Dynamic Bayesian networks as prognostic models for clinical patient management

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Abstract

Prognostic models in medicine are usually built using simple decision rules, proportional hazards models, or Markov models. Dynamic Bayesian networks (DBNs) offer an approach that allows for the incorporation of the causal and temporal nature of medical domain knowledge as elicited from domain experts, thereby allowing for detailed prognostic predictions. The aim of this paper is to describe the considerations that must be taken into account when constructing a DBN for complex medical domains and to demonstrate their usefulness in practice. To this end, we focus on the construction of a DBN for prognosis of carcinoid patients, compare performance with that of a proportional hazards model, and describe predictions for three individual patients. We show that the DBN can make detailed predictions, about not only patient survival, but also other variables of interest, such as disease progression, the effect of treatment, and the development of complications. Strengths and limitations of our approach are discussed and compared with those offered by traditional methods.

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1. Introduction

An important task in clinical patient management is to determine a prognosis for a patient that suffers from a disease, where we define prognosis as: the prediction of the future course of a disease process conditional on the patient’s history and a projected treatment strategy. This is non-trivial since the physician often has incomplete information and treatment itself can have a multitude of uncertain effects. As a result, predictions made by the physician can be poor [1,2] or miscalibrated [3]. Therefore, patient management can greatly benefit from the development of prognostic models that aid the physician in this task. Next to its use in clinical decision-making, prognostic models can also be of value to the patient, e.g., for notification and quality-of-life decisions, as well as to the policy-maker, e.g., for comparative audit, patient selection for clinical trials, and the development of treatment protocols [4,5].

Various approaches to the development of a prognostic model exist. Traditionally, a prognostic model consists of simple decision rules that are based on a prognostic score and classify patients into different risk categories. Such scores are often based on clinical variables, and have been constructed for the general patient population [6,7] as well as for specific patient subgroups [8]. Survival analysis takes a different approach, and models survival rate by taking into account patient-specific covariates, such as by means of the proportional hazards model [9]. In decision analysis, stochastic processes which evolve over time, known as Markov decision processes, are used as the basis for prognostic models [10]. More recently, techniques such as decision-trees, neural networks, support vector machines, and (dynamic) Bayesian networks, as developed by the artificial intelligence community, have become popular as prognostic models [11–13,5].
The above techniques have all proven their worth as a basis for constructing prognostic models in medicine, but most of them are not always applicable. Although sophisticated techniques, such as neural networks and support vector machines, generally improve upon the performance of simple decision rules, they also require the availability of large amounts of high-quality data. Unfortunately, these data are not always available and the only source of knowledge may be that of domain experts which is often condensed in the form of medical textbooks, thereby rendering the methods inapplicable. Another perceived deficiency is the fact that most of the described techniques do not provide insight into how a certain prognostic conclusion is reached; they are so-called black-box models, which is an undesirable property of clinical decision support systems [14]. For instance, even though the proportional hazards model has an interpretation in terms of patient-specific covariates that modulate patient hazard, the model cannot give a causal explanation of how the covariates interact and influence patient survival. Furthermore, the assumptions underlying a technique may not hold for a particular domain. The proportional hazards model, for instance, makes assumptions of proportionality, additivity, and linearity of the covariates.

In this paper, we will focus on dynamic Bayesian networks (DBNs) [15] as the formal basis for prognostic models in medicine. These models can be regarded as a generalization of Markov decision processes as they offer a factorized representation of the state of the process. Due to this fact, DBNs can be used to represent medical knowledge explicitly in terms of causes and effects as obtained from data, domain experts, and/or literature. Furthermore, no restrictive assumptions are being made about the interaction between domain variables. For these reasons, the DBN approach to prognosis promises to resolve some of the limitations of more traditional prognostic models. However, not much is known about how to construct a DBN for complex medical domains and the aim of this paper is to elucidate the steps that need to be taken in order to arrive at a satisfying prognostic model. We demonstrate these steps by means of the construction of a DBN for prognosis of patients that present with low-grade carcinoid tumors; a neuroendocrine tumor that displays a complex symptomatology [16]. We call the resulting model, henceforth, the carcinoid model.

We proceed by describing the concept of prognosis and the implementation of a prognostic model as a DBN in general in Section 2. In Section 3, we describe the steps that need to be taken in order to get from a clinical problem (in our case prognosis of carcinoid patients) to a functioning prognostic model (the carcinoid model). The carcinoid model is applied to retrospective patient data that has been collected at the Netherlands Cancer Institute (NKI) for clinical research purposes in Section 4. In order to obtain insight into the quality of the model, we focus not only on prognostic accuracy, but also on the intelligibility of the prognostic conclusions. We end with a discussion of the results in Section 5.

2. Prognosis using dynamic Bayesian networks

In order to understand the merits of dynamic Bayesian networks as the formal basis for prognosis, it is important to make clear what constitutes a prognosis. As mentioned, we define prognosis as the prediction of the future course of a disease process conditional on patient history and a projected treatment strategy.

Consider Fig. 1, which depicts the interaction between a patient and a physician in terms of a model of how the physician makes decisions, and a model of how the patient responds to decisions. With respect to prognosis, we wish to predict (part of) the state of the patient for a future time period. We therefore need to take into account how the state of the patient changes under the influence of choices made by the physician. This implies that we must know how the physician will respond in the future. That is, we need to know the treatment strategy under which the physician operates. Most traditional prognostic models sidestep the explicit representation of time by mapping the current state of the patient directly into the future time period of interest. However, the temporal nature of a problem is often essential to clinical decision-making as well [17].

