Decision support for medical diagnosis

Bert Kappen and Wim Wiegerinck, Nijmegen University
Edith ter Braak, University Medical Centre Utrecht,
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1 Introduction

"Do we need computerised Diagnostic Decision Support Systems in medical practice?"

Problems in modern medicine are often very complex, and evidence for the best choice to be made is often lacking. Decisions made by physicians are arbitrary and highly variable (within one physician and between physicians) and lacking explanation or “rationalisation” [1, 2]. Clinical examples of this phenomenon in diagnosis making are abundant.

The body of potentially useful knowledge that is relevant to even a relatively narrow diagnostic area may be too large to make the optimal (diagnostic) decision on the spot. Ironically, modern information technology (especially through the Internet) further increases the amount of available knowledge, potentially even further complicating this situation. Moreover, individual patients need “individualised” decisions, because their characteristics differ from the “average” and because of their individual wishes [3]. Apparently, individualising the general results of research may be cumbersome and time consuming, while on the other hand, modern medical practice demands for efficiency, cost-effectiveness and high technical quality.

The derivation of diagnostic protocols is a main problem in health care. In some environments diagnostic support as proposed in this proposal is not likely to influence physician’s decisions, e.g. on a neurological intensive care unit, since the diagnosis is often obvious [4]. In contrast, general internal medicine covers an enormous range of, sometimes relatively rare, diagnostic categories. Hence the tendency of medicine to be divided in superspecialties. A diagnostic decision support system covering general internal medicine may be appreciated by both generalists and super-specialists alike: by the generalist because this field of work typically covers a very broad range of diagnoses, by the super-specialist because he/she may not feel completely at ease outside his/her specific field of expertise.

It is readily understandable that the above comprises an enormous task and challenge for modern medicine in general and individual doctors in particular,
illustrating the need for decision support techniques. Obviously, computerised
decision aids may be very promising from a theoretical point of view. However,
the currently available systems have not yet been very successful and certainly
their use is still not widespread and not established in daily routine.
A variety of reasons may be responsible for this:

- **Lack of accuracy:**
  Those current systems that intend to cover a broad diagnostic domain of
  medicine [3, 6] generally lack diagnostic accuracy. This is mainly due to
  the levels of detail [7] (e.g. diagnostic categories at the level of ICD-10
  [8]) and completeness in the knowledge base. In contrast, systems that are
  based on detailed modelling of knowledge, resulting in good performance,
  are restricted to a relatively narrow field [9, 10].

- **Lack of transparency:**
  In the era of evidence based medicine the advise of “a machine”, function-
  ing as a black box is unacceptable: an advise must be accounted for on the
  basis of research published in the peer reviewed literature. The majority
  of conventional protocols and consenus guidelines also often fail to refer
  explicitly to the literature. Therefore, (diagnostic) advices suggested by
  a computerised tool should come with the appropriate references from the
  literature.

- **Users attitude:**
  In a subset of (potential) users there may be a misunderstanding about
  what computers can and cannot do for them. Generally, decision support
  systems need intelligent and responsible users, who are able to interpret
  the advise given and estimate its merit [11]. This, however is not ex-
  clusively a matter of users attitude. Producers of decision support tools
  should take this issue into account as well, especially when designing the
  user interface and deciding which facilities are needed.

- **Lack of integration of information:**
  Patient oriented decision support needs data from several sources. A de-
  cision support system will generate new information (e.g. a diagnostic
  advise) through inference, using patient-specific information. Integration
  of information, multiple usability of patient data, integration of databases
  and knowledge bases are common problems when using a heterogeneous
  Hospital Information System (HIS). In practice, the completeness of pa-
  tient information, and the accuracy and level of detail of diagnose stored
  in the HIS is often very poor [12].

- **Lack of a controlled terminology:**
  This is a problem that even might not be solved completely in the near
  future. Most standard classification systems are at a general level [8, 13],
  thus lacking the required detail, or specialised [14] and therefore too li-
  mited to meet the needs for a broad decision support system. Furthermore,
there is not always a standard classification available, for instance for specific terminology used in text books.

