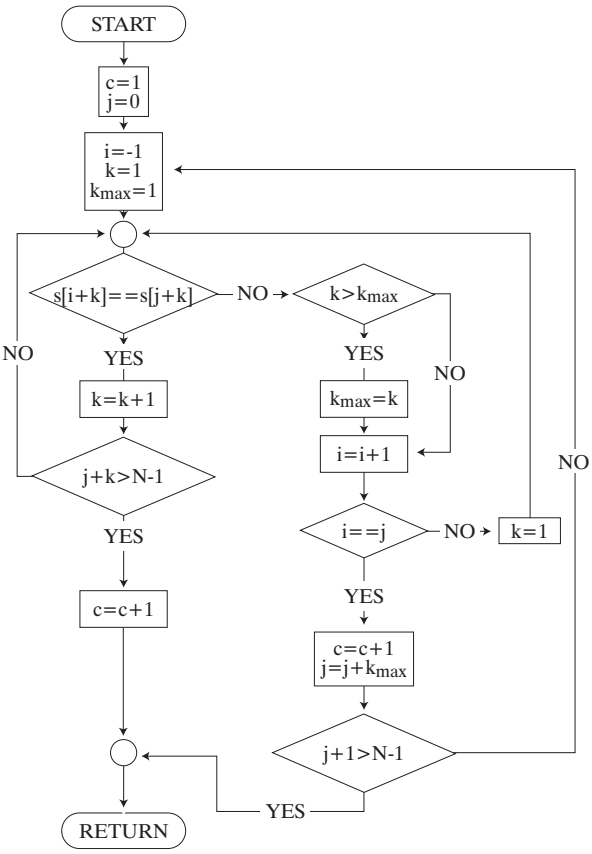
The Lempel-Ziv of the totally random sequence of length n consisting of two different symbols with equal probabilities is

$$b(n)=\frac{n}{log_2(n)}$$

If we divide the complexity of the sequence by the complexity b(n) of the random sequence, we get the normalized Lempel-Ziv C(n), which does not depend on the length of the sequence when n is large

$$C(n)=\frac{c(n)}{b(n)}$$

Figure 1. **Flow chart of the computer program for calculation of Lempel-Ziv complexity (modified from [10])**



Results

The mean values of Lempel-Ziv complexity for biomedical signals are:

1. The high L-Z complexity value for respiratory rate signal indicates that this time series is close to unstructured randomness.
2. The mean values of Lempel-Ziv complexity for angiogenic patterns are.
3. The Lempel-Ziv complexity values were growing with the FIGO stage of disease.

Conclusions

The values of normalized complexity measures for respiratory rate signal are high, what indicates that this time series is close to unstructured randomness. The Lempel-Ziv complexity values for angiogenic patterns were growing with the FIGO stage of disease. We conclude that Lempel-Ziv complexity may be a very helpful tool in analyzing the medical images and biomedical time series. It can be easily computed from the analyzed data.

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Development of the method of the bulbar conjunctiva images estimation for investigation of microcirculation state in cardiovascular diseases

Anishchanka U[1], Konstantinova E[2], Lapitskii V[1], Levshinskii L[1], Trukhan V[1]

[1] United Institute of Informatics Problems, Minsk, Belarus
[2] Belarussian Center "Cardiology", Minsk, Belarus

Abstract

Purpose: **The results of some studies specify the important role of microcirculation disturbances in ischemic heart disease (IHD) and essential hypertension (EH) pathogenesis. Among clinical methods of microcirculation research the most perspective is the biomicroscopy of bulbar conjunctiva. However, the outdated methods of application of semiquantitative criteria systems for the estimation of the microcirculation system condition cause subjectivity and incomparability of results received by different researchers. The purpose of this study is the creation of the algorithm and the medical-technological complex (MTC) for the automated quantitative estimation of the microcirculation system state and primary evaluation of its possibilities in clinical investigations.**

Material and methods: **To observe microcirculation on the bulbar conjunctiva we have used an intra-vital videomicroscopic system.**

Results: **We have worked out the computer tools for documentation and estimation of bulbar conjunctiva images. To quantitative evaluation images we have developed the qualitative-quantitative scale of Möriche and Volkov. The quantitative evaluation algorithm of bulbar conjunctiva images includes the calculation of the vascular and intravascular coefficients for arterioles, capillaries, venules and ones for extravascular space. For estimation of the algorithm and the MTC possibilities in clinical investigations we were observed microcirculation in healthy subjects, patients with IHD and EH.**

Conclusions: **Our findings have demonstrated that present algorithm and the MTC will permit to increase the informatively and diagnostic significance of the conjunctival biomicroscopy method and to create a single approach to the estimation of the microcirculation system state.**

Key words: microcirculation, biomicroscopy, bulbar conjunctiva, digital and analog engineering, images estimation.

ADDRESS FOR CORRESPONDENCE:
Uladzimir Anishchanka
United Institute of Informatics Problems
6 Surganova Str., Minsk, 220012, Belarus,
Tel. +375 17 2840985, Fax: +375 17 2840320.
e-mail: anishch@newman.bas-net.by

Introduction

At the present time the results of some researches specify the important role of microcirculation disturbances in ischemic heart disease (IHD) and essential hypertension (EH) pathogenesis. The attention which has considerably increased to microcirculation by cardiologists' part for last years is connected to its special value in operating cardiovascular system which consists of providing an optimum microenvironment of any tissue working structures. Therefore now the characteristic of blood system circulation condition are not be able considered enough full without detailed studying a microcirculation system. Among numerous clinical methods of microcirculation research the most perspective is the biomicroscopy of bulbar conjunctiva. The value of this method in clinical researches is caused its information completeness, availability, non-invasivity, nearness to natural conditions, an opportunity of supervision practically all parts microcirculatory network. So, the conjunctiva biomicroscopy allows to estimate a condition of microvessels (arterioles, capillaries, venules), perivascular spaces, structure of blood flow, kind and a degree of intravascular disorders of microcirculation. The modern level of digital and analog engineering development, computer methods gathering and storage of the videoinformation allows to receive on the personal computer qualitative microcirculatory network images and to carry out their automated processing that opens real opportunities for increase of diagnostic precision and information completeness of this method.

Now investigations of conjunctiva microcirculation with using computer added analytical systems are carried out in several research centers [1,2]. Thus authors are carrying out a quantitative estimation separate characteristics of a microvascular network: diameter of vessels, their form, flow structure or velocity in one kind vessels [3]. Such approach allows receiving the information about separate parts of microcirculatory net, but it does not give an opportunity to estimate a state of this system as a whole. It may be used in research of microcirculatory disorders at the established clinical forms of various diseases and an efficiency estimation of the influences directed to the correction of concrete abnormalities. Semi-quantitative criteria used for studying the microcirculation of system are the reason of significant subjectivity and, frequently, incomparability of the results received by various researchers.

The purpose of this study is the creation of the algorithm and the medical-technological complex (MTC) for the automated quantitative estimation of the microcirculation system state and primary evaluation of its possibilities in clinical investigations.

Material and methods

To observe microcirculation directly on the bulbar conjunctiva we have used an intra-vital video-microscopic system. It consists of slit lamp, adapter, videocamera and personal computer. We have worked out the computer tools for documentation and estimation of bulbar conjunctiva images. To quantitative evaluation images we have developed the qualitative-quantitative scale of Möriche [4,5] and Volkov [6]. The status of the conjunctival microcirculation was examined by taking the vascular and intravascular coefficients for arterioles (a), capillaries (c), venules (v) and ones for extravascular space. The quantitative evaluation algorithm of bulbar conjunctiva images includes the determination of mean vascular diameters, corresponding parameters characterizing the microcirculatory phenomena and calculation of the following coefficients: irregular of vessels diameter ($C_{id}^{(a,c,v)}$), vessels wind ($C_{w}^{(a,c,v)}$), capillary density (C_{s}^{c}), arteriole-venular ratio (C_{av}), arteriole-venular anastomosis density (C_{ava}), network area (C_{net}), haemorrhages (C_{hr}), extravascular oedema (C_{evo}) and deposits (C_{evd}) areas, irregular of blood flow ($C_{ibf}^{(a,c,v)}$), intravascular aggregation ($C_{agr}^{(a,c,v)}$), dissemination of aggregates ($C_{dar}^{(a,c,v)}$). Based on these parameters the vascular (VI), intravascular (IVI), extravascular (EVI) and summary microcirculatory (SMI) indices were determined. For primary estimation of a MTC with expert system possibilities in clinical investigations we were observed conjunctival microcirculation in 133 healthy subjects young (29-35) and middle (36-50 years) age, 45 patients with IHD 42-58 years and 16 people with early stage EH 33-41 years. Some specific clinical and laboratory methods of investigation were applied to exclude or diagnose IHD and EH.

Results

Four groups of healthy subjects were studied: young women – subgroup A (n=20; 31.2±0.4 years) and middle – subgroup B (n=20; 41.8±0.72 years) age, young men – subgroup C (n=20; 31.7±0.5 years) and middle – subgroup D (n=20; 41.5±1.8 years) age. It was not found a significant difference between subgroups in means following coefficients: $C_{id}^{a,c,v}$, $C_{w}^{a,v}$, C_{av}, C_{ava}, C_{net}, C_{hr}, C_{evd}, $C_{ibf}^{a,c}$, $C_{agr}^{a,c,v}$, $C_{da}^{a,c,v}$. But in middle age women it was significant lower C_{evo} (0.62±0.05 in compare with 0.91±0.08; 0.89±0.09 and 0.83±0.07 in subgroups A, C, D, respectively). In middle age men it was determined significant lowering of C_{s}^{c} (0.083±0.006 in compare with 0.13±0.007; 0.14±0.009 and 0.12±0.008 in subgroups A, B, C, respectively) and C_{ibf}^{v} (0.81±0.07 in compare with 0.95±0.05; 0.97±0.08 and 0.96±0.06 in subgroups A, B, C, respectively).

In next part of primary clinical investigation using the created MTC with expert system for the non-invasive automated quantitative estimation of microcirculation state it was observed two groups of people: the 1st – 45 patients with IHD (51.3±6.1 years) and the 2nd – 39 healthy subjects (48.4±5.2 years). Results of conjunctival microcirculation parameters calculation in each group are: in group 1 – C_{id}^{a}=0.81+0.08; C_{w}^{a}=0.91+0.1; C_{s}^{c}=0.04±0.003; C_{id}^{c}=0.78±0.08; C_{w}^{c}=0.81+0.079; C_{id}^{v}=0.82+0.085; C_{w}^{v}=0.7+0.072; C_{av}=0.34±0.04; C_{ava}=0.91+0.1; C_{net}=0.92+0.09; C_{hr}=0.97+0.09; C_{evo}=0.51+0.1; C_{evd}=0.94±0.09; C_{ibf}^{a}=0.78+0.08; C_{agr}^{a}=0.81+0.09; C_{da}^{a}=0.94+0.1; C_{ibf}^{c}=0.83+0.08; C_{agr}^{c}=0.80+0.09; C_{da}^{c}=0.97+0.09; C_{ibf}^{v}=0.76+0.08; C_{agr}^{v}=0.6+0.07; C_{da}^{c}=0.94+0.09; VI=7.54±0.59; IVI=7.43±0.62; EVI=2.42±0.27; SMI=17.3+1.52 and in group 2 – C_{id}^{a}=0.99+0.08; C_{w}^{a}=0.97+0.09; C_{s}^{c}=0.14±0.01; C_{id}^{c}=0.99±0.1; C_{w}^{c}=0.96+0.1; C_{id}^{v}=0.97+0.12; C_{w}^{v}=0.97+0.11; C_{av}=0.57±0.06; C_{ava}=0.97+0.09; C_{net}=1.0+0.006; C_{hr}=1.0+0.0; C_{evo}=0.91+ 0.1; C_{evd}=1.0±0.0; C_{ibf}^{a}=0.99+0.09; C_{agr}^{a}=0.99+0.1; C_{da}^{a}=0.99+0.1; C_{ibf}^{c}=0.98+0.1; C_{agr}^{c}=0.99+0.1; C_{da}^{c}=0.99+0.12; C_{ibf}^{v}=0.96+0.11; C_{agr}^{v}=0.98+0.1; C_{da}^{c}=0.99+0.11; VI=8.53±0.69; IVI=9.85±0.82; EVI=2.91±0.03; SMI=21.5±1.98.

For evaluation of creating MTC possibility to detect early EH microcirculatory sings 30 people (43.2±3.7 years) were observed without clinical EH manifestations. Blood pressure in conditions without physical and other loading in all observed subjects were normal. Results of retina examination were normal also. But after evaluation of bulbar conjunctiva microcirculation state observed subjects were separated in two group. In the first of them (n=14) it was obtained following data: C_{id}^{a}=0.98+0.08; C_{w}^{a}=0.92+0.09; C_{s}^{c}=0.13±0.01; C_{id}^{c}=0.97±0.1; C_{w}^{c}=0.93+0.09; C_{id}^{v}=0.97+0.1; C_{w}^{v}=0.95+0.08; C_{av}=0.57±0.06; C_{ava}=0.91+0.08; C_{net}=1.0+0.006; C_{hr}=1.0+0.0; C_{evo}=0.87+ 0.1; C_{evd}=1.0±0.0; C_{ibf}^{a}=0.99+0.09; C_{agr}^{a}=0.99+0.1; C_{da}^{a}=0.99+0.11; C_{ibf}^{c}=0.98+0.1; C_{agr}^{c}=0.99+0.1; C_{da}^{c}=0.99+0.12; C_{ibf}^{v}=0.96+0.11; C_{agr}^{v}=0.98+0.1; C_{da}^{c}=0.99+0.11. In the second group (n =16) means of microcirculatory coefficients were: C_{id}^{a}=0.96+0.09; C_{w}^{a}=0.91+0.1; C_{s}^{c}=0.08±0.01; C_{id}^{c}=0.9±0.08; C_{w}^{c}=0.87+0.08; C_{id}^{v}=0.89+0.09; C_{w}^{v}=0.86+0.07; C_{av}=0.34±0.04; C_{ava}=0.99+0.1; C_{net}=1.0+0.004; C_{hr}=1.0+0.0; C_{evo}=0.74±0.1; C_{evd}=1.0±0.0; C_{ibf}^{a}=0.93+0.09; C_{agr}^{a}=0.91+0.1; C_{da}^{a}=0.97+0.1; C_{ibf}^{c}=0.94+0.1; C_{agr}^{c}=0.89+0.09; C_{da}^{c}=0.93+0.09; C_{ibf}^{v}=0.86+0.08; C_{agr}^{v}=0.84+0.09; C_{da}^{c}=0.87+0.08.

According to bulbar conjunctiva examination results main differences between these group present as: more high degree of venules and capillary wind, significant decrease of capillary density and AV-ratio, increase of irregular blood flow and intravascular aggregation in venules in the second group in compare with the first. During following clinical examination in all subjects of the second group it was found the hypertensive reaction on physical exercise in condition bicycle test and with correspondence to clinical and laboratory examination it was diagnosed the early stage of EH. The found data in the part of microcirculatory alteration character in more late stages of EH are similar to the literature [7].

Discussion

Our results show that conjunctival microcirculatory changes in men middle age are presented as lowering of capillary density and increase of intravenous abnormalities degree. In this subgroup were observed increase plasma cholesterol level and blood viscosity at the low shear rate. Microcirculatory changes in healthy men middle age my reflect early vascular damage from IHD risk factors influence [8].

Obtained data show that in IHD there are increase of an irregular of microvessels diameter, extravascular oedema and degree of intravascular disturbances in arterioles, capillaries and venules, decrease of capillary density and arteriole-venular ratio. These microcirculation abnormalities were marked by other authors [9], but present system permits to obtain a quantitative evaluation of the visible alterations. Investigation of bulbar conjunctiva with using creating system may be more sensitive to microcirculatory sings of EH early stage than results of retinal microvascular abnormalities evaluation [10].

Conclusions

Thus, a developing system of the criteria based on quantitative definition of parameters of the main phenomena, which are registered at biomicroscopic observation of microcirculatory network, will allow to receive the objective information on a state of microcirculatory system as a whole and to create classification of normal and pathological conditions of conjunctival microcirculation, which are typical for early stages IHD and EH.

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Computer-aided processing ultrasonic diagnostic images of the children lymph nodes at lymphomas and reactive hyperplasias

Begun IV[1], Kulaha VV[2], Anishchanka UV[2], Spiridonov SV[2]

[1] Belarusian Research Center for Pediatric Oncology and Hematology, Minsk, Belarus
[2] United Institute of Informatics Problems, Minsk, Belarus

Abstract

Purpose: **The aim of our investigation is studying the quantitative indicators of the blood flow in LN of children and teenagers with the first discovered Hodgkin disease, non-Hodgkin's lymphoma and BL on the base of the computer-aided processing the ultrasonic diagnostic images.**

Material and methods: **Pathologically enlarged cervical lymph nodes were evaluated during the primary ultrasonic investigation of 65 children of both sexes of age from 2 to 17. Clinical (n=19 at benign lymphoadenopathy) and morphological (n=31 at Hodgkin's disease, n=9 at non-Hodgkin's lymphoma and n=6 at benign lymphoadenopathy) diagnosis verification was carried on with all patients. Maximal and minimal blood flow linear velocities in the main intranodal artery, resistance index and Color Pixel Density were determined. The program has been worked out for processing lymph nodes ultrasonic images obtained in one of four modes: gray scale; color flow mapping; power Doppler imaging; pulsed waved Doppler. The list of the measured parameters is defined in each mode.**

Results: **Were received results: 1) of the grayscale images analysis, 2) of the vascular patterns in a mode color flow mapping, 3) of the flow analysis and index of the intranodal resistive in the Hodgkin disease and lymphopathy. They confirm prospect of inclusion to the computer algorithm of differentiation lymphopathy and the affected lymph nodes of the information received by means of modern technologies of the diagnostic ultrasound at the time of acknowledgements of the morphological diagnosis. The developed method optimizing the description of the ultrasound image of the lymphatic tissue, allows to distinguish the signs in multistage process of classification with the purpose to achieve criteria of defeat in the lymphomas.**

Conclusions: **The work results consist in definition of the functional features being the pathognomic ones with the statistically acceptable probability at the differential diagnostics of lymphomas and reactive hyperplasias.**

Key words: lymphoma, cervical lymph nodes, Doppler sonography, vascularity index, computer method of the data identification, children.

ADDRESS FOR CORRESPONDENCE:
Igor Begun
Belarusian Center for Pediatric Oncology and Hematology,
P.O. Lesnoye-2, Minsk district 223052, Belarus,
Tel: +375 17 2022519, Fax: +375 17 2024222
e-mail: begun_igor@mail.ru

Introduction

Prospects of the lymphatic system organs ultrasonic investigation are determined by high resolution of the diagnostic equipment of the 4th generation and new Doppler technologies. According to the data of Ying M. et al., the lymph nodes (LN) sizes increase causes increase of the velocity of intranodal blood flow without substantial change of the resistance of intranodal blood flow [1]. Lymphomas hold the fourth place in the morbidity; structure and make-up approximately 13% of all the cancer diseases in children of the Republic of Belarus [8]. In many works the authors confirm the possibility of differentiation of benign from malignant lesions of LN during estimation of the intranodal resistance – in LN malignant lesions the resistance index (RI) has values over 0.8 [2-5]. Other authors consider RI over 0.72 [6] to be the indicator of the LN malignant lesion. There exist attempts of determination of the qualitative differential-diagnostic indicators for differentiation of lymphomas and reactive benign lymphoadenopathy (BL) on the basis of the semi-quantitative and qualitative indicators such as the LN shape, differentiation in the hilar area, vascularity appears [7-9]. There exist works on application of the contrast study with harmonic strengthening in studying vascularity of LN lesions [10] and high sensitive power Doppler in estimation of the vascularity of benign LN [11]. Accepting the decision about the

necessity of the lymphoid tissue histologic study is defined by the data of both clinic and instrumental methods of investigation. There are only single works on investigation of the vascularity appear of malignant lesions LN in cases of lymphomas and BL LN in children.

