Integrating model-based decision support in a multi-modal reasoning system for managing type 1 diabetic patients

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Received 15 January 2002; received in revised form 4 December 2002; accepted 17 March 2003

Abstract

We present a multi-modal reasoning (MMR) methodology that integrates case-based reasoning (CBR), rule-based reasoning (RBR) and model-based reasoning (MBR), meant to provide physicians with a reliable decision support tool in the context of type 1 diabetes mellitus management. In particular, we have implemented a decision support system that is able to jointly exploit a probabilistic model of the glucose–insulin system at the steady state, a RBR system for suggestion generation and a CBR system for patient’s profiling. The integration of the CBR, RBR and MBR paradigms allows for an optimized exploitation of all the available information, and for the definition of a therapy properly tailored to the patient’s needs, overcoming the single approaches limitations. The system has been tested both on simulated and on real patients’ data.

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Keywords: Decision support; Diabetes mellitus; Probabilistic modeling; Multi-modal reasoning

1. Introduction

Although there has been a strong emphasis on the definition of knowledge-based decision support systems in medicine, their application in the clinical routine is still very limited. It has been advocated by several authors that the major problems are related to architectural and usability issues and not to the availability of effective algorithms and tools [15,16]. The investigation of new strategies for supporting physicians in making
decisions is necessarily related to the definition of knowledge management (KM) platforms, that allows the user to collect data and receive advice, suggestions or alarms during the day by day workflow [40,43]. Within those platform, a methodological approach that seems particularly interesting to provide new ways for assisting decision-making is represented by the multi-modal reasoning (MMR) paradigm [42]. MMR is a reasoning approach that relies on the integration of different artificial intelligence methodologies, for problem solving and decision support purposes. The main advantage that MMR provides is the capability of exploiting all the available information, from the explicit (i.e. formalized) domain knowledge, to the operative know-how collected in the single organization where the application will be deployed. This is particularly important in the medical domain, where the introduction of hospital information systems into clinical practice has led to the storage of a huge quantity of data, extracted from day to day activity, thus making available a form of implicit knowledge, which embeds the unarticulated experience of individual workers. Both implicit and explicit knowledge need to be properly managed and made reusable, in order to support the complexity of medical decision making. Moreover, MMR seems a suitable way also to solve the classical dichotomy between model-based and heuristic-based reasoning: it may be useful to gain advantage from both approaches without inheriting their problems. In this paper we will investigate the integration of different reasoning strategies in the domain of diabetes mellitus. Diabetes mellitus is one of the major chronic diseases in the industrialized countries, involving up to 3% of the population. Seven to 20% of the total number of diabetic patients are affected by type 1 diabetes, and need to undergo intensive insulin therapy, consisting in three to four injections of exogenous insulin every day, in order to regulate blood glucose and to reduce the risk of later life complications. A correct implementation of intensive insulin therapy requires patients to perform a strict self-monitoring: they have to test blood glucose level (BGL) before every injection, and to record the measurements on hand-written diaries, together with the insulin doses really injected, and with additional information about their diet and lifestyle. Every 2–4 months they undergo periodical control visits, during which the physician evaluates also the diary data, and defines a suitable insulin administration protocol to be implemented, in order to optimize the patient’s metabolic behavior. The major long-term intervention trial on type 1 diabetic patients, the Diabetes Control and Complication Trial (DCCT) [12], has clearly shown that the definition and realization of an appropriate individual therapeutic goal, customized on the single patient’s needs, is the key to effective diabetes care. Defining a proper therapy is therefore a relevant decision problem to be addressed, that starts from the interpretation of a huge amount of information. The implementation of decision support systems for choosing the insulin protocol is a widely studied problem [23]. Traditionally, the approaches proposed in the literature have been subdivided into model-based and in algorithmic- or heuristics-based [24]. An interesting appraisal of model-based decision support tools for type 1 diabetes patients has been published by Lehmann and Deutsch [25]. In that paper the limits of model-based approaches are highlighted, and it is claimed that their role in patient’s care will be limited by the lack of the availability of data, such as for example the meal intakes. On the contrary, it is suggested that heuristics and algorithmic approaches may play a major role to generate advice and reminders to users of systems based on information technology (IT). Such a conclusion, although motivated by 20-years experience, can be only partially shared.
As a matter of fact, there are cases in which models are applicable to generate automatic advice, as shown by the experiences carried on in the DIAS project [10,17,18,29]. In particular, it seems that, among others, probabilistic models are more suitable to capture the variability of the patient’s response to a certain therapy during home monitoring [6]. It is therefore interesting to integrate model-based approaches in MMR systems in order to exploit their strengths and, at the same time, to overcome their weaknesses.

This paper is an attempt towards this direction. It will extend a simple model of the basic relationships between blood glucose and insulin intakes in a probabilistic framework; then it will integrate this model in a MMR system based on rules and case-based reasoning (CBR) [20]. The overall idea is to provide a system that is flexible enough in order to be able to provide advice in different situations.