![Fig. 1. An abstract representation of clinical decision making in terms of a physician model and a patient model. The current patient state influences the physician's decisions, which in turn influences the next patient state.](image-url)
During diagnosis, to know the temporal order and duration of symptoms can influence the diagnostic conclusions, the selection of treatments or tests may depend on the time at which the selection is made, and during prognosis, the disease dynamics is an unfolding of events over time that can only be approximated by a non-temporal prognostic model. Furthermore, new evidence often becomes available in time-points since prognosis is an ongoing process. This is not easily represented by more traditional prognostic models. The benefits of temporal modeling of clinical problems have become clear in practice, as illustrated by the work of Long [18], who used a representation based on Bayesian networks and time intervals [19] for diagnosing heart disease, which eliminated errors that were made by a non-temporal model. Similarly, it was found in [20] that a redefinition of a static Bayesian network for the diagnosis of ventilator-associated pneumonia (VAP) in terms of a dynamic Bayesian network that allows for temporal reasoning, increased diagnostic performance. Some other examples of (dynamic) Bayesian networks in medicine are presented in [21–23].

Another limitation of more traditional prognostic models is the fact that often an explicit interpretation in terms of causes and effects is lacking. This is regrettable since causal models allow for an accurate representation of domain knowledge. Therefore, they are more meaningful, accessible and reliable than models which merely capture associations [24,25]. Causation has in fact been used as a modeling strategy in some of the early medical expert systems (e.g., [26,27]). Furthermore, causal models are more easily constructed from domain literature and expert knowledge since knowledge concerning pathophysiology and the effect of treatment is normally described in terms of causes and effects [28], which is especially useful in case statistical data is lacking. Finally, causal models facilitate the explanation of drawn conclusions, which may increase the acceptance of decision support in medicine, both by the physician and by the patient [29,30].

We argue that the representation of a treatment strategy, the representation of the temporal nature of the medical problem, the ability to learn not only from statistical data, but also from domain literature and expert knowledge, and a causal approach to modeling are desirable features of any prognostic model. Dynamic Bayesian networks (DBNs) extend standard Bayesian networks and are a formalism that offers all of these features.

A Bayesian network $\mathcal{B} = (G, P)$ is a pair where $G$ is an acyclic directed graph, with nodes corresponding to a set of random variables $X$, and $P$ is a joint probability distribution (JPD) of variables in $X$, which factorizes as:

$$P(X) = \prod_{x \in X} P(X|\pi_G(x))$$

where $\pi_G(x)$ denotes the parents of $X$ in $G$. The representation of a JPD by a Bayesian network generally reduces the number of parameters that need to be estimated and allows for efficient probabilistic inference. In case we are dealing with problems of a temporal nature, we explicitly include time within a Bayesian network, by reasoning over random processes $X = \{X(t) : t \in T\}$ instead of random variables. The resulting model is known as a dynamic Bayesian network.

If it is assumed that the Markov property holds, which states that the future is independent of the past given the present, we obtain the following factorization:

$$P(X) = \prod_{t \in T} \prod_{x(t) \in X(t)} P(X(t)|\pi_G(x(t)))$$

with $X(t) = \{X(t) : X \in X\}$. In this work, we will focus on discrete-time and discrete-space random processes, which implies that $T \subseteq \mathbb{N}$ and $P(\cdot|\cdot)$ can be specified by a finite look-up table. If the structure of the dynamic Bayesian network is invariant for all times $t \in \{1, 2, \ldots\}$ then it can be specified in terms of:

- a prior model

$$P(X(0)) = \prod_{x(0) \in X(0)} P(X(0)|\pi_{G_0}(X(0)))$$

specifying the initial distribution of the joint process at time 0, and

- a transition model

$$P(X(t)|X(t-1)) = \prod_{x(t) \in X(t)} P(X(t)|\pi_{G_0}(X(t)))$$

specifying evolution of the process as it moves from time $t-1$ to time $t$ for $t \in \{1, 2, \ldots\}$.

A simple example of a DBN is shown in Fig. 2, where the influences between a disease, a complication, and health are shown in terms of a prior model and a transition model.
In the transition model, variables at time $t$ are represented by dashed objects, whereas variables at time $t+1$ are represented by solid objects. Note that the temporal nature of the problem is represented by the choice of the prior and transition model, while causal knowledge, such as the notion that a disease may cause a complication, and influence of disease and its complication on patient health is captured as well. In our experience, it is easiest to start with the construction of the transition model, and to derive the prior model from the transition model.