The aim of our investigation is studying the quantitative indicators of the blood flow in LN of children and teenagers with the first discovered Hodgkin disease, non-Hodgkin's lymphoma and BL on the base of the computer-aided processing the ultrasonic diagnostic images.

Material and methods

Pathologically enlarged cervical lymph nodes were evaluated during the primary ultrasonic investigation of 65 children of both sexes of age from 2 to 17 (age 9.7±0.6), that was carried on using the Logiq 500 (GE MS, USA) device. Investigation was carried on using the high frequency (13 MHz) linear transducer in the triplex mode.

Clinical (n=19 at BL) and morphological (n=31 at Hodgkin's disease, n=9 at non-Hodgkin's lymphoma and n=6 at BL) diagnosis verification was carried on with all patients. In 50% of all cases at Hodgkin's disease the variant of nodal sclerosis was stated, in the other cases – the mixed-cellular variant or lymphoid predominance. In the group of patients with non-Hodgkin's diseases the T-cellular tumors were prevailing.

Ultrasonic images of the lymph nodes were obtained in the gray scale modes, color flow mapping and power Doppler imaging modes when the index (Color Pixel Density) [12] and the intranodal vascularization character were estimated. During the pulsed waved dopplergraphy the check volume was placed in the visualization zone in the mode of color mapping of the arterial vessel in the region of the enlarged LN hilar projection. Maximal (V_{max}) and minimal (V_{min}) blood flow linear velocities in the main intranodal artery and RI were determined.

The program has been worked out for processing lymph nodes ultrasonic images obtained in one of four modes: gray scale (GRAY); color flow mapping (CFM); power Doppler imaging (PDI); pulsed waved Doppler (PWD). The list of the measured parameters is defined in each mode.

When opening the ultrasonic image the program, using the preliminarily trained neural network [13-15], automatically recognizes the operation modes of the ultrasonic diagnostic device, its settings, scaling coefficient. The recognized parameters are displayed on the input parameters panel and are supervised by a doctor-researcher. If necessary, e.g. in the case of erroneous recognition, the parameters can be edited in the manual mode. To start processing the doctor (operator) highlights the region of interest by a mouse and then initiates the processing mode by pressing the corresponding button on the modes control panel. After processing completion the results are displayed in the corresponding panel of the output parameters.

Statistical processing the data obtained was carried on using the standard methods. All the quantitative indicators after verification of the distribution normality are represented in the form M±m. Differences of the average values were considered reliable at $p<0.05$. The correlation analysis was carried out with calculation of the Pearson coefficient.

Results

The gray scale investigation of the LN in all the groups reflected their enlarged sizes, shape change, formation of the conglomerates, echogenicity reduction, the lack of the hilar region differentiation. The comparative analysis showed increase of the maximal longitudinal (L_1=32.3±2.4 mm) and cross (L_2=16.2±1.6 mm) dimensions for the LN in the non-Hodgkin's group in relation to the BL group (25.9±1.7 and 12.1±4.9 mm correspondingly, $p<0.05$). The most changed in a shape were the LN of the patients with the Hodgkin's diseases that is confirmed by the reliable reduction of the relation L_1/L_2 in comparison with the BL group ($p<0.05$) and is coordinated with the data of Papakonstantinou O. et al. [9].

The values of the blood flow linear velocities along the LN main artery for children with the BL exceeded those at Hodgkin's diseases (to the greater extent it was typical for V_{min}). The expressed differences in values of the blood flow finite diastolic velocity can indicate at more low intranodal blood flow resistance at BL that is confirmed by the RI values difference. The intranodal resistance of the circulatory bed of the patients with the non-Hodgkin's disease also exceeded the resistance for the BL group.

The L_2 and V_{min} correlation was noticed for children with the BL ($r=0.44$, $p<0.05$). The correlation was also obtained for L_2 and V_{max} and L_2 and V_{min} ($r=0.83$, $r=0.78$ correspondingly, $p<0.05$) for the patients with the non-Hodgkin's diseases that can reflect dependence of the intranodal circulatory bed properties from the degree of the lymphoproliferative process intensity. High resistance of the circulatory LN bed with the granulematosis lesion is evidently determined by its structure disorganization, presence of the diffuse fibrosis with the intranodal arterial network compression. Follicular hyperplasia at lymphadenopaties is accompanied by the small vessels proliferation that causes increase of the circulatory bed capacity and correspondingly reduction of its resistance.

The vascularity appear of the hyperplastic LN was characterized by the variety: from visualization of the short vascular pedicle at the hilar to visualization of the vascularity appear diffusion strengthening and tree-type structure with the foundation at the hilar region. Estimation of the Color Pixel Density indicator by the developed computer program showed its reduction in the group of patients with Hodgkin's disease relative to those with the BL ($p<0.05$). It is no necessary to note the variability of the intranodal vascularity appear in all the groups depending not only on the nosological and individual peculiarities of the concrete patient, but also on the diagnostic ultrasonic devise class and on its presenting.

Discussion and conclusions

The abilities of the computer-aided lymph nodes ultrasonic images processing at the reactive hyperplasias and lymphomas

in children are considered in the investigation. The technique is based on the ultrasonic images computer-aided analysis in the gray scale mode, color flow mapping and power Doppler imaging modes, estimation of the blood flow velocity characteristics and the intranodal resistance index in the mode of pulsed waved Doppler. The work results consist in definition of the functional features being the pathognomic ones with the statistically acceptable probability at the differential diagnostics of lymphomas and reactive hyperplasias.

The basic methods, which give the right for the lymphoma diagnosis formulation, are morphological and immunological investigations of the tumor substratum. The role and place of the ultrasonic method in the diagnostics of lymphomas in children are determined by the primary tumor localization and the tumor process spreading regularities [16]. Nevertheless, the data of the analysis of the blood flow linear velocity indicators, the circulation bed resistance and vascularization index confirm the perspective of differentiation of the reactive hyperplasia and lymphomas using the Doppler technologies by the moment of making the morphological diagnosis. These data can be applied as Doppler criteria in the differential diagnostics of the benign limphadenopathy and the malignant lymphoproliferative diseases in children on the stage of the primary diagnostics.

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Dipolar criterion in survival time prediction

Krętowska M

Białystok Technical University, Faculty of Computer Science, Białystok, Poland

Introduction

Analysing the survival data may focus on two main tasks: to predict the failure time corresponding to a new patient and to understand the relationships between measured variables and the survival time. In both cases the problem how to treat censored cases arises. Censoring is the characteristic feature of survival data. It is connected with lack of knowledge of the failure (e.g death) occurrence. In censored observations there is no exact information about the failure time, we only know that it is greater than patient's follow-up time.

Incomplete information causes many problems in understanding the nature of the relationships among variables in the data. The basic question is how to use this particular knowledge in the prediction tools. Simultaneously with statistical methods other techniques, which try to cope with the problem, are developed. In the paper the possibilities of using piecewise linear criterion functions in the survival time prediction are presented.

Dipolar criterion

The dipolar criterion function is based on the concept of dipoles [2]. The dipole is a pair of different covariate vectors (χ_i, χ_j) from the learning set. Mixed and pure dipoles are distinguished. Mixed dipoles are formed between objects that should be separated, while pure ones between objects that are similar from the point of view of an analyzed criterion.

The aim is to find such a hyper-plane $H(v)$ that divides possibly high number of mixed dipoles and possibly low number of pure ones. It is done by minimization of the dipolar criterion function. Two types of piece-wise linear and convex (CPL) penalty functions $\varphi_i^+(v)$ and $\varphi_j^-(v)$ are considered:

$$\varphi^+_j(v)=\begin{cases}\delta^j-<v,y_j> & \text{if} <v,y_j><\delta^j\\ 0 & \text{if} <v,y_j><\delta^j\end{cases}$$

$$\varphi^-_j(v)=\begin{cases}\delta^j-<v,y_j> & \text{if} <v,y_j>>\delta^j\\ 0 & \text{if} <v,y_j><\delta^j\end{cases}$$

where $y = [1, \chi^T]^T$ is an augmented covariate vector and $v = [-\theta, w_1, w_2, \ldots, w_N]^T$ is an augmented weight vector. Each mixed dipole (y_i, y_j), which should be divided, is associated with a function being a sum of two function with opposite signs

$$\varphi_{ij}^m(v)=\varphi_i^-(v)+\varphi_j^+(v) \text{ or } \varphi_{ij}^m(v)=\varphi_i^+(v)+\varphi_j^-(v)$$

With pure dipoles, which should remain undivided, we associate a function:

$$\varphi_{ij}^p(v)=\varphi_i^-(v)+\varphi_j^-(v) \text{ or } \varphi_{ij}^p(v)=\varphi_i^+(v)+\varphi_j^+(v)$$

The dipolar criterion function is a sum of penalty functions associated with each dipole:

$$\Psi(v)=\sum_{(i,j)\in I_p}\alpha_{ij}\varphi_{ij}^p(v)+\sum_{(i,j)\in I_m}\alpha_{ij}\varphi_{ij}^m(v)$$

where α_{ij} determines relative importance (price) of the dipole (y_i, y_j), I_p and I_m are the sets of pure and mixed dipoles, respectively.

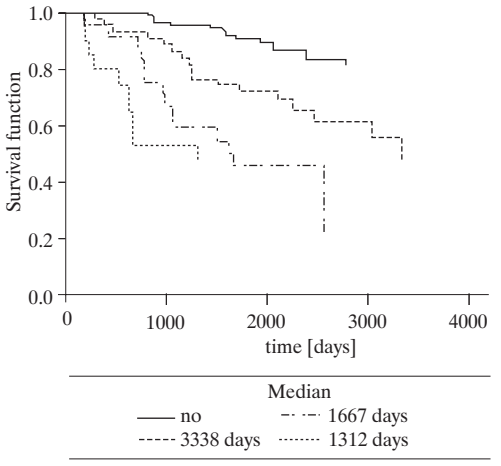
Because $\Psi(v)$ is the convex, piece-wise linear function, basis exchange algorithms, similar to linear programming, are used as a minimization method.

Prediction tools

Dependently on the presumed task the algorithm may lead to different solutions. The difference is connected with the way the dipoles are formed and the tool used. The above procedure may be used to search parameters of individual neurons in the

ADDRESS FOR CORRESPONDENCE:
Małgorzata Krętowska
Białystok Technical University, Faculty of Computer Science,
Wiejska 45a, Białystok, Poland
e-mail: mmac@ii.pb.bialystok.pl

Figure 1. **Kaplan-Meier estimates of the survival functions for distinguished subgroups obtained for *Malignant melanoma* data set**



artificial neural network or to search the splits in internal nodes of the regression tree.

Survival data: The i-th observation (patient) in survival data is described by a set (χ_i, t_i, δ_i) i=1,2,…,M, where χ_i is N-dimensional covariate vector, t_i – survival time, and δ_i – failure indicator. Failure indicator is equal to 1 for patients for whom the event of interest occurred (uncensored cases) and 0 otherwise (censored cases). Survival time may be also considered as a discrete variable. In that case the survival time t_i is divided into K disjoint intervals I_k (k=1, 2, ...,K), where $I_k=[t_{k-1}, t_k)$ and $0<t_1<t_2<...<t_K$, $t_0=0$, $t_K<\infty$. Each patient O_i is then described by a set (χ_i, I_i, δ_i), where I_i is the last time interval in which the subject O_i was observed.

Regression tree: Hierarchical and sequential structure of a tree recursively partition the feature space. The tree consists of terminal nodes (leaves) and internal (non-terminal) nodes. An internal node contains a split, which tests the value of an expression of the covariates. Each distinct outcome of the test generates one child node, which means that all non-terminal nodes have two or more child nodes. A terminal node generates no descendant [1].

The proposed method of regression tree induction aims at dividing the feature space into such areas, which would include the patients with similar survival time. It may be done by appropriate rules of dipoles formation. Pure dipoles are created between pairs of feature vectors, for which the difference of failure times is small, mixed dipoles – between pairs with distant failure times. Taking into account censored cases the following rules of dipole construction can be formulated:

a) a pair of feature vectors (χ_i, χ_j) forms the pure dipole, if
- $\delta_i=\delta_j=1$ and $|t_i-t_j|<\eta$;

b) a pair of feature vectors (χ_i, χ_j) forms the mixed dipole, if
- $\delta_i=\delta_j=1$ and $|t_i-t_j|>\zeta$;
- $(\delta_i=0, \delta_j=1$ and $t_i-t_j>\zeta)$ or $(\delta_i=1, \delta_j=0 \wedge t_j-t_i>\zeta)$.

Parameters η and ζ are equal to quartiles of absolute values of differences between uncensored survival times. The parameter η is fixed as 0.2 quartile and ζ – 0.6. The hyper-planes in the internal nodes of the tree are computed by minimization of dipolar criterion function. Each terminal node is described by median survival time and Kaplan-Meier estimator of the survival function.

Neural network: The analysis is focused on the prediction of the conditional failure probabilities (discrete hazards) in separate time intervals. The hazard rate in the k-th time interval is defined as $h_k=P(t\in I_k / t>t_{k-1})$. Taking into account the likelihood function one can show that for the i-th patient the censoring indicator d_{ki} can be treated as an estimator of the hazard h_{ki}. d_{ki} is equal to 1 for the last time interval in which the uncensored subject O_i was observed and equal to 0 otherwise.

Prediction of the conditional failure probabilities is done by using a modular neural network [3]. The network consists of K-1 ordered neural networks NN_k. Each network NN_k is trained to differentiate patients with the failure time belonging to the k-th time interval (the output equal to 1) from other patients being at risk in this time interval (0 at the output). The dipoles are formed according to following rules:

a) a pair of feature vectors (χ_i, χ_j) forms the pure dipole, if $d_{ki}\neq d_{kj}$,

b) a pair of feature vectors (χ_i, χ_j) forms the mixed dipole, if $d_{ki}=d_{kj}$.

Experimental results

The first analyzed data set contains the information on 205 patients (14 censored cases) with malignant melanoma following radical operation. The data was collected at Odense University Hospital in Denmark by Drzewiecki KT. Each patient is described by 4 features: sex, age, tumor thickness [cm] and ulceration.

The regression tree received for *Malignant melanoma* data consists of three internal nodes, which divide the feature space into four areas. The Kaplan-Meier survival functions are shown in *Fig. 1*.

The other data set contains the information from the Veteran's Administration (VA) lung cancer study. In this trial, male patients with advanced inoperable tumors were randomized to either standard (69 subjects) or test chemotherapy (68 subjects). Only 9 subjects from 137 were censored. Information on cell type, prior therapy, performance status at baseline, disease duration in months, and age in years at randomization, was available.

The survival time was divided into 3 time intervals [days]: <0,31); <31, 100);<100, ...). The modular neural network contains two networks: NN_1 and NN_2. The accuracy, sensitivity and specificity with 95% confidence interval of each network are [%]: NN_1 {acc: 78.8 (71.1; 85.4); sen: 73.2 (57.1; 85.8); sp: 81.3 (72; 88.5)}, NN_2 {acc: 73 (64.7; 80.3); sen: 74.7 (63.6; 83.8); sp: 70.7 (57.3; 82)}.

Conclusions

The dipolar criterion function is a flexible method to create different tools for survival time prediction. The main advantage of the technique is its ability to cope with censored cases, which are taken into account while dipoles construction.

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Uncover the relations between the discretized continuous-valued features with multiple correspondence analysis in medical domain

Navasiolava NA, Tom IE, Krasko OV

United Institute of Informatics Problems of The National Academy of Sciences of Belarus, Minsk, Belarus

Abstract

Purpose: The aim of this study was to explore a way in which continuous-valued and categorical features can be treated simultaneously in multiple correspondence analysis for the solution of a particular medical problem.

Material and methods: The exploratory analysis of medical data from Belarussian Research Center for Pediatric Oncology and Hematology (BRCPOH) was performed using the developed combined method, consisted of prior continuous-valued data discretization with subsequent correspondence analysis of frequency tables.

Results: The developed method allows to perform supervised discretization of continues features and significantly decreases the number of its values, to treat continuous-valued and categorical features simultaneously in multiple correspondence analysis, to analyze the quality of discretization of continuous-valued features.

Conclusions: The proposed combined method of exploratory data analysis allows discovering interactions between the different features of any initial type.

Key words: exploratory data analysis, continuous-valued feature discretization, multiple correspondence analysis.

Introduction

The results of data analysis in medical domain frequently are required to be interpretable to the medical expert, therefore in the most cases it's very important to find the critical values of the features, that can explain the data analysis model output. It is more convenient for the medical expert to analyze the features, represented with a few values, categorical features. Different methods of the discretization of continuous-valued features are introduced in the literature [1,2] as a technique allowing to improve the accuracy and to simplify the structure of many data analysis models (decision tree, neural networks). In this paper the combined method of exploratory data analysis is proposed, consisted of prior continuous-valued data discretization with subsequent correspondence analysis of frequency tables [3]. This method not only allows to discover interesting interactions between the different features of any initial type, but also to analyze the quality of discretization of continuous-valued features.

ADDRESS OF CORRESPONDENCE:
Navasiolava Natallia
Laboratory of Bioinformatics
United Institute of Informatics Problems
of The National Academy of Sciences of Belarus
6 Surganov Str., 220012, Minsk, Belarus
e-mail: novosel@newman.bas-net.by

Material and methods

The data of the children with acute lymphoblastic leukemia (ALL), collected in Belarussian Research Center for Pediatric Oncology and Hematology were analyzed with proposed combined method, consisted of prior continuous-valued data discretization with subsequent correspondence analysis of frequency tables. This method allows analyzing the interaction between the features of the different initial type.

The correspondence analysis of discretized medical data was performed using STATISTICA 6.0 software, StatSoft Inc.

Results

General

The main result of the study is the proposed combined method of exploratory data analysis, consisted of continuous-valued features discretization and the analysis of discretized and categorical features simultaneously with multiple correspondence analysis in order to reveal the interactions between them.

Continuous-valued features discretization

Several methods of data discretization have been described in the literature as the preprocessing step of data mining process [1,2]. They can be divided into two classes:

- unsupervised methods, which deal with data without classification information available;
- supervised methods, which take the classification information into account.

In the proposed combined data analysis method we use the Chi² algorithm [4], extended with the prior feature ranking according to entropy measure.

In our interpretation continuous-valued features discretization process consists of two stages:

- ranking of initial features according to their information gain for classification;
- Chi² statistical method of discretization.

All the initial features of patients with ALL are ranked according to their information gain for classification, which is calculated on the basis of entropy value or expected information for classification:

$$I(U)=-\sum_{c=1}^{N_c}\frac{n_c}{n}\cdot\log_2\frac{n_c}{n}$$

where n_c – the number of objects (patients), belonging to class c, and n – the total object number in the data set U.

Information gain, contributed by feature X_i is following:

$$G_i=I(U)-E_i,$$

$$E_i=\sum_{k=1}^{N_i}\frac{n_{ik}}{n}\cdot I(U_{ik}),\ I(U_{ik})=-\sum_{c=1}^{N_c}\frac{n_{ikc}}{n_{ik}}\cdot\log_2\frac{n_{ikc}}{n_{ik}},$$

U_{ik} is the subset of U with feature X_i for all objects equals k, $I(U_{ik})$ is the expected information for subset U_{ik}, n_{ik} – number of objects from U_{ik}, n_{ikc} – number of objects from U_{ik} belonging to class c.

After that, the features in the ranking order are propagated to discretization process with Chi² method. The Chi² method is based on χ^2 statistics and consists of two phases. In the first phase each feature is sorted according to its values. Then the following is performed:

- calculating χ^2 value for every pair of adjacent intervals;
- merging the pair of adjacent intervals with the lowest χ^2 value;
- merging continues until all pairs of intervals have χ^2 values exceeding the parameter, determined by defined significance level;
- process is repeated with decreased significance level until an inconsistency rate exceeds the predefined δ level.

