Managing Uncertainty in Medicine Final Report

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Final report

Petr Hájek (editor)
Bernard Richards (project manager)

Technical report No. 703

January 1997

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Abstract

This is the final report on the COPERNICUS grant No. 10053 (MUM).

Keywords
uncertainty, medical informatics, health care management, fuzzy logic, possibility theory, probability theory, expert systems

Third Framework Programme of European Community activities in the field of Research and Technological Development

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Final report

Project Number - 10053 **Project Acronym - MUM**
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Institute of Computer Science	Partner	CZECH REPUBLIC
Institute of Information Theory and Automation	Partner	CZECH REPUBLIC
Charles University	Partner	CZECH REPUBLIC
Consejo Superior de Investigacion Cientificas	Partner	SPAIN
Technical University of Wroclaw	Partner	POLAND

Date: December 14, 1996.

Contents.

Part A - Synopsis of Work Undertaken and the Results therefrom.

A1 - Objectives of the Project.

The objectives of the project were four-fold. These were (a) to produce some new theoretical results concerned with Uncertainty Theory, (b) to produce software systems which had applications in Uncertainty Theory and in Medicine; (c) to use this software systems in each country to derive new results and/or to assist clinicians in the more efficient care of the patient; and (d) to set up, and contribute to, an Educational and Research Centre (subsequently EUROMISE) to educate Physicians (clinicians, general practitioners and managers) in Medical Informatics, Statistics and Epidemiology for clinical research and practice.

It is the belief of the six MUM partners that all the planned objectives have been met. That is not to say however that more work cannot be made since extensions on almost all fronts have revealed themselves.

In more details, on the theoretical level, the aim has been to contribute to the emerging unifying theory of uncertainty management, including probabilistic, possibilistic, fuzzy and belief functional approaches. On the software level, the aim has been to draw consequences for diagnostic knowledge-based systems and intelligent systems of data analysis. On the application level, the aim has been to gain practical experience in medical data/knowledge processing and introduce software tools developed into selected medical institutions as well as to develop proven Decision Support Systems for use in various clinical departments with the aim of providing better patient care especially in those areas where there has been a shortage of clinical expertise.

Particular domains of application include: prediction of metastases in oncology, assessment of risk in cardiovascular diseases, treatment of patients in Intensive Care Units, supervision of patients undergoing cardiothoracic surgery and others. Developed methods are general, theoretically founded, and applicable in various other domains.

Data have been collected in several hospitals, methodologies have been developed and implemented, and resulting schemas have been used to treat patients in Critical Care Units and those undergoing Open Heart Surgery.

A2 - Work done.

The work which has been done is described in Parts B - E of this Final Report.

A3 - Deliverables.

The deliverables can be identified as being in close correpondence with the Objectives listed in (a) to (d) in Section A1 above. Thus the deliverables are

(a) new theories in Fuzzy logic, Probability theory and Pattern recognition as described in Part B and documented in the publication listed in Part E,

(b) new software systems (see Part C),

(c) new results and practices resulting from the use of software developed (see Part D),

(d) a fully functioning Educational and Research Centre which has used the teaching framework developed by the MUM partners,

Changes to the Project Plan.

The Project was extended by five months to obtain further important results, such developments not having been foreseen at the start of the Project; and to have material available to support the DGXIII team in the Information Forum in Prague in September 1996.

Dissemination of Products and Results.

The software products developed during the Project will be or have been made available to the Project Officer.

Part B. Description of the Theoretical work carried out.

The theoretical research concentrated on different problems connected with uncertain knowledge management and also to different types of uncertainty modelling. Regarding the mentioned types we concentrated mainly on approaches based on fuzzy logics and probabilistic models. Naturally, the research in this field put a special emphasis on the possibility of applications in medicine.

1. The common work of the Barcelona team and the team of the Institute of Computer Science of Prague focused on the clarification of the differences and possible links between uncertainty and vagueness. The main idea is that measures of uncertainty are mainly probabilities and also possibilities and belief functions, while fuzzy logic, as multiple-valued logic, does not deal with uncertainty at all. In this sense, Fuzzy logic is a logic of vagueness and it is well established. In the scope of MUM project, and based on the precedent work done by each team, the main results concerning this topic are contained in the following joint papers:
   (a) [29] deals with qualitative possibilities in the fuzzy setting,
   (b) [24] presents axiomatized theories of the Rational Pavelka logic characterizing probabilities and possibilities (an extended version with axioms characterizing also belief functions is now being submitted to a journal), and
   (c) [25] is a Hilbert style axiomatization, with completeness results, for the multiple-valued logic with product as conjunction. Similar results were known for Łukasiewicz and Gödel logics but product logic was surprisingly not studied. The results of this paper will be very interesting for the multiple-valued and fuzzy logic community.
   (d) In [17, 18] the goal has been to investigate to what extent the usual inference machinery used in fuzzy logic (in the broad sense), i.e. the combination-projection principle and the compositional rule of inference, is indeed logical deduction in a many-valued logic framework.

2. Graded consequence relations based on fuzzy similarity relations was another topic of our interest. Starting with a similarity relation between possible worlds, Ruspini provided a semantics for fuzzy logic. Following this idea, in [12] we studied the relations between this semantics and the semantics of possibilistic and fuzzy truth-valued logics. Moreover we defined and studied graded consequence relations based on similarities (see [8, 11, 7]) and a complete multi-modal system for it [13]. Applications to interpolative reasoning and case-based reasoning are also being studied (see [9, 105]).

3. The following papers contain further results on the interplay of beliefs, fuzziness and ([36]) to their relation to data mining. Daniel [4] and Kramosil [58] contribute to the Dempster-Shafer theory of belief functions, the paper [28] by Hájek and Harmancová introduces and axiomatizes an infinite-valued (fuzzy) modal logic

(of knowledge, S5), that by Godo and Hájek [17] presents a logical analysis of fuzzy inference. Kramosil's [56] paper is an axiomatization of truth-functional probability measures. [22] contributes to the relation of belief functions to Kripke models. Holeňa's paper [36] is an analysis of the hypothesis generation by the GUHA method from the point of view of fuzzy logic.