Prior to constructing a DBN, we need to choose an initial time (at what moment in time does the DBN start), a transition interval (how much time elapses between two subsequent points in time), and a horizon (at what point in time does the DBN end). Construction of a dynamic Bayesian network also requires a qualitative specification (defining the structure $G_0$ and $G_t$ of the DBN) and a quantitative specification (defining the parameters $P(\cdot|\cdot)$ of the DBN). Qualitative specification amounts to the identification of domain variables and the values they can assume, as well as the specification of network structure. Quantitative specification is realized by means of factor association and parameter estimation. Factor association refers to the definition of the functional form of $P(X|\pi_o(X))$ (how the outcome of a variable depends on its influencing variables). In case a variable is continuous then associated factors typically take on some suitable parametric form. In case a variable and its parents are discrete (take on a state from a finite number of states) then its associated factor can be interpreted as a simple look-up table, also known as a conditional probability table (CPT), that specifies the probability of taking a state given the states of all variables that influence that variable according to the graph $G$. In our model, we have assumed that all variables are discrete (or discretized in advance). Once factors have been attached, the final task is to estimate the parameters that complete the DBN.

A DBN is used as a prognostic model by entering the values of observed variables at past and current points in time and computing quantities of interest at future points in time. These quantities can be computed exactly or approximately using a variety of inference algorithms [31]. Fig. 3 depicts the prior and transition model in unrolled form for our example DBN.

After having discussed the required preliminaries with regard to DBNs, we now turn to the description of how a non-trivial prognostic problem can be modeled in these terms. The aim here is to convey the experiences that have been gained during the development of the model such that to-be-developed prognostic DBNs can benefit from the discussion.

3. Development of the carcinoid model

In this section, we describe the development of the carcinoid model; a dynamic Bayesian network for the prognosis of patients that present with a carcinoid tumor. The carcinoid model consists of 218 variables and 74,342 parameter estimates in total and is one of the largest models of its kind that have been constructed to date. The performance of the carcinoid model is compared with that of a proportional hazards model and demonstrated by means of three case studies. We will only focus on some of the most interesting aspects of the model, and refer to [32,33] for a more exhaustive description.

3.1. Problem description

A requirement for the development of a successful prognostic DBN is that prior to its conception, we have formulated a clear and unambiguous problem description. It is also important to properly restrict the problem domain in order to determine under which circumstances the model may be applied. Low-grade carcinoid tumors are a type of neuroendocrine tumor that can produce high levels of serotonin, kinins, prostaglandins, and other vasoactive peptides. They are most commonly found in the midgut and typically behave less aggressively than conventional adenocarcinomas [34]. During the early stages, carcinoid tumors often remain undiagnosed, where vague abdominal pain is commonly ascribed to irritable bowel or spastic colon. Neuroendocrine tumors that derive from other sites
often show markedly different behavior and hence need alternative models for prognostication [16]. Carcinoid tumor histology is determined by mitotic activity and tissue necrosis, and distinguished into well differentiated, or low-grade malignancies, and poorly differentiated, or high-grade malignancies [35]. A minority of patients presents with high-grade tumors, which grow faster but are biochemically less active, and require a different prognostic model. We therefore restrict ourselves to prognosis of carcinoids of the midgut with a low-grade histology.

3.2. Determining temporal characteristics

The choices for the initial time, interval, and horizon, should be motivated both by the properties of the domain (i.e., we need to be able to model the processes on the timescale in which we are interested) and by considerations with regard to available domain knowledge (i.e., domain experts need to be able to express the knowledge that is required to specify the model). For the carcinoid model we choose hospital admission as our initial time since this is a logical point to start the prognostic process. We choose a 3-month period as our interval time as this is the interval in between follow-ups within the clinic. We let the horizon be dictated by the survival time of individual patients whose follow-up we require.

3.3. Modeling patient health

Construction of a dynamic Bayesian network is a difficult process. The initial specification of network structure is a difficult undertaking, and the prime directive is to keep it simple. Simple models can gradually be extended to more complex models by adding detail to small domain fragments and evaluating the functionality of this fragment. Starting with complex models on the other hand makes it virtually impossible to evaluate functionality, since distant variables may interact in a complex ways.

We propose that the development of a prognostic DBN starts with the identification of the factors that have a direct influence on patient health. This is motivated by the fact that patient health is often of prognostic interest itself and has a wide impact on how the patient responds to different situations. The factors that directly influence patient health can be distinguished into patient characteristics, primary disease, complications, treatment of primary disease, and treatment of complications.

In oncology, one way to represent the patient’s health status is in terms of the performance status [36], which is distinguished into normal, mild complaints, ambulatory care, intensive care, and death, where we say that the health status is acceptable if it is at least in the ambulatory state. Fig. 4 depicts the various influences on carcinoid patient health and they can be categorized into the described factors. The variables age, gender, and (past) health determine patient health independent of the disease. The variable tumor mass represents the direct effect of the tumor on patient health. The variables chd (carcinoid heart disease), bowel obstruction and ischaemia, and carcinoid crisis are various complications that may arise as an effect of the primary disease. The variable bmd represents severe bone-marrow depression due to some of the treatments of the primary disease and plr (partial liver resection), rfa (radiofrequency ablation), and embolization are treatments of the primary disease that present a direct risk of dying. The same holds for bowel resection and cardiac surgery, which are treatments of particular complications.