The χ^2 value is calculated according to the following formula:

$$\chi^2=-\sum_{i=1}^{2}\sum_{j=1}^{k}\frac{(A_{ij}-E_{ij})^2}{E_{ij}},$$

Table 1. **Results of discretization of features from the medical data base**

Feature name	No values before discretization	No values after discretization
WBC1	60	5
WBC8	44	5
AGE	11	1
BL_ABS_8	24	5
HEP_8	12	3
CD10	32	1
CD20	37	3
CD45_14	46	2

k – number of classes, A_{ij} – no cases in the ith interval, jth class, R_i – no cases in the ith interval, C_j – no cases in the jth class, N total no cases, E_{ij} – expected frequency of

$$A_{ij}=\frac{R_i\cdot C_j}{N}$$

Along with discretization the selection of features is accomplished by removing those, having only one discrete value. Both discretization and feature selection retain the discriminating power of processed data (*Tab. 1*).

Correspondence analysis of frequency tables

Correspondence analysis is an exploratory technique for the analysis of frequency tables. It allows revealing the dependencies of medical features in order to fit the appropriate model to the problem in question. Another application of the correspondence analysis techniques is that it allows performing the equivalence of a multiple regression for categorical features, by adding supplementary data to the input frequency table. The display of the discretized continues-valued features along with categorical ones in reduced dimensional space provides an indication of the nature of the relationships between them.

The possibility to visualize positional relationship of different features, allows to select more significant ones for the task in question for further analysis with different methods, as for example neural networks or decision trees. The following combination of features was analyzed: three features with discretized values, viz Hepatomegaly, day 8 (HEP8, cm); Blasts, abs., day 8 (bl_abs8, 10^9/L); CD20 (%), CD45 (%) and one categorical feature Response on therapy on day 15 (RESP15).

The obtained coordinates of different features' categories in the selected two-dimensional space that preserves most of information about difference of frequency profiles of individual points are presented in *Tab. 2*.

The two-dimensional layout of different features' categories is presented on *Fig. 1*.

Category 0 of RESP15 corresponds to remission at the day 15, category 1 — absence of remission at the day 15. From the *Fig. 1* it can be concluded, that the relative row frequencies of categories of the feature RESP15 according to categories of other features are strongly different. There are relatively more patients with category 0 of RESP15 among patients with category 1 of CD45_14 and 2 of CD20, and with category 1 of RESP15

Figure 1. **Representation of features' categories in two-dimensional space**

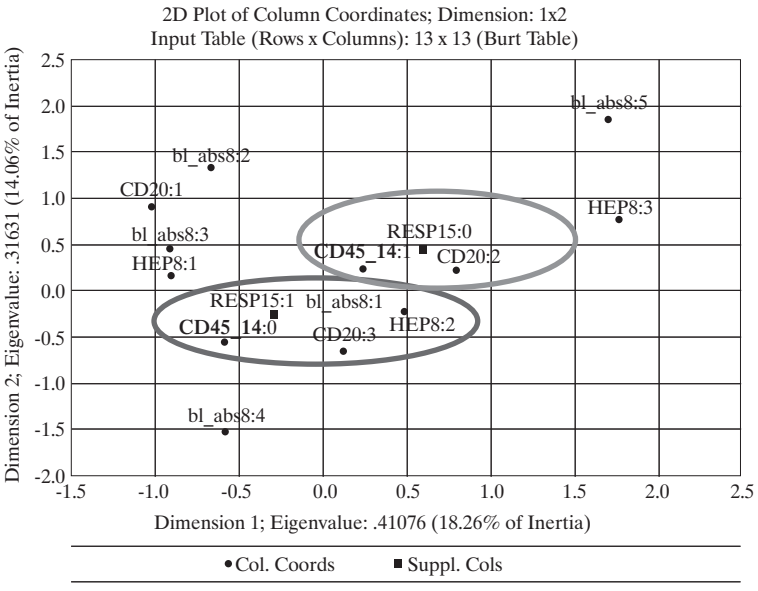

Table 2. **Coordinates and quality of representation of features' categories in two-dimensional space**

Feature	Row	Coordin1	Coordin2	Quality
HEP8:1	1	-0.88712	0.15889	0.584805
HEP8:2	2	0.48515	-0.23237	0.603148
HEP8:3	3	1.76494	0.75070	0.675892
bl_abs8:1	4	0.15641	-0.25785	0.661363
bl_abs8:2	5	-0.66448	1.32243	0.564276
bl_abs8:3	6	-0.90445	0.45886	0.566798
bl_abs8:4	7	-0.56815	-1.50782	0.730053
bl_abs8:5	8	1.70246	1.88259	0.883188
CD20:1	9	-1.01768	0.93388	0.696503
CD20:2	10	0.79206	0.20070	0.829504
CD20:3	11	0.14589	-0.63158	0.782826
CD45_14:0	12	-0.58271	-0.55839	0.666946
CD45_14:1	13	0.23882	0.22885	0.666946
RESP15:0		0.61981	0.47352	0.647287
RESP15:1		-0.29922	-0.22860	0.447287

among patients with category 0 of CD45_14 and 3 of CD20. Also the patients with category 1 of RESP15 strongly characterized with category 1 of bl_abs8. Therefore the interdependency of RESP15 and other more tightly related features can be further investigated with different statistical and data mining methods. Moreover the categories of the discretized feature that are close to each other in the two-dimensional space can be treated as one category without the loss of information, thus allowing to correct the results of discretization process.

Conclusions

The combined method of exploratory data analysis has been proposed, which allows solving the different tasks:

– to perform supervised discretization of continues features and significantly decrease the number of its values, keeping the discriminating power of a database;

– to treat continuous-valued and categorical features simultaneously in multiple correspondence analysis;

– to analyze the quality of discretization of continuous-valued features.

Acknowledgement

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Development of the information analytical system for childhood oncohematology: project ISTC #B-522

Tom IE[1], Krasko OV[1], Potapnev MP[2], Uglova TA[2]

[1] United Institute of Informatics Problems of The National Academy of Sciences of Belarus, Minsk, Belarus
[2] Belarussian Center for Pediatric Oncology and Hematology, Minsk, Belarus

Abstract

Propose: The main objectives were development of an information-analytical system (IAS) for processing personal, clinical, laboratory and other medical data, applying IAS in acute childhood leukemia particularly to select prognostic risk factors (PRFs) and to predict outcome of induction therapy based on the patient's profile of PRFs. Selection of adequate therapy was based on the results of analysis of individual profiles of PRFs for children with acute leukemias.

Materials and methods: The medical data were obtained in Belarussian Research Center for Pediatric Oncology and Hematology (BRCPOH). Altogether, data from 189 patients with acute lymphoblastic leukemia (ALL) and 74 patients with acute myeloid leukemia (AML) were analyzed. To verify the results of application the analytical system testing sample was obtained in Medical High School Hannover (collaborator of the project Prof. K.Welte).

Results: The IAS for selecting PRFs and for predicting outcome of induction therapy based on the patient's profile of PRFs. It can predict the outcome of induction therapy for protocols ALL BFM 90 M (Minsk, BRCPOH), ALL MB 2002 (Minsk, BRCPOH), ALL BFM 2000 (Hannover, MHSH), AML MM-2000 (Minsk, BRCPOH), AML MM-2003 (Minsk, BRCPOH).

Conclusions: The new PRFs and their combinations were explored by using IAS, the combinations were selected to predict outcome of induction therapy.

Key words: information-analytical system, prognostic risk factors, outcome of induction therapy.

ADDRESS FOR CORRESPONDENCE:
Igor E. Tom
Laboratory of bioinformatics
United Institute of Informatics Problems
The National Academy of Sciences of Belarus
6 Surganov Street, 220012, Minsk, Belarus
e-mail: tom@newman.bas-net.by

Introduction

The main objectives of the project were development of an information-analytical system (IAS) for processing personal, clinical, laboratory and other medical data, applying IAS in acute childhood leukemia particularly to select prognostic risk factors (PRFs) and to predict outcome of induction therapy based on the patient's profile of PRFs. Selection of adequate therapy was based on the results of analysis of individual profiles of PRFs for children with acute leukemias.

The main objectives have been reached by using the most progressive informational technologies for database design, access application development and the intelligent methods of medical data analysis.

The basis of an elaborated IAS is a three-tier (client – Web-server – database server) architecture that allows to part data storage and data handling and provides a security access to the data. Such an architecture means that only user dialogues is proceed on client's computer while business logic is checked by Web-server applications.

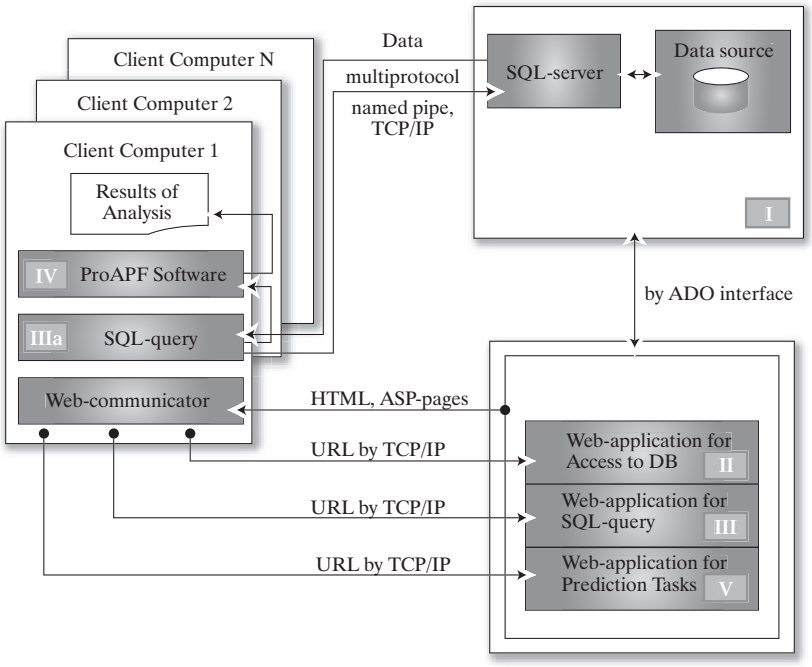
Material and methods

The medical data were obtained in Belarussian Research Center for Pediatric Oncology and Hematology (BRCPOH). Altogether, data from 189 patients with ALL and 74 patients with AML were analyzed. To verify the results of application the analytical system testing sample was obtained in Medical High School Hannover (collaborator of the project Prof. K.Welte).

Results

SQL-server was appropriated to store the data. We have used ASP-technology and Internet Information Server (IIS 5.0) to create user Web-application with ADO-components to

Figure 1. **The structure of IAS**



access the database server. The structure of IAS are as follows (see *Fig. 1*).

1. Subsystem #1: The Database for collecting (according the registration form) epidemiological, clinical and laboratory information in a form of relational database. We have chosen MS SQL Server as a Database Management System (DBMS) which is tight compatible with Windows NT/2000/XP platforms (the last is a preferable operational system in computer network of BRCPOH). The logical structure of the database corresponds the elaborated registration form. The form is clearly structured and contains data grouped by 7 mayor epidemiological, clinical and laboratory categories: personal information, history of disease, pre-diagnosis period, information about treatment, clinical manifestation, laboratory data, complications during induction therapy and toxicity. Registration form is created to fill computerized database for patient both with ALL and AML.

2. Subsystem #2: Web-application for a remote access to the database on purpose to add, view or edit information. According to the logical structure of the database we developed software for the basic function of data access (add, edit, delete) as stored procedures of Database server for different kind of data. We proposed to develop the client application based only on stored procedures, that restrict access to database for users, that means security and reliability of data of electronic register enhanced. The client application is designed in the format of sections of the registration form. We use three-tier "Client – Web-server – Database server" architecture, that grants remote access to data via Internet or Intranet. The user can access to data using only Microsoft Internet Explorer. The middle level (Web-server) ensures security exchange between client and Database server on ASP-platform. We constructed two kind of pages: DHTML-forms and action-pages. DHTML-forms only can read data from database and perform data for user. They also provide data input. Action-pages are handled by Web-server without exchange with client. This Web-application include more 175 ASP-pages.

3. Subsystem #3: Web-application for simplifying complicated SQL-queries generation to get necessary information from Database for further analysis. The subsystem for simplifying complicated SQL-queries generation is made in two versions for "Client – Web-server – Database server" and "Client – Server" architecture. Each of them can be adapted to database logical structure invisible for users. The query tools are based on the interactive query constructing using GUI. The user selects necessary criteria for query, after that subsystem translates them into SQL-query (Transact SQL-language is used in DBMS MS SQL Server 2000). The dialog with user helps to define input and output data. The query tools to electronic register data extract are created for further analysis in the subsystem #4 (ProAPF Soft). Query results are presented in form of a table where each row is a case, each column is a parameter. This table can be saved in various formats (.txt, .doc, .xls, .dbf) for further analysis.

4. Subsystem #4: The special software for multivariate statistical and intelligent of data analysis. The subsystem for multivariate statistical and intelligent data analysis is developed as a special software "Professional Analysis of Prognostic factors" (ProAPF). ProAPF software finds out prognostic factors and their combinations for medical classification and prediction tasks. The main reason in developing ProAPF is to create modern information technology for discovering combination of various prognostic risk factors (PRFs) for induction therapy

response in childhood acute leukemias. The main goal of ProAPF application is to enhance the efficacy of therapy using the estimation of patient's state based on the prognostic risk factors for selection an adequate intensity of therapy. ProAPF software actualizes the information technology of joint application multivariate statistical methods and intelligent neural network analyses of data with coherent input/output on the each stage of analysis.

5. Subsystem #5: Web-application for prediction task of induction therapy outcome for children with acute leukemias. The applied results are presented as subsystem #5 – Web-application for predict of induction therapy outcome for children with acute leukemias. This subsystem allows to review classification trees, scoring models, results of classification for as well as to predict outcome based on patient's PRFs profile (input by user) for the following group of patients:

1. male patients with B-lineage ALL, day 15 – early response
2. male patients with B-lineage ALL, day 33 – remission induction
3. female patients with B-lineage ALL, day 15 – early response
4. patients with T-lineage ALL, day 15 – early response
5. patients with T-lineage ALL, day 33 – remission induction
6. patients with AML, day 14 – early response
7. patients with AML, day 28 – response.

Using this subsystem it can predict the outcome of induction therapy for protocols ALL BFM 90 M (Minsk, BRCPOH), ALL MB 2002 (Minsk, BRCPOH), ALL BFM 2000 (Hannover, MHSH), AML MM-2000 (Minsk, BRCPOH), AML MM-2003 (Minsk, BRCPOH).

Conclusions

1. The information analytical system (IAS) was developed to predict the induction therapy outcome for patients suffering from acute leukemias. IAS was developed with the modern informational technology of database design, Web-access tools and the intelligent methods of medical data analysis. IAS was applied in Belarussian Research Center for Pediatric Oncology & Hematology (BRCPOH, Minsk, Belarus).

2. The database for prognostic risk factors (PRFs), collected at diagnosis and during early treatment course in children with acute lymphoblastic leukemia and acute myeloid leukemia, was created. Altogether, data from 189 patients with ALL and 74 patients with AML from BRCPOH were enrolled for analysis.

3. The information technology of analysis of prognostic risk factors actualized as ProAPF software was developed to identify patient-specific risk group to apply risk group – oriented chemotherapy in patients with ALL or AML.

4. The technique of accounting the individual profile of patient-specific PRFs and their association with response to induction therapy at critical timepoints for patients with ALL or AML was elaborated using statistical and intelligent neural network analysis methods.

Acknowledgement

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Nonlinear dynamics methods in the analysis of the heart rate variability

Kitlas A[1], Oczeretko E[1], Kowalewski M[2], Borowska M[1], Urban M[2]

[1] Institute of Computer Science, University of Białystok, Poland,
[2] 2nd Department of Children Disease, Medical University of Białystok, Poland

Abstract

Purpose: **We analyzed the heart rate variability (RR intervals) by means of nonlinear dynamics methods: Poincaré plot (return map), approximate entropy (ApEn) and detrended fluctuation analysis (DFA). The purpose of this study was the quantitative and qualitative assessment of heart rate variability by means of these nonlinear dynamics methods.**

Material and methods: **The Poincaré plot is a scattergram, which is constructed by plotting each RR interval against the previous one. Approximate entropy describes the complexity and irregularity of the signals. Detrended fluctuation analysis quantifies fractal-like correlation properties of the data.**

We analyzed two groups of patients: test group A – 15 diabetic children with diabetes type 1 and microalbuminuria and control group C – 24 healthy children. For each patient 24 hour ECG (RR intervals) was recorded. Statistical analysis was performed by means of nonparametric Mann-Whitney test.

Results: **Return maps of healthy children are mostly very complex. In the case of diabetic children we found torpedo-shaped plots. The values of ApEn were lower in diabetic children that indicated more regular heart rate in these patients. DFA method shows also differences between the investigated groups.**

Conclusions: **We concluded that using nonlinear dynamics methods we could quantitatively and qualitatively study the heart rate variability in healthy and diabetic patients.**

ADDRESS FOR CORRESPONDENCE:
Agnieszka Kitlas
Institute of Computer Science, University of Białystok,
64 Sosnowa Str., 15-887 Białystok, Poland,
Tel/fax +48 85 7457662,
e-mail: akitlas@ii.uwb.edu.pl

Key words: ECG signal processing, heart rate variability, Poincaré plot, approximate entropy, detrended fluctuation analysis.

Introduction

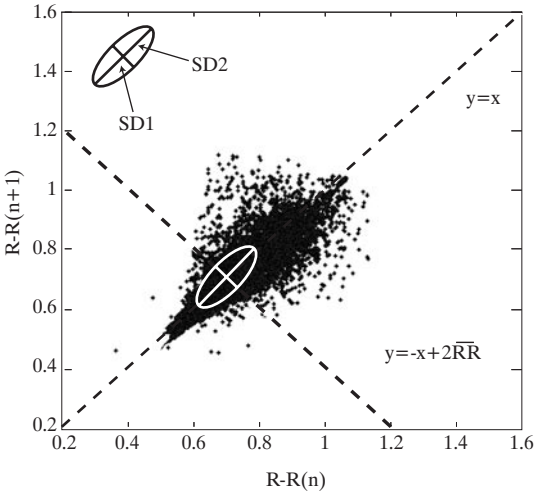
The analysis of heart rate variability is based mainly on analysis of RR intervals [1]. RR intervals are the series of time intervals between heartbeats [2]. We can observe RR intervals in electrocardiogram, which is simply graphic representation of the electrical forces produced by the heart [3].

The Poincaré plot (return map) is a scattergram, which is constructed by plotting each RR interval against the previous one [4]. The Poincaré plot may be analyzed quantitatively by fitting an ellipse to the plotted shape [5] (*Fig. 1*). The center of the ellipse is determined by average RR interval. SD1 means the standard deviation of the distances of points from y = x axis, SD2 means the standard deviation of the distances of points from $y=-x+\overline{RR}$ axis, where $\overline{RR}$ is the average R-R interval [6]. SD1 (instantaneous beat-to-beat variability of the data) determines the width of the ellipse, SD2 (continuous beat-to-beat variability) determines the length of the ellipse [7]. The ratio SD1/SD2 is the measure of heart activity.

Approximate entropy (ApEn) describes the complexity and irregularity of the signal [8,9]. ApEn is low in regular time series and high in complex irregular ones. It can be applied to both deterministic and stochastic signals and their combinations.

Detrended fluctuation analysis (DFA) quantifies fractal-like correlation properties of the data [10]. The root-mean square fluctuation of the integrated and detrended data are measured in observation box of various sizes and then plotted against the size of the box [11]. The scaling exponent represents the slope of this line, which relates log(F(n)-fluctuation) to log(n-box size). The short-term (F-fast) and long-term (S-slow) scaling exponents are also calculated [12].

