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EXPERT SYSTEM FOR HUMAN GENETIC STRUCTURE IDENTIFICATION

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Abstract

The human genetic structure identification (antigens detection) is very important process for the sake of its contribution to the adoption of transplatation of donor organs.
The whole procedure based on laboratory testings and huge mathematical work are fairly complicated. During the procedure many decisions are done through heuristic reasoning mechanism.
The part of this procedure namely **HLA** scoring is automatized employing expert system.
Throught friendly interface two most important informations are delivered:

a) possible **HLA** specificities of a serum
b) new testing suggestions for a serum

Keywords: **HLA** scoring, **HLA** antigens, **HLA** specificities, expert system

Introduction

The systematic study of **HLA** (human leukocyte antigens) characteristics has made an important contribution to the adoption of transplatation of donor organs as a rational component of clinical therapy.
It was already known from the fundamental animal experiments (Medawar 1946) that immunological procesess are responsible for rejection of transplants and that the antigen structures recognized by the recipient as foreign are to be found not only on the transplant itself, but also on other nucleated cells such as leukocytes.
Corresponding observations were made in man (Dausset 1954). It was

discovered that after blood transfusions antibodies to leukocytes develop react selectively with cells of individual donors.
The first antigen specifity was identified, named **HL-A2**. V.Rood and Payne found that antibodies are detectable in the sera of pregnant women which agglutinate the leukocytes of the husband and other, non-related persons. Up to present day antibody containg sera from multiparous and polytransfused donors have remained the important reagents for determination of **HLA** characteristics. Leukocytes from blood continue to yield the obtainable test cells. For this reason the nomenclature "transplatation antigens" has been displaced by "human leukocyte antigens". For determination of the **HLA** specificities monospecific antisera are required, i.e., antisera which under the conditions of the procedure react with only one specificity. Such sera are obtained from:

a) pregnant primi- and multiparous women
b) transfused patients

For the sake of great number of antigens (more than 100) and their issue in different combinations, correspondingly great number of tests have to be done on each serum of unknown structure, if that structure is to be identified effectively.
The microscopic readings of reactions coming out from cytotoxic tests on Terasaki test plates are done. Readings are done throught 72 fields (or more) on Terasaki test plate. Numbers of these plates form "test batery" as shown in figure 1.

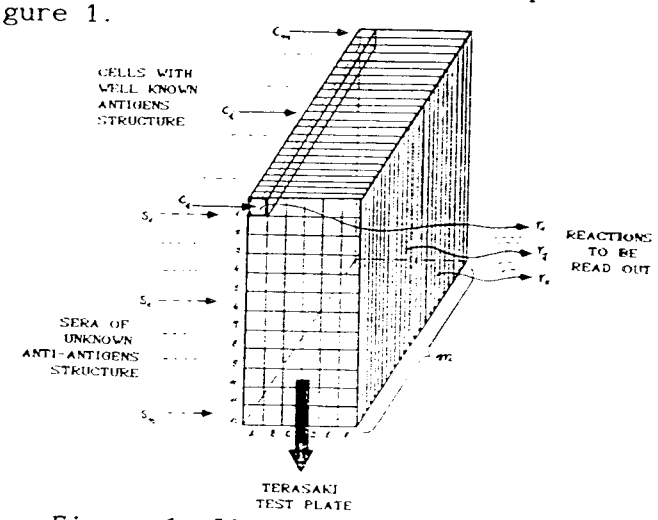

Figure 1. Ilustration of "test batery"

Next step is the determination of correlation coefficients between positive reactions of sera and the currently existing antigens. This computation involves great number of tiresome and time consuming mathematical operations.
Based on these accountings heuristic knowledge must be used for succesful interpretation of obtained data if accurance in determination of unknown anti-antigens structure of a sera is to be adopted.
For these reasons, we decided to automatize those accountings and decision makings coming out from these data by using appropriate expert system.

Expert system

The concept of antigens detection can be consider as identification process because the object model is final goal that can be reached throught experimental design. This is the case when it is necessary to design such an experiment that the obtained data should make

it possible to select the best model among a given set of competing ones and to determine its parameters at that.
The method we proposed in antigens detection is very similar to well known game called "Master Mind", but now expert system "plays the game" using data from files or from direct input.
Structure of experiment design used in forming our expert system is shown in figure 2.