The large number of conditioning variables that (partially) determine patient health, makes estimation of conditional probabilities for this variable very difficult. However, a large subset of these variables are risk factors that influence health only due to the fact that they may cause immediate patient death, thereby simplifying the specification as follows. Let \( U \subseteq X \) denote these risk factors, and let \( V = X \setminus U \) denote the complement. Then, the risk of immediate death \( P(health(t) = death|X) \) can be expressed as:

\[
1 - P(health(t) \neq death|V) \prod_{U \subseteq U} P(health(t))
\]

\[
\neq death|U, health(t-1)).
\]

This model is an adaptation of the well-known noisy-OR model [37,38] that takes the effect of past health into account. In a similar fashion, we obtain

\[
P(health(t) = h|X) = P(h|V) \prod_{U \subseteq U} P(health(t))
\]

\[
\neq death|U, health(t-1))
\]

Fig. 4. Representation of patient health where dashed objects denote past states and square objects denote treatments.
for $h \neq \text{death}$. These simplifications greatly reduce the number of parameters that need to be estimated and we have repeatedly applied similar modeling tricks when building our models.

In keeping with the prime directive, we do not propose to incorporate all the variables that influence patient health at once, but rather to incorporate these variables incrementally. A good starting point is to begin with a model that represents the healthy subject. That is, we model the effects of various patient characteristics. Subsequently, we model the main disease processes. The genesis and effects of various complications may be incorporated one by one, where one should start with those complications that have the largest effect on the variables of interest. At this point, we end up with a pathophysiological model of the patient. By incorporating the various treatments that may be given, we end up with a full prognostic model that is able to predict future patient state.

### 3.4. Representing the healthy subject

We represent the healthy subject by modeling the death rate in the general population. We focus only on modeling the probability of patient death under the assumption that changes in patient health are mainly influenced by disease processes. Since it is not our aim to take into account all possible risk factors, we make a distinction only between subpopulations according to age and gender. In order to estimate probabilities we will make use of data collected by the Central Bureau of Statistics (CBS), for the period 2000–2004 [39]. Based on this data we estimated male and female mortality quotients as shown in Table 1. For further details, we refer to [32].

<table>
<thead>
<tr>
<th>age($t$)</th>
<th>$P_1$</th>
<th>$P_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–30</td>
<td>$1.03 \times 10^{-4}$</td>
<td>$3.41 \times 10^{-5}$</td>
</tr>
<tr>
<td>30–40</td>
<td>$2.68 \times 10^{-4}$</td>
<td>$1.01 \times 10^{-4}$</td>
</tr>
<tr>
<td>40–50</td>
<td>$6.98 \times 10^{-4}$</td>
<td>$2.99 \times 10^{-4}$</td>
</tr>
<tr>
<td>50–60</td>
<td>$1.82 \times 10^{-3}$</td>
<td>$8.87 \times 10^{-4}$</td>
</tr>
<tr>
<td>60–70</td>
<td>$4.73 \times 10^{-3}$</td>
<td>$2.62 \times 10^{-3}$</td>
</tr>
<tr>
<td>70–80</td>
<td>$1.23 \times 10^{-2}$</td>
<td>$7.72 \times 10^{-3}$</td>
</tr>
<tr>
<td>80–90</td>
<td>$3.14 \times 10^{-2}$</td>
<td>$2.25 \times 10^{-2}$</td>
</tr>
<tr>
<td>$\geq 90$</td>
<td>$7.79 \times 10^{-2}$</td>
<td>$6.40 \times 10^{-2}$</td>
</tr>
</tbody>
</table>

### 3.5. Modeling the main disease processes

The main disease processes acting in a carcinoid patient are progression of the tumor and changes in tumor activity. The most prominent clinical sign of carcinoid disease is the carcinoid syndrome, which is mainly characterized by diarrhea caused by increased bowel motility due to serotonin overproduction, periodical flushing attacks due to the synergistic interaction between histamine, kinins, and prostaglandin released by the tumor into the general circulation, and less frequently wheezing [40]. Extreme cases of the carcinoid syndrome are known as a carcinoid crisis and may lead to cardiovascular collapse and ultimately death. Hormones released by carcinoid tumors are often destroyed by the liver before they reach the general circulation to cause symptoms, and therefore, only liver metastases or metastases that release hormones directly into the general circulation such as gonad or lung metastases, can produce the carcinoid syndrome. Since most of the hormone-producing tumor mass is accounted for by the liver, carcinoids are often accompanied by widespread hepatic metastases.

Fig. 5 depicts progression of a carcinoid tumor in detail. As described, the tumor may lead to various metastases, some of which may be biochemically active. Hepatic metastases are distinguished into different types, since hepatic treatment depends on this. The variable hepatic response captures the effect of hepatic treatment, whereas the
variable tumor response captures the tumor effect of systemic treatment. In the model, we only represent primary tumor localization, and not its size, since disease progression is mainly determined by metastatic disease. We found it useful to distinguish biochemically active from total metastatic tumor mass using separate variables, since the active mass fulfills a special function in carcinoid tumor biochemistry. We modeled the growth of metastases by estimating the probability that a transition occurs in 3 months to a more severe state. For example, for hepatic metastases (which accounts for the bulk of the metastases) we defined multiple states that represent what percentage of the liver is affected and how this changes over time. For other metastases, such as lung metastases we only modeled whether or not the lungs have become infected. For example, the development of lung metastases is given by

\[
P(\text{lung metastases}(t) = \text{present} | \text{lung metastases}(t - 1) = \text{absent}) \approx 8.9 \times 10^{-3}
\]

Although many different substances are thought to play a role in carcinoid disease, the exact interactions are as yet unclear, and in practice, diagnosis relies on the assessment of serotonin overproduction by measuring urinary 5-HIAA levels. Sometimes, excessive release of bioactive substances leads to a carcinoid crisis, which is characterized by severe flushing, severe diarrhea, and vomiting, and is thought to arise from an excessive release of vasoactive substances into the general circulation [41]. Plasma chromogranin A (CgA) levels can be used as a marker of tumor load, in terms of neuroendocrine activity [42] and tumor mass [43]. Fig. 6 depicts the causal relations between variables in the carcinoid model that together represent tumor biochemistry. It is shown that all metastases determine CgA production, whereas biochemically active metastases determine the release of various biochemical compounds, such as serotonin, whose product 5-HIAA can be measured in a urine sample. Note that the release of CgA and other biochemical compounds is influenced by the biochemical response of systemic treatment.

