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Application of Case-based Reasoning in Biomedical Research

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ABSTRACT

This paper describes the development of Case-Based Reasoning system intended to help doctors make a decision (diagnosis) based on biochemical tests and a complete blood count. A brief description of Case-Based Reasoning method and its main steps, known as R4 circle is given. Short analysis of available software CBR systems and platforms is presented. It is oriented to selection of appropriate software platform supporting the functionalities of current biomedical CBR system.

Keywords: Case-Based Reasoning, Analysis of CBR Systems, Biomedical CBR Systems.

INTRODUCTION

The study presents the application of Case-Based Reasoning methodology in biomedical researches. The Case-Based Reasoning (CBR) is a branch of artificial intelligence. It is based on human experience and the fact that similar problems (cases) have similar solutions. The CBR method [1] is oriented towards automation of reasoning based on cases. When a new problem (case) arises, the Case database is searched for the closest similar cases that have been solved in the past. If the new case coincides with an existing one in the database, then the solution of the old case is used to solve the new one. If there are no matches, then the decisions of the nearest cases are adapted to solve the new one, as the database is updated with the new case. In case of lack of closeness between the new case and those in the database, an expert solution of the new case is sought and after its validation the new case is added to the database. Case-based reasoning is a set of concepts [2] and techniques that relate to key issues, such as presenting knowledge, reasoning, and learning from experience. Software systems based on CBR method, initially, are widely used in solving problems in medical diagnostics and legal interpretation, and subsequently in virtually all areas where there is no need for a broad and complex formalization of the problems. One of the advantages of CBR-systems is that they can work in many areas where there are little known

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cases, without the need to extract a model of the field. Such a CBR-system can be created with a small amount of case and in the process of its work to develop gradually by adding new case to the Case Base database.

Description of CBR Reasoning Mechanism

The stages of reasoning in CBR systems, based on cases, are known as classical R4 cycle. Cases are the main objects in CBR systems. Each case represents expert knowledge of a solved problem in a specific domain. The case can be represented either as a free text, containing a list of question and answers, or as a structural type when the case is represented as a record or object in the reasoning database (Case Base).

All structural cases are described as a pair of problem-solution [1]. The problem $\mathbf{p_i} = (\mathbf{a_i}, \mathbf{v_i})$ is organized as a structure of attributes and values, described by the attribute vector $\mathbf{a_i} = (\mathbf{a_{i1}}, \mathbf{a_{i2}}, \ldots, \mathbf{a_{ir}})$ and the value vector $\mathbf{v_i} = (\mathbf{v_{i1}}, \mathbf{v_{i2}}, \ldots, \mathbf{v_{ir}})$. The solution $\mathbf{s_i}$ can be represented in the same way by number of solution attributes and their values $\mathbf{s_i} = (\mathbf{s_{i1}}, \mathbf{s_{i2}}, \ldots, \mathbf{s_{iq}})$.

For solving an actual problem, the following 4 main tasks of CBR R4 cycle are iteratively performed (Fig. 1) [1 - 3]:

Retrieve - process of extraction of one (nearest neighbor) or a group of cases (k-nearest neighbors) having closest definition to the current problem. The global similarity between the problems of these cases (the new $\mathbf{p_{new}}$ and the one in the case base $\mathbf{p_j}$) is presented by the following expression:

$$\mathrm{sim}(p_{new}, p_j) = \sum_{i=1}^{n} w_i \mathrm{sim}_i(p_{newi}, p_j), \text{ and } \sum_{i=1}^{n} w_i = 1$$

where $\mathbf{w_i}$ is the weight of i-th attribute $0 \le w_i \le 1$ and $\mathrm{sim}(p_{newi}, p_{ji})$ is the local similarity between i-th attributes of the cases.

For global similarity measure the following metrics are most used: weighted Euclidian distance, Manhattan's metric, Humming's metric, Tversky's metric, Tchebishev's metric, and

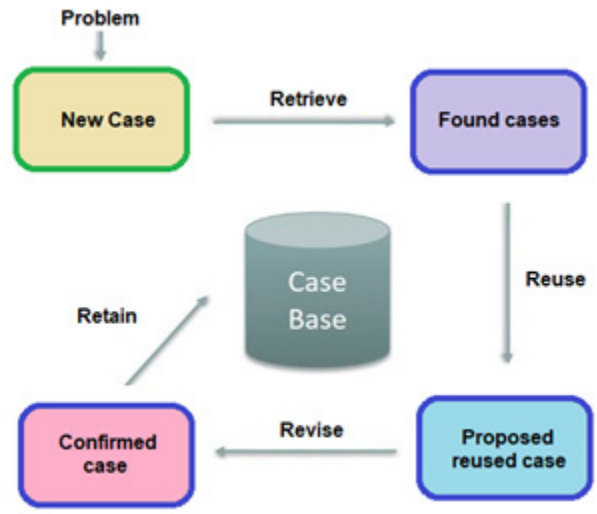

Fig. 1. Classical Case-Based Reasoning R4 circle.

minimum or maximum metrics, etc.

Reuse - reuse of the solutions of chosen in the first step one or k-nearest neighbors.

- When only one nearest case is chosen, the solution of the new problem $\mathbf{s_{new}}$ will be the solution of the chosen case $\mathbf{s_{NN}}$.
- When k-nearest neighbors are chosen, the solution of the new case is calculated on the base of adaptation of k-nearest neighbors' solutions or a part of them.

Revise - validate new solution made on the Reuse stage. This validation and test is mostly done by an expert or it is made based on simulation researches if there is a mathematical model available.

Retain - saving (retaining) the new solution (learned case) in the Case Base for future use, if it is successful.

Analysis of CBR Systems and Platforms

In our previous studies [4 - 7] a comparative analysis of most popular CBR software systems and platforms (jCOLIBRI, myCBR 3Workbench, CBR-Works 4.3.0 and myCBR ver. 2.6.6) has been done. The conclusions about their advantages and disadvantages can be summarised as:

- The software platforms, myCBR 2.6.6

[8](part of the ontology Protégé editor [9]) and myCBR 3 [10] use an incomplete R4 cycle and are therefore not suitable for more complex CBR applications. There are no interfaces for connection to both external databases and external systems. Knowledge and time for application programming are not required to develop a CBR application. It is only necessary to configure the cases. One of the disadvantages of myCBR is that they are not oriented to work with text-type attributes and cases.

