Adaptation and Case-Based Reasoning
Focusing on Endocrine Therapy Support

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Abstract
So far, Case-Based Reasoning has not become as successful in medicine as in some
other application domains. One, probably the main reason is the adaptation
problem. In Case-Based Reasoning the adaptation task is still domain dependent
and usually requires specific adaptation rules. Furthermore, in medicine adaptation
is often more difficult than in other domains, because usually more and complex
features have to be considered. We have developed ISOR, a system for endocrine
therapy support, especially for hypothyroidism. In this paper, we do not present
ISOR in detail, but focus on adaptation. We do not only summarise experiences with
adaptation in medicine, but we want to elaborate typical medical adaptation
problems and hope to indicate possibilities how to solve them.

Keywords:
Case-Based Reasoning, Therapy support, Adaptation, Endocrine

1. Introduction
Case-Based Reasoning (CBR) has become a successful technique for knowledge-based
systems in many domains, while in medicine some more problems arise to use this method.
A CBR system has to solve two main tasks [1]: The first one is the retrieval, which is the
search for or the calculation of most similar cases. For this task much research has been
undertaken. The basic retrieval algorithms for indexing [2], Nearest Neighbor match [3],
pre-classification [4] etc. were already developed some years ago and have been improved
in the recent years. So, actually it has become correspondingly easy to find sophisticated
CBR retrieval algorithms adequate for nearly every sort of application problem.

The second task, the adaptation means modifying a solution of a former similar case to fit
for a current problem. If there are no important differences between a current and a similar
case, a solution transfer is sufficient. Sometimes only few substitutions are required, but
usually adaptation is a complicated process. While in the early 90th the focus of the CBR
community lay on retrieval, in the late 90th CBR researchers investigated various aspects
of adaptation. Thouth theories and models for adaptation [e.g. 5, 6] and have been
developed, adaptation is still domain dependent. Usually, for each application specific
adaptation rules have to be generated.

Since adaptation is even more difficult in medicine, we want to elaborate typical medical
adaptation problems and we hope to show possibilities how to solve them.
2. Medical Case-Based Reasoning systems

Though CBR has not been as successful in medicine as in some other domains so far, several medical systems have already been developed which at least apply parts of the Case-Based Reasoning method. Here we do not want to give a review of these systems (for that see [7, 8, 9]), but we intend to show the main developments concerning adaptation in this area.

2.1 Avoiding the adaptation problem

Some systems avoid the adaptation problem. They do not apply the complete CBR method, but only a part of it, namely the retrieval. These systems can be divided into two groups, retrieval-only systems and multi modal reasoning systems. Retrieval-only systems are mainly used for image interpretation, which is mainly a classification task [10]. However, retrieval-only systems are not only used for image interpretation, but also for other visualisation tasks, e.g. for kidney function courses [11] and for hepatitic surgery [12]. Multi modal reasoning systems apply parts of different reasoning methods. From CBR they usually incorporate the retrieval, often to calculate or support evidences [13].

2.2 Solving the adaptation problem

A few medical systems have been developed that apply the complete CBR method. In these systems three main techniques are used for adaptation: adaptation rules, constraints, and compositional adaptation. Furthermore, abstracting from specific single cases to more general prototypical cases sometimes supports adaptation.

Adaptation rules. One of the earliest medical expert systems that use CBR techniques is CASEY [14]. It deals with heart failure diagnosis. The most interesting aspect of CASEY is the ambitious attempt to solve the adaptation task. Since the creation of a complete rule base for adaptation was too time consuming, a few general operators are used to solve the adaptation task. Since many features have to be considered in the heart failure domain and since consequently many differences between cases may occur, not all differences between former similar cases and a query case can be handled by adaptation operators. So, if no similar case can be found or if adaptation fails, CASEY uses a rule-based domain theory.

However, the development of complete adaptation rule bases never became a successful technique to solve the adaptation problem in medical CBR systems, because the bottleneck for rule-based medical expert systems, the knowledge acquisition, occurs again.

Constraints. A more successful adaptation technique is the application of constraints. In ICONS, an antibiotics therapy adviser [15], adaptation is a reduction of recommended therapies for a similar, retrieved case by constraints (contraindications of the query patient).