It can be difficult to incrementally build a prototype model. In practice, we have found the concepts of detailing, decomposition, and state revelation useful in order to add detail to our model. Detailing is the notion that we (partially) explain the influence of a variable \( Y \) on another variable \( X \) by introducing an intermediate variable \( Z \) such that \( X \rightarrow Z \) and \( Z \rightarrow Y \). For instance, the influence between release and health can be (partially) explained by the structure \( \text{release}(t - 1) \rightarrow \text{crisis}(t) \rightarrow \text{health}(t) \). If the influence is totally explained, then the original direct influence can be removed from the model. Decomposition is the notion that we decompose a variable \( X \) into constituents \( X_1, \ldots, X_n \). For instance, for the carcinoid model, we distinguish metastatic disease into metastases occurring in certain organs. A third, and important, way to refine a model is state revelation, which adds observable variables to the model that (partially) reveal the state of unobservable variables. Examples are measurable variables such as 5-hiaa and cga, but also directly observable variables such as flushing, since they partially reveal the underlying disease process.

![Fig. 6. Representation of tumor biochemistry.](image1)

![Fig. 7. Representation of carcinoid heart disease.](image2)

Detailing, decomposition, and state revelation are methods to incrementally add random variables to the model. Once sufficient detail has been added, it becomes useful to focus on context-specific independence that may hold between the states of random variables [44]. Context-specific independence refers to the fact that there may exist independence between random variables that is not apparent from the structure of a modeled graph. For example, suppose a random variable \( U \) has as its parents \( \pi_0(U) = X \cup Y \cup Z \). Then, after observing \( X = x \), it may hold that \( P(U|x, Y, Z) = P(U|x, Y) \) such that \( U \) is independent of \( Z \) in the context \( x \), thereby reducing the number of parameters that need to be estimated.

### 3.6. Modeling complications

Next to the representation of tumor biochemistry and tumor progression, we need to represent other components that are relevant to prognosis. One example is the set of possible complications, since this influences prognosis due to their influence on patient health. The release of biochemical compounds is for instance also responsible for the development of carcinoid heart disease (CHD). It is a consequence of enlargement and distortion of the endocardium and subendocardium of the tricuspid valve, leading to tricuspid insufficiency and decompensatio cordis. CHD may lead to right heart failure which is the cause of death in approximately half of carcinoid patients [45]; as the pump function of the heart deteriorates the patient’s health deteriorates rapidly.

The development of CHD is shown in Fig. 7. Note that thickening is a prerequisite for regurgitation, and CHD is defined as severe or extreme regurgitation in the presence
of thickening. This is an example of a deterministic variable, whose states are fully determined by the states of its parent variables. Following the definition of CHD in [46], we define:

\[
P(chd(t) = yes | thick(t), regurg(t)) = \begin{cases} 
1 & \text{if } thick(t) = yes \land regurg(t) > \text{moderate} \\
0 & \text{otherwise} 
\end{cases}
\]

Even though CHD is fully determined by thickening and regurgitation, it is still useful to represent the variable CHD in the model, as it facilitates subsequent parameter estimation. For example, elevated NT-pro-BNP concentrations indicate carcinoid heart disease [47], and are normally expressed conditional on the absence or presence of CHD. Here, we follow the results of [47], and distinguish NT-pro-BNP into normal (<200 ng/L) and elevated (≥200 ng/L) concentrations. Since all CHD patients had elevated NT-pro-BNP levels and 4 out of 23 non-CHD patients had elevated NT-pro-BNP levels, the distribution is specified by

\[
P(\text{NT-pro-BNP}(t) = \text{elevated} | \text{chd} = \text{no}) = 0.174, \\
P(\text{NT-pro-BNP}(t) = \text{elevated} | \text{chd} = \text{yes}) = 1. 
\]

Other complications of carcinoid disease that are modeled in a similar manner are carcinoid crisis and mesenterial fibrosis (shrinkage and fibrosis of the mesentery), which leads to bowel obstruction and/or ischaemia as represented in Fig. 7.

### 3.7. Modeling treatment

A prognostic model also requires the representation of decisions and their outcomes. For each treatment, we need to specify its negative and positive effects. Furthermore, we need to define the treatment strategy (the physician model of Fig. 1) that specifies under which conditions the various treatments are applied. This is important since we also need to take into account all future treatments the patient may receive when predicting the future state of the patient.