- jCOLIBRI [11] and CBR Works 4.3.0 [12, 13] implement a complete R4 cycle and have interfaces to various external databases. The use of jCOLIBRI requires excellent knowledge not only in the specific field of the developed CBR application, but also in programming. The creation of a CBR application in jCOLIBRI is a time-consuming and resource-intensive process related to defining the software requirements, database configuration, programming of the processes and the graphical interface, testing, configuration and verification of the developed software. Because CBR Works 4.3.0 is a final product (executable file), its integration into other systems is not possible.
- CBR Works 4.3.0 and jCOLIBRI can be used to develop both simple and complex CBR applications. The development of complex applications presupposes expert knowledge, not only in the field of artificial intelligence, but also in-depth knowledge in the specific subject area, in order to be able to formulate the rules for adaptation of precedents. Both versions of myCBR 3 are applicable to relatively simple, non-complex CBR applications with an incomplete R4 CBR cycle that have a small number of cases with a small number of attributes. No special knowledge is required to work with these platforms, except for those in the specific subject area.
- The graphical interfaces of CBR Works and jCOLIBRI have better functionality and capabilities for modelling and retrieving cases compared to the same versions of MyCBR.
- CBR Works has better case filtering capabilities than both versions of MyCBR. Navigating in its graphical interface among the extracted cases is better than in myCBR.
- CBR Works and jCOLIBRI support work with external databases, as well as import and export of cases, rules and functions for proximity to and from external databases.
- All platforms subject to benchmarking, with the exception of jCOLIBRI, have a drawback in working with text-type attributes that contain large amounts of information, especially in the visualization of extracted precedents. For this reason, they are not convenient when working with cases in which the solution to the problem is associated with long texts or prescriptions of actions. Creating and integrating applications with attributes of the above type could be done with jCOLIBRI, but it requires good programming skills and a lot of time to implement and test the code.
- Notwithstanding all the above, all analyzed platforms can be used to develop CBR systems for diagnostics in the field of biomedicine, which have precedents with a small number of attributes (up to 10 - 20). With a larger number of attributes, the visualization of the same involves multiple scrolls up and down the screen in order to analyze them.

Some of the mentioned systems (myCBR 3 and myCBR ver.2.6.6) are used in our researches in the field of predictive diagnostics and maintenance of technological [14 - 16] and metallurgical [17 - 20] units, biological wastewater treatment [21], for forming of extracurricular activities of the students [22], etc.

SELECTION AND DEVELOPMENT OF A CBR SYSTEM IN BIOMEDICAL RESEARCH

Based on the results of the comparative analysis of the non-specialized CBR systems and the specialized ones oriented to solving problems

in biomedicine [23 - 25] and medicine [25 - 28], a CBR platform was selected for diagnosis of patients using information for their complete blood count and biochemistry tests. The myCBR platform ver. 2.6.6 turned out to be the most suitable for this purpose. It provides excellent graphical interface and the ability to modify and adjust the attributes of cases, both in terms of adding and removing attributes and in terms of modifying the data type of an attribute, as well as the range of values of given attribute (maximum and minimum values). Another advantage is the ease of adding or excluding attributes to whether they describe the problem or solution of a case, as well as reconfiguring the similarity functions and the weight of a particular attribute.

Parameters of complete blood count and biochemical tests

Tables 1 and 2 show in tabular form the main parameters of complete blood count and biochemical tests that affect the diagnosis of a patient and which are introduced and used in the myCBR platform.

Table 1. Parameters of the complete blood count.

Name	Designation	Reference values
Hemoglobin	HGB	110-160 g L^{-1}
Hematocrit	HCT	0.370-0.540
Erythrocytes	RBC	3.50-5.50 10*12/l
Leukocytes	WBC	4.0-10.0 10*9/l
Carbon dioxide content	PCO_2	35.0-45.0 mm Hg
Oxygen content	PO_2	80.0-100.0 mm Hg

Table 2. Parameters of biochemical tests.

Name	Designation	Reference values
Transaminases	ALT	34.0-45.0 U/L
Transaminases	AST	31.0-35.0 U/L
Glucose	Glu-G	3.90-6.40 mmol L^{-1}
Creatinine	CREA-S	58.0-97.0 mmol L^{-1}
Urea	UREA	2.80-7.20 mmol L^{-1}
Lactate dehydrogenase	LDH	<=248.8 U/L
Cholesterol	TC	<=5.20 mol L^{-1}
Total protein	T-bil-D	2.00-21.00 mmol L^{-1}

Examples of complete blood count and biochemistry test

Patient 1

Name	Reference values
Complete blood count parameters:	
Hemoglobin (HGB) - 121 g L^{-1}	110 - 160 g L^{-1}
Hematocrit (HCT) - 0.383	0.370 - 0.540
Erythrocytes(RBC) - 4.45 .10*12/l	3.50 - 5.50 10*12/l
Leukocytes (WBC) 2.4 .10*9/l	4.0 - 10.0 10*9/l
Parameters of biochemistry:	
Transaminases 15.2U/L	34.0 - 45.0 U/L
Transaminases AST - 11.6 U/L	31.0 - 35.0 U/L
Glucose (Glu-G) - 7.39 mmol L^{-1}	3.90 - 6.40 mmol L^{-1}
Conclusion: It cannot be said that the patient has a disease compared to the low values of leukocytes and transaminases. The other parameters are normal	

Patient 2

Name	Reference values
Complete blood count parameters:	
Hemoglobin (HGB) - 107 g L^{-1}	110 - 160 g L^{-1}
Hematocrit (HCT) - 0.347	0.370 - 0.540
Erythrocytes(RBC) - 3.96.10*12/l	3.50 - 5.50 10*12/l
Leukocytes (WBC) - 8.8 .10*9/l	4.0 - 10.0 10*9/l
Parameters of biochemistry:	
Transaminases ALT 12.7 U/L	34.0 - 45.0 U/L
Transaminases AST - 12.1 U/L	31.0 - 35.0 U/L
Glucose (Glu-G) - 4.76 mmol L^{-1}	3.90 - 6.40 mmol L^{-1}
Creatinine (CREA-S) - 57.8 mmol L^{-1}	58.0 - 97.0 mmol L^{-1}
Conclusion: Low values indicate that the patient has anemic syndrome.	

Patient 3

Name	Reference values
Complete blood count parameters:	
Hemoglobin (HGB) - 134 g L^{-1}	110 - 160 g L^{-1}
Hematocrit (HCT) - 0.411	0.370 - 0.540
Erythrocytes(RBC) - 4.88.10*12/l	3.50 - 5.50 10*12/l
Leukocytes (WBC) - 14.5.10*9/l	4.0 - 10.0 10*9/l
Parameters of biochemistry:	
Urea (UREA) - 11.3 mmol L^{-1}	2.80 - 7.20 mmol L^{-1}
Glucose (Glu-G) -15.22 mmol L^{-1}	3.90 - 6.40 mmol L^{-1}
Creatinine (CREA-S) - 119.3 mmol L^{-1}	58.0 - 97.0 mmol L^{-1}
Conclusion: Viral infection or inflammatory process. Biochemistry shows that the patient has a kidney problem, it may be compensatory. He/she has hyperglycemia.	

