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A process model of diagnostic reasoning in medicine

Jürgen Stausberg *, Michael Person

Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University of Essen, Hufelandstr. 55, D-45122 Essen, Germany

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Abstract

The paper presents a model-based approach to diagnostic reasoning in medicine. A process model is defined on the levels of static elements, dynamic elements and reasoning control. Static elements, facts, hypotheses and different types of disease knowledge, are identified and variations relevant for hypotheses generation are described. Dynamic elements correspond to actions, which in turn modify static elements, but are also controlled and started by the expressions of the static elements. Hypothesis generation starts with the assessment of a given set of facts. According to their priorities, facts are used for the construction of a diagnostic differential: new hypotheses are considered, existing hypothesis refined or excluded. The purpose of hypotheses generation is to establish a complete diagnostic differential with disjunctive explanations which explain a given set of facts. The presented model could serve as a basis for an implementation in a model-based and process-oriented decision-support system. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Diagnostic reasoning is the classical objective of medical expert systems. There are several mechanisms for the generation of hypotheses from patient data: heuristic approaches as part of an expert system, neural networks which are influenced by neurophysiological concepts and model-based approaches based on clinical reasoning. The latter has become increasingly significant since the 1980s due to intensive work on knowledge engineering. In medicine, methodological issues have always been part of scientific debate, however, not as an issue of high priority [1–4]. In the work presented here, the authors aim is to formalize medical-

* Corresponding author. Tel.: +49-201-723-4512; fax: +49-201-723-5933; e-mail: stausberg@uni-essen.de.

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theoretical thoughts about a specific clinical process and to transfer them into an applicable structure. The article focuses on one part of diagnostic reasoning: the generation of hypotheses based on a given set of patient data. Concerning this process, the article demonstrates its complexity and diversity and offers a formal background for implementation.

Two basic assumptions underlie our work:

1. The inference mechanism in a medical knowledge-based system should be part of the knowledge base, representing the knowledge of experts on clinical processes. This might be in contrast to tools like CLASSIKA and PROTÉGÉ-II [5,6] providing inference mechanisms implemented in a shell. Using these tools a knowledge engineer will not be able to represent an approach of clinical reasoning different from the one implemented.
2. A model-based inference mechanism in a computer-aided medical decision-support system leads to better diagnostic results than an algorithm based only on mathematics. Although this hypothesis was not finally proven in the field of computer-aided decision-support, it is the central paradigm of all the work on expert systems.

The motivation for the methods used is described in Section 2. Sections 3–5 include the detailed description of the authors approach which is discussed in Section 6. With Section 3 the relevant sets of data are defined. In Section 4 the functions of the clinical process are introduced and combined in Section 5 to build up the complete process model. Some parts of this work are implemented in a prototype. Their implementations will be described shortly. Medical examples are provided in parentheses like hypothesis (cardiac arrest) as well as presented in a specific paragraph.

2. Methodology of process modeling

The work presented here considers one issue of diagnostic reasoning: the generation of diagnostic hypotheses based on facts. Hypotheses generation is part of diagnostic reasoning being one task within the whole process of medical reasoning. The developed model of hypotheses generation is based on Hucklenbroich's approach [7,8]. Hucklenbroich introduced the KliniC-model as an outline for clinical reasoning and the information and knowledge structures used within. We will refer to the KliniC-model whenever needed for understanding.

Modeling of inference processes is quite different from modeling of knowledge domains. The main task of the latter is to identify entities or objects and their relationships, to assign roles to the entities and relationships and to define access methods in object-oriented approaches. Methodologies for the support of these tasks were developed in projects among which PROTÉGÉ and GAMES-II are well known [6,9]. Inference mechanisms are also part of representation formalisms like belief, causal probabilistic, or hierarchical constraint networks. None of these methodologies provide advice for the modeling of clinical processes because the processes are part of the methodologies themselves. GAMES-II uses the 'Select and Test'-model (ST-model), PROTÉGÉ episodic skeletal-plan refinement and causal probabilistic networks the theorem of Bayes for example. Thus we had to develop a specific modeling approach for clinical processes.

In the following, we will distinguish three levels of clinical processes, the level of static elements, the level of dynamic elements and the control level which combines the dynamic elements to a unique model. Static elements represent variable information and knowledge structures. They could be created, modified and erased by dynamic elements. Dynamic elements correspond to actions, which in turn modify static elements, but are also controlled and started by the expressions of the static elements. These three levels are to some extend comparable with the lower three layers of KADS [10]. The main difference is the specific medical view in our approach.

The first step in our modeling approach is to identify static elements which serve as starting point, intermediate or final result of hypotheses generation. For the static elements relevant variations have to be identified which lead to different scenarios and strategies within hypotheses generation. The second step includes a detailed description of dynamic elements having a distinct and independent function. The variations of the dynamic elements have to be defined as well. Finally the dynamic elements are connected to reach a representation of the whole clinical process.

3. Static elements

3.1. Facts

In our model the starting point of hypotheses generation is a given set of facts. The typical environment in a clinical setting is rather uniform. The patient presents a limited number of complaints to the physician. This information is completed by the first impression of the physician about sex, age, general condition, eating habits, etc. of the patient.