Apart from its methodological interest, this work is also motivated by practical issues, and in particular by the different role that decision support systems are going to play in new IT-based services, such as telemedicine systems. In these services, the intelligent activity will be mainly devoted to automatically keep track of the current situation of each patient, to identify problems and to automatically provide suggestions only in simple cases, in order to leave time to health care professionals to deal with complex situations. The goal is therefore to provide a machinery that is able to perform the phases of problem identification, alarm generation and, when needed, decision support in a reliable way. It is therefore our opinion that also model-based approaches may play a role either to provide decision-theoretic support to patients or to assist physician in decision making; the crucial capability will be to rule-out models when they are inapplicable, by properly switching from one approach to another.

The following sections present a general overview of MMR systems, the methodological details of our new proposed model, the system architecture, and some results we collected, both on simulated and on real patients’ data.

2. Background: multi-modal reasoning approaches

A MMR scheme is usually designed to integrate different kinds of knowledge in the same decision support system, i.e. to integrate explicit and implicit knowledge [27]. Explicit knowledge corresponds to the already well established and formalized domain knowledge; it can be present in books and in written documentation, or can be represented by some formalisms for developing knowledge-based systems, such as taxonomies or rules, or finally by mathematical or probabilistic models; implicit or tacit knowledge consists in individual expertise, organizational practices, and past cases: it can be represented by heuristics that even experts are not fully aware of, or can be stored in databases and case libraries.

As a matter of fact, one of the most suitable methodologies for managing knowledge of the implicit type [39] is CBR [20]. CBR is a problem solving paradigm that utilizes the specific knowledge of previously experienced situations, called cases. It basically consists in retrieving past cases that are similar to the current one and in reusing (by, if necessary, adapting) past successful solutions; the current case can be retained and put into a case library. The case library enables one to keep track of the organization expertise, and can be
continuously and easily upgraded through the addition of new cases and (possibly) the deletion of old ones that proved to be out of date.

On the other hand, rule-based reasoning (RBR) and model-based reasoning (MBR) are helpful strategies for representing and managing knowledge of the explicit type.

A MMR methodology that integrates CBR with RBR or MBR (or with both) offers the possibility of taking advantage of all the available information within the organization, and of relying on it for automatic reasoning support. In the literature, the combination of CBR with RBR has received particular attention, since rules are truly the most successful explicit knowledge representation formalism for intelligent systems. Different levels of integration between the two paradigms have been proposed. In the majority of the examples, RBR and CBR are applied in mutually exclusive ways: first RBR, meant to deal with standard problems, is relied upon; if it fails in proposing a suitable solution, CBR is exploited, in order to retrieve similar cases from a library of peculiar and non-standard situations [41,44]. Other authors [8,5] rely on CBR for “contextualizing” rules, while RBR permits the extraction of more abstract and general concepts from cases. The methodology to be applied can be selected in a dynamic way, depending on the situation at hand: in particular, the rule base and the case memory can be searched in parallel for applicable entities; then the best entity (i.e. rule or case) to reuse (and therefore the reasoning paradigm to apply) can be selected, depending on its suitability for solving the current problem [5].

In other approaches, RBR is resorted to in the CBR adaptation step: if the memory does not contain suitable examples of adaptation to situations similar to the current one, the system will employ some general adaptation rules [21].

A few examples of a MMR strategy that integrate RBR, CBR and MBR can be found as well. In [36], for instance, RBR is applied to routine problems, MBR to more complex ones, and CBR on the few remaining cases, to improve system performances.

The common basis of all the above MMR approaches (except perhaps the work in [8]) is that the various paradigms are used in a quite exclusive way. These solutions do not guarantee to overcome the intrinsic limitations of the three reasoning methodologies, which can be summarized as follows:

- classical RBR systems do not have the capability of specializing the explicit knowledge embedded in the rules, by resorting to contextual knowledge (e.g. the single patient’s features). To deal with as many peculiar situations as possible, it would be necessary either to rely on a complex system, involving meta-rules or context-dependent parametrized rules, or to progressively enlarge the rule base, up to intractable dimensions: both approaches show problems related to the complexity of managing and maintaining the rule base itself ([34]; see also [32]);
- CBR just relies on the implicit knowledge stored in the case library. If the library presents competence gaps, i.e. it is too small, or biased by too specific examples, a misleading indication on how to solve the current problem may be provided;
- defining a suitable model to work with may be critical, especially when the available data are few or of poor quality, thus inadequate to be relied upon in the model identification.

In order to face such limitations, we propose a MMR system that will resorts to a very tight integration of RBR, CBR and MBR. The system is an evolution of a previous
methodology we implemented, that exploited only RBR and CBR [26], and was applied (and successfully tested) in the field of type 1 diabetes mellitus management. The current version incorporates also a mathematical model of diabetic patient’s metabolism. Case-based retrieval and the mathematical model are used as a means for specializing the behavior of a set of production rules, and for computing the optimal therapeutic suggestion, thus tailoring the proposed solution to the situation at hand. An added value of the MMR system is also the possibility of exploiting it in a modular way: in particular, the physician is allowed to rely on the CBR tool alone, to navigate the case library, and rebuild the patients’ clinical histories over time. CBR can therefore be seen as an independent operative KM methodology.