Patient 4

Name	Reference values
Complete blood count parameters:	
Hemoglobin (HGB) - 111 g L^{-1}	110 - 160 g L^{-1}
Hematocrit (HCT) - 0.335	0.370 - 0.540
Erythrocytes(RBC) - 3.86.10*12/l	3.50 - 5.50 10*12/l
Leukocytes (WBC) - 13.7.10*9/l	4.0 - 10.0 10*9/l
Parameters of biochemistry:	
Urea (UREA) - 32.42 mmol L^{-1}	2.80 - 7.20 mmol L^{-1}
Glucose (Glu-G) - 8.63 mmol L^{-1}	3.90 - 6.40 mmol L^{-1}
Creatinine (CREA-S) - 266.7 mmol L^{-1}	58.0 - 97.0 mmol L^{-1}
Transaminases ALT - 22.9 U/L	34.0 - 45.0 U/L
Transaminases AST - 23.6 U/L	31.0 - 35.0 U/L
Conclusion: The patient has an inflammatory process and compared to the high values in biochemistry, he has uremic syndrome.	

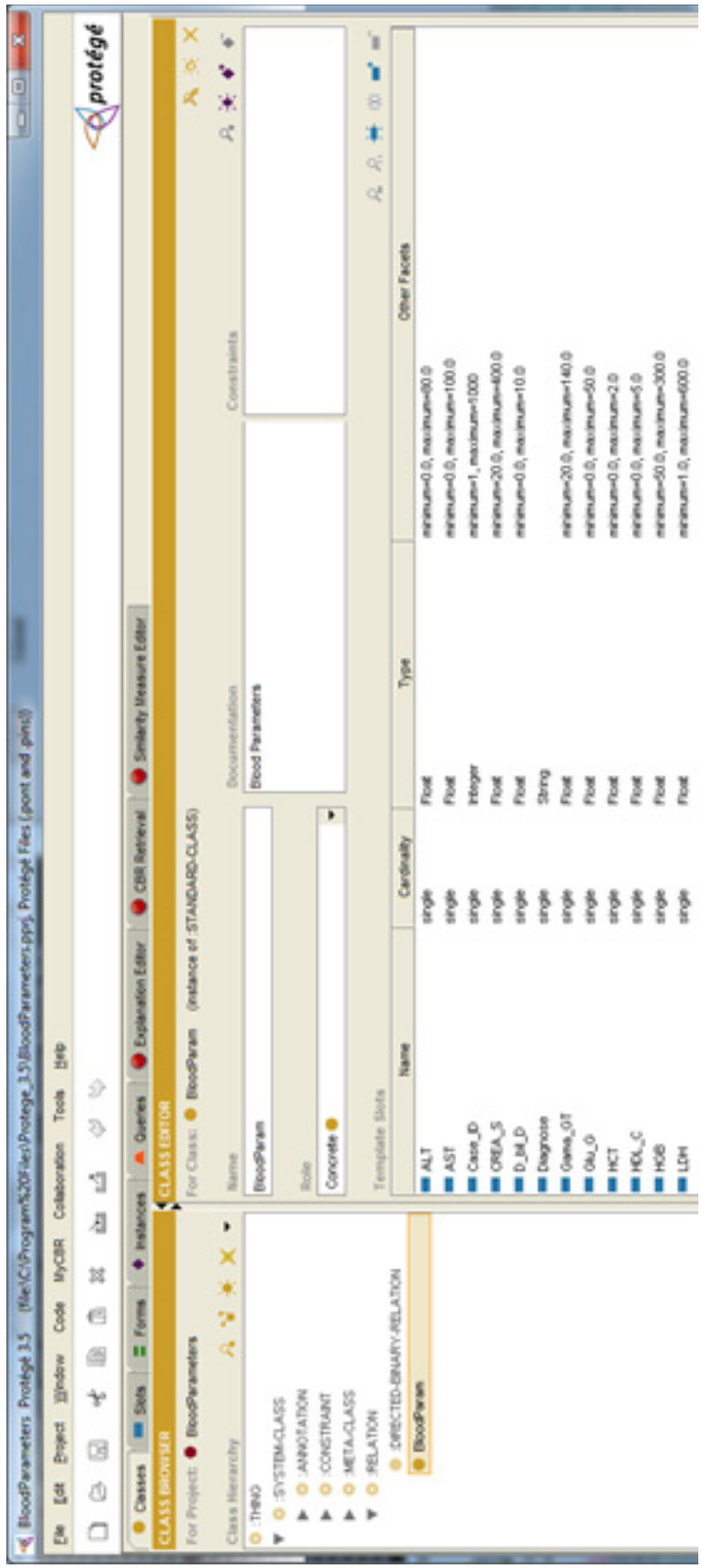

Fig. 2. Attributes (Slots) of the blood picture of a class.

Development of a system for diagnosis of the complete blood count and biochemical tests

The developed system for diagnostics of the blood count and biochemistry tests is implemented as a project Bloodparameters.pprj in the Protégé editor, in which the myCBR platform is integrated. The characteristics of the blood count and biochemistry are described by the following attributes (Slots) given in the right part of Fig. 2. The left part of the figure shows the pre-created class (case type) BloodParam to which the attributes belong. The right panel shows the software types of attributes (Integer, Float and String), as well as their maximum and minimum values.

Details of some of the cases with blood tests and diagnoses (conclusions) are given below. The names of the attributes in the system coincide with the names of the parameters of the blood picture or are close to them, because the system does not allow a hyphen in the name of a given attribute, therefore it is replaced by an underscore. As the actual data for a given patient may be above or below the reference values, the maximum and minimum values are determined after analysis of all studies (cases), including additional extensions of these limits in order to work out situations with new cases, which have larger or smaller values of an attribute, compared to its limit values.

The total number of all cases (cases in Case_Base database) is 50, and each case contains a specific number of blood or biochemical characteristics that may not be exactly the same in the other cases. The Fig. 3 shows the template of the attributes of the class, on the basis of which the individual precedents (blood tests) were subsequently introduced.

The Fig. 4 shows the cases entered (in the middle panel) as well as the specific values of the blood characteristics for the respective test. The name of each case is generated by the MyCBR platform, for example, BloodClass0, BloodClass1 or BloodClass0000, BloodClass 0001 and is specific at each system startup. The far right panel shows that not all attributes have values because, as noted, each study has a specific set of characteristics, but the case template contains all possible ones. In this case, the data for the selected case are shown (the second case at the top of the middle panel).