Facts are symbolized by s_1, s_2, s_3,..., s_n, a set of facts by $S = \{s_1,...,s_n\}$. Meaningful constellations of facts are given by $SK \subset S^\infty$ with S^∞ as the power set of S.

The following example clarifies the definition of facts: the anamnesis of a 45-year-old man leads to the facts s_1 = 'left sided heavy pain at the thorax', s_2 = 'age 45' and s_3 = 'male', i.e. a set of facts $S_{\text{example}} \subset S$ with S_{example} = {left sided heavy pain at the thorax, age 45, male}. SK represents all meaningful constellations of facts: SK = {{left sided heavy pain at the thorax}, {age 45}, {male}, {left sided heavy pain at the thorax, age 45}, {left sided heavy pain at the thorax, male}, {male, age 45}, {left sided heavy pain at the thorax, age 45, male}}.

A design-model for medical facts has been developed and prototypically implemented. The model is able to represent all textual data in a computer-based patient record that can be used by knowledge-based systems as well as by information systems. A detailed description of this model is provided in [11]. Medical facts are represented in a frame-like form, the case-data-sheet (see Fig. 1 for an example). With the use of case-data-sheets it is possible to represent simple object-attribute-value-triple as well as complex structures with iterations and multiple attributes of facts. Temporal, local and situation dependent correlations between facts as well as the outline between the patient and the fact are defined as slots. Temporal qualities from facts are represented in a distinct slot to support their complexity and special processing demands. Absolute (date, time) and relative temporal qualities (short time after the pain) can be represented. The existence of an object, attribute or value can be stated explicitly. Information on the relationship between the patient and the object or between objects is represented in the slots *source of cognition*, *causal relations to other facts* and *uncertainty*. The slot *causal relations to other facts* includes relationships between facts that are part of the information. The slot *basic relations* includes relationships between objects which are based on inferences.

object: **pain**
realization: **find out - known**
qualities
    attribute: **localization**, value: **thorax**
    attribute: **localization**
        qualities
            attribute: **side**, value: **left**
temporal qualities
    attribute: **time of onset**, value: **June 22, 1997**
context
    source of cognition: **anamnesis**
    causal relations to other facts
        kind: **accompanied by**, object: **high blood pressure**[1]
    uncertainty:
basic relations
    kind: **caused by**, object: **myocardial infarction**[1]

[1]respectively ID of the referred case-data-sheet

Fig. 1. Case-data-sheet. The names of the slots are presented in normal and the values of the example in bold font.

3.2. Hypotheses

The goal of hypotheses generation is to create unordered hypotheses. Under ideal circumstances the hypotheses can be described as a complete diagnostic differential, which consists of competing explanations for a given set of facts. Every explanation includes a set of hypotheses and every set of hypotheses has to explain all facts. A set of hypotheses is called a disjunction, for example ‘myocardial infarction and renal insufficiency’.

Single hypotheses are symbolized by h_1, h_2, h_3,..., h_n a set of hypotheses by $H = \{h_1,...h_2\}$. Meaningful constellations of hypotheses are given by $HK \subset H^\infty$ with H^∞ as the power set of H. The diagnostic differential is defined by $DD \subseteq HK$. The diagnostic differential denotes a special HK which is constructed by hypotheses generation.

The hypotheses h_1 = ‘myocardial infarction’ and h_2 = ‘hypertensive crisis’ for example result in a set of hypotheses $H_{\text{example}} \subset H$ with $H_{\text{example}} = \{$myocardial infarction, hypertensive crisis$\}$. The set of meaningful constellations of hypotheses is $HK = \{\{$myocardial infarction$\}$, $\{$hypertensive crisis$\}$, $\{$myocardial infarction, hypertensive crisis$\}\}$. The diagnostic differential includes elements of HK.

3.3. Disease knowledge

The dynamic elements of hypotheses generation use different types of knowledge to establish diagnostic hypotheses from data of a patient. Depending on the purpose of the dynamic elements only relevant parts of the disease knowledge are utilized. In comparison with the information structures (facts and hypotheses), the different types of disease knowledge are more closely related to the process of diagnostic reasoning. Thus it is not possible to model disease knowledge independent from the process model of diagnostic reasoning and vice versa. The diagnostic strategy of physicians is dependent and based on disease knowledge as well as the knowledge is developed to support specific dynamic elements.

Some types of nosological knowledge are more important in certain forms of hypotheses generation than other types. This includes knowledge of signs, symptoms and findings (symptomatological knowledge), knowledge of clinical profiles of diseases and knowledge of causal relationships between symptomatological entities and clinical profiles of diseases (pathophysiological and pathoanatomical knowledge).

W symbolizes the set of all disease knowledge. The set of symptomatological knowledge (lists of possible causes of symptoms, for example ‘possible diagnoses of left sided heavy pain at the thorax are myocardial infarction as well as hypertensive crisis’) is represented by $W^{\mathrm{S}} \subset W$, the set of pathophysiological and pathoanatomical knowledge (for example ‘the heart is mostly located in the left part of the thorax so that pain in this region is often caused by heart diseases’) by $W^{\mathrm{P}} \subset W$, the set of clinical profiles of diseases (descriptions of diseases, for example ‘myocardial infarction leads to left sided heavy pain at the thorax and is typically by male which are in a middle age’) by $W^{\mathrm{C}} \subset W$ and the set of general knowledge by $W^{\mathrm{G}} \subset W$.