3. A probabilistic model of the glucose–insulin system

As mentioned in the introduction, several models describing the interaction between insulin and glucose have been proposed in the literature [1,14,22,28,35]. In this paper we are interested in models that are able to predict BGL in response to a certain insulin protocol, without requiring additional information apart from previous BGL measurements and insulin dosages. These models typically make the assumption that the patient does not significantly change his/her lifestyle (including diet) for a certain period, so that the daily BGL dynamics may reach a “steady state” profile. Unfortunately, the extraction of a steady state profile from the BGL data is not a simple task, because of the high intra/inter-day variability that can be observed in diabetic patients. The classical solution to this problem is to derive the average daily profile (called the modal day) on a certain time span, typically a couple of months. The modal day may be soundly computed by resorting to structural time series analysis as described in [13].

Rather interestingly, the modal day can be viewed as the steady state value of a cyclo-stationary process with 24 h period, describing the BGL profiles. Although the cyclo-stationary assumption may seem too restrictive, it is actually what is applied in clinical practice to judge the appropriateness of an insulin protocol.

Under the cyclo-stationarity assumption the goal of a glucose–insulin model is to forecast the modal day (i.e. \( \text{BGL}(t, R_2) \)) in a subject given a certain insulin regimen.

To this end, we have exploited a stochastic extension of the model proposed in the UTOPIA system [13]. The model implemented in UTOPIA assumes that the change in the daily steady state values of BGL, caused by a change in the insulin therapeutic protocol from regimen \( R_1 \) to regimen \( R_2 \), is described by a linear differential equation, whose solution has the following form:

\[
\text{BGL}(t, R_2) = -S \int_{t-24}^{t} [(1 - r(\tau))Iarel(\tau) \exp\left(-k(t - \tau)\right)] d\tau + \text{BGL}(t, R_1)
\]

where \( \text{BGL}(t, R_1) \) and \( \text{BGL}(t, R_2) \) are the steady state values of BGL at day time \( t \), in response to insulin therapy regimen \( R_1 \) or \( R_2 \), respectively; \( Iarel \) is the difference between the daily insulin activity profile under \( R_2 \) and \( R_1 \), calculated as in [4]; \( r(t) \) is a periodic function with values in \([0,1]\) that expresses the daily insulin resistance profile and \( k \) and \( S \)
are the patient-specific model parameters: \( k \) is the rate of insulin-independent BGL elimination while \( S \) is the patient’s sensitivity to the insulin action.

The straightforward application of this model to the point estimate of the modal day suffers from a substantial problem: the point-based representation of patients’ behavior does not take into account the inter-day variability, that is caused by a variety of factors ranging from physiological reasons to the day by day small changes in the patient’s lifestyle. A decision based only on the average values is likely to be dangerous, since it neglects crucial information about the variability of the patient’s response.

In order to overcome such a problem, we have considered a stochastic formulation of the modal day, and consequently extended the model (1). The BGL time course in response to a therapeutic regimen \( R \) is modeled as a cyclo-stationary stochastic process, so that:

\[
P(BGL|t, R) = P(BGL|t + 24 \text{ h}, R)\tag{2}
\]

As a consequence, the BGL probability density function at any \( t \) is independent from the data previously collected. In this paper, we will suppose that BGL is suitably discretized into \( L \) levels, so that the probability distribution \( P(BGL|t, R) \) is described by a conditional probability table with elements \( P(BGL = l|t, R) = \theta_l(t, R), l = 1, \ldots, L. \)

When a new therapeutic regimen \( (R^+) \) is applied, a new probability distribution for BGL at the steady state is obtained. The new conditionals \( \theta(t, R^+) \) can be derived as a function of the past conditionals \( \theta(t, R) \), of the past and new regimens \( R \) and \( R^+ \) and of the time \( t \) by applying the model (1). In particular, if we run the model (1) by taking as initial value the central value of each discretization interval, we obtain a prediction that may lie in the same interval or in one of the other intervals. We therefore build a \( L \times L \) transition matrix \( M(t, R, R^+) \), containing only 0 and 1 elements, that mathematically expresses the forecast given by model (1) about the future location of the central value of the discretization intervals after the application of the new insulin regimen. The transition matrix may be used to compute \( \theta(t, R^+) \) as:

\[
\theta(t, R^+) = M(t, R, R^+)\theta(t, R)\tag{3}
\]

In general the \( m \) daily measurements are taken at fixed times, that we will refer to as time slices and we will denote with \( t_1, \ldots, t_m \). Then the stochastic version of the modal day is obtained considering the set of \( m \) probability distributions \( \theta(t_j, R) \).

Fig. 1 graphically depicts the paradigmatic shift introduced by the probabilistic model described in this paper. While the original approach forecasts the modal day in terms of point estimate of the average BGL (Fig. 1a), in the proposed approach a probability distribution is obtained for each time slice, thanks to a probability propagation mechanism based on the model (1) (Fig. 1b).

Once the vector \( \theta(t_j, R^+) \) has been forecasted for all \( m \) time slices, it is possible to apply standard utility theory to derive the optimal insulin regimen, by minimizing the expected cost \( \text{EC}(R^+) \):

\[
\text{EC}(R^+) = \sum_{j=1}^{m} \sum_{l=1}^{L} \theta_l(t_j, R^+)C_l\tag{4}
\]

where \( C_l \) is a suitable cost associated with each BGL discretization level.
Fig. 1. The basic philosophy underlying the proposed probabilistic model: (a) the original approach forecasts the modal day in terms of point estimate of the average BGL; (b) in the proposed approach a probability distribution is obtained for each time slice, thanks to a probability propagation mechanism based on the model (1).
In order to be applicable on a patient-by-patient basis, the stochastic version of the model (3) needs to be tailored by learning from data the probability density function of the current modal day \( \theta \) and the parameters \( S \) and \( k \) of the model (1).