Figure 1. **Return map of RR intervals with fitted ellipse to the plotted shape. SD1 means the standard deviation of the distances of points from y=x axis, SD2 means the standard deviation of the distances of points from y=-x+$2\overline{RR}$ axis. SD1 and SD2 determine the width and length of the fitted ellipse.**



Material and methods

We analyzed two groups of patients: test group A – 15 diabetic children with diabetes type 1 and microalbuminuria and control group C – 24 healthy children. For each patient 24 hour ECG was recorded. ECG records were divided into two segments, day (06:00 to 22:00) and night activity (22:00 to 06:00), respectively (A_{night}, $A_{day,}$ $C_{night,}$ C_{day}).

Programs written in Matlab (MathWorks Inc., USA), a high performance language for technical computing, were used to analyze the ECG signals. The SD1/SD2 ratio, the approximate entropy and DFA parameters were calculated. Statistical analysis was performed by means of nonparametric Mann-Whitney test for unpaired data.

Results

Return maps of healthy patients are mostly very complex. In the case of diabetic children we found (in most cases) torpedo-shaped plot. *Tab. 1* shows the mean values of SD1/SD2 ratio, approximate entropy and DFA exponents for groups: A_{night}, $A_{day,}$ $C_{night,}$ $C_{day.}$ The results are tabulated in the form mean ±standard deviation.

The values of ApEn were lower in diabetic children that indicated more regular heart rate in these patients. DFA method shows also differences between studied groups of patients.

Statistical analysis was performed between the following pairs of groups: A_{night} – C_{night} and A_{day} – C_{day} (*Tab. 2*). Approximate entropy values and long-term scaling exponents did not differ between A_{day} and C_{day} groups ($p>0.05$). Also long-term scaling exponents did not differ between A_{night} and C_{night} groups ($p> 0.05$). In other cases we found statistical significant differences between investigated groups of patients.

Table 1. **SD1/SD2 ratio, approximate entropy and detrended fluctuation analysis exponents in the studied groups**

Group	SD1/SD2 ratio	ApEn	DFA (Slow)	DFA (Fast)
A_{night}	0.257±0.079	1.344±0.152	1.053±0.105	1.034±0.179
A_{day}	0.175±0.044	0.997±0.190	0.984±0.072	1.273±0.141
C_{night}	0.396±0.130	1.454±0.153	1.002±0.124	0.896±0.176
C_{day}	0.231±0.069	1.112±0.186	0.984±0.060	1.145±0.158

Table 2. **Results of statistical analysis of investigated groups**

	SD1/SD2ratio		ApEn		DFA (Slow)		DFA (Fast)	
Groups	C_{night}	C_{day}	C_{night}	C_{day}	C_{night}	C_{day}	C_{night}	C_{day}
A_{night}	0.0004*		0.042*		0.279		0.045*	
A_{day}		0.019*		0.103		0.806		0.029*

*statistically significant differences ($p<0.05$)

Conclusions

We concluded that using nonlinear dynamics methods we could quantitatively and qualitatively study the heart rate variability in healthy and diabetic children.

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The dialogue-based principles of a textbook projection in a higher school distance learning

Korol AD

Department of Medical Biophysics, Grodno State Medical University, Belarus

Abstract

Purpose: **It is important to develop the principles of projection of the textbooks, which would help the student not only to obtain the necessary knowledge, but also simultaneously would develop experience of his creative activity as a component of the educational system.**

Material and methods: **The methodology of the research was based on the pedagogical works in the field of didactics of heuristic learning, psychology of the man speech-thought process, theory of the collective unconscious, philosophy of the dialogue between West and East. Used the method of generalizing analogies.**

Results: **We distinguish the following didactic components of a modern textbook: 1. dialogue in the contents of the educational material as a remedial unity of differentiation and integration of knowledge; 2. treasure-emotional component of the educational contents of the information; 3. component determining process of new knowledge creating by the students; 4. component ensuring reflexion of the students in their learning-cognitive activity.**

Conclusions: **We've made a conclusion, that heuristic dialogue, thinking of the man, and dialogue of two societies – eastern and western – are closely related. Thus development and introduction in higher school practice of such a form of a statement of the learning information which would comprise a combination of dialogue with the integrated form of a material are obviously important to us.**

Key words: heuristic dialogue, question, image and logic, civilization.

ADDRESS FOR CORRESPONDENCE:
AD Korol
Department of Medical Biophysics, Grodno State Medical University,
80 Gorky Str., 230015 Grodno, Belarus,
Fax: +375 152 33 53 41
e-mail: korandr2b@mail.ru

Introduction

The problems of educational system at the present stage is the necessity to help the student get the knowledge by himself, be guided in packed information space, that is to learn him to work creatively. The expanse of the distance education requires to project general principles of such types of education. It is important to note that the worktext is the important part of the distance educational process. It is important to develop the principles of projection of the textbooks, which would help the student not only obtain the necessary knowledge, but also simultaneously would develop experience of his creative activity as a component of the educational system.

Traditional knowledge-oriented medium assumes one-way influence of multicultural knowledge on the integral whole world of the student [1]. The response of the inner world of a student as not whole knowledge, potentially kept in him, on polycultural external influence is insufficiently effective for modern distant educational medium.

The opposite process looks logically proved, when the response of the student becomes a reason for influence on a polycultural educational component. Here the inner dialogue of the student while he is putting a question is on the foreground, rather than the external dialogue. Such a priority indicates the importance of the heuristic dialogue. Generally, the distance learning dialogue between a tutor and a student in which the activity in interrogation belongs to a student we called as the heuristic dialogue. In such a case, a question asked by a student can be considered as his own product of heuristic training activities.

Materials and methods

The methodology of the research was based on the fundamental works in the field of pedagogics conformable to nature (Lock J [2], Komensky Y [3], etc.), psychological and pedagogical bases of the heuristic learning (Kapterev PF [4], Hutorskoy AV[1]).

The basic directions of analysis of the given problem were to determine a role and a place of dialogue in historic-cultural life aspect of the man and reflectance of characteristic features of the dialogue interaction on the process of learning. A method of generalizing analogies of the philosophical and psychological categorical concepts describing development of a human society, such as "civilization", "culture", "religion" etc., allows to make a conclusion that in philosophical-psychologic aspect these concepts are connected with various systems of question-answer activity of the man.

Results

Considering the variety and depth of dialogue in culture history one can emphasize the priority significance of a question in the dialogue interaction. We distinguish the following didactic components of a modern textbook: 1. dialogue in the contents of the educational material as a remedial unity of differentiation and integration of knowledge; 2. treasure-emotional component of the educational contents of the information; 3. component determining process of new knowledge creating by the students; 4. component ensuring reflexion of the students in their learning-cognitive activity.

Let us consider the principles of modern textbook projection in details. Practically in all structural components of traditional knowledge-guided educational system, there is no unity of integral and differential knowledge as an educational dynamic process directed on the development of creative experience of the student. The analysis of the researches of philosophical, scientific, psychological-pedagogical problems of a question has allowed us to distinguish the two most important functions of a question in dialogue process of learning: integrating and differentiating.

The integrating function of a question is connected with variety and integrity of objects of the surrounding world, on cognition of which the question is directed. Development of skills of the students to put a question correctly to gain the necessary information about cognitional objects inevitably results in the necessity to integrate the intersubject and intrasubject knowledge in educational process.

The differentiative function of a question is closely related to the concepts of inner and external speech. The correctly put question (series of questions) allows to differentiate the complex object into its constituents, that is in essence to differentiate knowledge from ignorance.

The two mentioned above functions of a question: the differentiative and integrating, correlate with two constituents of thinking of the man: the logic thinking (interrupted or discrete) and creative thinking (continuous).

We consider the dialogue of the student with the teacher, in which the student by means of the question gets new knowledge, reflects dialogue of the integral and differentiative as:

1) interaction of external and internal speech, 2) dialogue of an image and logic of the man, 3) interaction of consciousness and unconscious, dialogue between East and West.

On the basis of the stated above, we've made a conclusion, that heuristic dialogue, thinking of the man, and dialogue of two societies – eastern and western – are closely related.

Thus development and introduction in higher school practice of such a form of a statement of the learning information which would comprise a combination of dialogue with the integrated form of a material are obviously important to us.

Discussion

As an example of the distance worktext we are presenting the integrated dialogue-based textbook "Integrated dialogue-based course in Medical and Biological Physics" which includes the educational materials of some natural sciences (physics, mathematics) and the humanities (philosophy, science of culture, history, mythology and others).

Such synthesis of integrated and dialogue-based forms of the educational material presentation has a number of advantages.

First, the dialogues of this textbook teach to prove one's own opinion and disprove another point of view. The question of the student proves to be an "instrument" of cognition and the efficiency of self-instructive gaining new knowledge depends on his skill to employ this so-called instrument since there is interrelationship (correlation) between an ability to put questions closely connected with already obtained knowledge and skills.

Secondly, integration of some disciplines of natural sciences and the humanities promotes the formation of the whole integrated image of the universe in students. This textbook allows the students "to turn time back" – to create the whole integrated image of human knowledge from differentiated, isolated fields of it.

Third, the information presented in the form of dialogues provides a student with better cognition of every subject in its integration with other disciplines, and allows to consider some complex aspects of a subject using such methods as comparison, generalizing analogy, etc.

Each dialogue in continuity with the topic of the lecture proof and disproof of a statement are given through consecutive questions. Such form of material presentation makes it possible for a student to get acquainted with the existing types of questions and ask them in proper succession.

Then the students are offered practical tasks for self-instruction and self-control, which include proofs and disproofs of the author's statement. The multidirection of thought operations of the student (when proving and disproving) results in intensifying his thinking, which is accompanied by generation of emotions as a whole [5,6]. The emotion of the heuristic dialogue enhances both the intensity of cognition of the student, and his reflexion. Actually, the emotion gave a rise to the development of western culture as well as to the development of the human activity concerning transformation (differentiation) of the world surrounding him [7,8]. In a projection to an educational plane, it is possible to state that the positive emotions promote the effective cognitional activity of the student.

An integrated form of knowledge presentation concerning the man and societies created by him is the most efficient for understanding close relationship between natural sciences and the humanities.

Proceeding from the principle of microcosm and macrocosm likeness the dialogue between the East and the West is reflected in the dialogue of image and logic, which is referred to the features of the distance heuristic dialogue [6,9]. Besides, the tasks were selected in such a way so that not only to develop students' logic when proving or disproving teacher's statement but to develop their visual thinking as well. Such synthesis of two complementary parts of man's thinking is the condition for creation.

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Importance of environmental risk factors for development of childhood pre-diabetes in Lithuania

Skrodeniene E[1], Marciulionyte D[1], Padaiga Z[2], Jasinskiene E[1], Sadauskaite-Kuehne V[1]

[1] Laboratory of General Endocrinology, Kaunas University of Medicine, Institute of Endocrinology, Kaunas, Lithuania
[2] Department of Preventive Medicine, Kaunas University of Medicine, Kaunas, Lithuania

Abstract

Purpose: To study what environmental factors predict islet cell autoantibodies (ICA) seroconversion in healthy schoolchildren.

Material and methods: Sera from 3053 non-diabetic schoolchildren living in Kaunas region of Lithuania were investigated for ICA autoantibodies. ICA were measured in undiluted sera by an indirect immunofluorescence method. Data from 13 ICA positive and 90 ICA negative schoolchildren were included in the analysis. Information on environmental factors was collected via questionnaires.

Results: The ICA positive schoolchildren tended to be more frequently breastfed than ICA negative (92.3% and 87.8%, respectively, $p=0.63$). ICA negative children were more frequently exclusively breastfed during the period of first month than ICA positive children (96.2% and 83.3% respectively, $p=0.07$). Allergy to cow's milk occurred more frequently among ICA positive than among ICA negative children ($p=0.05$). Mothers of cases took medicine during pregnancy more often, than mothers of controls ($p<0.001$). ICA positive children with neonatal icterus more often were treated with phototherapy and blood transfusions ($p=0.03$). 53.8% of ICA positive children lived in homes where family members were smoking indoors while this was recorded only for 27.8% controls ($p=0.06$).

Conclusion: Certain environmental factors have earlier been identified as risk factors for development of diabetes, and we can confirm that some of these factors increase the risk of developing ICA among Lithuanian children. Intake of medicine during pregnancy and indoor smoking of family members belong to the risk factors.

ADDRESS FOR CORRESPONDENCE:
Erika Skrodeniene
Laboratory of General Endocrinology, Institute of Endocrinology
Eiveniu 2, Kaunas, LT-50009 Lithuania
Fax: +370 37 733819, e-mail: Erika.S@takas.lt

Key words: pre-diabetes, schoolchildren, environmental factors, islet cell autoantibodies (ICA).

Introduction

Type 1 (insulin-dependent) diabetes is an autoimmune disease caused by the selective destruction of the insulin-producing pancreatic β-cell [1]. Islet cell autoantibodies (ICA) are markers of the ongoing β-cell damage during the asymptomatic prodromal period called pre-diabetes or pre-clinical diabetes [2]. Onset of type 1 diabetes is determined by genetic predisposition and environmental factors. The environmental risk factors generally found are short duration of breast feeding, early introduction of cow's milk and other food such as flour, eggs, meat [3-5]. Other factors such as maternal age, pregnancy period, baby infections [3] may also play a role in development of diabetes.

The aim of this study was to analyze whether risk factors related to type 1 diabetes also influence the development of childhood pre-diabetes in Lithuania.

Material and methods

Sera were collected under non-fasting conditions from 3053 non-diabetic schoolchildren living in Kaunas region of Lithuania [6]. The median age of children was 11.7, range 5.5-15 years. ICA were measured in undiluted sera by indirect immunofluorescence [7]. Data from 13 (6 boys and 7 girls) ICA positive and 90 (44 boys and 46 girls) ICA negative schoolchildren were included in the analysis. The mean age was 15.6±2.1 years for ICA positive and 15.5±2.2 years for ICA negative schoolchildren. The children and their parents were asked to fill questionnaires at provided the same time as blood samples were collected. The questionnaires gave information about pregnancy, neonatal period, duration of exclusive and total breast feeding, time of introduction of cow's milk, flour, meat, eggs and other solid foods. Questions regarding social factors, child infections were included as well [5].

Figure 1. **Prevalence of exclusive breastfeeding among ICA positive and ICA negative schoolchildren up to the age of 7 months**

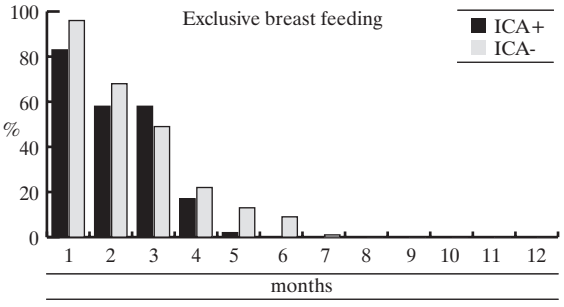
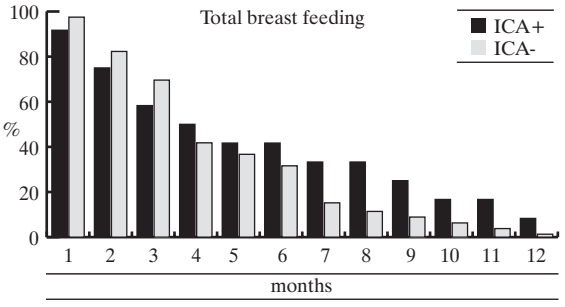


Figure 2. **Prevalence of total breastfeeding among ICA positive and ICA negative schoolchildren up to the age of 12 months**



Results

The ICA positive schoolchildren tended to be more frequently breastfed than ICA negative (92.3% and 87.8%, respectively, p=0.63). Prevalence of exclusive and total breast feeding up to the age of 12 month is presented in *Fig. 1* and *2*.

Average age at introduction of cow's milk was the same in both groups (4.9 months). However cow's milk was introduced at the age of 3 months or earlier twice more frequently for cases than for control children (25% and 13.8%, respectively, p=0.31). Allergy to cow's milk occurred significantly more often among ICA positive than among ICA negative schoolchildren (23.1% and 6.7%, respectively, p=0.05).

Mothers of cases statistically significantly more often took medicine during pregnancy (61.5% and 13.3%, p<0.001). Icterus in neonatal period was recorded somewhat more often for cases (23.1%) than controls (14.4%), p=0.42. ICA positive children with icterus significantly more often were treated with phototherapy and blood transfusions than ICA negative (33% and 0%, respectively, p=0.03). 53.8% of ICA positive children lived at homes where family members were smoking indoors while this was recorded only for 27.8% of controls, p=0.06.

Discussion

Short duration of breast feeding is a well-known risk factor for type 1 diabetes [5]. Our data showed that duration of breast feeding had an impact on the development of pre-diabetes. Early introduction of cow's milk can increase the risk of type 1 diabetes mellitus [3,5]. In the present study we did not detect significant results, but cow's milk was introduced before the fourth month twofold more often in ICA positive schoolchildren than in ICA negative. However, ICA positive children had allergy to cow's milk significantly more often than ICA negative, which in fact should lead to lower consumption of cow's milk later.

Mother's infections during pregnancy period, pre-eclampsia, blood group incompatibility are factors that might release autoimmune β-cell destruction [4,8]. Our data show that mothers of ICA positive children significantly more often took medicine during pregnancy infections may initiate an immune process in pancreas. Icterus in neonatal period was recorded more frequently between cases in our study. Treatment with phototherapy and blood transfusions could initiate the slowly progressing autoimmune process, later β-cell destruction and pre-diabetes [8]. We have obtained interesting data about smoking. The family members of 58.3% of ICA positive children were smoking indoors compared to only 27.8% of ICA negative children. Indoor and outdoor smoking, tobacco smoke exposure and its impact on children's health has been investigated in Sweden [9].

In conclusion, certain environmental factors have earlier been identified as risk factors for development of diabetes, and we can confirm that some of these factors increase the risk of developing ICA among Lithuanian children. Intake of medicine during pregnancy and indoor smoking of family members belong to the risk factors.

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Subsystem of prognostic risk factors analysis of childhood acute leukemias

Tom IE[1], Krasko OV[1], Zalessky BA[1], Novoselova NA[1], Suchkova AP[1], Sotikova EE[1], Skrygan NM[1], Potapnev MP[2], Uglova TA[2]

[1] United Institute of Informatics Problems of The National Academy of Sciences of Belarus, Minsk, Belarus
[2] Belarussian Center for Pediatric Oncology and Hematology, Minsk, Belarus

Abstract

Propose: The purpose was to create the electronic register formed as a database where the results of medical examination for each patient are stored and to develop the software for statistical and intelligent data analysis applied to medical tasks of prediction outcome of induction therapy and patient risk group classification based on prognostic risk factor (PRF) combinations in childhood acute leukemias.

Material and methods: Statistical and intelligent methods for data analysis, modern programming technologies for database and software development. The medical data were obtained in Belarussian Research Center for Pediatric Oncology and Hematology (BRCPOH).

Results: The subsystem for multivariate statistical and intellectual analysis of data is realized as a special software "Professional Analysis of Prognostic Factors" (ProAPF). ProAPF includes a number of statistical and neural network analysis methods that were selected, upgraded and adopted according to the applied aim of the project.

Conclusions: The database for prognostic risk factors (PRFs), collected at diagnosis and during early treatment course in children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), was created. The information technology of analysis of prognostic risk factors actualized as ProAPF software was developed to identify patient-specific risk group to apply risk group – oriented chemotherapy in patients with ALL or AML. The new PRFs and their combinations were explored, the combinations were selected to predict outcome of induction therapy.

ADDRESS FOR CORRESPONDENCE:
Igor E. Tom
Laboratory of Bioinformatics
United Institute of Informatics Problems
The National Academy of Sciences of Belarus
6 Surganov Street, 220012, Minsk, Belarus
e-mail: tom@newman.bas-net.by

Key words: data analysis, prognostic risk factors, outcome of induction therapy.