A first description of the design-model of disease knowledge and some remarks on the implementation are provided in [12]. The so called pathological states are represented in clusters of object-attribute-value-triple. Pathological states refer to an abstraction of entities such as signs, symptoms, findings, clinical profiles of diseases, etc. This abstraction is motivated by the non-existence of an exact distinction between symptomatological knowledge and clinical profiles of diseases (Is hypertension a disease or a finding?). The classification of pathological states in these categories has to be carried out according to the point of view and circumstances. One criterion for that differentiation might be the complexity of a pathological state.

Furthermore, our mind treats syndromes in the same way as pathological states in contrast to other approaches which construct syndromes to some kind of inference called abstraction, for example in case of the ST-model [13]. Syndromes, considered as sets of symptoms (Homer’s syndrome) or diseases (Down’s syndrome), represent one level of complexity between symptoms and clinical profiles of diseases in our model. Therefore, syndromes must not be considered separately in diagnostic reasoning. They could be treated like facts or disease profiles. As one consequence from the introduction of pathological states a common model of disease knowledge is reached. This refers to a common taxonomy of signs, symptoms, findings and clinical profiles of diseases. We can say that $W^{\mathrm{S}} \cap W^{\mathrm{C}} \neq \emptyset$.

3.4. Concepts

The combination of the introduced static elements (facts, hypotheses and disease knowledge) requires a common definition of the used terminology [14]. Standardization means the unambiguous definition of the used concepts, their denominations and relationships. We developed a data dictionary for the management of the used medical terminology [15]. This data dictionary serves as a link between the different modules: facts (cf. Section 3.1) in a computer-based patient record and disease knowledge (cf. Section 3.3) in a knowledge base.

The frame-oriented representation of the data dictionary defines several properties (slots) of terms. Examples of properties are denomination, hierarchic relationships (generalization, specialization) as well as the declaration of attributes and values.

To use this data dictionary in a terminology server a relational database model was developed, which yields a very flexible definition of concepts and supports a cooperative authoring of the terminological content. The basic idea of this approach is an elementary unit term. Term contains all terminological structures, independent from its exact denomination, for example a number, a word or a statement like 'left sided heavy pain of the thorax'. Terms could be related through link types, defined as terms in the same way. Any combination of terms and links could be used as a term. This representation of medical terminology facilitates the expression of facts and disease knowledge according to the presented models.

4. Dynamic elements

4.1. Need for action

Patient treatment starts or continues if there is a need for action, either diagnostic, therapeutic or preventive. This need for action determines the beginning of diagnostic reasoning as well as the end of clinical treatment. The end of diagnostic reasoning depends not alone on the explanation of all facts, which corresponds to a complete diagnostic differential. Just imagine a patient with an end-stage carcinoma. An unexplained symptom might be irrelevant because there is neither a diagnostic nor a therapeutic consequence. On the other hand it might be possible that facts (for example weight), which are not by itself pathological, are misinterpreted by the patient. In that case the misinterpretation of the patient is another fact that leads to clinical reasoning.

Definition 1. *The need for action for a constellation of facts* sk_i is tested by the function

$f_{action}\ SK \otimes (W^S \cup W^P \cup W^C)$

$\rightarrow \{0, 1\}$ with $f_{action}(sk_i, w_j) =$

- 1, if w_j implies that there is need for action for facts of sk_i
- 0, if w_j implies that there is no need for action for facts of sk_i

Definition 2. *The set of facts with need for action* $SK^+ \subseteq SK$ and the set of facts without need for action $SK^- \subseteq SK$ are defined by

$$SK^+ = \{sk_i / \exists\, sk_i \in SK: f_{action}(sk_i, w_j) = 1, w_j \in (W^S \cup W^P \cup W^C)\}$$

$$SK^- = \{sk_i / \exists\, sk_i \in SK: f_{action}(sk_i, w_j) = 0, w_j \in (W^S \cup W^P \cup W^C)\}$$

Usually, a constellation of facts including one pathological symptom, e.g. $sk_i = \{$left sided heavy pain at the thorax$\} \in SK$, is sufficient to define SK as SK^+.

4.2. Identification of unusual facts

New facts, which should be explained, have to be identified. These facts can be abnormal or pathological parameters (for example fever, hemoglobin concentration = 7 g/l). They are called unusual facts. We have to mention that the term abnormal is quite difficult to define. Demographic data such as age and sex are regarded as facts that have not to be explained. These facts are called ordinary facts.

Definition 3. *The need of explanation for a fact* s_i is tested by the function $f_{explanation}$: $S \otimes (W^S \cup W^G) \rightarrow \{0, 1\}$

- 1, if w_j implies that there is need of explanation for fact s_i
- 0. if w_j implies that there is no need of explanation for fact s_i

Definition 4. *The set of unusual facts* $S^+ \subseteq S$ and the set of ordinary facts $S^- \subseteq S$ are defined by

$$S^+ = \{s_i / \forall s_i \in S: f_{\text{explanation}}(s_i, w_j) = 1, w_j \in (W^S \cup W^G)\}$$

$$S^- = \{s_i / \forall s_i \in S: f_{\text{explanation}}(s_i, w_j) = 0, w_j \in (W^S \cup W^G)\}$$

A given set of facts $S = \{$renal insufficiency, female$\}$ of a female patient for example can be divided into a set of unusual facts and a set of ordinary facts by applying different disease knowledge:

$f_{\text{explanation}}$ (renal insufficiency, renal insufficien cy is a pathological state) $= 1$

$f_{\text{explanation}}$ (female, male and female are possib le values of sex) $= 0$

In this example the set of unusual facts is $S^+ = \{$renal insufficiency$\}$ and the set of ordinary facts is $S^- = \{$female$\}$.