The former problem can be easily solved in a Bayesian framework by resorting to the standard Bayesian updating scheme for discrete probability distributions, based on the multinomial-Dirichlet prior distributions. In particular, given a set of \( n(t_j) \) measurements collected in the \( j \)th time slice, the probability \( \theta_l(t_j, R) \) can be estimated as

\[
\theta_l(t_j, R) = \frac{b_{gl}(t_j, R) + \xi_l}{n(t_j) + \alpha}
\]

where \( b_{gl}(t_j, R) \) is the number of BGL data belonging to the \( l \)th discretization level collected during the application of the therapeutic regimen \( R \) and \( \xi_l \) and \( \alpha \) are the parameters of the Dirichlet a-priori probability distribution [9].

A more complex problem is related to the estimate of the model parameters \( S \) and \( k \). Those parameters play a crucial role in the calculation of the transition matrix \( M(t, R, R^+) \) and therefore in the calculation of the predictive probability distribution \( \theta(t, R^+) \).

For computational reasons that will be clear later on, we fixed the value of \( k \) on the basis of available knowledge, and we learned the probability distribution of the parameter \( S \) from the data. In particular, we have discretized \( S \) in a fine grid of \( D \) values. For each \( S_d, d = 1, \ldots, D \), given two therapeutic regimens \( R_1 \) and \( R_2 \), we can derive, for each time slice, a different transition matrix and therefore the predicted modal day, so that \( M(t_j, R_1, R_2) = M(t_j, R_1, R_2, S_d) \) and \( \theta(t_j, R_2) = \theta(t_j, R_2, S_d) \). Let us note that, since the transition matrix \( M(t_j, R_1, R_2, S_d) \) depends on the stochastic parameter \( S_d \), it turns out to be stochastic, too.

If a set of data \( bg(R_2) \) has been observed after the application of the insulin regimen \( R_2 \), we can use such data set to compare the model predictions with the observed values. To this end we can resort to the multinomial distribution to describe BGL measurements.

\[
P(bg, n, \theta | t = t_j, R) = \left( \frac{n(t_j)}{bg(t_j)} \right) \prod_{l=1}^{L} \theta_l(t_j)^{bg_l(t_j, R)}
\]

From (6) we can compute the posterior distribution of \( S \) given \( bg(R_2) \). In particular, given a uniform prior probability distribution for \( P(S) \), we obtain for the \( j \)th time slice:

\[
P(S = S_d | bg(t_j, R_2)) \propto \prod_{l=1}^{L} (\theta_l(t_j, R_2)^{S_d})^{bg_l(t_j, R_2)}
\]

\[
= \prod_{l=1}^{L} (M(t_j, R_1, R_2, S_d) \theta_l(t_j, R_1))^{bg_l(t_j, R_2)}
\]

where \( \theta_l(t_j, R_1) \) is estimated on the basis of the data collected after the application of protocol \( R_1 \) by using equation (5).

Since the data collected in the different time slices are assumed to be independent from each other, it is possible to derive the posterior probability distribution of \( S \) as

\[
P(S = S_d | bg(R_2)) \propto \prod_{j=1}^{m} P(S = S_d | bg(t_j, R_2))
\]
Once such a probability distribution is obtained, it is possible to apply it to revise the equation (3), that calculates the predictive probability distribution \( \theta(t, R^+) \). The equation becomes

\[
\theta_i(t_j, R^+) = \sum_{d=1}^{D} M(t_j, R, R^+, S_d) P(S = S_d | bg(R2)) \theta_i(t_j, R)
\]

(9)

Summarizing, the application of this model for forecasting the effect of a protocol change requires two consecutive phases: an identification phase and a prediction phase.

- In the identification phase the data coming from the assessment of two different regimens are considered; on the basis of this data the posterior probability distribution \( P(S = S_d | bg(R2)) \) is derived as in Eq. (7).
- In the prediction phase the Eq. (9) is applied to forecast the effect of a new regimen on the current probability distribution, estimated from the data collected after the application of the last therapeutic protocol.

It is finally important to remark that such new model may present two basic problems:

1. The identification procedure may lead to a very flat probability distribution for \( S \). This may be due to an insufficient change in insulin regimen related to the data exploited for identification, or to the inadequacy of the model in describing the data themselves: for example, the model is not able to capture rebound phenomena, such as the Somogyi effect [7,38]. Moreover, it must be noted that the model is designed to work “at the steady state”, i.e. it requires the collection of data coming from a sufficient number of weeks of application of a certain therapeutic protocol. In this light, it is different from the model used in DIAS [1], that is able to provide forecasts and optimization also on a day by day basis by paying the price of requiring information on the meal intakes.