4. Let us mention also the results contributing to the development of the probabilistic theory of uncertainty. These results are demonstrated by the following three achievements.

   (a) In papers [45, 48] a new viewpoint to the probabilistic models of uncertainty was developed. It was shown that most of the famous approaches can be interpreted as an iterative application of two types of I-projections. This approach provides not only new tools for proving theoretical results but also explains some problems connected with computational complexity of probabilistic algorithms.

   (b) A number of theoretical results have been achieved also in the field of chain graph models. These models, having advantages of both graphical models and Bayesian networks, can describe a wide class of different dependence structures. In a way they unify the wide class of graph models into a single approach. The most interesting results were published in papers [117, 118].

   (c) Among the third group of theoretical results let us mention the possibility of marginalization of graphical models, which was described in [119] and a new philosophy for construction of decision models manifesting nonmonotonic behaviour [47].

5. Another group of papers deals with the theoretical analysis of medical expert systems. Here let us cite [26, 27, 5, 99, 20]. Paper [26] is an abstract of the poster we had at the conference "AI in Medicine Europe" at Pavia; [27] is the corresponding full paper. The papers deal with the general problem in (medical) fuzzy expert systems, namely use of conditional probabilities as truth values of fuzzy implications. The paper [5] is a detailed critical, reader-oriented, analysis of the well-known fuzzy medical expert system CADIAG-2 (by Adlassing) showing its close relation to MYCIN-like systems, with which it shares both advantages and also disadvantages. The final version has been accepted for publication in the journal Artificial Intelligence in Medicine. [99] is a PhD thesis of P. Nguyen, written under the supervision of P. Hájek (the main advisor being Prof. Adlassnig); this is a thorough investigation of CADIAG-like systems containing, among other results, an elaboration of Möbius transform for CADIAG. The last topic is worked up in [33] for the first time. [20] is an internal report analyzing the Spanish system MILORD from the same point of view as we criticized CADIAG: the use of conditional beliefs as truth degrees in a way that may be dangerous due to the compositionality of fuzzy logic. The discussion of the possibilities of using fuzzy inference (which concerns vagueness, not degree of belief) to handle beliefs is ongoing.

6. Other types of theoretical results we want to mention are the results that were achieved when solving problems connected with application of probabilistic models for uncertain knowledge representation in medicine. Above all, let us mention design of algorithms for solution of inconsistent marginal problem connected with the knowledge integration process. We have proposed methods based on the algebraic approach [65, 67, 68] and methods based on modification of the famous *Iterative Proportional Fitting procedure* [52].

7. An automatic design of a graph structure, either of a graphical model or of a Bayesian network, is recently the center of interest of researchers. Our contribution to this field is a result of collaboration with the University of Salzburg [49, 50]. Another practical problems are connected with dimensionality of distributions representing the knowledge. These problems were both theoretically and algorithmically tackled by several groups of MUM partners and are solved e.g. in [140].

8. Research on data reduction and constitution problems: The research in this field has been of probabilistic nature. We prepared a special seminar in the frame of the MUM project where the overview of methodologies for feature selection and extraction was given. In the frame of the project we prepared a very detail overview of discriminant analysis [97] and regression analysis in connection with the selection of variables, and we prepared an overview of the information theory approach to data reduction and constitution problems. Based on the results of the seminar we concentrated in our research on the development of new methods and algorithms based on the information theory approach for data reduction and the constitution problem, where also the weight of features can be considered. The developed approach was presented at different conferences and workshops [139, 140, 131], and shown also in connection with real applications [142, 131, 135] based on our research. We have not decided to prepare any programs connected with classical statistical approaches because we found that strong tools already have been included in different commercial software packages. For this purpose a special software called CORE (Constitution and Reduction of data) has been developed and tested on medical data. First results have been presented at the Medical Informatics Congress 95 in Copenhagen [141] and further results are submitted for publications and presentation at forthcoming conferences.

9. Research on data analysis in epidemiological, clinical and genetic studies: Research in this part was using mostly probabilistic approaches: only in the part concerning the GUHA methods was the exploratory data analysis applying also some tools of logic. First, we have analyzed the methods and tools used in the epidemiology. We made an evaluation of the statistical software used for these purposes. According to our evaluation we decided to prepare the program Epidemiology Tools (E.T.) that will be useful for practical applications. We found that some methods were not involved in any known statistical software packages, e.g. methods of standardization. Papers [128, 127] connected with this topic were published and results presented at some conferences as lectures or posters.

For both clinical and epidemiological studies we tested some other methods, e.g. survival analysis [136] and others [42]. We have developed some new approaches for analysis of data in genetic studies.

10. Decision support tools: We have decided to formulate real decision making problem in cardiology, i.e. how to optimize therapy of hypertension. The idea was to build into the program clinical experience in the therapy of arterial hypertension for general practitioners and to include also the real prices of drugs used. The model for this purpose was developed and the program HYPERTENSION prepared in the Czech language. The developed method and the program (first and later versions) were presented as papers or posters on the occasion of national and international conferences [135, 102, 103] and a full paper will appear in the international journal [104].

Part C. Software developments and Extensions.

Intensive Care Unit Expert System: ICUES (Manchester).

A team led by Professor Bernard Richards had previously produced two computer Expert Systems which were widely acclaimed and which received international recognition in many world-wide conferences. These were an Expert System as an aid to the anaesthetist in Cardiac-by-pass (Open Heart) Surgery; and an Expert System for diagnosis and therapy of acid-base and electrolytes in an Intensive Care Unit.

The proposal in the MUM project was to build on the experience and collaboration previously established to add a further in-depth module to the Intensive Care System.