After entering the cases, the weights of each of them are set, with which they will participate in the subsequent search queries (Retrievals) in the database of precedents. In Fig. 5 higher weights of cholesterol (HCT-2) and hemoglobin (HGB-3) are set, and the weights of the other attributes are the same - 1. The discriminant column specifies (marked in the check box) the attributes describing the problem (all without Case_ID and Diagnose) and the attributes describing the solution (Diagnose). The Case_ID attribute describes the patient number (study) and is used for internal purposes and is not relevant to the solutions proposed by the system when a new case arises.

In the Fig. 6 the setting of a symmetric similarity function of the ALT attribute is shown. The symmetric similarity function means that the similarity search with respect to values less than or greater than the value sought in the request will be of the same weight (linear function), while in the example of Fig. 7, when searching for similarity for the HGB (hemoglobin) attribute, when searching in the direction of a higher value, the nonlinear graphical dependence will be used.

Fig. 8 shows the formation of a query to search for the closest solutions (cases) in the Case-Base database of cases when a new case arises. In this case, the values of the attributes of the new case:- hemoglobin (HGB value 120) and WBC value 2.2 are set (left part of the figure - Query). The search is triggered by pressing the Retrieve button. The retrieval results are given in the middle and right panels. One can see

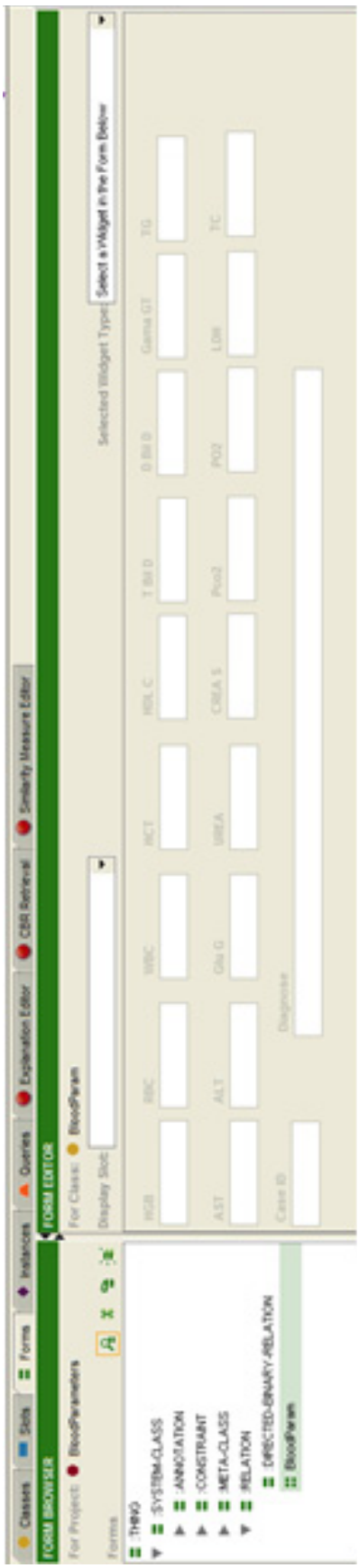

Fig. 3. The template of the class attributes.

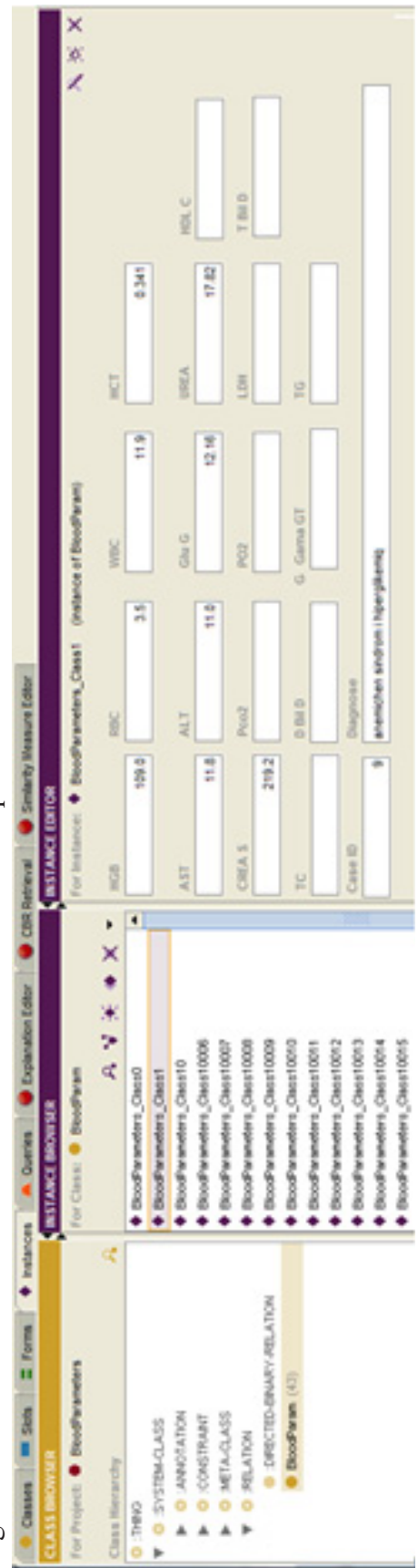

Fig. 4. The cases in the Case-Base database and the data for the specific one.