• Careful introduction:
  Introduction of a decision support system should be done as careful and thorough as is done for drugs that are new on the market. Oddly enough this tradition of careful introduction (and marketing!) is common in the field of therapeutics, but not quite as established for support tools in general and for diagnostics in particular. After introduction, the decision support system will need constant monitoring of users needs and maintenance to keep up with the latest results of medical research.

• The need of an integrated clinical workstation:
  The appropriate infrastructure and workstations are not yet available in all hospitals. Physicians will need on-line support during the implementation of the various functionalities of a reliable clinical workstation, that integrates all the required information.

In conclusion, modern medicine is in need of computerised decision aids both to meet its own high standards and to keep pace with the stage of development in other domains such as manufacturing or the services industry. Although decision support appears to be exceptionally suitable for the medical domain, computer aided decision making in medicine is still in its infancy. The development, implementation, assessment and further improvement of decision support systems in medicine still need a lot of research.

2 Our approach

Diagnostic reasoning in the medical domain is a typical example of reasoning with uncertainty. This uncertainty has different sources: missing patient information, uncertainty in medical tests results or observations, and the uncertainty about the physiological processes involved. A model on which a DSS is based should be able to deal with these uncertainties. The different systems that have been developed so far use a variety of modeling approaches which can be roughly divided into two categories: The large systems, that attempt to cover the whole of internal medicine use a rule-based approach with some rather heuristic method to quantify uncertainty. These methods perform poorly in practice [5, 6]. The main reasons are that the modeling of the relations between diseases and findings is at a very coarse level. Therefore, the diagnoses suggested by these systems are too superficial for clinical use. Secondly, the diagnostic process requires reasoning from causes to effects (diseases → finding) and vise versa at the same time. The rule based approach, together with the heuristics for uncertainty, is not well suited for such bidirectional reasoning.

For smaller systems, the probabilistic approach is typically used. The probabilistic approach has the important advantage of mathematical consistency and correctness. In particular Bayesian networks (see e.g. [15, 16, 17]) provide a
powerful and conceptual transparent formalism for probabilistic modeling. In addition, they allow for easy integration of domain knowledge and learning from data. Systems that are based on detailed modeling have been restricted to a relatively small domain [9, 10]. The reason for this restriction is that Bayesian networks will become intractable for exact computation if a large medical domain would be modeled in detail.

To proceed one has to rely on approximate computations. Recently, variational methods for approximation are becoming increasingly popular [18, 19, 20]. An advantage of variational methods techniques is that they provide bounds on the quantity of interest in contrast to stochastic sampling methods which may yield unreliable results due to finite sampling times. Until now, variational approximations have been less widely applied than Monte Carlo methods, arguably since their use is not so straightforward. We argue that variational methods are indeed applicable to large, detailed Bayesian networks for medical diagnosis constructed by human experts.

Although the formalism of Bayesian networks is very powerful, the construction of networks for medical diagnosis is not straightforward. A learning approach depends crucially on the availability of high quality patient data. In particular, rare disorders should be well covered. In general, unfortunately, this is rather exception than rule [12]. Therefore, to reach a successful diagnostic DSS requires explicit modeling effort by human experts. The existing medical literature is not sufficient to define the probabilistic model. Not all probabilistic relations between variables have been documented. But it provides a useful starting point for model design. Once a minimal performance is thus obtained, the model can be improved by learning from patient data.

3 Probabilistic modeling in the medical domain

We here outline what the structure of a broad and detailed Bayesian network will typically look like. This is based on an extrapolation of our current modeling experiences. Details of the medical domain are beyond the scope of this paper and are discussed elsewhere [21].

The variables to consider in the network are of different types. There are diseases variables, which are typically of the binary type, signalling whether a disease is present or not. The findings encode the results from laboratory measurements, physical examination etc. As a simplification, these variables are discretized, with medically relevant cut-off points. In practice, such discretisation does not lead to significant loss of information. In addition, there are prior variables that describe the patient, such as sex and age.

In constructing the graph for the Bayesian network, human experts mostly use “causal” relationships between variables as a guideline (the arrows in fig. 1). Often, the expert can relate (large numbers of) variables via additional hidden variables. These hidden variables may represent pathophysiological variables
that are known to have certain relations to the observable variables, but are
themselves not accessible during clinical investigation. Often, the use of hidden
variables results in a simplified and more transparent network.