Introduction

The modern information technologies of data collection, data storage and data analysis are effectively used for the different goals, in particular in the health care. Augmented clinical opportunities for specialized medical care for childhood leukemia currently require their selection based on particular sets of parameters, including diagnostic and prognostic factors. Selection the adequate strategy of therapy will result in shorten treatment course to reach recovery, better quality of patient's life, higher rate of survival and, finally, decreased cost of therapy. Sets of parameters to be taken into account are markedly increased and require their computing for medical decision making.

The purpose was to create the electronic register formed as a database where the results of medical examination for each patient are stored and to develop the software for statistical and intelligent data analysis applied to medical tasks of prediction outcome of induction therapy and patient risk group classification based on prognostic risk factors (PRFs) combinations in childhood acute leukemias.

Material and methods

Statistical and intelligent methods for data analysis, modern programming technologies for database and software development were used.

The medical data were obtained in Belarussian Research Center for Pediatric Oncology and Hematology (BRCPOH). Altogether, data from 189 patients with acute lymphoblastic leukemia (ALL) and 74 patients with acute myeloid leukemia (AML) were analyzed. To verify the results of application the analytical system testing sample was obtained in Medical High School Hannover (collaborator of the project Prof. K.Welte).

Results

The subsystem for multivariate statistical and intelligent data analysis is developed as a special software "Professional Analysis of Prognostic Factors" (ProAPF). This is one of the main parts of information analytical medical-oriented system. ProAPF software finds out prognostic factors and their combinations for medical classification and prediction tasks.

The main reason in developing ProAPF is to create modern information technology for discovering combination of various prognostic risk factors (PRFs) for induction therapy response in childhood acute leukemias.

The main goal of ProAPF application is to enhance the efficacy of therapy using the estimation of patient's state based on the prognostic risk factors for selection an adequate intensity of therapy.

ProAPF software actualizes the information technology of joint application multivariate statistical methods and intelligent neural network analysis of data with coherent input/output on the each stage of analysis.

Joint application of statistical and intelligent analysis is necessary for mutual compensation of their intrinsic limitations. The results of neural networks application are implicit, cannot be easy interpreted or modified. But they have low sensitivity to the form of analyzed data, hence they have high generality. The results of application of the statistical analysis are explicit and easy interpreted. The numbers of statistical and intelligent analysis methods are adapted to medical tasks of discovering prognostic risk factors in ProAPF software. Moreover, some special analytic methods were developed for ProAPF. This software can be used for solution the following tasks:

1. **Decrease of the dimension** of clinical and laboratory data **and** its **preprocessing**: digitalization and coding of continuous variables, normalization. This task is provided by univariate analysis (by t-tests, Chi-square tests), principal component analysis (statistical and neural network versions), multiple correspondence analysis, combined algorithm of entropy estimation and maximum-likelihood Chi-square test.

2. **Selection of the combinations** of the most significant PRFs for classification and prediction. This task is provided by stepwise algorithm for PRFs selection in linear regression, exhaustive search on full sets of PRFs, stepwise discriminant analysis based on Mahalanobis distance (stepwise with addition and exhaustive search).

3. **Verification of the selected combinations** by test cases classification and prediction. This task is provided by linear discriminant analysis; multilayer perceptron with different learning algorithms and different normalization type; self-organizing Kohonen networks for classification tasks.

4. **Prediction the outcome of induction therapy** and identification of patient's risk group by his/her individual profile of prognostic risk factors. This task is provided by multiple regression algorithms with exponential and logistic functions, multilayer perceptron for regression tasks, classification CART-trees (decision trees) with automatic and interactive construction type.

We have positive experience in processing of real oncohematological data that approves the efficiency of the developed information technology, especially ProAPF software for comprehensive processing and analysis of heterogeneous (laboratory, clinical, epidemiological) data based on joint using various statistical and intelligent neural network analysis.

The technique for PRFs combinations selection and patient's PRFs profile estimation to predict outcome of induction therapy are developed and applied in BRCPOH in cooperation with medical scientists from BRCPOH. According to the agreement the ProAPF software was successfully tested in Medical High School Hannover, collaborator of the project Prof. K.Welte.

For children with **acute myeloid leukemia** the detection at diagnosis more than 3.5% of apoptotic cells (PI+ cells) in blast population in patient's bone marrow (BM) is one of the most significant favorable PRFs of early response to induction therapy (on day 14 of therapy). The simultaneous identification of <3.5% of apoptotic cells and >70% of initial blasts in PB predict an unfavorable (poor) early response to therapy, estimated on day 14. Besides, the unfavorable PRFs of early response to therapy on day 14 are initial content of BM blasts of >80%, initial blasts in peripheral blood (PB) $>70{\cdot}10^9$/l as well as a high amount of CD34+ blasts (>70%) and HLA-DR+ blasts <70% in bone marrow. Significant PRFs for unfavorable treatment response to therapy on day 28 in children with AML are the combination of >10% blasts in BM (day 14-15) sample with the initial WBC of $>70\times10^9$/l and with a large number (>60%) of CD7+ blasts and of t (8;21). Unfavorable response on day 42 of therapy can only be associated with initially defined cytogenetic abnormalities in BM blasts – rearrangement 11q23 without t (9;11).

For children with **B-lineage acute lymphoblastic leukemia** the PRFs for unfavorable response to induction therapy (day 33 – 36 of protocol) are gender (boys), the presence of blasts in BM on day 15 of therapy >10%, initial count of CD2+ blast cells in BM>10%. The significant PRFs for early response to induction therapy (on day 14-15 of protocol) are gender, age at the moment of diagnosis, (more or less than 10 years old) in combination with initial WBC, WBC and blasts' count on day 8 of therapy, bone pains, initial count of CD 34+ blast cells in BM. Among PRFs the unfavorable early response to induction therapy for girls was related to: age >12 years, associated with the initial WBC of $>20\times10^9$/l, WBC count on day 8 of therapy $>2\times10^9$/l, initial count of blasts PB >70%, the persistence of blasts in PB on day 8 of treatment >10%, initial high level (>85%) of CD34+cells and the simultaneous identification >10% cyIgM+ and ≤10% sIgM+ blasts of in patient BM sample. Among boys the PRFs of unfavorable early response to therapy were: initial blasts in PB>70%, WBC count $>7\times10^9$/l on day 8 of therapy, the persistence of $>1\times10^9$/l of blasts or >1% of blasts in PB on day 8 of treatment, initial content of >10% CD2+ cells and low level CD20+ blasts in BM, hepatomegaly after day 8 of therapy.

The PRFs of unfavorable response to the induction therapy (on day 33 of protocol) in children with T-lineage acute lymphoblastic leukemia were: the persistence of >10% of blasts in BM on day 15 of therapy or combination the next factors – the presence of blast cells and especially >20% CD117-expressing and >30% CD34-expressing BM cells at diagnosis, as well as

the blast count of $>1\times10^9$/l on day 8 of therapy. The PRFs of unfavorable early response to induction therapy (day 15) are: blasts content $>1\times10^9$/l in PB on day 8 therapy, the absence of CD10-expressing BM cells. Myelocoexpression (CD13) on BM blast cells is also an unfavorable PRF for early treatment response (day 15) the children with T-lineage ALL.

Conclusion

1. The information technology of analysis of prognostic risk factors actualized as ProAPF software was developed to identify patient-specific risk group to apply risk group – oriented chemotherapy in patients with ALL or AML.

2. The technique of accounting the individual profile of patient-specific PRFs and their association with response to induction therapy at critical timepoints for patients with ALL or AML was elaborated using statistical and intelligent neural network analysis methods.

3. It was estimated, that for children with AML detection at diagnosis more than 3.5% of apoptotic cells (PI+ cells) in blast population in patient't bone marrow (BM) is one of the most significant favorable PRFs of early response to induction therapy (on day 14 of therapy). The simultaneous identification of <3.5% of apoptotic cells and >70% of initial blasts in PB predict an unfavorable (poor) early response to therapy, estimated on day 14. Unfavorable response on day 42 of therapy was associated with initially defined cytogenetic abnormalities in BM blasts – rearrangement 11q23 without t (9;11).

4. For children with B-lineage ALL the PRFs for unfavorable response to induction therapy (day 33-36 of protocol) were gender (boys), the presence of blasts in BM on day 15 of therapy >10%, initial count of CD2+ blast cells in BM>10%. The significant PRFs for early response to induction therapy (on day 14-15 of protocol) are gender, age at the moment of diagnosis, (more or less than 10 years old) in combination with initial WBC, WBC and blasts' count on day 8 of therapy, bone pains, initial count of CD 34+ blast cells in BM.

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Different approaches to missing data in discrimination applied to medical problems

Ćwiklińska-Jurkowska M[1], Jurkowski P[2], Kukulska-Pawluczuk B[3], Kołtan A[4], Dróżdż W[5], Hilemann W[2]

[1] Department of Theoretical Background and Medical Informatics; Collegium Medicum; Nicolaus Copernicus University, Poland
[2] Department of Informatics and Research Methodology; Collegium Medicum; Nicolaus Copernicus University, Poland
[3] Department of Neurology; Collegium Medicum; Nicolaus Copernicus University, Poland
[4] Department of Pediatrics, Hematology and Oncology; Collegium Medicum; Nicolaus Copernicus University, Poland
[5] Clinical Neuropsychology Unit; Collegium Medicum; Nicolaus Copernicus University, Poland

Abstract

Purpose: **The aim of the work was the comparison of different methods' usefulness for managing incomplete explanatory data in aiding the recognition for new patients, by different methods of multidimensional discriminant analysis, and in visualizing medical classification problems.**

Material and methods: **Different methods as casewise deletion, single and multiple imputations for different discriminant methods and the distance-based discrimination built on Gower's distance, modified for missing data, were used for supporting diagnosis. The examination was done on three real medical data sets (recognition of childhood asthma, predicting the endpoint of childhood leukemia and diagnosis of neurological stroke kind.**

Results: **The performance of classification was a little worse for discrimination after single and multiple imputation than for casewise deletion. Distance-based discrimination with Gower's distance was next applied. We obtained only 1% decreasing of the patients correctly classified for examined medical data sets comparing the starting complete data set to the set with even about 30% of incomplete data patients – with randomly generated places for removing data, i.e. for artificial creating missing data. Multidimensional metric scaling using Gower's distance in visualizing neurological stroke groups, with mixed variables and missing values, gave similar visualization of patients as ordinary canonical discrimination, which is appropriate for complete data sets.**

Conclusions: **Gower's distance, handling missing values, can be successfully used for distance-based discrimination and visualization of classification problems.**

Key words: aiding medical diagnosis, discrimination, single and multiple imputation, missing values, mixed variables.

ADDRESS FOR CORRESPONDENCE:
Małgorzata Ćwiklińska-Jurkowska
Department of Theoretical Background
and Medical Informatics; Collegium Medicum
Nicolaus Copernicus University
ul. Jagiellońska 13-15, 85-067 Bydgoszcz; Poland
Fax: 052-585-3308;
e-mail: mjurkowska@cm.umk.pl

Introduction

Characteristic features of medical data are occurrences of values being lacking – "missing values" and also the mixed quantitative-qualitative character of variables. We examined different methods of handling missing data to use incomplete sets with known clinical diagnosis for the purpose of aiding diagnosis for new patients by discrimination procedures and for the aim of visualizing multidimensional medical classification problems.

Material and methods

Different known methods of treating missing values assume that data are missing at random (MAR – the missing observation may depend on the observed values, but not on the missing values) or even more – missing completely at random (MCAR – the probability of having a missing value is unrelated to the value of this variable or to any other variables in the data set). In other words: for MCAR cases with complete data not differ from cases with incomplete data and for MAR cases with complete data differ from cases with incomplete data and the probability, that the values are missing, depend on the observed values, but not on the missing values. If the pattern of missing data is not random, we call it nonignorable. There is no way to check if the condition of MAR is met, but the MCAR assumption is testable by Little's [1] chi-square test. Missing values in discriminant analysis can be treated in the following ways:

1) casewise (list-wise) deletion: the method is biassed and admissible only, when the number of missing data points is very small (i.e. <5%); assumption – MCAR SPSS, Statistica;
2) omit the most incomplete variables;
3) filling in missing data with plausible values;

3a) Single Imputation: means in groups substituting (or modes for categorical variables) SAS, SPSS, Statistica; multiple regression methods (for categorical variable – discriminant analysis) Solas; Last Value Carried Forward (longitudinal data); Hot decking (identify the most similar case to the case with missing value) Solas; EM (Expectation Maximization) SPSS, SAS

3b) Multiple Imputation (MI) – assuming MAR SAS, Solas: predictive imputation technique Solas, Propensity score SAS, Solas; MCMC (Monte Carlo Markov Chains) SAS.

EM method (Expectation-Maximization) [2,3] is an iterative procedure of missing data estimation by maximizing the likelihood. Rubin's [4] multiple imputation procedure MI replaces each missing value with a set of plausible values that represents the uncertainty about the right value to impute. Just 3-5 imputations are sufficient to obtain good results of filling in data. These multiple imputed data sets are then analysed by using the same discriminant procedures for obtained completed data sets. Next the results of discrimination are combined. MI is forgiving for departures from imputational model [5,6].

The used discriminant methods were: linear, quadratic, kernel and nearest neighbor one [7]. Radii for kernel methods and number of neighbors were chosen to obtain the smallest leave-one-out classification error.

We studied real medical data from Collegium Medium Departments – with mixed variables and many really or artificially missing values. Examined medical data sets are: Treated leukemic children with naturally missing values (21 mixed variables, 114 patients, classification into 2 groups – predicting relapse or death and without the event); Asthmatic children – complete set and the one for discrimination's results comparison – with randomly generated missing values (28 mixed clinical variables and chosen 7 the most discriminating ones, 170 patients, 2 groups – asthma, no asthma); Neurological patients – complete set and the one with randomly generated missing values (25 mixed variables, 170 patients, 4 groups of different cerebral stroke kinds).

The casewise deletion and also single imputation EM and multiple imputation for filling in missing data were used. The applied method of multiple imputation was for example EM is (Expectation-Maximization with importance resampling) by King et al. [8]. The number of imputed data sets is five.

Results

The best cross-validation result of all considered discriminant classifiers was obtained for the kernel normal discrimination as well for incomplete data, after casewise deletion, as for single and multiple imputed data. The results of variables' selection, for data sets completed by multiple imputations, are nearly the same as for real data set after casewise deletion. We obtained similar results of discrimination effectiveness for single imputation and multiple imputation.

Discrimination after single and multiple imputation gave little worse percentage of correctly classified patients than after casewise deletion. Thus, we used modified algorithm for calculation of Gower's distance, also appropriate in the situation with missing values. Complete data of patients from Department of Neurology were entered to our program and we compared results with the same set, where 33 randomly selected patients have missing values. Good classification results for using this method are also confirmed for set with missing values in about 30% of patients – for the diagnosis of asthmatic children. At this point, we obtained only 1% decreasing of correct classifications.

Using multidimensional metric scaling (MDS) [9], technique and Gower's distance [10] we visualized four group neurological patients, described by mixed variables and with missing values. First we obtained a plot of four neurological group means. Next we incorporated individual variability of four neurological diseases onto the same plot using Gower's [11] adding-a-point technique and Gower's distance. The procedure was done for full data set and for the set with randomly rejected 33 values of variables, as described above. In this way we obtained scatterplots of neurological patients after MDS on general diversity distances [12] and add-a-point procedure. These two scatterplots are similar to the plot of patients in two canonical variates space for full data set.

Discussion

We obtained little worse results of classification correctness for MI and EM, than for casewise deletion. It may be caused by changed related size of smaller group. However, recently the questions for validity of multiple imputations are raised [13]. So we also suggest another approach to missing values – the programmed by us modification of Gower's [10] distance between two observations (patients) with possible missing values in mixed variables. This enables using discrimination with missing values by applying distance-based discrimination [14], based on inter-observations (patients) distance.

Using Gower's measure for distance-based discrimination we obtained decreasing percentage of the correct classifications for examined medical data set only by 1%, comparing the beginning complete data set and the set with even about 30% of patients – chosen randomly – with generated randomly places for removing data.

Gower's distance can be also very successful, as applied to visualize groups of patients, when occur missing data.

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Polish on-line resources for community nurses

Cisek M[1], Górkiewicz M[2], Brzostek T[1]

[1] Jagiellonian University of Cracow, Collegium Medicum, Institute of Nursing, Department of Environmental Nursing, Cracow, Poland
[2] Jagiellonian University of Cracow, Collegium Medicum, Institute of Public Health, Department of Epidemiology and Population Research, Cracow, Poland

Abstract

Purpose: The purpose of this paper was to present our experiences in supplying seminars for community nurses and other their self-educational activities with Polish on-line resources free distributed in the Internet. We didn't pretended to give scrupulous review of all Polish medical and health Web sites. The choice was got subjectively, but all links mentioned in the paper were find useful in own Author's didactic practice.

Material and methods: In the paper several Web hosts were classified into five categories: legal and organizational information; handbooks and readings for nurses' self-education; didactic aids and readings for patients; diagnostic and organizational tools; mailing lists for nurses.

Results: It was stated that Polish on-line resources to assist community health nurses implement their role are becoming more accessible. There are observed somewhere lack of up-to-date information, but more frightening away is lack of credible guidance on the trustworthiness of health-related information.

Conclusions: The on-line resources should not be treated only as tool for making our lessons more brilliant. The main goal there is to train the practical skills necessary for reading and critically evaluating medical literature, to make students sensitive to the reliability and credibility of information.

Introduction

The key role of the community health nurses includes health promotion and illness / injury prevention for individuals, families, groups and all communities representing wide-ranging ages, social position, health status [1]. In this they collaborate with other health workers, but their medical and pedagogical literacy was critical commonly [2]. Till 2003 the Polish nurses preferred printed literature in their self-educational activities [3]. There are known many users' guides to the medical literature which encourage us to start reading them critically [4], introduce us to research and statistical methodology [5,6], point on included discussion [7] or on this, how use it in caring for the reader's patients [8,9]. Currently, in the Poland the Internet has become the most widely-used communication medium, in this by nurses too [10,11]. The above guides keep their usefulness but they must be completed with some guidance on the trustworthiness of a Web health-related information [12], because it should be considered that there besides trustworthy good medical journals and editors anyone can set up a Web site and publish any kind of data which is then accessible to all. The eEurope 2005 Action Plan proclaim that "it is critical that e-health content and services are developed efficiently, are available for all and health related web sites comply with established quality criteria" [13]. What about health-related hosts in the English language the problem was there overcoming with some specialised hosts like http://discern.org.uk; http://www.quick.org.uk; http://www.biome.ac.uk; http://www.medcertain.org, and in the French http://www.chu-rouen.fr. For Polish hosts it arises now as a challenge of a great importance.

ADDRESS FOR CORRESPONDENCE:
Maria Cisek
Jagiellonian University of Cracow, Collegium Medicum,
Institute of Nursing, Department of Environmental Nursing
ul. Kopernika 25, 31-501 Kraków, Fax: +48 12 4294872
e-mail: mxcisek@cyf-kr.edu.pl

Material and methods

Besides the governmental hosts www.mzios.gov.pl; www.unuz.gov.pl; www.csioz.gov.pl; www.gis.mz.gov.pl the Main Chamber of Nurses and Midwives (http:// www.izbapiel.org.pl) and the Polish Nurses Association (http://www.zgptpiel.waw.pl) took the leading position in providing the legal and organizational information to nurses with some other useful links in the matter. Some specialised hosts provides legal information concerning their area of interest, for example: http://www.pck.org.pl/ for international law or http://www.ratownictwo.pl/ for emergency

medicine. The profuse free educational material and advises for patients offers page http://zdrowie.medicentrum.pl and for medical specialists the page http://www.mediclub.pl/club/mp/, both connected with Praha Communications, the editor of JAMA (Journal of the America Medical Association). The leading Polish editor of the medical journals, the Medycyna Praktyczna Co, carries on some professional web hosts, in these the great http://www.mp.pl. Tree other great educational hosts for no-professionals are offered by Allcore Co (http://www.mediweb.pl/) and by Medical Web Designs Co (www.zdrowie.med.pl) and www.zdrowemiasto.pl. Besides encyclopaedic hosts a set of specialised hosts offer the educational aids, for example: www.parkinson.med.pl; www.oko.info.pl; www.alergen.info.pl; www.udarmozgu.pl; www.leki.med.pl; www.onkolink.pl; www.cukrzyca.pl; www.dzieci.org.pl; www.warman.com.pl/~osteo. The ready to use Power Point and video presentations provides specialised host http://www.rakpiersi.pl. Some specialised hosts offered interactive tests for medical and psychological diagnoses: www.acpp.edu.pl; http://www.psychologia.edu.pl/ (Michigan Alcoholism Screning Test, Adult Alcoholic's Child, Alcoholic's Wife, Social Readjustment Rating Scale, Fagerstrom test for smokers, Affect Balance Scale, Workoholic Test, Internet Dependence); www.telezdrowie.pl (tests: I hear, I speak, I see); www.nadcisnienie.pl; www.ptk.waw.pl/ (IBM, coronary risk, Fagerstrom's test). Almost all above hosts provide chat and mailing lists for their users.