4.3. Definition of priorities

Consider the situation of unusual facts and an empty diagnostic differential, represented by $S^+ \subseteq S$ and $|S^+| > 1$ with $DD = \emptyset$ We have to select one fact, that starts the hypotheses generation and the further ordering of the facts. This assessment is called definition of priorities. The definition of priorities takes into account several criteria. Most important criterion for the generation of diagnostic hypotheses is the heuristic significance of the fact. Facts with a high heuristic significance are called cardinal symptoms. The reason of starting with a cardinal symptom is to find explanations of all unusual facts as quickly as possible. In clinical practice two other criteria have to be considered: the patient's acute risk and his distress. Both criteria are more important for the assessment of the hypotheses than for hypotheses generation. Thus we will concentrate on the heuristic significance.

The heuristic significance combines two requirements. First, the explanations of the cardinal symptom should explain the facts with lower heuristic significance. Second, the diagnostic hypotheses should be as detailed as possible. The predictive value is a parameter for the first requirement. It is calculated by the combination of sensitivity, specificity and prevalence using the theorem of Bayes. It depends strongly on the population on which the values are based. In general, exact values are not known for signs and symptoms. Second, the predictive value of a disease (p(disease/fact)) has to be combined with the diagnostic selectivity of a fact. But there are only qualitative values in symptomatological knowledge to assess the selectivity. Statements like specific or unspecific are being used. Both parameters provide a broad range for the determination of heuristic significance.

Definition 5. *A cardinal fact can be identified by the function*

f_{cardinal}: $S^+ \otimes W^S \rightarrow \{0, 1\}$

with $f_{\text{cardinal}}(s_i^+, w_j) =$

- 1, if w_j implies that s_i^+ is a cardinal symptom
- 0, if w_j implies that s_i^+ is not a cardinal symptom

Definition 6. *The set of cardinal facts* $S^C \subseteq S^+$ is defined by

$$S^C = \{s_i / \forall s_i \in S^+: f_{\text{cardinal}}(s_i, w_k) = 1, w_k \in W^S\}$$

The cardinal fact $s_3 =$ 'left sided heavy pain at the thorax' is identified having the set of facts $S^+ = \{$fear, cold sweat, left sided heavy pain at the thorax$\}$. The set of cardinal facts is defined by $S^C = \{$left sided heavy pain at the thorax$\}$.

4.4. Generation of diagnostic hypotheses for an unusual fact

As a prerequisite for the construction of the diagnostic differential, diagnostic hypotheses have to be generated for each unusual fact. Starting from the top level disease this function queries the lattice of clinical disease profiles. The goal is to derive the most detailed occurrence of the fact as a manifestation of one disease or syndrome. That search in the lattice of clinical disease profiles ends under the following conditions:

- The manifestation of a disease (left sided heavy pain at the thorax as manifestation of myocardial infarction) is identical with the fact (left sided heavy pain at the thorax). The disease is taken as hypothesis for this fact.
- The manifestation of a disease (left sided heavy pain at the thorax as manifestation of myocardial infarction) is more detailed than the fact (pain at the thorax). The disease is taken as hypothesis for this fact.
- The manifestation of a disease (left sided heavy pain at the thorax as manifestation of myocardial infarction) is less detailed than the fact (heavy pain at the upper part of the left side of the thorax) and no further specialization is provided. The disease is taken as hypothesis for this fact.
- There is an explicit remark in a clinical profile (cardiac arrest) that refers to the nonexistence of this fact (high blood pressure).

In case that a pathophysiological condition is being used as hypothesis, the known causes of that condition are used as hypotheses. A simultaneous occurrence of two diseases that are both relevant for the fact is not considered in this dynamic element. Necessary for the outlined process is an ordering of the knowledge about clinical disease profiles based on clinical practice, i.e. the refinement of disease profiles according to the description of their manifestations. A medico-theoretical ordering, for example following epidemiological parameters, may lead to wrong results performing this function.

Definition 7. *Hypotheses for a fact si can be checked by the function*

$$f_{\text{hypothesis}}\colon S \otimes (W^S \cup W^P \cup W^C) \otimes H \rightarrow \{0, 1\}$$

with $f_{\text{hypothesis}}(s_i, w_j, h_l) =$

- 1, if $(f_{\text{explanation}}(s_i, w_k) = 1, w_k \in (W^S \cup W^G)) \wedge (w_j$ implies that h_l is a hypothesis for fact $s_i)$
- 0, if $(f_{\text{explanation}}(s_i, w_k) = 0, w_k \in (W^S \cup W^G)) \vee (w_j$ implies that h_l is a hypothesis for fact $s_i)$