Briefly, the system takes in initial information on the patient (e.g. age, sex, diagnosis) and then attempts to control the patient's Heart Rate, Blood Pressure, and Central Venous Pressure. It does this by asking the clinician to input these three parameter values. The ICUES then prescribes a treatment (drugs, or ventilator settings) which will improve the patient's condition. Normally the physician will follow this recommended treatment. However, the system gives provision for the physician to suggest, and use, an alternative treatment (possibly because the suggested drug may not be available). This cycle of input-of-parameters followed by treatment is repeated until the patient reaches normality. However, additional facilities are provided. Should the patient go into a cardiac arrest state there is a tutorial explaining to the nurses or doctors exactly how to deal with this situation. Further, if more detailed information is required on the patient's condition it may be necessary to insert a Pulmonary Artery Catheter (PAC). Firstly there is a tutorial on how this should be done. Then, with the catheter in position, it becomes possible to obtain additional parameter values (e.g. cardiac output etc.) which, in turn, allow the physician to more selective and more precise in the treatment of choice. The ICUES includes a sub-module making a provision for treatment using the PAC. This amounts to a whole new set of treatments as there are now five, not three patient-parameter values to be analysed. So, throughout the ICUES there are some 300 treatments based on the three parameter system and further 81 treatments based on the PAC sub-module. Finally, for every treatment (which occupies one full screen of information) there is a corresponding "Explanation" screen. This holds true for both the HR/BP/CVP System and the PAC System. Thus the grand total of information screens, forming this knowledge base, is almost 1000.

The ICUES software package was produced in Manchester at UMIST and both tested and refined at the Manchester Royal Infirmary under the personal supervision of Dr Barry Doran.

The ICUES is described in full in the various publications and Reports [37, 38, 39, 40, 41] and[110, 111, 112, 113, 114, 115].

GUHA (ICS Prague).

GUHA is a method of automatic generation of hypotheses based on empirical data. GUHA (General Unary Hypotheses Automaton) distinguishes from various statistical packages (enabling one to test hypotheses that have been formulated) by its explorative character: it automatically creates hypotheses from data, by the means of computer procedures. The hypotheses are general in character; they express statements concerning all objects from the data sample. Clearly the data cannot guarantee the truth of such a hypothesis with certainty; they support the hypothesis, make it plausible.

GUHA is primarily suitable for exploratory analysis of large data. The processed data form a rectangle matrix, where rows correspond to objects belonging to the sample and each column corresponds to one investigated variable. A typical data matrix processed by GUHA has hundreds or thousands of rows and tens of columns. GUHA systematically creates all hypotheses of interest from the point of view of a given general problem and on the basis of given data. Thus GUHA is a *method of data mining.*

PC-GUHA is an implementation of the GUHA procedure ASSOC for PC AT/XT personal computers. See [34], [35] and references thereof.

The program PC-GUHA contains tools for data description and preparation, easy choice of run-time parameters, saving and changes of parameter choices, saving and printing of results. It offers options for easy interpretation of results, survey reports on data and results, and various kinds of sorting of the results etc.

ASSOC is a GUHA procedure processing dichotomous and/or categorical data. ASSOC processes a matrix representing the behavior of dichotomous variables (values 0,1) or, more generally, categorical (finitely valued) variables possibly with some missing data items. It systematically creates composed properties of objects (elementary conjunctions), like

AGE:YOUNG & NOT COLOR:GREEN & WEIGHT:HEAVY

ASSOC generates and evaluates relevant queries on associations of the form $A \sim S$ (read "A is associated with S") or $A \rightarrow S$ (read "A makes S likely"), where A and S are elementary conjunctions of literals, $\sim$ is a notion of *association* (quantifier), $\rightarrow$ is a notion of *implication.* In a given run, the quantifier is fixed and so is the condition (if any); antecedent and succedent vary. Each generated relevant query is *evaluated* as a statement concerning the data matrix. Six quantifiers are at one's disposal, each having several parameters. Results are saved in a solution file containing all necessary information. The solution file can be sorted and then printed.

The software system PC-GUHA was mainly developed before MUM, but was continuously improved in the Institute of Computer Science, Academy of Sciences, Prague, during MUM. The software surrounding GUHA which was developed fully inside MUM is the system WIN-GUHA, described in the sequel.

The goal of the project was to implement a prototype of a new generation of GUHA software. A former implemented subprogram ASSOC in FORTRAN was used for generation and verification of hypotheses. A focus inside the MUM project was on a development of a new interface working under WINDOWS.

The system WIN-GUHA working on personal computers under WINDOWS was implemented. The programming language VISUAL-BASIC was used. The main features of the system WIN-GUHA are:

The system WIN-GUHA reads data from database files of the type *.dbf (FoxBase, Dbase), it is easy to implement possibilities of reading files of types *.mdb (ACCESS) and *.pdx (PARADOX). The input file is further understood as an analysed data matrix.

It is possible to define new quantities derived from columns of the analysed data matrix. New names, missing values and categories (possible values) are defined for each quantity.

There are three types of quantities: Boolean, codes, and intervals.

Categories of a Boolean quantity are YES/NO.

Categories of a quantity of type "codes" are defined as lists of values of the corresponding data matrix column.

Categories of a quantity of type "intervals" are defined as lists of intervals of real values.

Names, missing values, and categories of new quantities, can be defined both for particular quantities and for groups of quantities in a very simple way.

It is also possible to define all further parameters (antecedent and succedent quantities, generalised quantifier, etc.) of the subprogram ASSOC in a very easy way.

It is possible to store the set of defined quantities and parameters and to use it repeatedly.

It is possible to run the subprogram ASSOC and to interpret a resulting set of hypotheses.

It is possible to define a subset of a resulting set of hypotheses. Conditions concerning 12 statistical characteristics, conditions on lengths of antecedent and succedent, and conditions concerning presence of particular quantities and/or their values, can be used to define each subset of hypotheses.