What about methodology let us now turn to ask what specific skills and attitudes we should seek to develop. Currently it is no problem to find a lot of texts including wanted key words with Web browse tools. The problem is how to distinguish useful from useless or even harmful reading-matters. We introduced student to that art by leading them from passive work to active tutored and active self-reliant work. During passive readings the students deal with material selected by a teacher. It is, however, important that at least some of the students' readings should involve an active participation in looking for an appropriate texts for different sorts of their tasks. During tutorials a teacher prompts the validation criterions to students and step by step he/she restricts it to discussion on criterions proposed by students.

Results

It was stated that Internet stands currently a prepared source of health-related educational Polish readings for patient and nurses. Nevertheless, the not experienced users should be there supported with professional tutors because of lack of credible on-line guidance on the trustworthiness of health-related information.

Discussion

Medicine is a persistently developing science, day after day new research results change some previous medical standards with the new ones. Moreover, human error is always possible. In practice various on-line tools were applied with aim to describe and evaluate patient-oriented health information on the Internet. All they are very expensive rather and they need constant support from a team of trained experts. Among them there are sites held by commercial and non-commercial organizations. For example each of about 6000 pages for patients and consumers in www.eMedicinehealth.com is reviewed by 2 physicians and a PharmD. Besides, the eMedicine Clinical Knowledge Base contains 30000 multimedia files suitable to medical education for physicians, nurses, and optometrists. The Discern: http://discern.org.uk questionnaire which can be used to judge the reliability of a publication was funded from 1996-7 by The British Library and the NHS Executive Research & Development Programme. The QUICK: http://www.quick.org.uk designed to be used as a teaching aid in an educational setting is supported by UK Health Development Agency and the UK Centre for Health Information Quality. The OMNI (Organising Medical Networked Information): http://www.biome.ac.uk gateway to evaluated quality Internet resources in health and medicine, aimed at students and practitioners is created by a core team of specialists based at the University of Nottingham Greenfield Medical Library, and is funded by the Joint Information Systems Committee through the Resource Discovery Network (RDN). The MEDCERTAIN: http://www.medcertain.org for a self and third-party rating system enabling patients and consumers to filter harmful health information and select high quality information established a part of the project of the Action Plan on promoting safer use of the Internet (Decision no 276/ 1999/ EC) of the European Parliament and of the Council of 25 January 1999.

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The web based archive of digital images of laryngeal and eye diseases

Uloza V[1], Paunksnis A[1], Marozas V[2], Jurkonis R[2], Severgardh P[3], Uloziene II[1]

[1] Kaunas University of Medicine, Kaunas, Lithuania
[2] Kaunas University of Technology, Kaunas, Lithuania
[3] Euromed Networks AB, Stockholm, Sweden

Abstract

Medical image management is one of the hottest areas in the medical device market, which is experiencing a high degree of dynamism and competition. Otolaryngology and ophthalmology are well positioned to take advantage of telemedicine and images archiving and transmission using telemedicine and Internet facilities because diagnostics in these specialties is mostly based on evaluation of the live images and graphical data.

Purpose: An international Baltic MedWeb project was devoted to the creation of Internet based data archive of the images of laryngeal and eye diseases.

Material and methods: Several alternatives of obtaining and collecting medical images were used: "frozen" still pictures from video laryngostroboscopic examination, images from surgical microscope and slit lamp as well as CT and MRI data. The images are systemized and archived according the classification of laryngeal and eye diseases.

Results: Up to date about 1500 clinical cases containing more than 8000 digital clinical images of various laryngeal and eye diseases are included into the structural systematical archive.

Conclusions: The benefit of international Baltic MedWeb project consists of implementation of new technologies and possibilities for education, consultations for medical society and finally, for the best medical care for the patients.

Key words: educational databases, image management, telemedicine, larynx, eyes.

ADDRESS FOR CORRESPONDENCE:
Virgilijus Uloza
Department Otolaryngology, Kaunas University of Medicine
Eiveniu 2, LT-50009 Kaunas, Lithuania
Fax: +370 37 326862
e-mail: uloza@kmu.lt

Introduction

Medical image management is one of the hottest areas in the medical device market, which is experiencing a high degree of dynamism and competition [1,2]. Otolaryngology and ophthalmology are well positioned to take advantage of telemedicine and Internet images transmission because diagnostics in these specialties is mostly based on evaluation of the live images and graphical data [3-6].

The task of an international Baltic MedWeb project is to create an Internet based data archive of the images of laryngeal and eye diseases. This project was running in cooperation among the Departments of Otolaryngology and Ophthalmology of Kaunas University of Medicine, Kaunas University of Technology (Lithuania) and Euromed Networks AB (Sweden) and supported by Stockholm County Council.

Materials and methods

The medical images were collected using telemedicine systems (Euromed Eurotel I), which are connected with medical examination devices. Telemedicine systems are equipped with frame grabbers (Matrox Meteor II) for image digitalization. Several alternatives of obtaining and collecting medical images were used: "frozen" still pictures from video laryngostroboscopic examination (KAY Elemetrics RLS model 9100) of the laryngeal patients, images from surgical microscope (Moller-Wedel Universa 300 and 3CCD video camera attached) obtained during direct microlaryngoscopy under general anesthesia as well as CT and MRI data of the same patients. Images of eye diseases were obtained using slit lamp (Topcon SL-8Z) with 3CCD video camera (Sony DXC-950P) attached.

The specialized software was used for acquisition of images and formation of clinical objects-cases. The "cases" consisted of information related to the patient's clinical data (history, complains etc.) and information related to the images itself (comments, explanations, technical data). The images were

systemized and archived according to the working classification of laryngeal and eye diseases.

The cases were stored in relational databases: local (MS Access) and central (MS SQL Server 2000). Also all descriptions of the fields of the input form to the database were stored in the database itself. This feature allows the connection of different clients and dynamic formation of the data input forms. The central database is linked with Web server (MS IIS server), thus updated database can be reached immediately using Web based interface. Web based interface is used for user authorization as well as for browsing and searching the educational database.

Results and discussion

The demand for contemporary, systemized and highly qualified medical information for medical students, specialists, researchers, teachers and other people working in the field of health care has rapidly increased. Evaluation of the clinical images is extremely important in diagnostics of laryngeal and eye diseases. Therefore both, otolaryngology and ophthalmology are uniquely positioned to use effectively the benefits of images archiving and transmission using telemedicine and Internet facilities.

An international Baltic MedWeb project was a fruitful extension of previous pilot Swedish-Lithuanian telemedicine Litmed project [7]. Consequently, in Baltic MedWeb project less effort was needed to build working team and infrastructure. Therefore, Baltic MedWeb project was devoted to the creation of Internet based data archive of the images of laryngeal and eye diseases and concentrated on software solution development, involving new medical specialties and intercommunication.

Up to date about 1500 clinical cases containing more than 8000 digital clinical images of various laryngeal and eye diseases are included into the digital archive.

An extensive database of clinical images collected in systematic structure has a great value not only for education of medical students, but for improvement of the qualification of medical specialists, as well.

Collection and archiving of medical images of rare clinical cases (diseases) would allow sharing an experience with colleagues from other medical institutions.

Another very important feature of the archiving of laryngeal images is the possibility of documentation of the results of laryngeal microsurgical operations. This allows explaining and discussing the result of the operation with the patient. The possibility to document and discuss later consequent steps of the operation contains a great educational potential for practical training of residents and young physicians. Moreover, such archive of pre-surgical and post-surgical laryngeal images could be of great importance in some difficult contentious medico-legal situations.

The ophthalmologic database has been created in order to promote and facilitate the development and implementation of training, professional development and information programs for eye-disease patients. This database will assist the general practitioners to diagnose and differentiate acute eye diseases.

In addition, the practical integration of Internet based archive of images of laryngeal and eye diseases with electronic patient records, hospital information system and connection to picture archiving communication systems will form the basis for the development of decision support system [1,2,9]. The case based reasoning is particularly suitable approach to problem solving and learning in decision support systems [10].

Conclusions

At the present the benefit of international Baltic MedWeb project consists of implementation of new technologies and possibilities for education, consultations for medical society and finally, for the best medical care for the patients. The utility of Baltic MedWeb project is based on international and very fast exchange of information, participation in distant education.

The use of Baltic MedWeb archive of images of laryngeal and eye diseases in combination with Web technology is certainly among the factors that will make these technologies to be available to mainstream hospitals and medical universities.

Acknowledgements

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First step for information technologies implementation into eye injury prevention programme among children

Speckauskas M[1], Miseviciute V[2], Paunksnis A[1], Puodziuviene E[3]

[1] Department of Ophthalmology, Institute for Biomedical Research, Kaunas, Lithuania
[2] Distance Learning Centre of Kaunas University of Medicine, Kaunas, Lithuania
[3] Eye Clinic of Kaunas Medical University Hospital, Kaunas, Lithuania

Abstract

Purpose: About 100 cases every year serious eye injuries among children are registered in the largest Kaunas University Hospital in Lithuania. Most of prevention recommendations were prepared as written materials and in this paper is presented new experience of information technologies use in children health education. Having in mind the fact that eye injuries among children have very serious consequences, we decided to create a new kind of educational material for eye injuries prevention.

Material and methods: Statistics of in-hospital patients, who were treated at the Department of Ophthalmology in Clinics of Kaunas University of Medicine, was used for the analysis of eye injuries among children in 2001-2003 years.

Results: The retrospective study of all children admissions into Eye Department of Clinics of Kaunas University of Medicine during three years (2001-2003) was performed. Total number of 308 cases was analyzed. The analyses showed what accidents are most likely to happen; they were related with four groups of causes:

- contusion of an eye by throwing an object, e.g. a snowball,
- eye injury with explosive devices,
- eye injuries by observing adults work,
- accidents that happen while falling down.

Health education material was created using Macromedia Flash MX for children under 10 years old. The total length of it is 1.5 minutes.

Conclusions: The health educational material could be a new tool for prevention of eye injuries among children and should become a part of eye injuries prevention program in children gardens and schools.

ADDRESS FOR CORRESPONDENCE:
Martynas Speckauskas
Department of Ophthalmology
Eiveniu str. 4, LT-50009 Kaunas, Lithuania
e-mail: speckauskas@kmu.lt

Key words: eye injuries, children, prevention, information technologies.

Introduction

Every year 100 cases of serious children's eye injuries are registered in the largest Kaunas University Hospital in Lithuania. The Department of Ophthalmology of Institute for Biomedical Research in Kaunas University of Medicine in close relation with Eye Clinic of Kaunas Medical University Hospital is involved in implementation of national eye diseases prevention and control program. The Department of Ophthalmology has a lot of experience in evaluation of eye health situation among children and preparation of preventive programs in children gardens and schools in Lithuania [1,2].

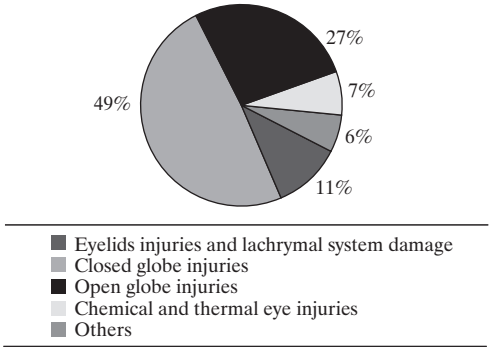
Most of recommendations were prepared as written materials and in this paper is presented a new experience of information technologies (IT) use in children health education. Having in mind the fact that eye injuries among children have very serious consequences, we decided to create a new kind of educational material for eye injuries prevention. The literature describes several examples of powerful videos about preventable burn injuries [3,4], brain and spinal cord injury [5] and others [6].

Medical doctors [7,5] and nurses [3] as well are very active in creation of videos. Unfortunately we didn't find articles, which describe the use of IT for the creation of informational animation. Our experience with educational eye injury prevention informational animation is the first case in Lithuania.

Material and methods

Statistics of in-hospital patients, who were treated at the Department of Ophthalmology in Clinics of Kaunas University of Medicine, was used for the analysis of eye injuries among children in 2001-2003 years. During those three years near 300 cases

Figure 1. **Main causes (%) of eye injuries among children (Clinics' of Kaunas University of Medicine data 2001-2003)**



of serious eye injuries were registered in the largest Kaunas University hospital in Lithuania. Those eye injury causes were very important for the creation of educational material. For the prevention of eye injuries among children the health education material was created. Macromedia Flash MX was applied for this animation.

Results

The retrospective study of all children admissions into Eye Department of Clinics of Kaunas University of Medicine during three years (2001-2003) was performed. Total number of 308 cases was analyzed. The distribution of major causes of eye injuries is presented in *Fig. 1*. Half of the cases (49%) were classified as closed globe injuries and nearly third case (29%) as open globe injuries. In 11% of cases eyelids were injured or lachrymal system was damaged. Chemical and thermal eye injuries were not very frequent i.e. 7%. The absolute number of eye injury cases in different groups were very similar during three year period. The analyses of eye injuries showed that they are most likely to happen as accidents and were related with four groups of causes:

- contusion of an eye by throwing an object, e.g. a snowball,
- eye injury with explosive devices,
- eye injuries by observing adults work,
- accidents that happen while falling down.

The health education material was created as informational animation, trying to describe the above mentioned situations in the understandable way for children. The total length of educational material is 1.5 minutes and it is easily handled by the user. The educational material is adapted for children under 10 years old.

Discussion

The creation of health educational material using information technologies was the first step of new prevention methods application in eye injury prevention program among children. Authors describe a lot of good examples when the video becomes a powerful tool for burn injuries, pedestrian related injuries among children [3,4,6], but there is no experience about the use of new information technologies for children education. Cook DJ [5] in his study have shown no difference in experimental and control groups of new cases of brain and spinal cord injury in children ice hockey players, but showed some improvement in children's knowledge, concerning the mechanism of injuries. We are going to carry out a pilot study in children gardens and schools for the evaluation of the effectiveness of educational material. We intend to show the animation to the children and check if they understand what they shouldn't do to prevent eye injuries.

Conclusion

The health educational material created using Macromedia Flash MX could be a new tool for prevention of eye injuries among children and should become a part of eye injuries prevention program in children gardens and schools.

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Receiver operating characteristic (ROC) and other curves measuring discriminability of classifiers' ensemble for asthma diagnosis

Jurkowski P[1], Ćwiklińska-Jurkowska M[2], Doniec Z[3], Szaflarska-Popławska A[4]

[1] Department of Informatics and Research Methodology; Collegium Medicum; Nicolaus Copernicus University, Poland
[2] Department of Theoretical Background and Medical Informatics; Collegium Medicum; Nicolaus Copernicus University, Poland
[3] Institute of Tuberculosis and Lungs Diseases, Rabka, Poland
[4] Department of Pediatrics, Allergology and Gastroenterology; Collegium Medicum; Nicolaus Copernicus University, Poland

Abstract

Purpose: **The aim was studying the discriminability by ROC curves and gain charts for simple fixed combining of constituent classifiers, for asthma severity diagnosis, and also for bagging and boosting.**

Material and methods: **ROC shows a performance over a range of relative costs and probabilities a priori. Area under ROC curve (AUC) is the measure of separability of two probability distributions, for example of classifying functions. We examined ROC curves of different discriminant methods such as logistic regression, classification trees and neural networks. Next we combined these constituent classifiers and compared the obtained curve with curves of constituent classifiers. The analogous analysis was made on other methods of classifiers' ensemble: bagging and boosting. Besides ROC-in the same way we examined also another curves, measuring discriminability cumulative and non-cumulative lift charts. Social and simple clinical data of 439 patients from three groups of children, hospitalized at the Institute of Pulmunology in Rabka, were used to find classification functions for existing and severity of asthma. We studied also two-group classification problems: asthmatic and non asthmatic children to elaborate automatic predicting of asthma.**

Results: **We found out features with biggest discriminant properties in the differentiation groups of existing and severity of asthma. The improvement of performance after combining classifiers was proved by examining errors of classification and curves measuring discriminability.**

Conclusions: **Performance of ensemble method can be visualized in one graph and compared with joint graph of constituent classifiers.**

Key words: aiding medical diagnosis, childhood asthma, discriminability, ROC, gain chart, combining classifiers.

ADDRESS FOR CORRESPONDENCE:
Piotr Jurkowski
Department of Informatics and Research Methodology
Collegium Medicum; Nicolaus Copernicus University,
ul. Techników 3; 85-801 Bydgoszcz, Poland
Fax: 052-52193;
e-mail: jurkomal@atr.bydgoszcz.pl

Introduction

Receiver Operating Characteristic curve (ROC) is an indicator of performance of two classification rules. The purpose of the work was examining the discriminability by ROC curves and gain charts for combining of constituent classifiers for asthma severity diagnosis and comparing the usefulness of them.

Material and methods

Assessment of performance [1] can be made by:

1) discriminability (error rates: apparent=resubstitution, true=actual=conditional, Bayes error rate; holdout estimate, where set is divided into train and test subsets, cross-validation, jack-knife, bootstrap);
2) reliability (imprecision)
3) ROC curves (only for two classes).

The Receiver Operating Characteristic (ROC) curves can be used as indicators of performance for two-populations classification rules. ROC is a plot of the sensitivity as the function of (1-specificity). ROC curves are also called Lorentz diagrams. Charts with reversed axes are called ODS – Ordinal Dominance Curves.

The positive likelihood ratio is the slope. For discriminant Bayesian rule:

slope= $c_2\Pi_2/c_1\Pi_1$ where:

c_1, c_2 are costs of misclassifications to groups 1 and 2;
c_1 and c_2 are probabilities a priori for groups 1 and 2.

Straight lines of constant costs (iso-performance lines) are such that gradients are equal to the slope. Minimum loss is obtained where line of loss contour are tangential with ROC. In practice precise costs are not known – ROC shows a performance over a range of relative costs. AUC – Area Under Curve does not depend on the relative costs of misclassifications [1]. Area under ROC curve (AUC) is the measure of separability of two probability distributions, for example of two classifying functions: excellent for AUC values bigger than 0.9, good for 0.8-0.9, fair for 0.7-0.8, poor for 0.6-0.7 and fail for values smaller than 0.6. ROC shows a performance over a range of relative costs and probabilities a priori.

In multivariate normal case AUC has the simple and clear probabilistic interpretation – it is a probability that classification function to one group is stochastically larger than classification function to the other group [2]. ROC curve is concave, if densities in two groups have a monotone likelihood ratio [3]. During last years some publications on modelling the classifying functions based on the area under ROC curves have appeared. For example, Ferri et al. [4] propose a novel splitting criterion in decision trees, which chooses the split with the highest local area under curve.

In order to avoid the possible loss of information, classifiers can be pooled. Diversity among individual classifiers of the team is expected to be important for effectiveness in classifier combination. The recognition rate of a combination is usually better than that of each individual classifier. Multiple classifier systems have been attempted in a variety of pattern recognition fields [1].

We examined simple fixed combining method of different constituent classifiers and bagging and boosting fusion.