Definition 8. *The set of hypotheses* $H^s \subseteq H$ of the fact $s_i \in S^+$ is defined by

$$\begin{aligned} H^s = \{h_l / \forall h_l \in H\colon & f_{\text{hypothesis}}(s_i, w_x, h_l) \\ &= 1 \vee f_{\text{hypothesis}}(s_i, w_y, h_l) \\ &= 1 \vee f_{\text{hypothesis}}(s_i, w_z, h_l) \\ &= 1, w_x \in W^S, w_y \in W^P, w_z \in W^C\} \end{aligned}$$

This definition allows to find the set of hypotheses for a fact such as $s =$ ‘left sided heavy pain at the thorax’ by analyzing different disease knowledge in the defined sequence. The sequence is used to find the possible hypotheses in the most efficient way, starting from the explicit listing of possible diagnoses for one fact in symptomatological knowledge if available. For example $s=$ 'left sided heavy pain at the thorax', $h=$ 'myocardial infarction' and $w=$ 'a possible cause of left sided heavy pain at the thorax is a myocardial infarction' as an element of W^{S} matches with

$f_{\text{hypothesis}}$ (left sided heavy pain at the thorax, a possible cause of left sided heavy pain at t he thorax is a myocardial infarction, myocar dial infarction) $=1$

In this case the set of hypotheses for the fact s is $H^{S}=\{\text{myocardial infarction}\}$.

4.5. Construction of the diagnostic differential

4.5.1. Adoption of single hypotheses

If the differential is empty, the set of hypotheses H^{s} of the cardinal fact s is transferred to the differential.

Definition 9. *Given a set of cardinal facts* $S^{C}\subseteq S^{+}$ with $/S^{C}/=1$, the set of hypotheses H^{s} for the only fact $s\in S^{C}$ and $DD=\emptyset$ then all elements of H^{s} are transferred to the diagnostic differential as disjunctions

$DD:=\{\{h_{s}\}/\forall h_{s}\in H^{s}\}$

Starting with an empty diagnostic differential, i.e. no unusual facts have been considered, the first given fact such as $s=$ 'left sided heavy pain at the thorax' with its set of hypotheses $H^{s}=\{$myocardial infarction, hypertensive crisis,…$\}$ leads to the following diagnostic differential: $DD=\{\{$myocardial infarction$\}$ $\{$hypertensive crisis$\}\ldots\}$

4.5.2. Assessment whether an unusual fact is well explained

An unusual fact is well explained by a diagnostic differential if each hypothesis of the fact is included adequately in at least one disjunction. The simultaneous occurrence of several explanations for one fact is not considered here. A hypothesis is included adequately in a disjunction if:

- The hypothesis appears in the disjunction.
- One element of the disjunction (heart disease) is a generalization of the hypothesis (myocardial infarction).
- One element of the disjunction (myocardial infarction) is a specialization of the hypothesis (heart disease) and that specialization is compatible with the fact (pain at the thorax).

Definition 10. *Given a set of hypotheses* H^{s} for the fact $s_{i}\in S^{+}$ then a hypothesis $h_{l}\in H^{s}$ is *included adequately* in a disjunction $D_{k}\in DD$

- if $h_{l}\in D_{k}$
- if $h_{m}\in D_{k}$ and h_{m} generalization of h_{l}
- if $h_{m}\in D_{k}$ and h_{m} specialization of h_{l} and h_{m} compatible with s_{i}

Definition 11. *Given a fact* $s_{i}\in S^{+}$ that must be explained, a set of hypotheses H^{s} for the fact s_{i} and $DD\neq\emptyset$, $s_{i}\in S^{+}$ is *well explained* if $\forall\, h_{l}\in H^{s}\ \exists\, D_{k}\in DD: h_{l}$ *is included adequately in* D_{k}

Definition 12. *The set of well explained facts* $S^{E}\subseteq S^{+}$ and the set of not well explained facts $S^{N}\subseteq S^{+}$ are defined by

$$S^{E}=\{s_{i}/\forall s_{i}\in S^{+}: s_{i}\ \textit{is well explained}\}$$

$$S^{N}=\{s_{i}/\forall s_{i}\in S^{+}: s_{i}\ \textit{is not well explained}\}$$

The next example explains this definition. The diagnostic differential includes two disjunctions of a previous fact such as $DD=\{\{$kidney disease$\}$, $\{$heart disease$\}\}$. A new fact $s=$ 'left sided heavy pain at the thorax' with its set of hypotheses $H^{s}=\{$myocardial infarction$\}$ should be checked for membership of the set of well explained facts S^{E}. The fact s is well explained because all hypotheses of s ($h=$ 'myocardial infarction') are included adequately in at least one disjunction of the diagnostic differential DD, i.e. the element of the disjunction $D=$ {heart disease} is a generalization of $h=$ 'myocardial infarction'.

4.5.3. Combination of hypotheses

In case that a hypothesis of a fact is not included adequately in the diagnostic differential, that hypothesis is added to each disjunction of the differential.

Definition 13. *The diagnostic differential* $DD \neq \emptyset$ is combined with the set of hypotheses H^s of the fact $s_i \in S^N$ by

f_1: $DD \otimes H^s \rightarrow DD$

with $f_1(D_i, h_j) =$

- $D_i \cup \{h_j\}$, if h_j is not included adequately in DD
- D_i, if h_j is included adequately in DD

A fact such as $s=$ 'renal insufficiency' with its set of hypotheses $H^s=$ {heart disease, glomerulonephritis} is an element of the set of not well explained facts if the existing diagnostic differential looks like $DD=$ {{myocardial infarction}, {hypertensive crisis}}. In this situation the defined combination of hypotheses leads to the new diagnostic differential $DD=$ {{myocardial infarction, glomerulonephritis}, {hypertensive crisis, glomerulonephritis}}.