Another example for applying constraints is GS.52, a diagnostic program concerning dysmorphic syndromes [16]. The retrieval provides a list of dysmorphic syndromes sorted according to their similarity in respect to the query patient. The provided list is checked by a set of explicit constraints. These constraints state that some features of the query patient either contradict or support specific syndromes.

A typical application domain for applying constraints is menu planning [17], where different requirements have to be served: special diets and individual factors, not only personal preferences, but also contraindications and demands based on various complications.

Compositional adaptation. A further successful adaptation technique is compositional adaptation [18]. In TA3-IVF [19], a system to modify in vitro fertilisation treatment plans, relevant similar cases are retrieved and compositional adaptation is used to compute weighted average values for the solution attributes. In TeCoMed [20], an early warning system concerning threatening influenza waves, compositional adaptation is applied on the most similar former courses to decide whether a warning against an influenza wave is appropriate.
Abstraction. Since one reason for the adaptation problem is the extreme specificity of single cases, the generalisation from single cases into abstracted prototypes [16] or classes [21] may support the adaptation. The idea of generating more abstract cases is typical for the medical domain, because (proto-) typical cases directly correspond to (proto-) typical diagnoses or therapies. While in GS.52 all prototypes are organised on the same level, in MNAOMIA [21], a hierarchy of classes, cases, and concepts with few layers is used.

3. Adaptation problems in endocrine therapy support

We have developed ISOR, a system for endocrine therapy support in a children's hospital. Here, we focus on adaptation problems within ISOR to illustrate general adaptation problems in medicine. For technical details of ISOR see [22].

All body functions are regulated by the endocrine system. The endocrine gland produces hormones and secretes them in blood. Hypothyroidism means that a patient's thyroid gland does not produce enough thyroid hormone naturally. If hypothyroidism is undertreated, it may lead to obesity, brachicardia and other heart diseases, memory loss and many other diseases [23]. Furthermore, in children it causes mental and physical retardation. If hypothyroidism is of autoimmune nature, it sometimes occurs in combination with further autoimmune diseases such as diabetes. The diagnosis hypothyroidism can be established by blood tests. The therapy is inevitable: thyroid hormone replacement by levothyroxine. The problem is to determine the therapeutic dose, because the thyroxin demand of a patient follows only very roughly general schema and so the therapy must be individualised [24]. If the dose is too low, hypothyroidism is undertreated. If the dose it too high, the thyroid hormone concentration is also too high, which leads to hyperactive thyroid effects [23, 24].

There are two different tasks of determining an appropriate dose. The first one aims to determine the initial dose, while later on the dose has to be updated continuously during a patient's lifetime. Precise determination of the initial dose is most important for newborn babies with congenital hypothyroidism, because for them every week of proper therapy counts.

3.1 Computing initial doses

For the determination of an initial dose (Fig. 1), a couple of prototypes, called guidelines, exist, which have been defined by commissions of experts. The assignment of a patient to a fitting guideline is obvious because of the way the guidelines have been defined. With the help of these guidelines ranges for good doses can be calculated.

![Figure 1 - Determination of an initial dose](image-url)
To compute an optimal dose, we retrieve similar cases with initial doses within the calculated ranges. Since there are only few attributes and since our case base is rather small, we use Tversky's sequential measure of dissimilarity [25]. On the basis of those of the retrieved cases that had best therapy results an average initial therapy is calculated. Best therapy results can be determined by values of a blood test after two weeks of treatment with the initial dose. The opposite idea to consider cases with bad therapy results does not work here, because bad results may be caused by various reasons.

So, to compute an optimal dose, we apply two forms of adaptation. First, a calculation of ranges according to guidelines and patients attribute values. Secondly, we use compositional adaptation. That means, we take only similar cases with best therapy results into account and calculate the average dose for these cases, which has to be adapted to the query patient by another calculation.

Example. The query patient is a newborn baby that is 20 days old, has a weight of 4 kg and is diagnosed for hypothyroidism. The guideline for babies about 3 weeks age and normal weight recommend a levothyroxine therapy with a daily dose between 12 and 15 μg/kg. Since the baby weighs 4 kg, a range of 48-60 μg is calculated. The retrieval provides similar cases that must have doses within the calculated range. These cases are restricted to those where after two weeks treatment less than 10 μU/ml thyroid stimulating hormone could be observed. Since these remaining similar cases are all treated alike, an average dose per kg is computed which subsequently is multiplied with the query's weight to deliver the optimal daily dose.