It is possible to order the defined subset of hypothesis according to 21 criteria or their combinations.

Some parts of the system WIN-GUHA were also experimentally implemented under the UNIX system as a basis for an assumed system SUN-GUHA.

Other software from ICS Prague:

Description of *CRACTES*:

From a mathematical point of view, the task of the risk-assessment with time dependent covariates is solved, from a medical point of view it is a task of the estimation of cancer patients prognosis based on tumor markers follow-up and cytological prognostic factor measurements in oncology.

The authors proposed an original multidimensional model of survival analysis with indirectly diagnosed failure realized with the help of long-term monitoring of selected parameters (tumor markers). Every marker's follow-up is modelled with the help of a bivariate failure-time model; there are two possible failures, tumor markers increase (or just change behaviour) without clinical evidence of a recurrence (we will call it clinical latency) or recurrence, recurrence being the last possible failure. As there are cases when recurrence is not preceded by marker rise, the first failure may be either clinical latency or recurrence. The covariate vector includes covariates of two types:

1) fixed covariates connected to the primary tumor, such as the estrogen receptor for breast carcinoma patients

2) covariates which represent the marker behaviour (time dynamics), e.g. robust estimation of the time of tumor marker increase, rate of increase, etc.

Finally, risk estimation of cancer recurrence serves the clinician as a signal for more detailed clinical investigation about metastases (using sonography, computer tomography, x-ray, etc.).

Description of *BIANTA*:

Fuzzy Bayesian network is applied to the cases when clinical examination admits two or more possible locations of a tumor, or when metastases are diagnosized without any precise specification of origin. Tumor markers may contribute some useful information concerning the unknown site of the primary tumor and it is a common practice to take their measurement in such a situation. Our network give probabilities of different cancer diagnoses based on tumor marker results, sex, and age. Fuzziness is because each measurement has its own CV (coefficient of variation) and biological age is generally not exactly equal to real age.

There are three main problems to be solved:

1) find the dependencies between each diagnosis and each marker

2) find the dependencies among markers (for a given diagnosis)

3) overcome the incompleteness of the database.

Because usually only 2-3 markers are measured from a possible 42 markers, the method of reconstruction of a multidimensional distribution from partial, less dimensional (marginal), distributions was applied. The bayesian network serves as a useful tool for the clinician. It provides a display of prior probabilities (incidence rates) of the diagnoses known from epidemiology. Then, these probabilities are modified on the basis of measured markers. The network enables the clinician to exclude a subset of (from the clinical point of view) non-probable diagnoses and to find out which additional marker measurements could further modify the probabilities.

CRACTES as well as BIANTA exist as running prototypes, capable of practical use. We note that the results of this research and implementation have been used outside MUM to produce commercial fully fledged versions of CRACTES and BIANTA that are in practical use in several hospitals.

Software from Charles University.

The Charles University group developed three new programs and all these programs are running in PC versions.

Program E.T. (Epidemiology Tools) has been developed for analysis of data from case control and cohort studies and for standardization. The program is written for English speaking users and a more detailed description of the program is given in Part G. In the MUM Project, the program was used especially for data analysis of a large longitudinal study of atherosclerosis in Prague's male population. Moreover the program is widely used in education at Charles University in the pre-graduate and post-graduate courses as well as in European courses organized by the EuroMISE Center. The program was used by many students from these European courses and it was donated to them for their own research and applications. In this way the program is in use in countries like Poland, Romania, Hungary, Bulgaria, Slovenia, Croatia, and Bosnia and Hercegovina.

Program CORE (COnstitution and REduction) was developed in ACCESS for data constitution and reduction using information theory tools. The program is written for English speaking users and a more detailed description of the program is given in Part G. The program has been used for the analysis of data from a large longitudinal study of atherosclerosis in Prague's male population and for analysis of a sample of data gathered in Wroclaw Chest Hospital.

The program HYPERTENSION was developed to support the therapeutical process for patients sufferring from hypertension. The program is written for Czech speaking users and a more detailed description of the program is given in Part G. Moreover the program is using data on drugs and their costs distributed by the Czech General Insurance Company. Due to language restrictions, it cannot be directly used abroad. However, we intend first to obtain in-depth experience with this program in the Czech environment, especially to estimate its value for Czech general practitionners. The program is also widely used in Czech courses organized by the EuroMISE Center these being mainly for physicians.

MILORD (IIIA Spain)

The IIIA team, before the starting of the MUM project, had developed an architecture for knowledge-based systems, called MILORD II, whose main features were the modularity and the local reasoning facilities, in the sense that it was possible to choose, for each module, the most appropriate finite multiple-valued logic according to the particular application being developed. In this framework the IIIA team has extended the local reasoning facilities in two different directions:

- The first extension was to enhance the knowledge representation power of the MILORD II system by allowing the possibility of defining modules using probabilistic reasoning on Bayesian networks and integrate them with non-probabilistic modules in hybrid knowledge bases.
- The second extension, which is not yet completely finished, is a tool for helping the expert in choosing the most appropiate finite local multiple-valued logics and the renaming functions needed for the combined use of two different modules of the system with different local logics.

A general language description of the current MILORD II system can be found in [108].

The MILORD II system is on the Internet and it is freely available for MUM partners. It has also been installed in Prague in the Institute of Computer Science, and in the EUROMISE Center, and it has been presented, together with RENOIR (a decision support system on Rheumatology built on MILORD), in a joint seminar with the Prague partners of MUM. Renoir is also used for educational purposes in the EUROMISE Center in Prague.

The following software is available:

1. The MILORD II system (Mac and Unix platforms, very soon also on PC)

2. RENOIR, Expert system on Rheumatology built on MILORD I (on Mac platform).

3. Expert System Prototype in Oncology (on Mac platform).

Systems PME and OM (IITA Prague).