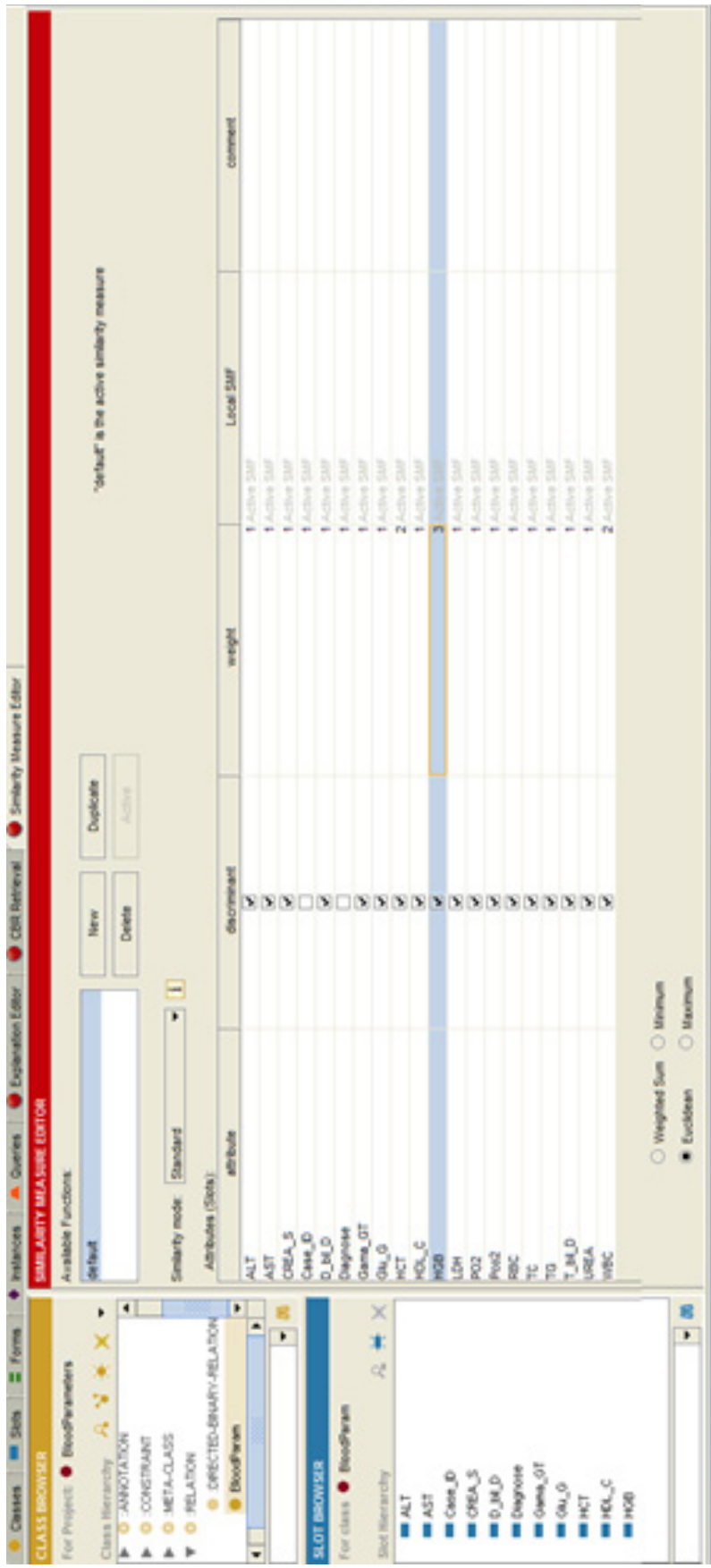

Fig. 5. Entering precedent weights.

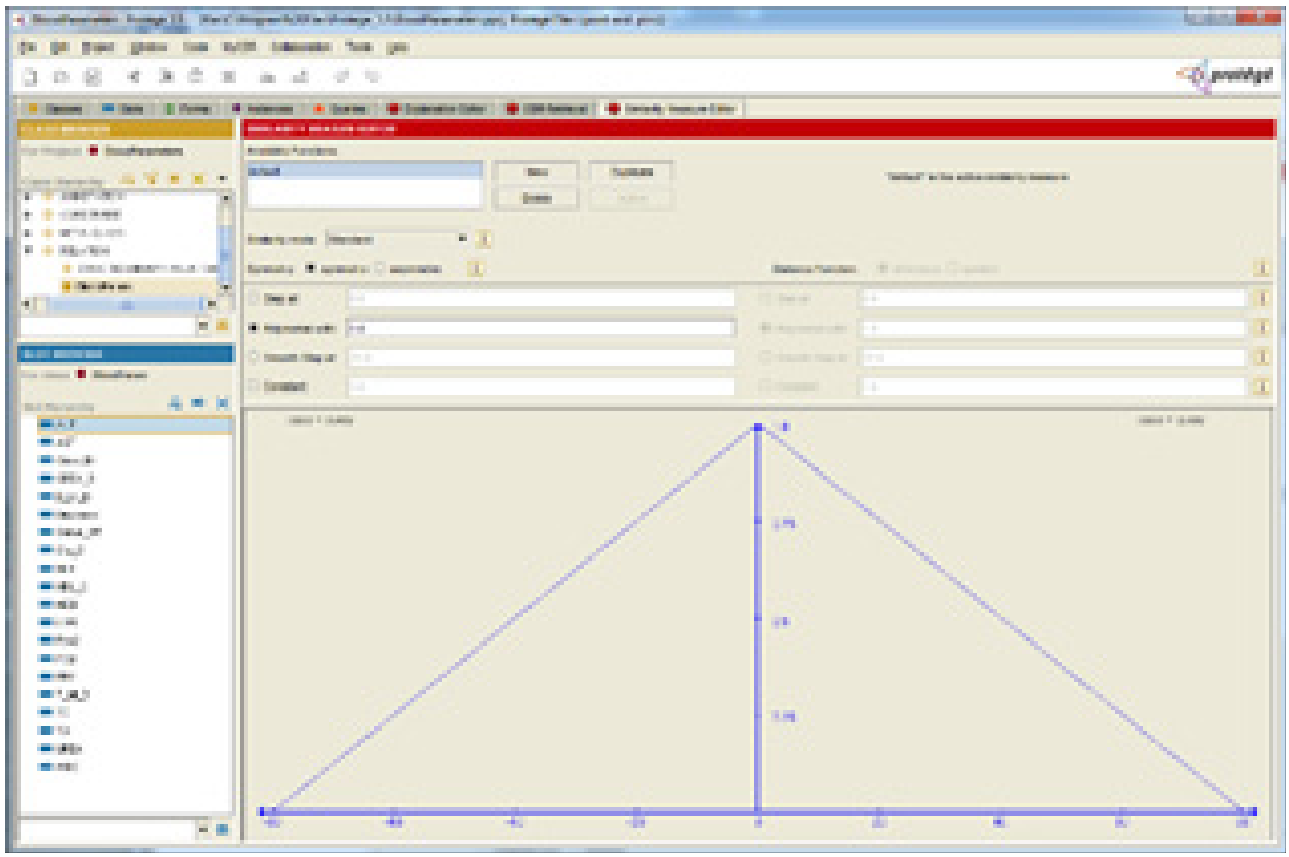

Fig. 6. Setting symmetric function.