The majority of probabilistic relations between the variables involve only
a small number of parents. Consequently, modeling using explicit probability
tables is feasible. These are estimated on the basis of data in the literature or
on “educated guesses” based on local statistics/experience if no data from the
literature are available.

Medical experts tend to divide knowledge concerning a medical domain into
sub-domains with a relatively small overlap. Therefore, the network will typi-
cally have a modular structure (cf. fig. 1). Each module represents a disease
with its relevant findings. In practice, the modules are rather small, containing
between 20-50 variables. Different modules are connected via shared variables
(e.g. pathophysiological variables that are relevant in different modules), com-
mon prior nodes, and/or common findings nodes. The computational complex-
ity of the network $N_1$ consisting of the modules and their parents (black nodes
in fig. 1) can be assumed to be tractable.

The probabilistic relations for the findings require somewhat more care. For
example, ‘hemoglobin level’ (Hb) is a variable whose value is affected by many
diseases. Such nodes may have parents in many sub-domains. This makes the
use of a conditional probability table not feasible, as the size of the table grows
exponentially in the number of parents. Fortunately, this is neither necessary,
since medical experts are likely to agree with a ‘sum of univariate relations’
between this finding and its parents. Such simplified conditional probability
tables require only the specification of order $k$ parameters, where $k$ is the number
of parents.

Even though the conditional probability tables are modeled in a compact
way, inference is still intractable.

4 Variational Approximations

In general, the problem of inference is to find the conditional probability dis-
tribution $P(S_i|E)$ of each of the nodes $i$ given the evidence $E$. If $P$ is in-
tractable, one has to approximate these conditional probabilities. In the vari-
ational method, the intractable probability distribution $P(S|E) = P_E(S)$ is
approximated by a tractable distribution $Q(S)$ (on the non-evidential nodes).
Then $Q$ is used to compute the node probabilities $Q(S_i)$. To construct $Q$, one
first has to define a tractable graphical structure for $Q$: $Q(S_i) = \prod \gamma Q(S_{\gamma}\|\gamma)$,
[22, 23, 20]. The next step is to optimize the parameters of $Q$ such that the
Kullback-Leibler (KL) divergence between $Q$ and $P_E$,

$$D(Q, P_E) = \sum_{\{S\}} Q(S) \log \frac{Q(S)}{P_E(S)}$$  \hspace{1cm} (1)
is minimized. The KL-divergence is related to the difference of the marginals of $Q$ and $P_E$, 
\[
\max_i |P(S_i|E) - Q(S_i)| \leq \sqrt{\frac{1}{2} D(Q, P_E)} \tag{2}
\]
(see [24]).

$D(Q, P_E)$ depends on the numerical values of the conditional probability tables $Q(S_i|\pi_i)$. Setting the gradient of $D$ with respect to these parameters equal to zero, yields a coupled set of non-linear equations that can be solved numerically.

The quality of the approximation depends strongly on the structure of $Q$. The simplest approach is the so called mean-field approach, in which the graph of $Q$ is completely disconnected, i.e. $Q(S) = \prod_i Q(S_i)$. The other extreme is to factorize $Q$ according to a triangulated graph [15, 17] of $P$. In this case, one obtains the exact solution $Q = P_E$ and $D = 0$. This solution is only theoretically of interest, since its computational complexity is equal to the original inference problem. However, it indicates that the variational approach using structure interpolates between the standard mean field theory and the exact solution. In general one must choose a structure for $Q$ that is a good compromise between approximation error and complexity.

In figure 2 we plotted the maximal error $\max_d |Q(s_d) - P(s_d|s_f)|$ as a function of the network size for an artificially generated network. We also plotted the required computer time for exact and approximate inference as a function of the network size. We conclude that variational methods using structure significantly improves the quality of approximation, within feasible computer time. In a
network with tractable substructures, as can be expected in medical diagnosis, these substructures provide a useful starting point for the approximating model. For more information on the variational approach see [25].