4.5.4. Refinement of disjunctions I

A refinement of disjunctions is carried out if hypotheses h_m (heart disease) of a disjunction (heart disease and renal insufficiency) in the diagnostic differential is a generalization of the explanation $h_l \in H^s$ (myocardial infarction) of a new fact $s_i \in S^+$. In case that all previously considered facts $s_n \in S^+$ (cold sweat) and $s_m \in S^-$ (male) which are compatible with h_m, are also compatible with h_l, h_l replaces h_m in the disjunction.

Definition 14a. *The diagnostic differential* $DD \neq \emptyset$ is refined by

f_{2a}:$S \otimes W^C \otimes DD \otimes H^s \rightarrow DD$

with f_{2a} $(s_i, w_j, D_k, h_l) =$

- $(D_k/h_m) \cup \{h_l\}$, if h_l is a specialization of h_m and for all $s_n \in S^+$ Definition 11 is met and h_l is compatible with all $s_m \in S^-$
- D_k, in all other cases

4.5.5. Refinement of disjunctions II

Furthermore a refinement is possible concerning facts s_i (female) $\in S^-$. Let H^h the set of specializations of congenital hemorrhagic diathesis with $H^h=$ {hemophilia A, Willebrandt's syndrome}. In that case the specialization h_l (hemophilia A) replaces an explanation h_m (congenital hemorrhagic diathesis) $\in D_k$, if the previously considered facts $s_n \in S^+$ (nasal bleeding) and $s_m \in S^-$ (age 5), which are compatible with h_m, are also compatible with h_l.

Definition 14b. *The diagnostic differential* $DD \neq \emptyset$ is refined by

f_{2b}: $S \otimes W^C \otimes DD \otimes H^h \rightarrow DD$

with f_{2b} $(s_i, w_j, D_k, h_l) =$

- $(D_k/h_m) \cup \{h_l\}$, if h_l is a specialization of h_m and for all $s_n \in S^+$ Definition 11 is met and h_l is compatible with all $s_m \in S^-$
- D_k, in all other cases

4.5.6. Exclusion of disjunctions

If an element h_l (renal insufficiency) of a disjunction D is not compatible with fact s_k (creatinine clearance $=100$ ml/min) $\in S$ this disjunction is excluded, indicating a contradiction between the fact and the description of the clinical disease's profile. In this dynamic element unusual facts are used as well as ordinary facts.

Definition 15. *Disjunction* $D_i \in DD$ with $h_l \in D_i$ is excluded by

f_3: $DD \otimes W^C \otimes S \rightarrow DD$

with $f_3\ (D_i, w_j, s_k) =$

- DD/D_i, if $h_l \in D_i$ is not compatible with s_k
- DD, if $h_l \in D_i$ is compatible with s_k

5. Scenarios

5.1. Combination of facts and hypotheses

Inference processes in diagnostic reasoning may be characterized by the combination of starting points (i.e. facts) and final results of the hypotheses generation (i.e. the diagnostic differential). Two versions of the diagnostic differential have to be distinguished in view of hypotheses generation: First, absence of any explanation. Thus we can skip the question: 'Is it possible to explain a new fact with existing hypotheses?'

Second, there are some explanations. Also the occurrence of only one fact versus the occurrence of a high number of facts might lead to different strategies of diagnostic reasoning. The search of the cardinal symptom could be skipped in the first situation and is a complex task in the second. Six combinations of facts and the diagnostic differential can be distinguished.

1. A patient who is not known by the physician reports one symptom or a pathological finding is discovered without any complaints. The set of facts which have to be explained S^+ is given by $S^+ \subseteq S$. We have $|S^+| = 1$ with $DD = \emptyset$.
2. A patient under treatment reports a new symptom or a pathological finding is discovered. We have $S^+ \subseteq S$ and $|S^+| = 1$ with $DD \neq \emptyset$.
3. A patient under treatment reports a couple of symptoms to his physician or a couple of new pathological findings is discovered. This represents also a typical clinical situation. We have $S^+ \subseteq S$ and $|S^+| > 1$ with $DD \neq \emptyset$.
4. A patient seeks medical attention with a restricted set of symptoms or pathological findings. We can suggest that this refers to the most usual situation in clinical practice. We have $S^+ \subseteq S$ and $|S^+| > 1$ with $DD \neq \emptyset$.
5. A physician who is asked for his advice receives a detailed clinical report on the condition of a patient. A comparable situation is characterized by a physician, who has to consider the whole circumstances in a difficult diagnostic situation independent from any previous diagnostic hypotheses. We have $S^+ \subseteq S$ and $|S^+| \gg 1$ with $DD = \emptyset$.
6. A large number of new pathological findings, for example laboratory values, are discovered from a patient under treatment. Today, this might be an increasingly common situation. We have $S^+ \subseteq S$ and $|S^+| \gg 1$ with $DD \neq \emptyset$:

Having in mind the implementation in a decision-support system the variety of cases can be restricted to number 3. The cardinal fact is treated according to case 1, other facts according to case 2. Case 3 corresponds to case 4 after the explanation of the cardinal fact. Case 5 and 6 increase the complexity of diagnostic reasoning, but do not have to be distinguished further, given the power of computers to handle these cases.