(1) PROBABILISTIC MODEL EDITOR (PME)

In the field of medical diagnostics, there exists an amount of inherent uncertainty that cannot be simply neglected as is the case in deterministic (logical) expert systems. Among different formalisms for dealing with uncertain information (e.g. *fuzzy set approach, Dempster-Shafer theory, possibility*) an important position is taken by *advanced probabilistic models*.

These are known as the best models as far as prediction is concerned. The claim holds if there is enough data (statistical material) and/or additional *pieces of knowledge* (e.g. types of conditional dependence among variables). In these situations probabilistic models outperform other approaches.

The reason why they are not used on a wider scale lies in the fact that they are very complicated, difficult to understand, and the work with them may be cumbersome.

The aim of the developed software is to serve as a tool for easy construction of *Bayesian networks* and *graphical models* that can be used as inputs to *diagnostical expert systems*. The user friendliness of the programme was assessed by comparing different alternatives: two codes were written. PME is one of them.

The programme was developed by the group led by R. Jiroušek in the Department of Decision-Making in the Institute of Information Theory and Automation, Czech Academy of Sciences, Czech Republic.

(2) OLIGODISTRIBUTION MANAGER (OM)

Oligodistribution Manager was developed as an alternative to PME and therefore the motivation is the same for both products. (Oligodistributions are less-dimensional distributions, considered to be marginals of a joint distribution that represents the universal model in the probabilistic paradigm.) The differences between PME and OM are the following:

1. OM is written in Visual Basic for DOS. (PME is in Visual C++.) Background utilities are stand-alone programs written originally in C language.

2. OM can run under MS DOS in less then 640 kBytes of memory and it is therefore more universal than PME which requires 4 MBytes.

3. The graphics of OM are not as "professional" as those in PME.

4. OM has a more open architecture where separate utilities (e.g. for IPFP algorithm, building of Bayesian networks and construction of graph models) are called with the help of *spawn* functions and are not integrated firmly in the body of the presentation and dialogue windows as is the case with the PME.

Details on OM are given in the *Oligodistribution Manager's User Manual* by O.Kříž [66]. The theory is given in the *Probabilistic Model Editor User Manual* by N. Kushmerick [64]. The programme was developed by the group led by R. Jiroušek in the Department of Decision-Making in the Institute of Information Theory and Automation, Czech Academy of Sciences, Czech Republic.

Software from Wrocław.

(1) Software tools for data acquisition (KOSTAT, KARTAIOM, POBYTY)

First of all there is KOSTAT-1, a Paradox 3.5 application for DOS, which has been used for collecting hospital management data for all patients discharged from the hospital. The following data has been put on all wards on special forms: personal data (including ICD9 code), names and code-numbers of all diagnostic and therapeutic procedures performed, as well as drug brand names and total doses administered for each patient. The actual unit costs of each item have also been filled in. Two versions of this system have been developed and installed in the Operation Theatre Module, to collect some data on surgical procedures (in a compatible format). The system had been revised several times (until Spring 1996). A companion system KARTAIOM for collecting not only patient management, but also more detailed, clinical, data on medical problems and medical procedures at the Intensive Care Unit had been in routine use since July 1995. There are a number of other patient management data bases, created and updated manually from source documents (books), using Paradox format, not incorporated into the above systems; namely: HISTPAT - histological diagnoses for lung cancer patients, BRCHZGON and ZGONYWR - mortality data, TERPRZ - details on bone marrow transplants, TERONK - general data on alternative forms of treatment for lung cancer patients (chemotherapy and radiotherapy). Some PAS- like data has been imported from an old PAS UNIX-based system, installed at the Admission room on an informal basis (only general personal data). All data bases have been found incomplete, uncorrelated, and with a great number of mistakes or missing values. Consequently it was decided to develop a new unified data collection system for all aspects of the hospital patient management process, using and unifying available data from other sources. The new system POBYTY was installed initially only to assist this research project, but the idea has been accepted by the hospital authorities and the full scale system is planned.

(2) Software tools for data analysis.

Firstly there is the ANALIZY software package, an independent Paradox 4.0 application for DOS, for automatic analysis and partial correction of hospital patient management data from Wrocław, stored in KOSTAT-1 and POBYTY format. This package currently incorporates the previous version of the HSI-P1 module, designed to analyse similar data bases from Bristol. Secondly two modules of the PROFILE1 software package, BAZY-FCE and CASE-MIX, have been developed which are able to perform analyses. All analyses may be performed for a very specific set of parameters, defined by the user; it is possible to restrict analyses (and also all experiments under the other PROFILE1 system option) to a specific period, patients from a particular district, of a particular sex, treated at specific ward, etc.

(3) Software tools for decision support (PROFILE1-3, ODCZYT)

There are currently three prototypes of a Patient Management Decision Support System PROFILE: PROFILE1 - actual version of a Paradox-based DOS application (requires Paradox 4.0), incorporating all the above-mentioned decision support and some of the data analysis modules (the system has been in use at WCH in Wrocław since 1994); PROFILE2 which is an independent DOS application, partly integrating data collection and decision support systems at WCH, consisting of three problem-oriented modules: PAS DATA (interfacing unified data structures of PROFILE1 type with incompatible DOS/PC-MOS/UNIX hospital data collection systems at WCH and external data sources), HOSPSTAY (an extended version of POBYTY system), QUERIES (which will be offering all data analyses of the PROFILE1 type and data visualisation techniques; currently only sample queries may be assisted with bar charts) and supportive TOOLS module (offering operations on coding systems, including automatic conversion of clinical/histological diagnoses from source data bases, written in Polish or Latin, into unified terms; this module will also offer transformation of PROFILE- type resulting data bases into GUHA compatible format, it is now offered by a separate ODCZYT program); PROFILE3 - a WINDOWS 3.1x application, intended as next step to integration of all decision support systems at WCH, consisting of all PROFILE2 modules and incorporating modules linking POBYTY-data bases and PROFILES-analyses to standard tools (EXCEL and WORD macros); it is planned to introduce links of the same type to WIN-GUHA and ICUES-PL. All above systems use the same data structures and executables - the same DLL libraries.