Figure 2: Left: The maximal error as a function of the network size. Right: CPU-time in Matlab seconds for exact and approximate inference as a function of the network size.

5 Promedas, a demonstration DSS

Promedas (PRObabilistic MEEdical Diagnostic Advisory System)\(^1\) is a DSS that we are developing for the problem of anaemia. The aim is to use Promedas to assess the usefulness of approximate methods for a DSS in practice. The problem domain anaemia is chosen because we expect that the computational problems described in the previous sections will be encountered in this domain. For instance, anaemia can be subdivided in a large number of sub-domains, each of which share a large number of findings. Furthermore, anaemia is a common medical problem. This facilitates evaluation in practice. To cover the domain completely, we expect that approximately 1000 nodes are needed.

To develop Promedas, we use our internally developed software environment, called BayesBuilder. BayesBuilder has graphical tools for network construction, evaluation, and maintenance. So far, Promedas covers megaloblastic anaemia. It is currently based on a network of 91 variables, and is still tractable for exact algorithms.

Promedas consists of a graphical user interface (GUI) to enter patient data and for diagnostic consultation (fig. 3). It provides a differential diagnosis, i.e. the probabilities of potentially relevant diagnoses and the probabilities of potentially involved underlying mechanisms (e.g. pathophysiology) as percentages (ranked in descending order). These probabilities are computed on the basis of the available findings entered in the system. In addition, Promedas computes which additional tests it expects to be most informative to decide

\(^1\)A demonstration version of Promedas is available on CD-ROM. See www.sbfys.kun.nl/research/promedas
Figure 3: The Promedas diagnostic decision support system.

about a diagnosis, specified by the user. This information is computed given the values of the variables previously entered and is defined as 

\[ I(D,T) = \sum_{D,T} P(D,T) \ln \left( \frac{P(D,T)}{P(D)P(T)} \right) \]

with \( P(D,T) \) the joint probability of diagnosis and test result, and \( P(D), P(T) \) the marginal probabilities of diagnoses and tests, respectively. These probabilities are computed by marginalizing over all the missing variables in the network. The information is normalized between 0 and 100, and displayed in descending order. In addition, Promedas provides help information, medical background information and pointers to the literature.

6 Utilisation

Taking into account the need for decision support system in general and diagnostic decision support in particular, we strongly believe that a diagnostic decision support system is viable and, eventually, marketable. However, even a pilot regarding the implementation and assessment a diagnostic decision support system that covers only a relatively narrow diagnostic field (i.e. anaemia) will need careful, preferably step-wise, introduction to its target users, followed by continuing support and mutual feedback. It is expected that this will result in growing acceptance and enthusiasm by its target users and finally leading to
wide-spread use.

The physicians that participate within this project work in daily hospital practice as well. They have good contacts in the medical community in many
fields of medicine (general internal medicine, oncology, endocrinology, haematology) within Utrecht University Hospital, affiliated (regional) hospitals and
various professional circles. In addition, the user group includes specialists in
internal medicine from other academic hospitals. Therefore, we feel that we
are able to "market" and to follow up a diagnostic decision support system at
least for research purposes (assessment) in The Netherlands. Wide spread
acceptance of computer aided diagnostic decision support tools will probably need
some "trend setters", who are most likely to be found in the academic circle.

7 Discussion
The development of a DSS for comprehensive medical diagnosis in internal
medicine represents a great challenge for AI. A broad and detailed probabilis-
tic network is intractable for exact inference in this context. It is currently
unknown, whether variational or other approximate methods are sufficiently
powerful to provide a practical solution. The "quality of approximation" is to
a large extent a user defined (medical) issue, since (1) comparison with exact
inference is not possible due to the size of the networks and (2) errors in the
approximation will be judged as acceptable not just on their numerical values
but more importantly on their medical implications. The only way to assess
the usefulness of approximate methods for modeling medical domains is by ac-
tually building such a system and evaluating it by users. The Promedas model
must be extended to 500-1000 variables in order to be able to address this issue
properly.

Further reading on graphical models can be found in [16, 26]. Further reading
on diagnostic decision support systems can be found in [4, 2].

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