5.2. Linking with disease knowledge

Linking facts, hypotheses and disease knowledge with their variations establishes two main clinical settings. The first setting is characterized by the existence of unusual facts and missing of any diagnostic hypotheses. We have $S^+ \subseteq S$ and $|S^+| >= 1$ with $DD = \emptyset$. The first inference in that constellation is the determination of the unusual fact (i.e. sign, symptom or finding) from which diagnostic reasoning has to be started. In a second step explanations for that fact are inferred, initially using explicit symptomatological knowledge. If there is no symptomatological knowledge, pathophysiological and pathoanatomical knowledge on causal relationships (anatomical, functional) are considered. Finally explanations need to be searched which refer to the question 'Is there any disease with that fact as a manifestation?' That leads to a search in all clinical profiles of diseases. The last-named inference is to some extend comparable to the logical category abduction, defined by Peirce in the late 19th century for example [16]. Overall, the knowledge is used in the following sequence: symptomatological knowledge; pathophysiological/-anatomical knowledge; and clinical profiles of diseases.

The second clinical setting is characterized by existing diagnostic hypotheses in a clinical situation. We have $S^+ \subseteq S$ and $|S^+| >= 1$ with $DD \neq \emptyset$. Diagnostic reasoning starts along two different lines. On the one hand it is proven whether clinical profiles of existing hypotheses in the diagnostic differential explain a new unusual fact. A new unusual fact is well explained, if there are no unconsidered hypotheses of the fact retrieved from the investigation of symptomatological knowledge. On the other hand an inference mechanism is started comparable to the first clinical setting to identify other relevant diagnostic hypotheses through the use of the other knowledge types.

Two requirements have to be considered linking facts, hypotheses and disease knowledge in a knowledge-based system. The model of facts has to be compatible with the description of manifestations of clinical profiles of diseases. The detailed design models in our work ensure this compatibility. The terminology used has to be standardized or at least transformed. This is provided by the data dictionary approach.

5.3. Reasoning control

Hucklenbroich's model of clinical reasoning [8] consists of a cyclic sequence of the four information structures, facts, hypotheses, indications and actions. Every sequence can lead to a new set of facts with a combination of used and new facts. This set of facts has to be assessed in the first step. he assessment includes the determination whatever action is needed, identification of new facts and the definition of priorities of new unusual facts (Fig. 2). The construction or the modification of the differential starts when this assessment is carried out for all facts.

The following functions of the diagnostic hypotheses generation are performed individually for every fact (Fig. 3). The sequence of unusual facts is determined by their priority. The initial differential consists of the hypotheses of the cardinal symptom. The cardinal symptom is defined by the fact with the highest priority. In the second and the following sequences of Hucklenbroich's cyclic way of reasoning, the cardinal symptom is considered like all others. The other facts are used for the modification of the diagnostic differential.

The criteria of Section 4.5.2 have to be used for every fact to perform the differential modification (Fig. 4). The list of criteria is being used to determine whether a fact is explained by an existing disjunction in the differential. It is not the goal to combine all possible hypotheses. Given a cardinal symptom and the exclusion of two independent causes of one fact, a fact is adequately explained if each possible cause of the fact is included in at least one disjunction of the diagnostic differential. Causes that are not considered in the differential are combined with the existing disjunctions. In that case all

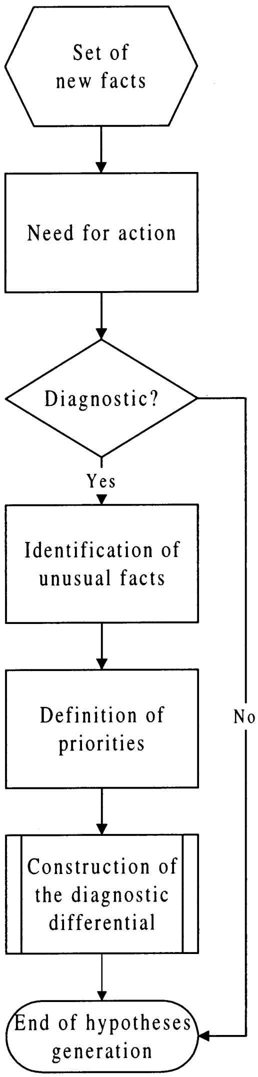

Fig. 2. Beginning of hypotheses generation.

combinations are explicitly used. The hypotheses generation ends if all unusual facts are explained according to Definition 11 and all ordinary facts are used for the refinement and exclusion of disjunctions.

6. Conclusion

Our model of hypotheses generation is based on a clinical view on medical processes. Therefore the model is strongly different to others starting from methodologies of artificial intelligence techniques or philosophical and logical theories. An important influence of the latter on model-based decision support is the introduction of the logical category abduction. For example, abduction is used by Stefanelli's ST-model [13]. But abduction does not mirror clinical practice because strategies based on compiled knowledge are not considered. Furthermore abduction is not sufficient from a computing point of view. So one major advantage of our process model is the consideration of compiled and deep knowledge, i.e. symptomatological and pathopysiological knowledge.