Survey of Wrocław software:

a - KOSTAT-1, version 5 - Borland Paradox 3.5 application for DOS, a modified software application for collecting patient management data, currently used only in the Operation Theatre Module at the Wroclaw Chest Hospital (WCH); to be replaced in 1997 with a module of a new version of POBYTY (see below)

b - KARTAIOM, version 3 - Borland Paradox 4.0 application for DOS used for collecting patient management data (including clinical data on medical problems and medical procedures) at the Intensive Care Unit; routinely used at ICU WCH since July 1995; to be replaced in 1997 with a module of a new version of POBYTY

c - POBYTY, version 0.5./1.0 - a Borland C++ 4.53 software package (object oriented, protected mode) for collecting patient management data, superseding KOSTAT software and compatible with its Paradox format databases; routinely used at WCH since September 1996

d - ANALIZY - currently an independent Paradox 4.0 application for DOS, a software package used for automatic analysis and partial correction of hospital patient management data stored in KOSTAT-1 and POBYTY format; implemented in WCH from October 1995; incorporates previous version of the HSI-P1 module (see below)

e - HSI-P1 software module of the PROFILES system - a Paradox 4.0 application for DOS, a software package used for automatic analysis and partial correction of in-patient hospital management data stored in SW regional PAS format in the UK; implemented for 1993-1994 data from Bristol and District Health Authority from October 1995; currently within ANALIZY software package,

f - PROFILE1 (PX), a new prototype of a Patient Management Decision Support

System - Paradox 4.0 application for DOS, incorporating DSS shell, analytic modules (BAZY-FCE, CASE-MIX, STRUKTURY, PROFILE, SCHEMATY, PROCESY) and utility modules, implemented in WCH for analysing all 1994-1996 patient data management data, stored in KOSTAT/POBYTY format and pre-processed by ANALIZY package

g - PROFILE2 (DOS Turbo Vision), version 1.0 - a BC++ 4.53 software package (object oriented, protected mode), intended as the first step to integration of all decision support systems at WCH; incorporates modules of POBYTY (both systems and all other applications use the same DLL libraries and the same data structures, defined in INI files); includes the prototype modules interfacing with incompatible PC MOS systems and UNIX based systems installed at WCH; implemented at WCH in November 1996

h - PROFILE3 (WIN 3.1x), version 0.2 - a BC++ 4.53/5.0 software package (object oriented, protected mode), working on the same DLL libraries and the same data structures as other applications, intended as the next step to integration of all decision support systems at WCH; incorporates modules linking POBYTY-data bases and PROFILES-analyses to standard MS tools (EXCEL and WORD macros). It could include links of the same type to WIN-GUHA and ICUES-PL; preliminarily tested at WCH since Autumn 1996

i - ODCZYT2 - a modified utility for transforming resulting data bases of the PROFILES.PX system into GUHA-compatible format (currently Borland C++ version 3.1 for DOS, enabled to work with GUHA 3.2E)

j - ESICU-PL (version 0.1.) - a prototype extension of the original ICUES expert system for intensive care developed at UMIST, and partly translated into Polish; an MS ACCESS 2.0 application, with a separate SHOCK.EXE Turbo-Pascal executable module; incorporating a translated and partly adapted interface and main treatment database/rule base, as well as a modified version of SHOCK - an expert system for diagnosing and treating cardiogenic shock, currently attached as a module of the ESICU expert system.

Part D. Applications and testing of software. Data and knowledge acquisition.

(1) Expert system ICUES.

Collaboration between England, Poland, and the Czech Republic has resulted in the development, testing, and use of software developed as part of the MUM project. In Manchester the software package ICUES was developed, tested and refined.

After two refinement cycles ICUES was then installed in the Intensive Care Unit and the Post-operative Cardiac Surgery Unit in the First Medical Faculty in Prague. The intention here was that the Consultant Physicians in these two Units, Dr J. Valenta and Dr B. Scrovina respectively should evaluate the system from the point of view of it being both an educational / training tool for junior doctors and as a therapeutic regime which could be recommending the use of drugs available in Prague. Both these physicians were very enthusiastic: such was there enthusiasm that they were each joined in their evaluation by a further colleague, these being respectively Dr Balik in the case of the Intensive Care Unit and Dr J. Mokrejs in the case of Cardiac Surgery.

Subsequently, after these first trials in Prague, the ICUES software was installed in the Chest Hospital in Wroclaw by Dr Marek Lubicz. The intention here was similar to that in Prague, viz both educational and therapeutic. However, the enthusiasm of the staff in Wroclaw was such that a further sub-module was designed and tested. This supplementary module, SHOCK, was developed in Wroclaw for dealing with patients in acute stages of shock in the Chest hospital, Wroclaw. Details of this sub-module are in the references [73, 78, 79, 80, 81]. The success of this implementation in Wroclaw has been due in no small part to the enthusiasm of both Dr Lubicz but also of Dr Sypula, the Hospital Director.

The results from the work done within this MUM project are these. Firstly a unique collaboration was established between the team in Manchester (at both UMIST and the MRI) and the workers in both Prague and Wroclaw. Secondly, the field-trials showed which drugs needed to be replaced within the system to meet the special circumstances (e.g. availability, cost etc.) required in the hospitals in Prague and Wroclaw.

The publications [37, 38] describe in detail treatment of individual patients, their HR/BP/CVP parameter values, the suggested drug treatment, and the patient's response in terms of improvements in these parameter values. Patients from all three Units have been included in these publications.

Thus the ICUES package has been in use in the Chest hospital Wroclaw, and in two Departments in the Intensive Care Unit and the Cardio-thoracic Unit in the First Medical Faculty Prague, as well as in the Intensive Care Unit in Manchester where the original testing was done. The results are very interesting in that (i) the package has proved itself as a Decision Support System carrying the confidence of the physicians on the varous sites, and (ii) the system is valuable as a source of guidance for the junior clinic staff both in their service role and also as an educational aid.