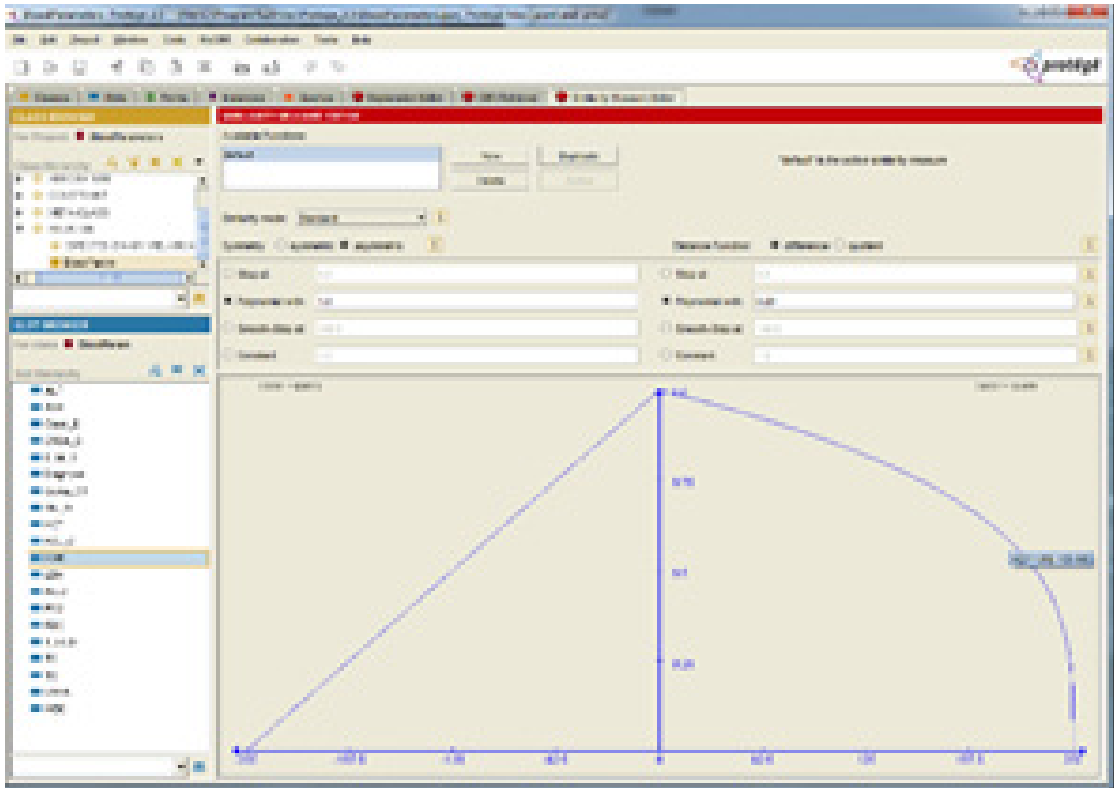

Fig. 7. Setting asymmetric nonlinear function.

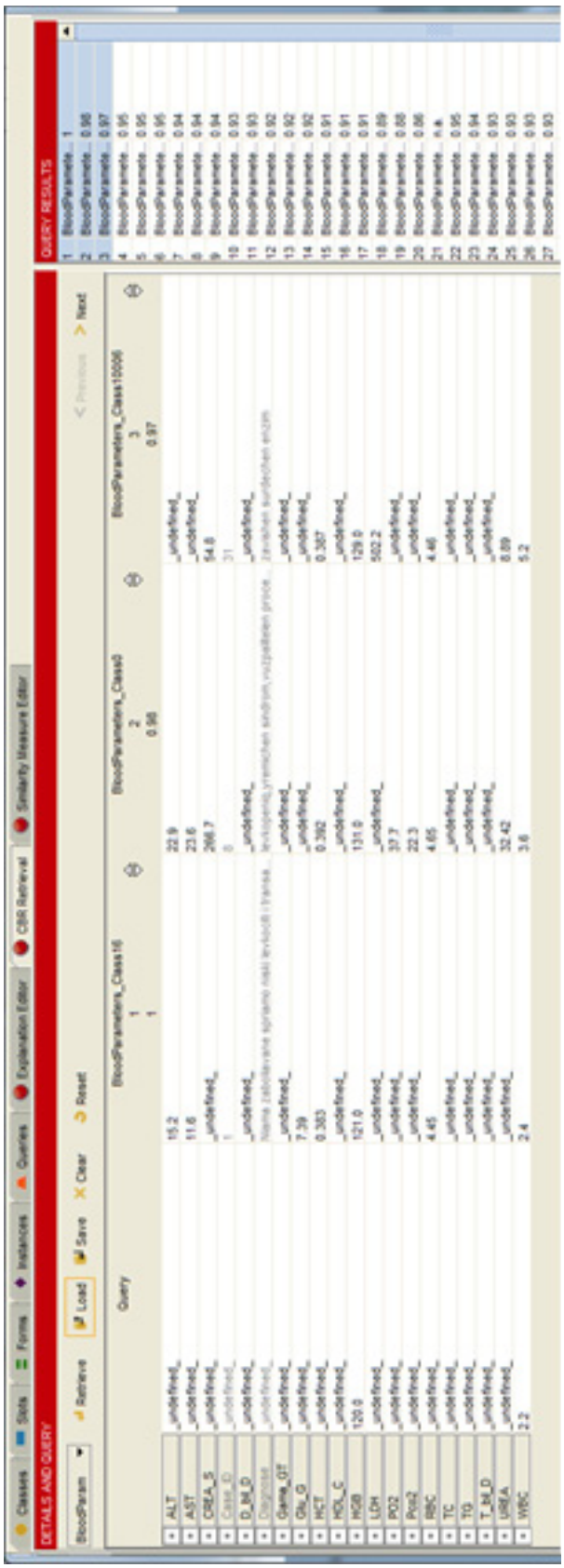

Fig. 8. Sorted precedents with the nearest decisions.