2. The dose optimization procedure may be extremely time-demanding: each probability propagation requires the calculation of a different matrix \( M(t_j, R, R^+, S_d) \) for each discretization level of \( S \) and for each time slice. The number of computation would have been grown in a combinatorial way by considering also \( k \) as a discrete stochastic parameter. In any case, if a large number of different therapeutic regimens must be compared, the solution of the optimization problem turns out to be intractable. Therefore, the use of the model should always be coupled with the use of suitable heuristics to reduce the search space.

In the following, we will describe the integration of the model in a MMR system, and we will show how the MMR strategy is able to cope with the problems of the model described above.

4. The system architecture

In the field of type 1 diabetes care, the therapy revision process is typically articulated in four consecutive tasks; in our implementation, the completion of the process is scheduled by a RBR system, within which each task is mapped into a specific set of rules, fired
through a forward chaining mechanism. In detail, the reasoning paradigm proceeds as follows:

1. Data analysis: to interpret the effects of a therapy, we resort to the probabilistic description of the *modal day* of the patient presented in the previous section. In particular, we extract the BGL modal day, through a generalization of the Eq. (5) able to handle missing data (see [30]), after a discretization and aggregation of BGL values performed on the basis of qualitative abstractions [2].

2. Problem identification: the results of the modal day extraction trigger the identification of hyperglycaemia or hypoglycaemia problems in the different periods of the day. The RBR system can complete this task independently, or its behavior can be specialized resorting to the integration with case-based retrieval. The concept of *case* is mapped to the one of periodical control visit. We structured the case library resorting to a taxonomy of prototypical classes, representing the most common diseases associated with diabetes, or clinical course conditions which paediatric patients may incur. Each case belongs to one and only one class. It was thus possible to implement case-based retrieval as a two-step procedure: (i) classification of the input case as belonging to a precise class in the taxonomy, and (ii) retrieval of past similar cases, on the reduced search space found by classification. In particular, in the problem identification task, only classification results are exploited (see Fig. 2), to tune specific rule parameters, thus tailoring the identification of metabolic alterations to the single patient’s needs (see [26] for details).

3. Suggestion generation and selection: for each detected problem, a set of suggestions on how to modify the current insulin therapy are proposed; the most effective ones are selected resorting to the concept of insulin *competence*. The most competent insulin, that has the stronger effect on the moment of the day in which the problem has been found, is identified. Competence is evaluated relying on the pharmacokinetics of the different insulin types [19].

![Fig. 2. Implementation of the integration between RBR, CBR and MBR in the automatic reasoning process for therapy revision.](image-url)
4. Therapy revision: the RBR system proposes an adjustment to the current insulin therapy, in accordance with the selected suggestions. It is meant to be general enough to be safely applicable in a variety of different situations: therefore, it typically proposes small variations to the current protocol insulin doses, quantitatively speaking. Even though the RBR behavior was judged correct and quite satisfactory in a formal evaluation study [31], it came out to be sometimes not sharp enough to promptly face the patient’s alterations. A way of overcoming this weakness is by integrating the RBR results with MBR or with CBR. In particular, we propose to use the model described in Section 3 to calculate the optimal insulin doses increase or decrease, in the direction identified by the generated suggestions. Unfortunately, as mentioned before, not always does the model turn out to give reliable predictions, in particular when a clear causal effect of insulin doses on the BGL cannot be identified in the data (for example because of the presence of “brittle control” or “Somogyi effect”).

To detect this problem, a two-level strategy is applied:

1. During the model parameter identification phase, we evaluate if the posterior distribution of $S$ is not statistically different from a uniform distribution: in this case, since all the discrete values of $S$ have the same probability given the data, we conclude that the model is not able to correctly represent the patient’s data, and it is not exploited in the MMR process.

2. After having selected the new therapy by minimizing the expected cost (EC) (4), the modal day forecast is calculated. If such a forecast has a higher EC than the current modal day (i.e. $EC(R^+) > EC(R)$), the solution does not succeed in ameliorating the patient’s metabolic behavior. In this case the system rolls back and again does not make use of the model suggestions.

When these situations hold, the integration process goes on by performing the CBR retrieval step, restricted to the most probable class(es) identified during the problem identification phase. In more detail, the physician is allowed to choose whether to retrieve only cases belonging to the most probable class, or to a set of very probable classes. In both situations, cases are retrieved by resorting to metrics able to cope with the problem of missing data, and to treat both symbolic and numeric variables [26]. Some simple statistics are calculated on the retrieved cases, to set the insulin adjustments width that will then be applied to the current protocol. Therefore, MBR and case-based retrieval are used in a mutually exclusive way to specialize the rules behavior (see Fig. 2). In any case, if the system is not able to retrieve a sufficiently large number of past similar cases, integration with CBR will not take place, and the reasoning process will be completed relying only on RBR.

As stated in Section 2, CBR can also be seen as an independent implicit KM tool. From an implementation viewpoint, each case in the library is linked to the previous and to the following ones, in terms of time, by two chains of pointers; in this way, it is easy for the user to navigate the whole patient’s history, and to visualize the transitions from one class to another, together with the therapeutic choices that made possible the transitions themselves. Moreover, the classification procedure provides an added value: the identification of the most probable class(es) for the input case allows to detect a suitable context for interpreting the case itself; the metabolic alterations experienced can be evaluated in the
light of the patient’s features, and the therapeutic suggestion can be adapted to them. Finally, classification focuses the attention only on the relevant parts of the case library, thus speeding up retrieval of past cases and making it more efficient.