Many benefits have come out of the collaboration between partners, viz. these in Manchester, Wroclaw, and Prague, during this MUM exercise. Firstly it has enabled the physicians in the First Medical Faculty in Prague and in the Chest Hospital in Wroclaw to experience for the first time a good computerised Expert System. It has enabled them to asses for themselves the role that a Decision Support System can play in the overall scheme of patient care. Secondly, in Wroclaw the system has raised so much enthusiasm in the clinicians that they have been able to build an additional module SHOCK for giving guidance in the treatment of patients admitted to hospital in a state of cardiogenic shock. This module is proving very beneficial in Wroclaw and is under trials in Manchester. The third area where this system has proved to be of value is in training the junior staff. The pressure on the senior staff is very great on account of the large number of patients entering hospitals in Prague and Wroclaw. Here the junior staff have an alternative means of learning.

Finally there are economic benefits emerging from the use of the system. Here reference is made specifically to the pharmacological regimes emboddied in these computer programs. Because the computer system can incorporate these drugs of local preference, the consultants will know what will be the likely costs of treating patients in their care.

So what are the conclusions at this point in time. The systems are in use in the hospitals in Manchester, Prague, and Wroclaw and will continue to be used. Further evaluation is still needed to cover every possible combination of patient parameter values (of HR/BP/CVP) and to check the response from the chosen drug therapies. It must be remembered that the ICUES is written to permit a drug-usage matched to the individual hospitals. It would be the wish of all those involved in these three cities that the work should continue.

(2) GUHA, CRACTES , BIANTA

We first mention two successful applications of the GUHA method of automated hypothesis generation to medicine. First, Dr. Pecen, in collaboration with Prof. Kaušitz, M.D. from Slovakia, processed by GUHA data on carcinomas of the breast. Some unexpected hypotheses have been obtained that were found rather interesting by the doctor; they were then additionally investigated by different statistical methods. A paper [53] describing this is in final stages of preparation. Second, Hájek visited Florida State University at Tallahassee, invited by prof. Bandler and paid by a COBASE short term grant; even if his main activity was developing fuzzy logic with Prof. Kohout and processing environmental data by GUHA with Dr. Stabile (Kohout's wife), he additionally processed Dr. Stabile's set of data on ectopic pregnancies and its diagnosis using various markers. Many runs were made and Dr. Stabile found the results interesting enough for preparation of an article for a medical journal: [21] is a short report on the results obtained. Our third medical application, concerning Italian data on AIDS, has still not been brought to an end; we made first a set of GUHA runs, sent the results to Dr. Pezzotti and invited him to come and discuss them; but apparently due to lack of time he still has not come. We hope to bring this application to a conclusion later. A report on the present state of processing is contained in [116].

A fourth medical application concerning epileptic patients was presented at a EuroMISE Conference "Information, Health and Education" at Prague (October 1995) [137]. Furthermore, GUHA has been successfully applied to psychological data (on health care for medical students, [107].

Collaboration between Professor Richards and Dr. Lubicz resulted in the latter collecting data which was subsequently processed by the team in Manchester using GUHA and also the software package CLUSTAN. Lubicz collected demographic, socio-economic, and clinical data on some 1500 patients, and 350 variables were recorded on each patient (data set for 1994). The results revealed new associations between the variables and gave to the hospital information which will be valuable for budgeting, man-power planning and for clinical guidance. Full details can be found in the report [71].

Additional series of computer experiments using GUHA software have been performed in Wrocław for larger sets of data on patients with lung cancer and other pulmonary diseases. The experiments were carried out on data bases collected in 1995 in Wrocław (approx. 10000 admissions) and Bristol (approx. 8000 FCEs). The research aimed at identifying relationships between patient management features (length of stay, cost) and selected clinical and socio-economical variables, as well as internal relationships among wards, and patients with specific clinical features (small cell versus non-small cell lung cancer). Full details can be found in [70, 71].

(3) Cooperation of IIIA (CSIC), ICS (AS CR), and Charles University, concerning development and applications of expert systems on MILORD II language and CRACTES.

A prototype of a diagnosis support system on Oncology, built upon MILORD II language, was developed and it is currently running. This prototype is a result of the collaboration of the three teams. The IIIA provided MILORD II, and installed it at ICS and the EUROMISE Center in Prague for research and training purposes, explaining its capabilities in a seminar. The knowledge base for the prototype was provided by the team of Prof. Topolčan from the Charles University, Medical Faculty at Plzeň (Pilsen). The knowledge engineers that built the prototype are from IIIA and from ICS. The prototype also made use of a probabilistic module containing a Bayesian network about tumor markers provided by Dr. Pecen of ICS (author of CRACTES system). The collaboration was realised by several fruitfull visits and also by e-mail.

(4) Cooperation of the Technical University of Wroclaw and Wroclaw Chest Hospital with Charles University testing of CORE and E.T. programs

The program E.T. (Epidemiology Tools program) has been tested in Poland for epidemiological data analysis and for education. Moreover the sample of data gathered at the Wroclaw Chest Hospital was transferred to Prague and the tools developed in the program CORE were used for testing of the program CORE on Polish data. There was also research cooperation in transferring the knowledge gathered in the field of information theory in Polish and Czech scientific schools.

(5) Cooperation of Institute of Information and Automation, Academy of Sciences, Charles Universtity and Wroclaw Hospital in testing programs PME and OM

The program PME developed at the Institute of Information and Automation was tested on data gathered at the First Faculty of Medicine, Charles University, in Prague.