Carcinoid tumor treatment is distinguished into interventions and systemic treatments (symptomatic treatment is disregarded since this does not influence disease progression). Treatment of a carcinoid tumor often amounts to surgical intervention, and although curative surgical removal of the primary tumor is the treatment of choice for small localized tumors, it is almost impossible in the presence of intra-abdominal or hepatic metastases. In the context of the prognostic model, it is assumed that the patient has already received appropriate primary tumor surgery. The remaining interventions are shown in Table 2. The intervention cardiac surgery simply influences tricuspid valve thickening, whereas the intervention bowel resection influences mesenterial fibrosis. Hepatic treatments influence the degree of hepatic metastases via the hepatic response. The effect of hepatic treatment is modulated by the metastatic type, which can be localized, multiple, or diffuse. The risk that is associated with performing these interventions is modeled by variables shown in Fig. 4.

Systemic treatment focuses on reducing overall tumor activity and tumor growth, and can be distinguished into the treatments shown in Table 3. Systemic treatment is administered in case of biochemically active metastases in conjunction with extreme 5-HIAA levels and/or both severe diarrhea and flushing. We call these conditions the systemic conditions. In general, systemic treatment is characterized by positive effects (such as tumor reduction and reduction of biological activity), and possible side-effects, such as bone-marrow depression. The effect of systemic treatment can be quantified in terms of reductions in tumor growth as well as reductions in tumor activity.

Fig. 8 depicts tumor and biochemical response of systemic treatment. The effect of some of these treatments is modulated by other variables (not shown). For f-soma, tumor and biochemical response are conditioned on a variable increase, which captures whether the f-soma dosage has recently been increased, since this induces stronger response. Tumor and biochemical response of f-soma and r-soma is modulated by the variable octreoscan, since these treatments are ineffective in case of a negative octreotide scan. Similarly, tumor and biochemical response of r-mibg is conditioned by a variable mibgscan, since the treatment has no effect in case of a negative mibg scan. Positive effects of tumor response and biochemical response have already been shown in Figs. 5 and 6.

The protocol for the various treatments needs to be incorporated in the model as well in order to model which treatments are expected to be performed in the future. These protocols can be very simple, such as in case of cardiac surgery, where we normally treat in case of carcinoid heart disease given an acceptable health status.

### Table 2

<table>
<thead>
<tr>
<th>Interventions for carcinoid tumors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel resection</td>
<td>Performed in case of severe mesenterial fibrosis</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Performed in case of carcinoid heart disease</td>
</tr>
<tr>
<td>Partial liver resection</td>
<td>Treatment of mild liver metastases</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td>Treatment of moderate liver metastases</td>
</tr>
<tr>
<td>Embolization</td>
<td>Treatment of severe liver metastases</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Systemic treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmacological somatostatin</td>
<td>Synthetic form of native somatostatin</td>
</tr>
<tr>
<td>Interferon</td>
<td>Synthetic compound that stimulates the immune system</td>
</tr>
<tr>
<td>Radiolabeled somatostatin</td>
<td>Radioactive somatostatin used for autoradiation therapy</td>
</tr>
<tr>
<td>Radiolabeled MIBG</td>
<td>Radioactive MIBG used for autoradiation therapy</td>
</tr>
<tr>
<td>Farmacological MIBG</td>
<td>Inhibitor of mitochondrial respiration of tumor cells</td>
</tr>
</tbody>
</table>
“Normally” refers here to the fact that there may be unmodeled causes that preclude cardiac surgery. This is represented by means of a so-called stochastic policy:

\[
P(\text{cardiac surgery}(t) = \text{yes}|\text{chd}(t) = \text{yes}, \text{health}(t) > \text{ambulatory}) = 0.90.
\]

For systemic treatments, the protocols are more complex. Consider for instance the treatment strategy for \textit{f-soma} (Fig. 9). The figure depicts that the systemic conditions must be present and the octreoscan must be positive in order to administer \textit{f-soma} treatment. It is also shown that if biochemical and tumor responses are absent despite \textit{f-soma} treatment, then there is tumor progression despite treatment (\textit{f-soma progression}). This progression determines whether \textit{f-soma} treatment dosage is increased, or whether \textit{f-soma} treatment fails. Finally, if the patient comes in with severe or extreme amounts of tumor mass then the patient receives \textit{f-soma}, possibly together with other systemic treatment.

### 3.8. Specifying a prior model

Once the transition model for the pathophysiological and treatment components has been specified, we need to define a prior model. This prior model can be generated in part from the independencies that are already represented in the transition model, although we need to take into account possible associations between random variables and have to reestimate parameters for some of the random variables. For example, patient age is conditioned by both patient gender and the primary localization of the tumor since these variables are correlated at admission time. This way of constructing a prior model from a transition model is summarized as follows:

1. Add a variable \(X(0)\) to \(G_0\) for each variable \(X(t) \in G_t\).
2. Add an arc \((X(0), Y(0))\) to \(G_0\) for each arc \((X(t), Y(t))\) in \(G_t\).
3. For all variables \(Y\) with arcs \((X(t-1), Y(t))\) in \(G_t\), such that \(X \neq Y\), determine if there are variables \(Z(0)\) in \(G_0\) that condition the prior distribution of \(Y(0)\) and add arcs \((Z(0), Y(0))\) to \(G_0\).
4. Reestimate distributions that have changed due to the above transformations.