Nevertheless there are some unsolved problems in our approach. The alteration of dynamic elements, which is the aim of evolutionary or genetic algorithms, is beyond this methodology as well as the assessment of competing diagnostic hypotheses. In some of the dynamic elements only parts of solutions are provided: the assessment of the patient's distress and the combination of two causes for one fact for example. A further task will be the differentiation of the relevant elements of our model-based approach for a computational model of diagnostic reasoning. The presented work includes a detailed suggestion. The static elements are implemented successfully yet. In the future the whole cyclic

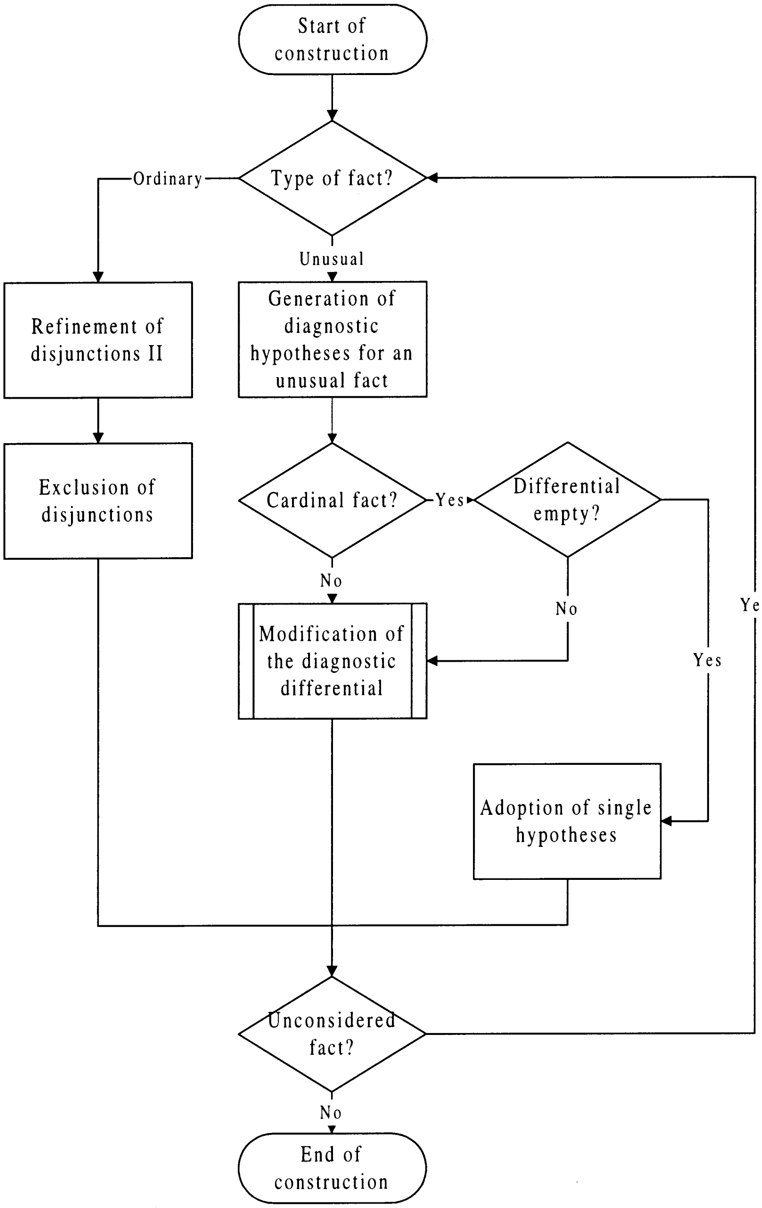

Fig. 3. Construction of the diagnostic differential.

way of reasoning has to be modeled taking into account diagnostic, therapeutic and preventive aspects. The authors assume that this integrative, comprehensive and model-based approach of medical reasoning leads to useful and intuitive decision-support systems to support the physicians needs.

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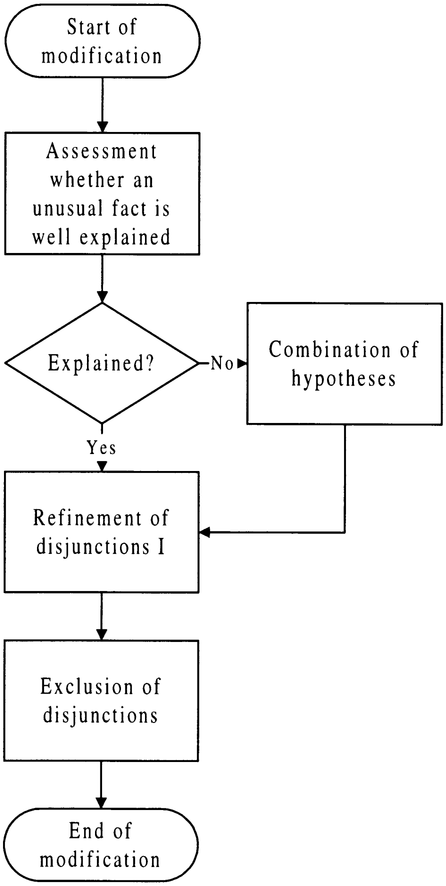

Fig. 4. Modification of the diagnostic differential.

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