Social and simple clinical data of 439 child patients from three groups of children, hospitalized at the Institute of Pulmunology in Rabka, were used to find classification functions for existing and severity of asthma. We studied two classification problems:

Classification A
group 1= non asthmatic children (n=101)
group 2= mild and moderate asthma (n=62)
group 3= severe asthma (n=176)

Classification B
group 1= non asthmatic (n=101)
group 2= asthma (n=338).

The social information was collected from family of hospitalized patients by the questionnaire.

We applied the real medical data with mixed variables and known disease diagnosis (children's asthma) as the training set for aiding diagnosis for new patients. We examined ROC curves of different discriminant methods such as: logistic regression, classification trees and neural networks with comparing theirs AUCs to the global classification errors.

Next we combined above constituent classifiers and compared the obtained curve with the curves of constituent classifiers. The analogous analysis was made on other methods of classifiers' ensemble: bagging and boosting [1].

In a lift chart [5], also known as a gains chart, for a nonbinary grouping variable, all observations from the scored data set are set in order from highest expected profit to lowest expected profit. For a binary target, the scored data set is sorted by the posterior probabilities of the event level in diminishing order. Then the individuals are grouped into deciles. Patients with actual profit values greater than the cutoff value are classified as responders (for binary targets: individuals with a posterior probability of the event level greater than or equal to 0.5). If the model has high predictive power, then the positive responses are concentrated in the highest deciles.

We analysed percent response and the percent captured response. To compute the exact model for the grouping variable, observations are sorted in diminishing order by actual profit. The exact model quickest captures all of the responses.

We compared obtained plots with the baseline (corresponding to the random classification) and with the exact model plot.

Results

The data set consisted of much incomplete information. From 90 variables we rejected the most incomplete ones, obtaining 49 variables. Next we performed single imputation of missing data and we found out features with biggest discriminant properties in the differentiation of groups: home contact with a dog in the past or actually, passive smoking by child in the past, active or passive smoking by mother during pregnancy, number of children in the family (or the number of pregnancy or the number of childbirth), pregnancy week when birth, days of staying in the hospital after birth, age of home building, kind of water heating.

For the described in presented paper asthmatic data we obtained the satisfying results. Classification effectiveness was high for different discriminant methods. Kernel discrimination with prior probabilities proportional to group sizes and with normal kernel attained the smallest assessment for the new trial error by cross-validation method. Simple fixed combining some of not such effective methods and of different construction character among them improved effectiveness of classification comparing to constituent classifiers errors.

Examples of charts for simple fixed combining and bagging or boosting are presented in figures of ROC and gain charts. We observed the improvement of combining by examining errors of classification and also curves measuring discriminability.

Discussion

Improvement of effectiveness for fusion of classifiers is confirmed by classification errors and by graphs measuring discriminability. Performance of ensemble method can be visualized in one graph, such as ROC or gain chart, and compared with the joint graph of constituent classifiers. For the case of more then 2

groups we can use other than ROC curves, measuring discriminability, such as gain charts. Similarly to ROC, cumulative lift chart for a model with good predictive power is superior over the line for a model with bad predictive power. In the contrary to ROC, they can be applied for more then 2 groups. However, the interpretation of those curves is different.

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Osteoporosis is dangerous but preventable: needed extensive health education and exercises

Ciszek E[1], Szczygieł A[1], Górkiewicz M[2], Bac A[1]

[1] Academy of Physical Education in Cracow, Faculty of Physical Therapy, Cracow, Poland
[2] Jagiellonian University of Cracow, Collegium Medicum, Institute of Public Health, Department of Epidemiology and Population Research, Cracow, Poland

Abstract

Purpose: **The pilot study on efficacy of the new program for health education was examined. The program combines supervised exercises at the class with patient's self-reliant individual exercises at their homes and, in other plane, it combines physician's lectures with patient's discusses about own experiences and readings about rehabilitation in osteoporosis.**

Material and methods: **The study engaged 71 women at the age of 51-80 with osteoporosis diagnosed by densitometry (BMD: 2.6-4.2). The physical examination were made twice, on the beginning and on the end of the 6 month' program. The class tests and discussions were made every three weeks.**

Results: **The improvement of patient's health in the group was significant: the number of the best class progressed from 0 to 9 persons and of the worst class depreciated from 8 to 3 persons.**

Conclusions: **It was stated that patients can successfully exercise at the home settings. The group meetings enlarge the educational and therapeutic effects.**

Key words: osteoporosis, health education, therapeutic group, self-reliant exercises.

ADDRESS FOR CORRESPONDENCE:
Elżbieta Ciszek
Academy of Physical Education in Cracow,
Faculty of Physical Therapy
Al. Jana Pawła II 78, 31-571 Cracow, Poland
Fax: (012) 683 13 00
e-mail: ecisz@gazeta.pl

Introduction

World Health Organisation defines osteoporosis as a value of BMD that is more than 2.5 SDs below young adult mean value [1]. Osteoporosis is a silent disease, which in itself causes no symptoms, but the morbidity of osteoporosis arises from bone fragility and the subsequent fractures. This result, causing not only pain, but also deformity and even immobility. It was estimated that in the USA and in Europe more than 50% of post-menopausal white women are osteopoenic and about 30% are osteoporotic [2,3]. Thus, there is a great need for appropriate early intervention before fracture occurs [4,5]. The physiotherapeutic approach based there on evidence that physical activity showed prevention effect of falls in old patients too [6], with observed the positive group's effects [7]. In the literature [4,5,7] there are showed a plenty valuable ways to prevent the disabling disorders, but in our opinion, on the beginning of each group therapy, we must carefully consider the goals which differ from one group of patients to another. While many physiotherapists are likely to focus only on transmitting knowledge and on training self-physiotherapeutic skills, many patients are likely to have trouble with their anxiety and other negative attitudes or beliefs towards rehabilitation. Such factors can impede efficacy of therapy or can induce patients to give up. In our opinion the other important goal of a therapy is to make patients more informed, critical readers of current news stories and Web advices on this how live safety with osteoporosis. The monthly face-to-face meetings with patients a physiotherapist should utilize to provide hands-on guidance. There the discussions among patients should not be considered as relax only but as helpful activity that strengthens the relationship between patients and physiotherapist, reduces stress, makes a meetings more interesting, and, if relevant to the subject, may even enhance recall of the consultations. All therapy must be developed in partnership with and between the patients.

Material and methods

During 6 months of the program the patients were obligated to 20 minutes of exercises at home every day. The class tests and discussions were made every three weeks. During each of such meeting the physiotherapist demonstrated some new exercise and patients learned it under his/her supervision. Besides patients reported their feelings and demonstrated their skills on all past exercises. The exercises was aimed to reinforce the pliability of patients, strengthen and endurance of their muscles. The 41 patients from initial 71 took active part to the end of program. The all above 30 leaves were not caused by decrease of a health or a danger of this.

The features of patients posture were examined with Metrecom computer-based system [8]. The obtained anatomical pictures were classified by physiotherapist into four ordered classes with double-blinded procedure (unknown patient and unknown time of measurement, that is either before or after program). The results of therapy were verified with chi-square test.

Results

The significant ($p=0.01$) improvement of patient's health in the group of 41 women was stated: the number of the best class progressed from 0 to 9 persons and of the worst class depreciated from 8 to 3 persons. Moreover, all group of 71 women found this program interesting and helpful, but to more embarrassing for 30 of them.

Discussion

The generally acknowledged goal of the primary prevention in the osteoporosis is to improve the health-related quality of life for people with possible musculoskeletal disorders. The results of classical physiotherapy are there very hopeful but the cost is unacceptable. The key to this is to reduce ambulatory exercises under continuous therapeutic supervision. Consequently, physiotherapists are faced with the challenge of deciding how to maximize patients self-learning and self-reliant exercising. The other challenge is to minimize patient's anxiety and disaffection. The most obvious difficulty in the situation of the increasing patient's self-learning is that the physiotherapist has to learn new terminologies with aim to easy guide discussion using the notions from patient's readings.

Conclusions

The results of our pilot study encouraged us to continue the research. The used health educational program was intended for big group of patients rather, but is also fits for small groups or individual tutoring.

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Making nurses familiar with data explanatory analysis and visualization

Kołacz J[1], **Górkiewicz M**[2]

[1] Jagiellonian University of Cracow, Collegium Medicum, Institute of Nursing, Department of Management in Nursing, Cracow, Poland
[2] Jagiellonian University of Cracow, Collegium Medicum, Institute of Public Health, Department of Epidemiology and Population Research, Cracow, Poland

Abstract

Purpose: The purpose of this paper is to provide our well-tried approach to develop statistic education based on the use of spreadsheets and then, to propose way of continuing evolution to Internet aided education in the introductory statistics for medical (nurses) students.

Material and methods: Paper expresses Author's personal opinions and was based on their experiences in preparing statistic textbook and spreadsheet's instructions, and then in using these in a computer room.

Results: In small groups, 10 to 20 students, the students quickly learned by hands-on experience to solve real-life problems following in exemplary solutions described in spreadsheet's instructions. Owing to restricted use of mathematics we obtain more time to discuss a practical interpretation of a research problem and for the student's presentations in the class.

Conclusions: The main goals of the presented approach was to familiarize students with the data explanatory analysis and visualization on the elementary level, giving them a good starting point to their nearest works in the matter and ability to recognize problems they were incapable of solving on their own. In our opinion the presented approach appeared useful to reach assumed goals.

Key words: statistic education, explanatory analysis, spreadsheet, interactive pages.

ADDRESS FOR CORRESPONDENCE:
Janusz Kołacz
Jagiellonian University of Cracow, Collegium Medicum,
Institute of Nursing, Department of Management in Nursing,
ul. M. Kopernika 25, 31-501 Cracow, Poland,
Fax: +12 421 40 10
e-mail: jkolacz@cm-uj.krakow.pl

Introduction

The patient's education and health promotion is getting more and more importance in nurses' daily duties. Some of the graduate nurses are engaged to active participation in research work. Nevertheless, all other professional roles need the continuous professional learning. Thus, the concept of education in computer science and statistics must be in advance adjusted to new challenges. We suspect there is general accord between educators that teaching computer sciences and statistics for medical students must substantially differ from teaching it for others, e.g. for engineers or statisticians. There a deep understanding of technical details and statistical methodology is not necessary but a more emphasis on the applied part is. The medical students should obtain a fairly clear picture of the activities associated with data analyses in practice. Moreover, they should be able to accurately formulate a question and they should distinguish practical task where they are and where they are not sufficiently experts. On the end, they should be able to successfully communicate the results to their intended audience. The Material & methods section of this paper describes our approach aimed to reach these goals, based on a set of the separate mini-tasks or entities which can be combined into the nets leading to solution. Section Results summarises our experiences in the matter. Section Discussion relates to some similar didactic approaches.

Material and methods

At Institute of Nursing on Jagiellonian University of Cracow from some years the statistic education based on small group cooperative learning approach [1]. This approach de-emphasized the traditional method-oriented approach, typically focusing on formulas and separated statistical tasks, and shift the focus to the looking for complete solutions to practical problems [2]. This approach allows students to supplement what they have heard and read about data analysis by actually doing analyses and then by giving oral presentations and discussing results. The

peer interactions, an atmosphere of cooperation and mutual helpfulness, and individual accountability fitted to individual mathematical and other abilities can change initial negative students' attitudes towards all mathematics [3,4].

From other hand, this approach requires a significant time and efforts necessary to implement all system, and then, a fitting amount of instructor's vigor and creativity at the class. Our first step as teaching coordinators was to design such structure of the statistics teaching resources which can be easy modifying, e.g. adopted to various statistics curses. Our second step was to choose the software, which keeps preparation time for instructors and for students as short as possible.

For software the best pragmatic advice is, if possible, do not design your own, use someone well-tried else's. Moreover, we have to provide software that students can easy use at home, at university, everywhere. Some years ago the seemly choice was the Excel spreadsheet program [5,6]. Excel has some advantages: first, it gives us opportunity to divide all didactic material into separate mini-tasks, each placed in separate spreadsheet. Next, the Excel spreadsheet program includes a lot of ready to use subroutines, named Excel functions and Excel procedures, in this as a minimum about 90 statistical functions and 17 procedures in special statistic add-in named Analysis Tools. Then, there every step in the solution is visible in the spreadsheet and easy to carry out by the students themselves. Alas, it is known that original Excel's help to statistics used strange terminology sometimes, moreover, it misconstrued some elementary statistical notions [7]. The Polish translation followed in this the English original. Thus, we are under necessity to write own explanations to each statistic mini-task. Our instruction to any mini-task points out how to prove if it can be applied (namely: which other mini-task use to do it) and then, where the results of this mini-task can be used. Moreover, there are suggestion what to do if necessary conditions (e.g. normality) was not fulfilled.

Working on set of statistic mini-task one may single out some Excel procedures ready at hand to our didactic purposes, in our opinion they are 8 following tasks: ANOVA – Single Factor, ANOVA – Two Factors without Replications, F-Test Two-Sample for Variances, Random Number Generation, Regression, t-Test Paired Two Sample for Means, Z-Test Two-Sample for Means, XY graph with options Trend. Than, 6 procedures needed a little extensions: Descriptive Statistics (there differences between mean and median and/or values of skew and curtosis should be used to discuss normality; then box-plot graphs need the explicit limits of the confidence interval), ANOVA – Two Factor with Replication (there graph of means makes evident an interaction if it occurs), Correlation (it needs some formulas to estimate a significance of correlation), t-Test Two-Sample Assuming Equal/Unequal Variances (there, except to more conservative F-test, some criterions is needed to use proper variant of t-test), Chi-square test (needed formulas to compute table of expected frequencies). Moreover, we recognised as indispensable 8 new own mini-tasks: Confidence interval for variance or standard deviation from normal distribution, Confidence interval for probability on the base of number of success in Bernoulli experiment, Confidence interval for odds ratio, Cronbach's alpha for questionnaires, histograms, Mann-Whitney test for medians (as nonparametric alternative for t-test), t-Test on the base of known sample means and variances (for data from literature). It makes 8+6+8=22 basic mini-tasks. Our textbook [8] includes description of 135 mini-tasks, in this about 40 intended for the introductory courses.

During last years step by step the web on-line interactive pages become the main position in the student's statistical works. There are specialized Excel sheets like htttp://espse.ed.psu.edu/spsy/Watkins/software/ROCanalysis.xls for evaluating diagnostic performance on a clinical test under study. Besides, there are ready to us interactive pages like: http://members.aol.com/johnp71/javastat.html or http://home.clara.net/sisa/ that perform wide variety of statistical calculations. Currently, The Excel statistical instructions [8] are all time ready to use at our computer laboratory, but each of our mini-task has own web-based substitution, that can be freely applied by students.

Results

Our approach to statistic education was shown to be a working method that allowed students to enrich their statistical competencies. On the end of semester at the first glance there were no distinct differences in students knowledge and skills obtained with cooperative learning or by more traditional learning oriented on average student: about the same majority of the graduated students can carry out not more than 2-4 procedures practiced themselves and usually had some troubles with interpretation. Nevertheless, there are two measurable benefits. First, in the cooperative class some leaders appeared which could explain, compute and interpret many more tasks, because in the same time in a class divided into some working groups the students can to practice about three-four times more statistical procedures than a teacher can proceed and explain in a class working together (like chorus). The second advantage is that some years later students after cooperative learning are more eager to undertake statistical tasks, for example as an candidate for the master's degree.

Discussion

The cooperative learning in the statistical class can be carried out in many ways [9]. The commonly acknowledged great advantage is a class-room can be a not of a kind of a torture-room, neither for students nor for statisticians. It rather seldom pointed out that this approach can be very embarrassing for teachers at the preparatory stage and in the field, during lessons without fixed scenario [10,11]. It seems that our approach makes preparatory work distinctly easier.

Conclusions

Although Excel has a great deal to offer at the elementary level, it is of limited use to more professional data analysis, there is no many procedures offered by a good statistical package, like fitting maximum likelihood approach to regression and multi-factor analysis of variance, generalised linear models. Thus the

next step in practical course of statistics should base on some chosen statistical package that interfaces with Excel.

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Forgotten duties: universities should be anxious for students' learning styles

Rosochacka W[1], Górkiewicz M[2]

[1] University of Warsaw, Faculty of Psychology, Warsaw, Poland
[2] Jagiellonian University of Cracow, Collegium Medicum, Institute of Public Health, Department of Epidemiology and Population Research, Cracow, Poland

Abstract

Purpose: The purpose of this paper is to demonstrate a need of a pedagogical and psychological support for Polish students to develop by them their style of studying, especially for first and second course students with aspect to academic cramming. Moreover, the paper was aimed to show the examples of organizational frames for such support successful practiced at American universities.

Material and methods: The questionnaire investigation on coping with stress and attitude to academic cramming was carried out among 200 Polish students. The results were validated with histograms and Cronbach's alpha and then compared with known from literature results of analogous research on 161 American students using 95% confidence intervals. The survey of American academic sites was made in aspect of a pedagogical and psychological support for students.

Results: It was stated that Polish students are quite similar to their American peers, so they both need similarly extensive support in the matter.

Conclusions: Polish universities should develop organizational forms for a pedagogical and psychological support for their students. It seems that American experience can be helpful there.

Key word: academic cramming, tutoring, learning assistance.

Introduction

American universities and colleges contain the structure charged with mission defined in such words as: supporting the university commitment to ensure a balance between high academic achievement and holistic personal development. Then, they provide suggestions how about coping with stress, anxiety and attitude to procrastination. In this area they encourage students to require for individual consultations and diagnostic testing, especially in the dangerous situations: In case you feel that your coursework is overwhelming, in case if you have three exams in five days and you are now in justifiable panic – don't be afraid to ask for help! All they put great effort on academic cramming. There focus can be on negative effects related to academic defeats and/or to health' emergency. The Polish universities didn't manifested a noticeable activity in this area yet. The hypothetic cause could be that it is superfluous here. Alas, Authors of this paper carried out two-years investigation on cramming behaviour among Polish students [1,2]. Generally, it was proved that all three Polish groups under study from 1st, 2nd and 3rd course, are in this quite similar to their American peers described in [3], so they all need similarly extensive support in the matter.

Material and methods

The 200 Polish students were reviewed. The used cramming questionnaire [3] included seven items, each with four-level Likert scale: frequency of cramming for exams during the current semester (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always), general preference to not cram or to cram for exams (1 = definitely not cram, 2 = probably not cram, 3 = neutral, 4 = probably cram, 5 = definitely cram), how often one crammed by choice (preferring to wait to study even if one didn't have to) and by necessity (being forced to because of work, lack of time, or other external circumstances) (1 = never, 5 = always), how often one gave oneself enough time to study (1 = never, 5 = always), overall level of satisfaction with study habits (1 = very dissatisfied, 2 = somewhat dissatisfied, 3 = neutral, 4 = some what satisfied, 5 = very satisfied), and frequency of engaging in last-minute or last-second cramming just before an exam is passed out in class (1 = never, 5 = always). The standard Cop-

ADDRESS FOR CORRESPONDENCE:
Maciej Górkiewicz
ul. Brzozowa 16/4, 31-050 Kraków
Tel: (012) 4241365, Fax: (012) 4218660
e-mail: mygorkie@cyf-kr.edu.pl

ing Inventory for Stressful Situations (CISS) consist of 48 items [4]. The responders showed good attitude to research. The non-response rate was about 5%. The histograms for CISS principal components were regular, Cronbach's alpha was about 0.80.

The survey of American universities was made by general Internet browsers with key words like Academic Success Center or Academic Resource Center, Learning Assistance Center, and then with key words: academic cramming, academic procrastination.