Furthermore, the efficiency of the PME and OM methodology was tested on the following data:

1.
   - Domain: *Cardiovascular diseases*
   - Size: 6 variables, 1000 cases
   - Source: Prof. Reinisch, IV. Internal Clinic, I. Faculty of Medicine, Charles University, Czech Republic
2.
   - Domain: *Rheumatology*
   - Size: 4 diagnoses, 34 variables, 1089 cases
   - Source: Prof. Rejholec, IV. Internal Clinic, I. Faculty of Medicine, Charles University, Czech Republic
3.
   - Domain: *Tuberculosis*
   - Size: 111 variables, 370 patients
   - Source: Dr. Marek Lubicz, Lower Silesian Centre for TB & Pulmonary Diseases, Wroclaw Chest Hospital, Poland

Models were tested with the help of a professional expert system called HUGIN that was developed by Jensen, Lauritzen in Aalborg, Denmark.

(6) Testing of the program HYPERTENSION developed at Charles University on real cases from Czech general practitioners and clinicians.

For the purpose of its quick penetration into medical practice in the Czech republic the program was developed in the Czech language. For this reason it cannot be directly used in medical practice in other countries. However, the ideas of this program were communicated to other MUM partners on joint meetings as well as being introduced in conferences, workshops and publications presented in English. The program was also used as a teaching tool in different courses.

(7) Medical data and knowledge collection.

Fulfilling the aims of the project we collected and used a large data set from the longitudinal study of atherosclerosis as well as several small medical data sets. The idea of the longitudinal study is described in the report of Tomečková et.al and Zvárová et.al. [123, 124]. During the project we have been transferring data of men with risk factors of atherosclerosis stored in paper form at the Second internal clinics, First Faculty of Medicine, Charles University, Prague into a computer format. The longitudinal study started in 1974 and therefore data have been collected for more than 15 years already on 1417 men. New data have been collected also during the duration of the project. This work was very time consuming due to the data analysis and problems with verification of the data using logical and statistical tools to find incorrect or misclassified data. We have prepared the transformation of all data stored in paper questionnaires using program EPIINFO. Finally, after cleaning the data, we could use the data for newly developed software, E.T. [135, 128, 127, 136, 133] and CORE [139, 131, 142, 135, 141]. From small medical data sets we mention the data on epilepsy patients analyzed by GUHA methods [138, 141]. Other medical data and knowledge was collected at the Second Internal Department, First Faculty of Medicine, Charles University for the program HYPERTENSION [136, 102, 104, 103, 132] and at in the Intensive Care Unit and the Cardio - thoracic Unit in the First Faculty of Medicine, Prague.

(8) Cooperation of Wrocław and Manchester in data acquisition and analysis using PROFILES, GUHA, and CLUSTAN.

(a) Hospital data bases from Wrocław, Poland. There is a system of unified databases on hospital treatment/patient management processes in 1994-1996: WR94-WR96 are sets of yearly databases on ALL patients admitted in a year, each consisting of 9 files: PACJENT (admissions), POBYT (FCEs), ROZPOZNA (ICD codes), PAC-xxx where xxx stands for DIAGnostic procedures, LABoratory tests, OPERations etc. At present there are verified data on (approx.) 20,000 admissions of 10,000 persons, stored as 300,000 records of relational databases (80,000 records are personal data, the rest - patient management data), but only about 30% of 1996 data has been processed as yet; WR - is a set of specialised data bases, concerning: ICU activity (5,000 records), Operation theatres activity (80,000 records), histological diagnoses etc. (30,000 records). These data have also been processed at UMIST cf [71, 120].

(b) In-patient databases from Bristol, England. The databases describing hospital treatment processes in hospitals related to Bristol and District Health Authority (currently Avon Health) have been extracted from the general regional PAS of the SWRHA. The data have been reprocessed and files compatible with Polish databases from Wrocław have been created (PACJENT, POBYT, ROZPOZNA, PAC-OPER only). There are three sets of source databases: one for 1992-1993 in-patients only with diagnoses corresponding to those treated by the hospital in Wrocław (35,000 records), one for all in-patients in the first half of 1994 (55,000 records), one for pulmonary medicine&surgery in-patients in 1994-1996 (40,000 records, not finally processed as yet); all of them have been reprocessed to create BR92-BR96 sets of databases (corresponding to Polish files). There are also additional databases with economical data (approximate indicative prices per case for each speciality at each hospital site under each provider).

Sample results for Wrocław databases: Those are presented in HSC report [98].

Sample results for Bristol databases: Those are presented in HSC report [87].

Part E. Educational aspects of the Project.

The transfer of research knowledge was realized in the international Medical Informatics courses (1995, 1996) and Medical Statistics and Epidemiology course (1995). In these courses programs E.T., CORE were used and methodologies in information theory approach, discriminant analysis, regression analysis and survival analysis were presented. A further program HYPERTENSION was presented in courses for Czech physicians [132, 133]. Programs HYPERTENSION and E.T. are also used in pre-graduate and post-graduate education at Charles University. RENOIR (an expert system for rheumatology built on MLORD II system) was used in a seminar of MUM at the EuroMISE Center.

The European Center for Medical Informatics, Statistics and Epidemiology of Charles University and Academy of Sciences has been established as the joint department where the Institute of Computer Science is the representative of the Academy of Sciences and the Faculty of Mathematics and Physics is the representative for Charles University. It was one of the tasks of the MUM project. The report [143] about the EuroMISE Center establishment was prepared and the Center was ceremonially opened at the occasion of the EuroMISE Working Conference in May, 1994. The EuroMISE Center has been responsible for the preparation of conferences e.g. EuroMISE 94 in Harrachov [126] and EuroMISE 95 in Prague [134] on the international level, as well as some workshops at the national level in the field of Medical Informatics and Health Telematics, Prague, November 1996 [134], MEFA, Brno, November 1996 [144]. Further the EuroMISE Center was involved in the transfer of research knowledge through its educational and training activities. Besides, several pre-graduate and post-graduate students have worked on the problems of MUM under the guidance of members of MUM team (Gunn, Švejda, Nguyen and others).

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