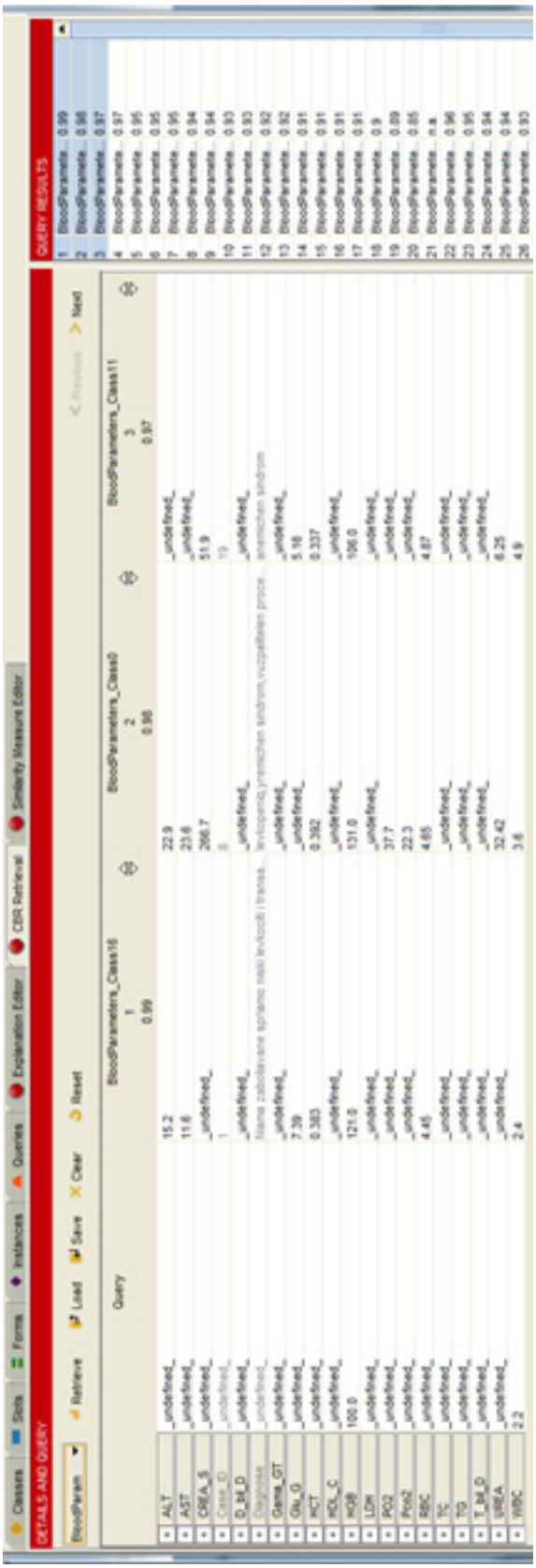

Fig. 9. Modification of the query from the previous search (HGB 100) and new results.

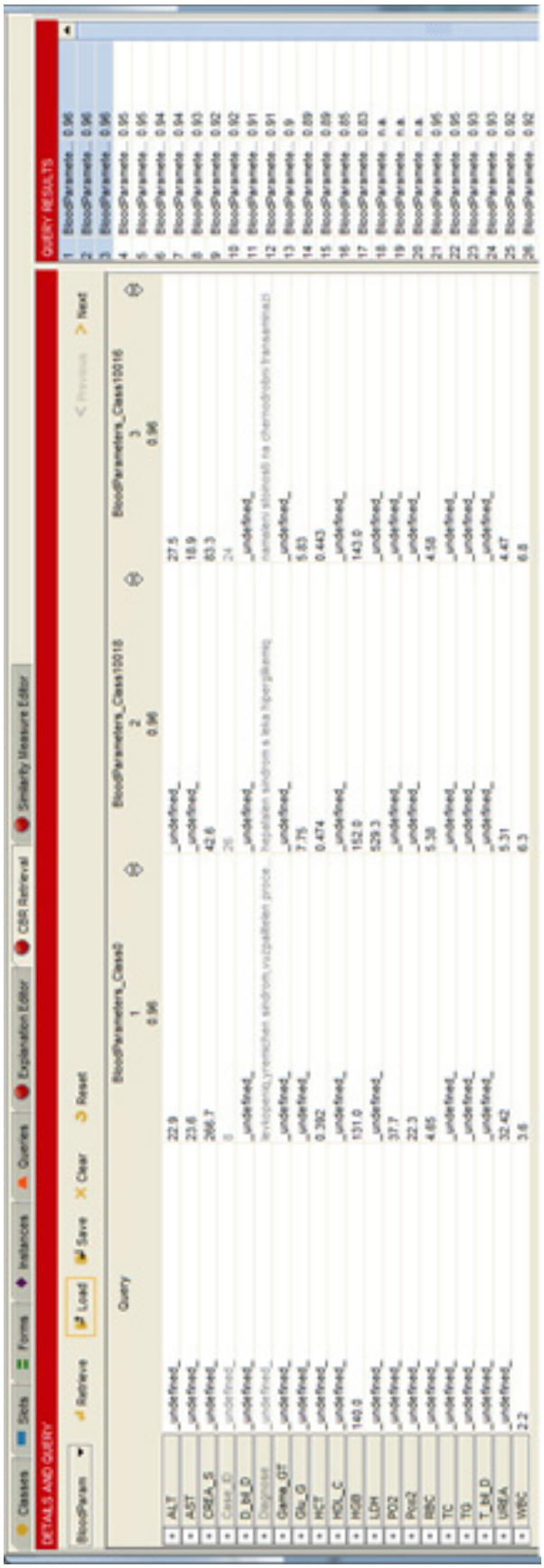

Fig. 10. Modification of the query from the previous search (HGB 140) and new results.

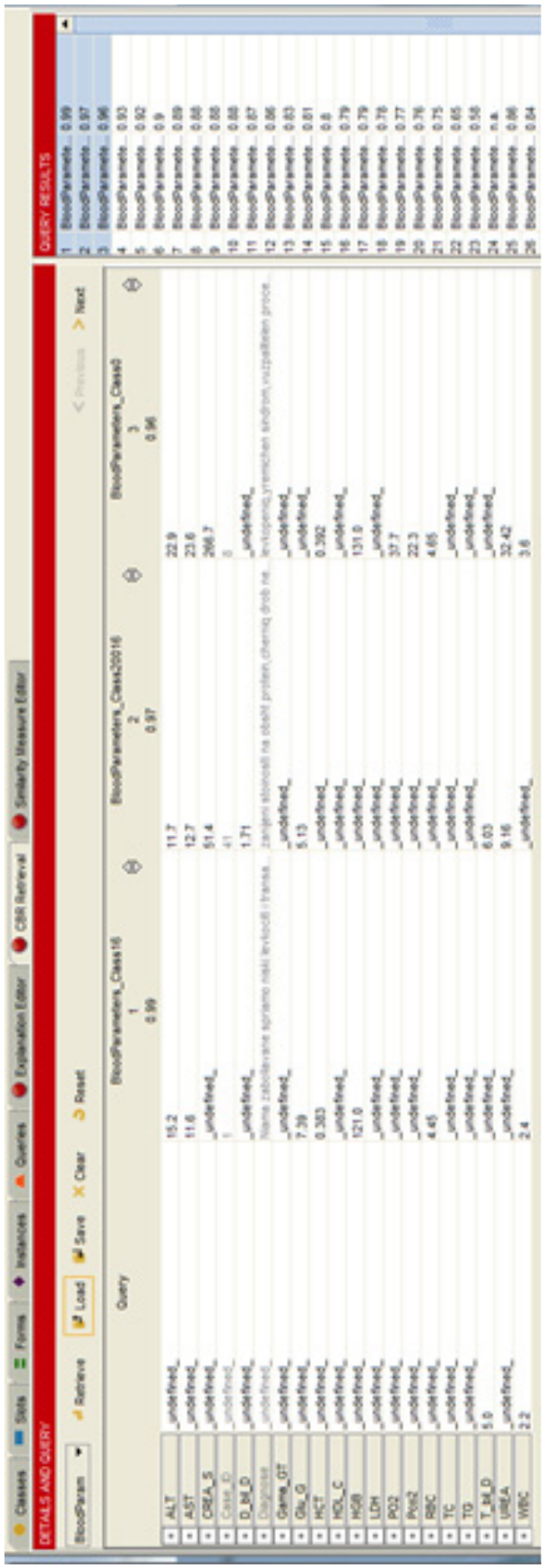

Fig. 11. New query with attributes (T_bil_D 5.0 and WBC 2.2) and new results.