5. Experimental results

The approach presented in this paper has been evaluated through a three-step procedure: first, we have evaluated the performance of the model-based decision support system on simulated data, by making a comparison of the proposed solutions with the optimal ones, calculated relying on the model that was used to simulate the data [11]; second, we evaluated the overall MMR system performance prospectively on simulated data, obtained through the same realistic diabetic patient simulator; third, we have retrospectively evaluated the system on a set of real patients data. In this paper, we have studied the problem with three time slices ($m = 3$), i.e. breakfast, lunch and dinner, five discretization values ($L = 5$) for BGL, 20 discretization levels for $S$, $k = 0.125$ h$^{-1}$ and, as a cost function, the $M$ index [37].

5.1. Evaluation of the model-based decision support system

To evaluate the performance of the model-based decision support strategy described in this paper we carried out a simulation study. In this study we have used a diabetic patient simulator [11] to generate a set of modal day profiles, that are prototypes of challenging decision support problems that the system may have to deal with. For each of the generated profiles, the system suggested an insulin plan revision, which effect could be easily computed through the simulation model. Such effect have been quantitatively evaluated by calculating the $M$ index on the new daily profile. The derived index has been compared with the index obtained by the optimal solution to the problem, i.e. the insulin protocol that minimizes the $M$ index on the 24 h simulated profile. Let us note that such a comparison mimics the complexity of decision making in the clinical routines: our decision support system has to provide the new insulin plan on the basis of three noisy measurements per day, while the optimal decision could be obtained only by knowing the data on the 24 h BGL profile.

In more detail, the evaluation of the system has been carried out as follows:

- **Modal day profiles generation.** We have run the diabetic patient simulator proposed by [11] in 21 different cases, corresponding to three different values of insulin sensitivity (normal: $s_i = 0.004781$/(h pmol), high: $s_i = 0.00961$/(h pmol), low: $s_i = 0.00241$/(h pmol)), and seven different meal plans, shown in Table 1. Each meal plan corresponds to a particular life style. In each case we took the same starting insulin protocol (5 units of regular insulin at breakfast, 15 units of regular insulin at lunch and dinner and five units of NPH insulin at nighttime) and the same patient weight (70 kg). We therefore obtained twenty-one 24 h profiles; starting from those profiles we generated 60 days of noisy data in three time slices (breakfast, lunch and dinner) by adding Gaussian noise.

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1 The $M$ index is defined as $M = \sum \theta_{\text{measur}} |10 \log_{10}(\text{BGL}_i/90)|$. 

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with zero mean and standard deviation equal to 20 mg/dl. The modal day was then calculated in all cases.

- **Suggestion generation.** On the basis of the different modal days generated, the model described in this paper has been identified and then used to generate the suggested insulin plan. In order to understand the performance of the model-based approach independently from the RBR suggestions, we have derived the insulin protocol with the lowest $M$ index through an exhaustive search among all possible insulin plans, obtained from the original one by varying any of the dosages of a maximum of three units.

- **Optimal solution generation.** The optimal solution for each of the 21 problems has been derived by searching the insulin protocol that minimizes the $M$ index, computed on the basis of the simulated 24 h profile.

- **Performance comparison results.** In Table 2, we show the percentage variation of the $M$ index obtained by applying the model-based decision support system with respect to the one of the starting profile. Table 3 shows the percentage increase of the $M$ index obtained by applying the model-based decision support system with respect to the one obtained with the optimal solution.

Not all the 21 cases have been correctly simulated due to numerical problems, so that only 19 have been considered. It is possible to note that in four cases the model turned out to be not possible, since the forecasted penalty obtained with the suggestion was more than

**Table 1**
The different meal plans used in the model evaluation

<table>
<thead>
<tr>
<th>No.</th>
<th>Meal plan (g)</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>40</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>60</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>40</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>40</td>
<td>30</td>
<td>130</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>40</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>10</td>
<td>120</td>
<td>40</td>
</tr>
</tbody>
</table>

**Table 2**
Percentage variation of the $M$ index obtained by applying the model-based strategy with respect to the one of the starting profile

<table>
<thead>
<tr>
<th></th>
<th>Meal plan (g)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td>-35.6400</td>
<td>2.9700</td>
<td>62.3200</td>
<td>-38.2600</td>
<td>-98.3500</td>
<td>-2.3400</td>
<td>0.8100</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>6.2600</td>
<td>-2.1500</td>
<td>NA</td>
<td>-10.4300</td>
<td>NA</td>
<td>26.7600</td>
<td>9.1100</td>
</tr>
</tbody>
</table>

The positive values denote an improvement in glycemic control, while the negative ones denote a worsening. The model turned out to be not applicable in four cases, since the forecasted penalty obtained with the suggestion was more than 10% higher than the original problem one (negative values).
10% higher than the original problem one (see negative values in Table 2). The best solutions have been obtained in cases with normal insulin sensitivity and standard or nearly standard meal plans. This fact confirms the validity of the model in a limited range of conditions.

For what concerns the comparison with the optimal solutions, it is possible to note that in 9 cases over 19 the distance between the two solutions is less than 50%. Since the optimal solution is calculated without noise and on a grid of 96 values, the performance of the proposed model, which relies only on three points per day, can be considered to be satisfactory.