3.2 Dose updating in a patient's lifetime

For monitoring the patient, three laboratory blood tests have to be made. Usually the results of these tests correspond to each other. Otherwise, it indicates a more complicated thyroid condition and additional tests are necessary. If the tests show that a patient's thyroid hormone level is normal, it means that the current levothyroxine dose is OK. If the tests indicate that the thyroid hormone level is too low or too high, the current dose has to be increased resp. decreased by 25 or 50 μg [23, 24]. So, for monitoring adaptation is a calculation according to well-known standards.

Example. Figure 2 shows an example of a case study. We compared the decisions of an experienced doctor with the recommendations of ISOR. The decisions are based on the basic laboratory tests and on lists of observed symptoms. Intervals between two visits are approximately six months.

Figure 2 - Dose updates recommended by ISOR compared with doctor's decision. V1 means the first visit, V2 the second visit etc.
In this example there are three deviations, usually there are less. At the second visit (v2), according to laboratory results the levothyroxine should be increased. ISOR recommended a too high increase. The applied adaptation rule was not precise enough. So, we modified it. At visit 10 (v10) the doctor decided to try to decrease the dose. The doctor’s reasons were not included in our knowledge base and since his attempt was not successful, we did not alter any adaptation rule. At visit 21 (v21) the doctor increased the dose because of some minor symptoms of hypothyroidism, which were not included in ISOR’s list of hypothyroidism symptoms. Since the doctors decision was probably right (visit 22), we added these symptoms to the list of hypothyroidism symptoms of ISOR.

3.3 Additional diseases or complications

It often occurs that patients do not only have hypothyroidism, but they suffer from further chronic diseases or complications. So, the levothyroxine therapy has to be checked for contraindications, adverse effects and interactions with additionally existing therapies. Since no alternative is available to replace levothyroxine, if necessary additionally existing therapies have to be modified, substituted, or compensated (Fig. 3) [23, 24]. ISOR performs three tests. The first one checks if another existing therapy is contraindicated to hypothyroidism. This holds only for very few therapies, namely for specific diets like soybean infant formula, which are typical for newborn babies. Such diets have to be modified. Since no exact knowledge is available how to do it, ISOR just issues a warning saying that a modification is necessary. The second test considers adverse effects. There are two ways to deal with them. A further existing therapy has either to be substituted or it has to be compensated by another drug. Since such knowledge is available, we have implemented corresponding rules for substitutional resp. compensational adaptation. The third test checks for interactions between both therapies. Here we have implemented some adaptation rules, which mainly attempt to avoid interactions. For example, if a patient has heartburn problems that are treated with an antacid, a rule for this situation exists that states that levothyroxine should be administered at least 4 hours after or before an antacid. However, if no adaptation rule can solve an interaction problem, the same substitution rules as for adverse effects are applied.

![Figure 3 - Levothyroxine therapy and additionally existing therapies](image)

4. Conclusion: Adaptation techniques for therapeutical problems

In this paper, we firstly reviewed how adaptation is handled in medical CBR systems and secondly enriched the experiences by additional examples from the endocrinology domain, where we have developed a support system. For medical therapy systems, that intend to apply the whole CBR cycle, at present we can summarise useful adaptation techniques. However, most of them are promising only for specific tasks. Abstraction from single cases to more general prototypes is a promising implicit support. However, if the prototypes
correspond to guidelines they can even explicitly solve some adaptation steps (see section 3.1). Compositional adaptation at first glance does not seem to appropriate in medicine, because it was originally developed for configuration [18]. However, it has been successfully applied for calculating doses (e.g. in TA3-IVF [19] and see section 3.1).

Constraints are a promising adaptation technique too, but only for a specific situation (see section 2.2), namely for a set of solutions that can be reduced by checking e.g. contraindications (in ICONS) or contradictions (in GS.52).

Adaptation rules. The only technique that seems to be general enough to solve many medical adaptation problems is the application of adaptation rules or operators. Unfortunately, the technique is general, but the content of such rules has to be domain specific. Especially for complex medical tasks the generation of adaptation rules often is too time consuming and sometimes even impossible. For therapeutic tasks some typical forms of adaptation rules can be made out, namely for substitutional and compensational adaptation (e.g. section 3.3), and for calculating doses (e.g. section 3.2).

5. References