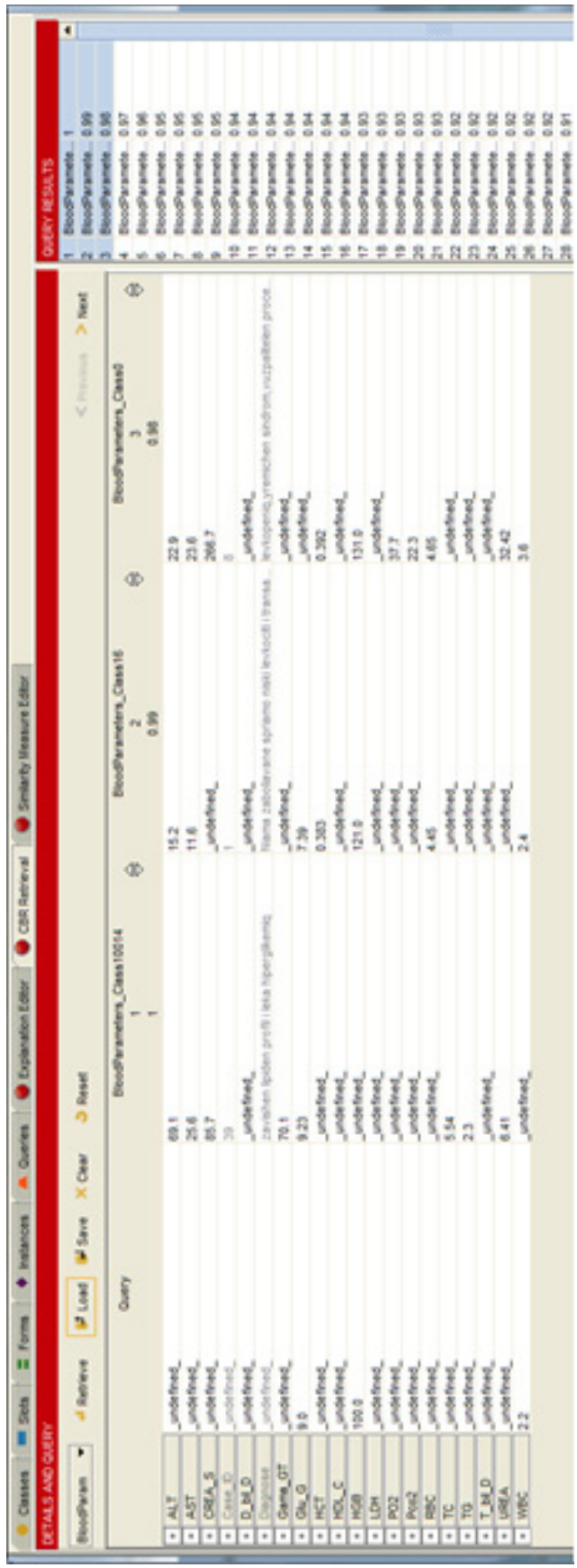

Fig. 12. Modification of the query from the previous search (Glu_G 9.0 and HGB 100.0) and new results.

the values of the closest solutions found in the database of cases. Immediately after the Query (new case) are the first three cases sorted by similarity to it. In the right panel are given all the precedents, sorted by degree of similarity from the nearest to the farthest. In this case, the closest precedents are those with numbers (Case_ID) 1, 8 and 31, which correspond to values of proximity, respectively 100 %, 98 % and 97 %. The final decision, as well as the specification of the other attributes of the search is in the hands of the medical person.

In the next request (Fig. 9) the value of hemoglobin (HGB) is reduced to 100 and now the solutions proposed by the system are related to cases with numbers 1, 8 and 19 from the base with cases and respective proximity 99 %, 98 % and 97 %. And here the decision is in the hands of the competent medical person.

In the next request (Fig. 10) the value of hemoglobin (HGB) is increased to 140 and as a result the solutions proposed by the system are related to cases with numbers 8, 26 and 24 from the Case Base database and a corresponding similarity of 96 % for all detected in the base. And here the decision is in the hands of the competent medical person.

In this new case (Fig. 11) the values of T_bil_D and WBC are set to 5.0 and 2.2, and the solutions proposed by the system are related to cases with numbers 1, 41 and 8 with similarity of 99 %, 97 % and 96 % from the Case Base database.The diagnoses (leukopenia, uremic syndrome, inflammatory process, hepatic syndrome, mild hyperglycaemia) are not a decision of the given disease in relation to the entered values of the parameters. The decision is made by a competent medical person.

In next request (Fig. 12) the valus of Glu_G is set to 9.0 and the values of HGB and WBC are set 100.0 and 2.2. The solutions proposed by the system are related to cases with numbers 39, 1 and 8 with similarity of 100 %, 99 % and 98 % from the Case Base database. Proposed solutions (It cannot be said that the patient has a disease compared to the low values of leukocytes and transaminases; OR leukopenia, uremic syndrome; OR underestimated total protein) are not a final solution of the given disease in relation to the entered values of the parameters. The decision is made by a competent medical person.

CONCLUSIONS

The stages of reasoning in Case-Based Reasoning systems are described. A brief comparative analysis of the existing non-specialized and specialized medical and biomedical CBR systems and platforms has been done.

As a result of the analysis, an appropriate platform was selected for the development of a diagnostic system, which is based on the parameters of the complete blood count and the biochemical tests of the patient.

The developed system uses the myCBR ver. 2.6.6 plugin of the ontological editor Protégé. A Case-Base database with cases has been created, containing parameters (attributes) of the complete blood count and the biochemical tests of 50 patients.

Studies on the operability of the system have been made, generating different requests to solve new cases, using a different number of attributes describing the problem with different weight combinations.

The results obtained, even with a minimum number of attributes of the query, offer solutions with high reliability (95 % - 99 % proximity). The result that the system gives us is not the final decision for the specific case of the patient. The final decision is made by a qualified medical professional.

In any case, the developed system assists physicians in making decisions and diagnoses and can be of great benefit to physicians with little experience.

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