Results

For seven items of the cramming questionnaire there are not any significant differences between group of American students [3] and all three Polish groups under study. In aspect of frequency of cramming for exams the second and third course Polish students don't differ from the American ones, but the first course Polish students (95%CI: 2.7÷3.2) differ significantly from American ones (95%CI: 3.4÷3.7). Simiraly, only first course Polish students declared (95%CI: 2.2÷2.6) that they rarely crammed by choice (preferring to wait to study even if one didn't have to) than American ones (95%CI: 2.8÷3.1). All Polish groups differ significantly (95%CI: 1.9÷2.4; 2.2÷2.8; 1.9÷2.7) form American group (95%CI: 3.4÷3.75) in aspect of in last-minute or last-second cramming just before an exam is passed out in class. The opinions about goals of academic studying don't correlate with attitude to cramming and they were omitted there, besides they were discussed in our earlier papers [1,2].

The Web survey showed great activity of almost all American universities in fighting with academic craming among their students. Usually, they provide 24/7 access to their online collection of the supplemental instruction named like Study Guides and Strategies web site; Guidelines for Taking Multiple Choice Exams; see for example: http://www.studygs.net; http://www.questia.com/aboutQuestia/eventsj.html; http://www.american.edu/privacy.html. (http://www.eiu.edu/~lrnasst/finals.htm; http://www.usu.edu/arc/idea_sheets.php?site_id=30&page=test_anxiety; http://www.ncwc.edu/Offices/Student_Support/academic_skills_enrichment.htm). For example http://www.ignoututor.com/does-last-minute-cramming-help.html argues: There are a few very good reasons why you should not cram for your exams. The biggest one is that it doesn't work. Here are some others: Your anxiety level will go up; You will lose sleep and eat poorly because of this; You will get sick more easily because of this. Similar warnings can be found in many other sites: http://success.oregonstate.edu/study/testprep.cfm; http://www.arc.sbc.edu/testpreparation.html;http://www.american.edu/ocl/asc/studyskills/timemanagement.html;http://www.umass.edu/sas/html/skills.html. The http://www.stfrancis.edu/arc/study.htm cited the thought by Huxley TH: "Perhaps the most valuable result of all education is the ability to make yourself do the thing you have to do, when it ought to be done, whether you like it or not; it is the first lesson that ought to be taught". Some hosts, like http://www.studygs.net; and http://www.dso.iastate.edu/dept/asc/handouts/cramming.doc represent another philosophy: Although students been told to avoid cramming (studying the night before), there are times when they left with no other choice – thus they need guidance on how to cram. The task-oriented advices for cramming include: preview material to be covered; write out own a course summary; be selective: skim chapters for main points; concentrate on the main points. The health-oriented advices include: Get at least 6hrs sleep. If you have an exercise program, stay with it, and don't forget to eat well!

Discussion

The most confusing result is that student's opinions about goals of academic studying don't correlate with attitude to cramming. It means that some ambitious and prudent students don't restrict cramming at all, just in contrary they perceived it as ordinary learning strategy, as way to get more time for their holistic development [5,6]. Then, some Authors avowal their disappointment that academic cramming persists in spite of all obstinate counteraction [7,8]. Nevertheless, there the general agreement should be noted that costs of academic cramming distinctly exceed the eventual benefits from this, and that the looking for effective ways to overcome it should be continued.

Conclusions

Polish universities should develop organizational forms for a pedagogical and psychological support for their students. The practicable American strategy in the matter includes 24/7 access to specialized sites in the Web, usual talks for all students groups and individual consultation given by specialized university's pedagogues and psychologists.

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Visual inspection of the osteoporosis functional disability using rescaled standard anatomical pictures

Szczygieł A[1], Ciszek E[1], Górkiewicz M[2]

[1] Academy of Physical Education in Cracow, Faculty of Physical Therapy, Cracow, Poland
[2] Jagiellonian University of Cracow (Poland), Collegium Medicum, Institute of Public Health, Department of Epidemiology and Population Research, Cracow, Poland

Abstract

Purpose: This paper promotes use of a 3-dimensional computer-based digitizer to repeated scoring the osteoporosis functional disability of the patients during physiotherapy. The direct purpose is to present our research on the use an standardized anatomical pictures enabled by this technology. The novel method for judging the validity of scores drawn from visual inspection was proposed.

Material and methods: For each patient from group of 41 women menaced with osteoporosis the collection of four skeletal pictures was obtained. Two double-blinded scoring of these pictures were carried out by experienced physiotherapists. The statistical analyses were focused on probability (Pr) that scoring was made by random.

Results: It was proved that probability $Pr<1$ significantly. Moreover, with maximum likelihood estimate (MLE) value of Pr was approximated as $Pr<0.2$.

Conclusions: The visual inspection, carried out by comparing one standardized image with another, or one with many, offers there a good alternative to questionnaires used to examine health-related quality of life. Moreover, there measurements carried out with 3-dimensional digitizer can be used instead of (or as completion to) more expensive and more invasive measurements like radiography or ultrasonography.

Key words: osteoporosis, physiotherapy, visual inspection, non-invasive.

ADDRESS FOR CORRESPONDENCE:
Andrzej Szczygieł
Academy of Physical Education in Cracow,
Faculty of Physical Therapy
Al. Jana Pawła II 78, 31-571 Kraków, Poland
e-mail: wrszczyg@cyf-kr.edu.pl

Introduction

The aims of an individual physiotherapy program should be formulated in terms of functional independency and recommended levels of physical activity or, more generally, in terms of health-related quality of life. In common use there are numerous questionnaires, in these strictly related to disability under study [1]. But it is known that adaptation of questionnaire or even a simple Likert scale to use them in other language or/and in other social environment constitutes a burdensome and long-time process, without any guarantee of a success [2]. The visual inspection, carried out by comparing one standardized image with another, or one with many, offers there a good alternative [3] on condition of keeping proper procedures for data acquisition and statistical analyses [4]. Before all, there the anatomical (histological) pictures should be distinguished from diagnostic ones. The latter need not be accurate in all details, but just opposite, they must allow the user to extract useful information. The practical problem was how prepare the anatomical images, which should be physiologically representative for examined patients as well as standardized for blinded comparisons. Authors recommended there data visualization approach used in the computer system Metrecom [5]. The main idea is to deal with basic three-dimensional anatomical model, which can be modifying accordingly to given patient's properties. In other words, the used algorithms are similar to that of the Chernoff faces [6], but they operate with three-dimensional surface [7] instead two-dimensional curves.

Material and methods

In the experiment the therapeutic group of 41 women were twice examined with Metrecom computer-based system. This instrument uses a touch probe that was placed on various palpated landmarks of the patient's body. The computer recorded positions of probe and then created 3-dimensional image in its memory, that can be used to display and print 2-dimentional pic-

tures. There two quite different approaches may be taken to the subjective scoring of visual information. Under the traditional one the pictures were collected into patient's histories and the physiotherapists score each history separately from others. In this study the double blinded scoring was organized in a simple, uncomplicated way. First, all identification data about patients and time of measurements were hidden on the pictures. Then physiotherapists two times divided all collection of 82 pictures into 9 ordered classes of preference basing on his/her subjective, holistic opinion. The raw statistical material obtained in such way consists of two independent orderings of the same set (in our experiment: 82) pictures, what gives a good starting point to many classical statistical procedures like Sperman rank correlatiom, Kendall's coefficient of concordance, test of goodness-of-fit (e.g. chi-square) [8].

Results

Examined approach was shown practicable and valuable. Two session of a preferential ordering, separated with enough long relax, took together no more than 1-2 hours. The statistical analyses rejected hypothesis that scoring were by random with significance $p<0.0001$. Moreover, with maximum likelihood estimate (MLE) value of random scoring was approximated as $Pr<0.2$.

Discussion

It was obvious that radiography cannot be applied in repeated examinations during rehabilitation. The 3-dimensional computer-based digitizer dominates over other possible technologies with respect to time and expenditures necessary to obtain diagnostic material. Owing their low volume resulting digital information can be easy copied, transmitted, analysed and communicated in a lot different ways. Nevertheless, there some serious doubts on an accuracy and validity of these data arose [5,9,10]. Our research showed adequate application area (it mean a supervising progress of rehabilitation in therapeutic group) and a proper procedure for data acquisition that makes all method reliable.

Conclusions

We have conducted experiment which confirmed our expectation in the matter and encouraged us to continue the research.

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Creation of the software for the acute leukemia automatic differentiation

Belevtsev MV[1], Kulaga VV[2], Spiridonov SV[2], Savva NN[1], Aleinikova OV[1]

[1] Belarussian Research Center for Pediatric Oncology and Hematology, Minsk, Belarus
[2] United Institute of Informatics Problems, Minsk, Belarus

Abstract

Purpose: The aim of our works was created the software for automatic classification of the acute leukemia by immunological subtypes on the basis of the immune marker analysis of blasts, which can used as the "Decision Making Support System".

Material and methods: At The Belarussian Center for Pediatric Oncology and Hematology (Belarus, Minsk) one of the most wide diagnostic immune marker panels is used, that is recommended by the research group (EGIL-95). The panel contains the following monoclonal antibodies: Control, CD45, CD14, CD1a, CD2, CD5, CD7, CD3, CD4, CD8, CD19, CD20, CD22, CD10, HLA-DR, CD34, CD13, CD33, CD15, CD117, CD11c, mIgM, cy IgM, CD79a, MPO, TdT. Positiveness and negativeness of these monoclonal antibodies on the tumor cells is defined by the flow cytometry method using the corresponding devise. The search algorithm is realized by the modern optymalization algorithms application.

Results: To avoid the logical algorithm for finding the solution has been worked out, which allows to find correct solutions by partial estimation of information about the markers. On the basis of the modern knowledge in the area of the differential diagnostics of acute leukosis in children, where the definite combination of positive (1) and negative (0) markers corresponds to each type of the acute leukosis. The developed algorithm forms the basis of the calculation program. The essence of the algorithm consists in the fact, that influence of only the definite markers set is typical for the definite groups of diseases with possible co-expressions. Consider this in more detail and describe the algorithm of diagnostics for every type of acute leukosis, multistage process of classification with the purpose to achieve criteria of defeat in the lymphomas.

Conclusions: Hence the task of acute leukemia immune marker diagnostics automation can be surely referred to the decision making support tasks, which imply conformation or refute of this or that hypothesis. The final decision is made by a person with consideration of recommendations obtained as a result of the software operation. Besides this, the created software can be used as a teaching program by specialists for acute leukemia diagnostics.

Key words: childhood leukemia, immunophenotyping, automatic, subtype.

Introduction

Contemporary classification of acute leukemia is based on the tumor cells immune marker definition [1,5,7]. Utilization of the wide panel of monoclonal antibodies (over 25) for this purpose raises the diagnostics self-descriptiveness, but also increases number of positive and negative expression combinations, that substantially complicates comparison of the combination obtained with the required subtype of acute leukemia. Therefore, the immune marker diagnosis requires deep and long-time period of training specialists, who, except knowledge in immune marker techniques, have also got knowledge in the area of positive and negative monoclonal antibodies expression combination comparison with the leukemia subtype [2-4,6]. The aim of our works was created the software for automatic classification of the acute leukemia by immunological subtypes on the basis of the immune marker analysis of blasts, which can used as the "Decision Making Support System".

Material and methods

At The Belarussian Center for Pediatric Oncology and Hematology (Belarus, Minsk) one of the most wide diagnostic

ADDRESS FOR CORRESPONDENCE:
Michael Belevtsev
Belarusian Center for Pediatric Oncology and Hematology,
P.O. Lesnoye-2, Minsk district 223052, Belarus,
Tel: +375 17 2024089, Fax: +375 17 2024222
e-mail: HYPERLINK mailto: Belevtsev_m@mail.ru

immune marker panels is used, that is recommended by the research group (EGIL-95). The panel contains the following monoclonal antibodies: Control, CD45, CD14, CD1a, CD2, CD5, CD7, CD3, CD4, CD8, CD19, CD20, CD22, CD10, HLA-DR, CD34, CD13, CD33, CD15, CD117, CD11c, mIgM, cy IgM, CD79a, MPO, TdT. Positiveness and negativeness of these monoclonal antibodies on the tumor cells is defined by the flow cytometry method using the corresponding devise. The search algorithm is realized by the modern optimization algorithms application.

Results and discussion

To solve the task directly is extremely complicated, as it requires selecting a single one from 771 possible solutions by the numerical value of 27 markers. Utilization of some special algorithms can only slightly decrease the computational complexity. Therefore, for finding this task solution in the real time it is required to apply some restrictions and admissions in the solution. The analysis that has been carried out allows defining the value for every marker, which has been named "the threshold value". In the case of exceeding this value it is possible to affirm with the great credibility value, that this marker has the great influence on the general process of diagnostics. During this hypothesis verification it was stated, that introduction of these restrictions does not effect anyhow the task solution accuracy. As a result we can substantially reduce the task computational complexity by application of the information, represented in the binary system, during the task solving process. It means, that in case of exceeding the positiveness criterion by the marker (20% and for some of them 10%), it is assigned a unit value, otherwise – zero value. Although such problem formulation substantially simplifies the solution searching process, however, it is also very complicated and difficult in formalization. It is caused by the fact, that when searching the solution "directly" one has to solve the complicated combinatorial task of estimation of 134217728 possible combinations of the markers and selection of a single solution. The process of writing the software for estimation of all possible variants can take much time. To avoid this logical algorithm for finding the solution has been worked out, which allows finding correct solutions by partial estimation of information about the markers. On the basis of the modern knowledge in the area of the differential diagnostics of acute leukosis in children, we have constructed the table (*Tab. 1*), where the definite combination of positive (1) and negative (0) markers corresponds to each type of the acute leukosis. The developed algorithm forms the basis of the calculation program. The essence of the algorithm consists in the fact, that influence of only the definite markers set is typical for the definite groups of diseases with possible co-expressions. Consider this in more detail and describe the algorithm of diagnostics for every type of acute leukosis.

For diagnostics of the B-linear ALL with possible co-expressions the section corresponding to the markers of the B-linear ALL (CD19, CD20, CD22, CD10, cy IgM, s IgM, CD79a, CD45+CD14, CD34, HLA-DR, TdT) and markers, which can be met in the form of co-expressions (CD3, CD4+CD8-, CD4-CD8+, CD4+CD8+, CD5, CD7, CD1a, CD11c, CD14, CD13, CD33,CD117, MPO) is chosen from the general *Tab. 1*. Further every possible combination (sequence) of 0 and 1 is recorded as a binary number, which then is converted into the decimal one. Positions during the conversion are represented by the sequential numbers of markers. For example, the sequence, corresponding to the Pro-B ALL, recorded in the binary system, is equal to 00000000111000100000000001111, that corresponds to the number 125847296 in the decimal system. Such manipulations are made for all possible combinations of the selected markers. As a result 31 numbers are obtained corresponding to the B-linear ALL. After it has been defined, that the obtained sequence unambiguously belongs to the selected group, a search of possible co-expressions in *Tab. 1* is carried on.

During diagnostics of the T-linear ALL with possible co-expressions the section corresponding to the markers of the T-linear ALL (CD2, CD3, CD4+CD8-, CD4-CD8+, CD4+CD8+, CD5, CD7, CD1a, TdT, CD34, CD45+CD14) with all possible co-expressions (CD19, CD20, CD22, CD10, cy IgM, s IgM, CD79a, CD14, CD13, CD33, CD117) is formed from the general *Tab. 1*. Every possible combination (sequence) of 0 and 1 is recorded as a binary number, which is then converted into the decimal one in the same manner as it was described earlier. As a result of the transformations 84 numbers are obtained corresponding to the T-linear ALL.

For diagnostics of the AML with possible co-expressions of the lymphoid markers the markers typical to the AML (CD13, CD33, CD15, CD117, CD11b, CD11c, CD14, MPO, CD45+CD14, CD34, HLA-DR) with possible co-expressions of B-lymphoid (CD19, CD20, CD22, CD10, cy IgM, s IgM, CD79a, TdT) and T-lymphoid markers (CD2, CD3, CD4+CD8-, CD4-CD8+, CD4+CD8+, CD5, CD7, CD1a, TdT) is chosen from the general *Tab. 1*. Every possible combination (sequence) of 0 and 1 is recorded as a binary number, which is then converted into the decimal one in the same manner as it was described earlier. As a result of the transformations 72 numbers are obtained corresponding to the AML. After definition of the fact, that the obtained sequence unambiguously belongs to the selected group, the search of possible co-expressions is carried on. Diagnosis of the acute bi-phene leukosis is formed from the previous groups in the case, if the number of co-expressions exceeds 4 by any separate variant of coincidence.

Conclusions

Hence the task of acute leukemia immune marker diagnostics automation can be surely referred to the decision making support tasks, which imply conformation or refute of this or that hypothesis. The final decision is made by a person with consideration of recommendations obtained as a result of the software operation. Besides this, the created software can be used as a teaching program by specialists for acute leukemia diagnostics. Creation of the (universal) software second version is planned, which could be applied at any modification of the monoclonal antibodies diagnostic panel.

Acknowledgments

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Table 1. Marker overflows

Marker	Pro-B ALL	Common B ALL	Pre-B ALL	Transitory Pre-B ALL	Mature-B ALL	Probably Co-expression	Pre-T ALL	Cortical-T ALL	Mature-T ALL	Atypical-T ALL	Probably Co-expression	Early and Intermediately AML	Mature AML	AML	Probably Co-expression	B-lymphoid +Myeloid	T-lymphoid +Myeloid
CD2	0	0	0	0	0	1/0	1/0	1	1	1/0	-	0	0	0	1/0	0	1
CD3	0	0	0	0	0	0	0	1/0	1	1/0	-	0	0	0	0	0	1/0
CD4+ CD8-	0	0	0	0	0	0	0	0	1/0	1/0	-	0	0	0	1/0	0	1/0
CD4- CD8+	0	0	0	0	0	0	1/0	0	1/0	1/0	-	0	0	0	0	0	1/0
CD4+ CD8+	0	0	0	0	0	0	0	1	0	0	-	0	0	0	0	0	1/0
CD5	0	0	0	0	0	0	1	1	1	1	-	0	0	0	1/0	0	1
CD7	0	0	0	0	0	0	1	1	1	1	-	0	0	0	1/0	1/0	1
CD1a	0	0	0	0	0	0	0	1	0	0	-	0	0	0	0	0	1/0
CD19	1	1	1	1	1	-	0	0	0	0	0	0	0	0	0	1	0
CD20	1/0	1/0	1/0	1	1	-	0	0	0	0	0	0	0	0	0	1/0	0
CD22	1	1	1	1	1	-	0	0	0	0	0	0	0	0	0	1	0
CD10	0	1	1	1	0	-	0	1/0	0	0	0	0	0	0	0	1/0	0
cy IgM	0	0	1	1	0	-	0	0	0	0	0	0	0	0	0	1/0	0
s IgM	0	0	0	1	1	-	0	0	0	0	0	0	0	0	0	0	0
CD79a	1	1	1	1	1	-	0	0	0	0	0	0	0	0	0	1	0
CD13	0	0	0	0	0	1/0	0	0	0	0	1/0	1/0	1	1	-	1	1
CD33	0	0	0	0	0	1/0	0	0	0	0	1/0	1	1	1	-	1	1
CD15	0	0	0	0	0	1/0	0	0	0	0	1/0	1/0	1/0	1/0	-	1/0	1/0
CD117	0	0	0	0	0	1/0	0	0	0	0	1/0	1	0	1/0	-	1/0	1/0
CD11b	0	0	0	0	0	0	0	0	0	0	1/0	1/0	1/0	1/0	-	1/0	1/0
CD11c	0	0	0	0	0	0	0	0	0	0	1/0	0	1/0	1/0	-	1/0	1/0
CD14	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-	0	0
MPO	0	0	0	0	0	1/0	0	0	0	0	1/0	1/0	1	1	-	1	1
CD45+ CD14-	1/0	1/0	1/0	1	1	-	1/0	1	1	1	-	1/0	1	1	-	1/0	1/0
CD34	1	1/0	1/0	0	0	-	1	1/0	0	1/0	-	1	0	1/0	-	1	1
HLA-DR	1	1	1	1	1	-	0	0	0	0	0	1	0	1	-	1	1/0
TbT	1	1	1/0	1/0	0	-	1	1	0	1/0	-	0	0	0	1/0	1	1

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Index of Authors