Fig. 3 shows in three different cases the performance of the model-based decision support solution with respect to the original problem and the optimal profile. The continuous line represent the 24 h original profile, the dash-dotted one depicts the solution proposed by the decision support system, while the continuous line shows the optimal solution. It is possible to note that, in all three cases, the profiles derived by the decision support system do not strongly differ from the ones obtained by the optimal solution.

5.2. Prospective evaluation

To perform prospective evaluation, for each test 21 days of BGL measurements were generated; then the therapeutic suggestions proposed by the RBR system, and the ones obtained by specializing rules resorting to MBR or to CBR, were collected. Finally, an additional period of 21 days, following the application of each therapy, was simulated: in this way, it was possible to compare the performance of different MMR solutions. In particular, Fig. 4a shows the comparison between RBR and MBR–RBR integration, on a simulated patient entering the clinical remission phase, affected by hypoglycaemia problems in the morning and over night. Both the methodologies suggest therapy changes that ameliorate the initial metabolic behavior, but the model proves to be much more sharp, since it totally recovers from hypoglycaemia. A second test was performed by simulating a patient suffering from typical puberal problems, leading to frequent hyperglycaemia. This time, the application of our proposed probabilistic model suggestions led to a situation of a flat posterior distribution of $S$, in which also the expected cost function was higher than the actual one; therefore, as described in Section 4, the MMR system identified a condition of non-applicability of the model, and rolled back, exploiting the CBR–RBR integration. Fig. 4b shows the comparison between the therapy suggested by applying RBR, and the one obtained by specializing the rules through past cases retrieval. CBR clearly improves the efficacy of the rules, allowing for larger adjustments in the competent insulin doses.

<table>
<thead>
<tr>
<th>Meal plan (g)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>56.1479</td>
<td>40.6401</td>
<td>28.5248</td>
<td>80.7526</td>
<td>44.3214</td>
<td>35.3529</td>
<td>13.6413</td>
</tr>
<tr>
<td>High</td>
<td>88.5651</td>
<td>86.8797</td>
<td>2.5643</td>
<td>115.2431</td>
<td>201.9436</td>
<td>13.9856</td>
<td>86.5116</td>
</tr>
<tr>
<td>Low</td>
<td>60.9227</td>
<td>55.2734</td>
<td>NA</td>
<td>66.4573</td>
<td>NA</td>
<td>36.4925</td>
<td>27.5090</td>
</tr>
</tbody>
</table>

Table 3

The percentage increase of the $M$ index obtained by the model-based solution with respect to the optimal one.
Fig. 3. Daily simulated BGL profiles (24 h) in response to different therapeutic regimens: comparison between the starting profile (continuous line), the model-based decision support system solution (dash-dotted line), and the optimal solution (dashed line). The circles represent the mean of the measurements available to the model-based system. (a) A simulated patient with a normal insulin sensitivity and following meal plan 5. The two approaches show nearly similar profiles: the patient profile at bedtime is only slightly improved in both cases; (b) a simulated patient with a high insulin sensitivity and following meal plan 3. The two approaches show again nearly similar profiles; in both cases the original hyperglycemic profile is properly handled in order to generate a normo-glycemic one; (c) a simulated patient with a low insulin sensitivity and following meal plan 7. The model-based decision support system shows a sub-optimal capability of normalizing the blood glucose profile, although the solution does not show strong differences from the optimal one.
Fig. 4. Comparison between RBR and MBR–RBR integration in stabilizing a simulated patient entering the clinical remission phase. Both the methodologies suggest therapy changes that ameliorate the initial metabolic behavior, but the use of the model largely increases efficacy, allowing a total recovery from hypoglycaemia.
The MMR system was retrospectively evaluated on 26 real cases, derived from the data of 10 patients monitored in the M²DM (Multi-Access Services for the Management of Diabetes Mellitus) telemedicine project (funded by the EU: http://aim.unipv.it/m2dm) for a period ranging from 6 months to 2 years.

The model turned out to be not applicable in five cases due to problems in the identification of the probability distribution of the parameter \( S \) (see Section 4). On the remaining 21 cases we evaluated the potential effectiveness of the different strategies through the prediction of the BGL values and their calculation of the expected cost (see Eq. (4)). Table 4 shows the improvement (in percentage) of the \( M \) index obtained by the RBR and MBR–RBR with respect to the current situation. It is possible to note that a slight amelioration of the initial metabolic behavior can be obtained through RBR, while the MBR–RBR integration obviously leads to the greater improvement. We must, however, note that in cases 12–16, corresponding to a single patient, the forecasted improvement is only marginal. Table 5 reports the two cases where the CBR–RBR integration gave a