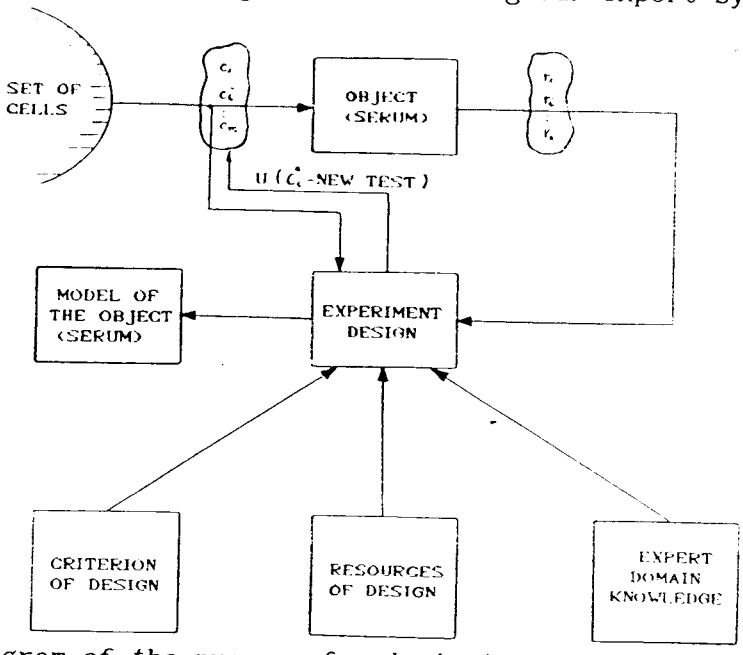

Figure 2. Diagram of the process for designing experiments with object

Structure of expert system is accomplished taking in consideration the whole scenario of process of antigens detection and automatization basic tasks.
Hierarchic structure of expert system is shown in figure 4.

Two levels, depending on knowledge of antigens detection process can be seen.

At first level ES acquires data, makes intelligent interpretation of data (see figure 3.) forming temporary knowledge base, and carries out basic computation and analyse.
Model of problem solving strategy, we introduced at this level, can be expressed as classification model.

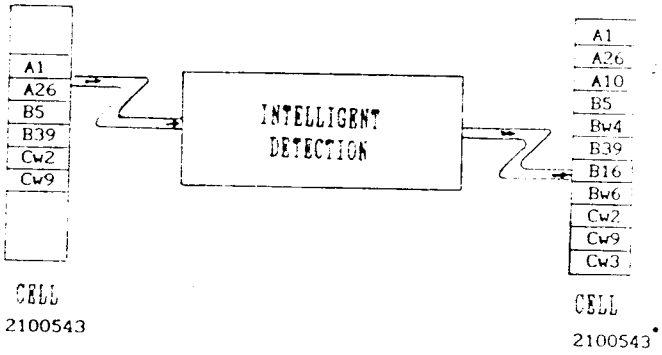

Figure 3. Intelligent interpretation of input data

Output (see figure 5.) from this expert subsystem transfer data to expert system at second level and/or to user.