As a simple example, if we focus on \(P(\text{luna metastases}(t)|\text{luna metastases}(t-1))\) then we need to remove the dependence on lung metastases\(t-1\) and estimate the prior probability \(P(\text{luna metastases}(0) = \text{present}) = 0.15\).

Now that we have described the steps that are involved when constructing a prognostic DBN, we demonstrate the performance of the carcinoid model by comparing it with a proportional hazards model and by applying it to three patient cases.

### 4. Evaluation of the carcinoid model

In order to determine if the performance of the carcinoid model is satisfactory, we examined its performance by determining a detailed prognosis for three individual...
patients. For the purpose of comparison, we have also employed a proportional hazards (PH) model. The PH model assumes that the hazard (death risk) at time $t$ can be expressed as $h_0(t) \exp(\theta^T x)$ where $h_0(\cdot)$ is the baseline hazard and $\theta$ is a vector of coefficients for covariates $x$.

We have estimated the parameters using a clinical database that has been obtained from the NKI and contains data on 129 patients with a diagnosed low-grade midgut carcinoid tumor. The PH model uses variables that are known at admission time as covariates, with estimated coefficients as in Table 4.

The negativity of some of the coefficients show that, unexpectedly, the presence of particular “risk factors” is beneficial for patient survival according to the database. The presence of mesenterial fibrosis, for instance, has a strong positive effect on patient survival, and was in fact the strongest effect found. Clearly, this does not match with the carcinoid model, which predicts that mesenterial fibrosis has a negative effect on patient survival. A possible explanation might be that the absence of many of these risk factors is atypical and atypical patients are more difficult to treat than typical patients. An alternative explanation is that the assumptions made by the PH model are just not fulfilled by the data. This difficulty of interpreting results demonstrates one of the problems associated with learning prognostic models from a limited amount of data. This being said, the PH model actually performed somewhat better than the carcinoid model when predicting survival for patients in this database. This is however not surprising since the model was learnt from the very same data, and it is questionable how well the PH model generalizes to unseen patient data. Furthermore, as we will demonstrate, the carcinoid model can make more detailed predictions.

In the following, we focus on individual patients, where patient data, as taken from the database, is supplemented with more specific clinical evidence as found in the physician’s paper records. It is demonstrated that the carcinoid model has the advantage that (1) it can make use of evidence that becomes available over time, (2) it may answer other types of queries, such as the expected cause of death or the expected future treatment, and (3) since the carcinoid model is an explicit causal model of disease progression, the drawn conclusions are more understandable. These features considerably improve both the quality and detail of the prognosis.

### 4.1. Patient A

Patient A is a 70-year-old male that came into the hospital with a small-bowel tumor and some health-related problems. The patient had elevated 5-HIAA levels, and suffered from diarrhea, flushing, and obstruction, but it was found that the patient was free from hepatic metastases and other malignancies. There was no indication of carcinoid heart disease, and both octreo and mibgscans were

### Table 4

Estimated coefficients $\theta$ for covariates $x$ in the PH model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Variable</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender(0)</td>
<td>0.8660</td>
<td>bowel obstruction(0)</td>
<td>0.5314</td>
</tr>
<tr>
<td>age(0)</td>
<td>1.0454</td>
<td>hepatic metastases(0)</td>
<td>-0.3146</td>
</tr>
<tr>
<td>5-hiaa(0)</td>
<td>0.0043</td>
<td>octreoscan(0)</td>
<td>1.2103</td>
</tr>
<tr>
<td>cga(0)</td>
<td>0.7091</td>
<td>mibgscan(0)</td>
<td>-0.3952</td>
</tr>
<tr>
<td>diarrhea(0)</td>
<td>0.3371</td>
<td>primary localization(0)</td>
<td>-0.1812</td>
</tr>
<tr>
<td>flushing(0)</td>
<td>-0.5039</td>
<td>mesenterial fibrosis(0)</td>
<td>-1.2263</td>
</tr>
</tbody>
</table>

Fig. 10. Prediction of patient A’s health according to the carcinoid model and the prediction of patient death according to the PH model.
positive. The patient eventually died of wasting 5 years and 2 months after admission.

The predictions of the carcinoid model and the PH model for patient health are shown in Fig. 10. The figure shows that, according to the carcinoid model, the patient starts with an ambulatory health status, where, over time, the chance of needing nursing care first increases and then decreases since the patient’s chance of dying increases. The PH model can only predict the probability of patient death over time, and the figure demonstrates that, due to the negative contribution of the covariates, the PH model assigns a very high probability to patient death. According to the physician this estimate is unrealistically high, since it is not expected that almost all patients that suffer from the same symptoms as patient A would have died after 5 years.

During hospitalization, the patient was given several treatments. He received a bowel resection at admission due to obstruction. After 10 months, pharmacological somatostatin treatment was initiated, due to the development of serotonin-producing metastases. Thirteen months after admission, the patient received pharmacological MIBG for 4 months since deterioration in health precluded other treatments. After 3 years and 9 months, the patient received another bowel resection due to the development of mesenterial fibrosis. We condition on the evidence that is present during admission and on observations that are made over time; namely, the development of serotonin-producing metastases after 1 year (which we take here to be hepatic metastases), a deterioration in health after 18 months, and the development of mesenterial fibrosis after 45 months. Fig. 11 depicts the predictions of the carcinoid model for the treatments that patient A will receive.