### Table 4
Percentage decrease of the cost function using RBR and MBR–RBR

<table>
<thead>
<tr>
<th>Case number</th>
<th>RBR</th>
<th>MBR–RBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−0.89</td>
<td>−17.64</td>
</tr>
<tr>
<td>2</td>
<td>−0.91</td>
<td>−18.18</td>
</tr>
<tr>
<td>3</td>
<td>−0.63</td>
<td>−17.71</td>
</tr>
<tr>
<td>4</td>
<td>−2.43</td>
<td>−17.5</td>
</tr>
<tr>
<td>5</td>
<td>−3.4</td>
<td>−20.02</td>
</tr>
<tr>
<td>6</td>
<td>−21.20</td>
<td>−66.76</td>
</tr>
<tr>
<td>7</td>
<td>−5.08</td>
<td>−24.52</td>
</tr>
<tr>
<td>8</td>
<td>−1.37</td>
<td>−13.54</td>
</tr>
<tr>
<td>9</td>
<td>−0.84</td>
<td>−14.77</td>
</tr>
<tr>
<td>10</td>
<td>−16.72</td>
<td>−41.37</td>
</tr>
<tr>
<td>11</td>
<td>−16.85</td>
<td>−42.46</td>
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<tr>
<td>12</td>
<td>−0.34</td>
<td>−4.09</td>
</tr>
<tr>
<td>13</td>
<td>−2.52</td>
<td>−18.73</td>
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<tr>
<td>14</td>
<td>−0.39</td>
<td>−3.69</td>
</tr>
<tr>
<td>15</td>
<td>−0.47</td>
<td>−5.95</td>
</tr>
<tr>
<td>16</td>
<td>−0.49</td>
<td>−6.08</td>
</tr>
<tr>
<td>17</td>
<td>−0.75</td>
<td>−19.99</td>
</tr>
<tr>
<td>18</td>
<td>−0.79</td>
<td>−26.09</td>
</tr>
<tr>
<td>19</td>
<td>−2.54</td>
<td>−19.17</td>
</tr>
</tbody>
</table>

### Table 5
Percentage decrease of the cost function using RBR, RBR–CBR and MMR

<table>
<thead>
<tr>
<th>Case number</th>
<th>RBR</th>
<th>RBR–CBR</th>
<th>MBR–RBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>−0.75</td>
<td>−5.76</td>
<td>−19.99</td>
</tr>
<tr>
<td>21</td>
<td>−1.15</td>
<td>−12.03</td>
<td>−15.33</td>
</tr>
</tbody>
</table>
different suggestion with respect to the RBR. In this case the CBR–RBR solution shows a better performance than the RBR alone.

We must remark that, however, the model was applicable in more than 80% of the cases. When the model could not be effectively used, the joint use of the RBR system and the CBR–RBR integration represented a way for obtaining a sub-optimal therapeutic advice.

6. Conclusions

MMR strategies represent a suitable way to integrate model-based and heuristic or case-based reasoning into a common KM framework. In this paper we have presented a MMR system for supporting decisions in diabetes management based on a tight integration between different reasoning approaches: rules and cases are used to perform patient’s profiling, while a new probabilistic model of the patient’s metabolic behavior is used as a means for deriving optimal insulin dosages. Such a MMR approach is also able to automatically diagnose situations of poor performance of the model-based therapy revision, and to propose alternative solutions based on heuristics and past relevant cases. When a sufficiently large number of past similar cases can be retrieved, CBR–RBR integration represents a way for obtaining sub-optimal therapeutic advice. When the case library content is poor, the retrieval results may lead to an unfit rule specialization. In this condition, the MMR system can exploit RBR alone, thus providing a reliable (even if not patient-tailored) solution. It is interesting to note that the overall system is able to improve its competence during the data collection process: the model is able to learn the model parameters from data in a progressively reliable way, while the growth of the case library increases the competence of the CBR system and therefore the performance of the therapy assessment mechanisms.

It is important to remark that the conjunction of models and heuristics seems particularly interesting in this application domain. As a matter of fact, the relative low number of daily measurements with respect to the blood glucose dynamics and the possible absence of available information on food intakes, makes it difficult to exploit a classical mathematical formulation of the problem. Even in the probabilistic framework, the long-term modeling of BGL time series with dynamics influence diagrams, as performed in DIAS [1], is feasible only in presence of quantitative information on glucose intakes. In this paper we have exploited some reasonable simplification assumptions to derive a steady state probabilistic model: first, the system is assumed to possess a cyclo-stationary behavior; second the daily measurements are assumed to be independent from each other, given the model parameters and the cyclo-stationary assumption. The first assumption is more critical, since it may not hold when the patient suffers from intercurrent diseases or changes his/her lifestyle. In those cases, in order to obtain a nearly cyclo-stationary behavior, it may be necessary to detect and remove the trend component from the BGL time series [3]. For what concerns the second assumption, it must be remarked that, in case of sparse daily measurements, the BGL values collected in different times of the day are only weakly mutually dependent [33]. Therefore, the independence assumption turns out to be applicable in the majority of the cases. When both assumptions do not hold and the
model is not applicable, the MMR system herein proposed is able to provide a solution resorting to heuristic strategies based on clinicians’ experience. This capability makes the system able to detect complex situations and to handle them in a more robust way.

The evaluation procedure described in this paper has been carried out resorting both to simulated and to real patients’ data, monitored within the telemedicine project M²DM. The encouraging results obtained has motivated the implementation of the MMR system as a decision support facility of the M²DM project.

Acknowledgements

The paper is part of the IST project M²DM (Multi Access Services for the Management of Diabetes Mellitus), funded by the European Commission. The authors acknowledge the anonymous reviewers for their help in improving the paper.

References