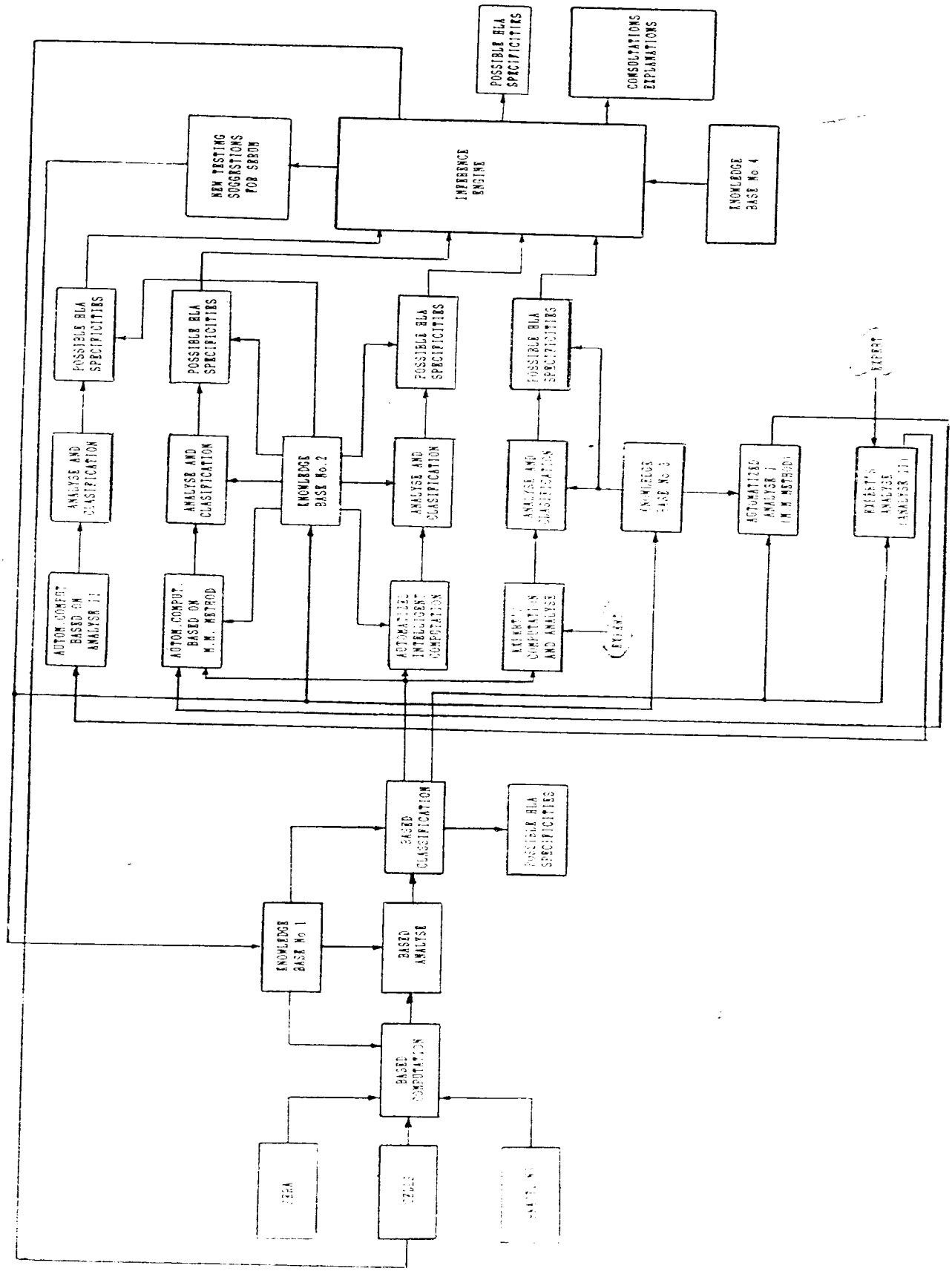

Figure 4. Expert system structure

TEST BATERY No.: T-117
SERUM CODE: 9300064

DATUM OF COMPUTATION: 28-03-1993
TEST PLATE POSITION: A1

BLA SCORING

TOTAL NUMBER OF CELLS USED IN TESTING: 72

N O T E: REACTIONS BORDERS: 8 6 4 -4 -6 -8

AG	NUMBER OF CELLS WITH AG	INCLUSION INDEX	TOTAL NUMBER (+8)(+4)	STRENGHT INDEX	A ++	B +-	C -+	D --	CORRELATION COEFFICIENT	CHI-SQUARE (A*B*C*D)
A2	7	100	6 1	85	7	0	8	57	.639	29.3
A1	3	100	3 0	100	3	0	12	57	.406	11.8
B17	3	100	2 0	66	3	0	12	57	.406	11.8
B8	3	66	0 0	0	2	1	13	56	.235	3.97
A28	4	50	2 0	100	2	2	13	55	.174	2.17
B16	5	40	2 0	100	2	3	13	54	.128	1.17
Bw22	3	33	1 0	100	1	2	14	55	.064	.29
B38	3	33	1 0	100	1	2	14	55	.064	.29
Bw4	10	22	3 0	75	4	14	11	43	.019	.02
B15	5	20	1 0	100	1	4	14	53	-.006	0
A24	1	0	0 0	999	0	1	15	56	-.061	.26

Figure 5. Obtainable date at first level of analyse

Fundamental tasks for expert system at second level is to check results of basic analyse, if necessary, and to solve the problem of ambigous results using heuristic reasoning throught Master Mind method (see figure 6.).

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DATUM OF COMPUTATION: 28-03-1993
TEST PLATE POSITION: A1

SECOND LEVEL OF BLA SCORING M.M. METHOD

AG	NUMBER OF CELLS WITH AG	INCLUSION INDEX	TOTAL NUMBER (+8)(+4)	STRENGHT INDEX	A ++	B +-	C -+	D --	CORRELATION COEFFICIENT	CHI-SQUARE (A*B*C*D)
K11	16	93	11 1	73	13	1	0	56	.959	66.2
K7	13	100	11 1	84	13	0	2	57	.915	63.2
K8	13	92	9 1	75	12	1	3	56	.826	49.1
K9	13	92	9 1	66	12	1	3	56	.826	49.1
K1	10	100	9 1	90	10	0	5	57	.782	44
K2	10	100	8 1	80	10	0	5	57	.782	44
K3	10	90	8 1	66	9	1	6	56	.693	33.5
K10	9	88	7 0	62	8	1	7	56	.639	28.8
K4	8	100	7 0	82	8	0	9	57	.557	24.6
K5	8	83	6 0	66	7	1	10	56	.484	15.5
K6	8	83	6 0	40	7	1	10	56	.484	15.5

POSSIBLE SPECIFICITIES OF A SERUM
Combination of antigens with correlation coefficient greater than .85

Combination	Correlation coefficient
K11	.959
K7	.915

RESULT
Combination of antigens A2 A1 B17 B8 is deduced like the most possible specifity of the serum in position A1

EXPLANATION
M.M. method was used

Figure 6. Obtainable data at second level of analyse

At second level we adopted combination of blackboard model and classification ones as problem solving strategy.

At third level inference engine compares results from the first two levels and deliver the best possible result, i.e. the most probably anti-antigens structure of unknown sera. Also, in the case of still ambigous results user is adviced how to perform new experiment (test), i.e. expert system proposes antigens structure of cells to be used in next experiment (test).

"The game Master Mind in Master Mind can be played again."

Conclusion

In this paper we described an expert system that plays main role in the automatization of the process of antigens detection. Expert system design involves elements of control theory.

Domain knowledge is presented through production rules and implemented through classification model.

Problem solving strategies, classification model and its combination with blackboard model, are chosen.

We suggested new concept of antigens detection through method called Master Mind.

The automatizated process of **HLA** scoring we have been created can be used in futher research in field of immunology and can be regarded as powerful help to aim of **HLA** serology - the selection of compatible organ donors.

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