Fig. 11 is in accordance with the physician’s expectations. At admission, the model suggests bowel resection with high probability. This probability drops to zero at 18 months since health has deteriorated, and shows a small increase at 45 months due to the development of mesenterial fibrosis. The model also predicts that pharmacological somatostatin is administered early on and continued indefinitely. Finally, the probability that pharmacological MIBG is administered increases when it is found that health has deteriorated.

4.2. Patient B

Patient B is a 68-year-old male of which the primary localization is unknown. He came in with extreme CgA levels, but no signs of the carcinoid syndrome or other malignancies, and only minor health problems. The patient had a negative result on the octreoscan, and a positive result on the mibgscan. After 5 months the patient started to receive pharmacological somatostatin. From 11 to 15 months, the patient received interferon. After 14 months, it was found that the patient had elevated NT-pro-BNP levels. Currently, 17 months after diagnosis, the patient starts to receive radiolabeled MIBG. The patient remains alive today, and we wish to predict patient health and projected treatment for the next 5 years.

Fig. 12 shows the predictions for patient health. Note that at 17 months, the model predicts that the patient either has mild complaints, or is ambulatory, since treatment with radiolabeled MIBG requires an acceptable health status. Over time, the probability of being in these states decreases, and the probability of requiring nursing care/
dying increases. Five years later, the patient is predicted to have a 34% chance of remaining alive. Note that the predicted course of events for patient B is very different from that of patient A in Fig. 10, which demonstrates that the carcinoid model is sensitive to changes in patient characteristics. The PH model again predicts patient death with high probability due to a similar negative contribution of the coefficients of patient covariates.

Even if NT-pro-BNP levels were elevated, the model assigned a low probability to the development of carcinoid heart disease. This is consistent with the physician’s expectations, since diarrhea and flushing were absent at time of admission (indicating that CHD due to elevated serotonin levels is unlikely) and cardiac surgery was not performed immediately after elevated NT-pro-BNP levels were noticed. The model also assigned low probabilities to the development of other complications such as a crisis or mesenterial fibrosis, and therefore did not prescribe treatment for these complications. For treatment with pharmacological somatostatin, the data in the database is not consistent with the model; since the octreoscan of the patient is negative, the model predicts that pharmacological somatostatin is not administered. In reality the patient was given this treatment since his condition at that time precluded other treatment. Upon entering this evidence, the model responds by giving no biochemical or tumor response, which is in accordance with the observed progressive disease of the patient, and by the discontinuation of this treatment for the remaining time. For the same reason, the model predicts that radiolabeled octreotide will not be administered in the future. The only remaining applicable systemic treatments are then radiolabeled MIBG and pharmacological MIBG. The carcinoid model predicts that the patient has a small chance of receiving radiolabeled MIBG once more over the next few years since this requires an acceptable health status, whereas pharmacological MIBG has a small chance of being administered for a longer period of time, as this only requires a normal blood pressure, for which there is no contraindication.

4.3. Patient C

Patient C is a 59-year-old male that came into the hospital with a small-bowel tumor, carcinoid syndrome, and minor health problems. The patient had a positive octreoscan, and it was found during admission that the patient suffered from cardiac valve thickening together with moderate tricuspid valve fibrosis and mesenterial fibrosis. An important question is to determine at admission time the probability that the patient will receive cardiac surgery. Fig. 13 depicts this probability for the coming 5 years, and shows that this probability is at a reasonably high level after 13 months, which is the time at which the patient actually underwent cardiac surgery.

Next to predicting future patient health and projected treatments, we may employ the model in order to distinguish between different scenarios. For instance, for a patient that has developed carcinoid heart disease after 1 year, we may compare the expected course of events in case the patient receives cardiac surgery between 12 and 15 months with the expected course of events in case the patient never receives cardiac surgery. This comparison is shown in Fig. 14 and motivates the physician’s choice of performing cardiac surgery since this is expected to improve long-term survival. The figure also shows that performing this type of surgery may lead to patient death in a
minority of cases and, unfortunately, patient C also died 1 month after surgery. The sudden increase in survival probability after 1 year is implied by the treatment which the patient received at that time. If an inference engine were used that performed smoothing instead of filtering then we could also have incorporated this information to update the past to infer that the patient must have been alive up to that point. However, for the purpose of prognosis this is not required since we want to make predictions about future events. Note that the prediction of survival by the proportional hazards model is in-between the two different treatment regimes, illustrating that the PH model is unable to model the effect of treating versus not treating for this patient.

With respect to mesenterial fibrosis, the model predicts that there is a 78% chance that bowel resection is performed immediately. It was found however that the patient did not receive such a surgical intervention. After some deliberation, it was found that the operationalization of mesenterial fibrosis in the model differed from that in the database. In the model, the presence of mesenterial fibrosis indicates severe fibrosis, which warrants the intervention, whereas in the database, presence of mesenterial fibrosis also indicates mild fibrosis, which does not warrant such an intervention.

5. Discussion

In this study, we have explored the use of dynamic Bayesian networks as the basis for the construction of prognostic models for clinical patient management. We have described the basic steps that need to be taken in order to arrive at a fully specified model and presented some guidelines that streamline this process. The usefulness of the approach is demonstrated with the development of the carcinoid model; a DBN for prognosis of patients that suffer from low-grade midgut carcinoids. The carcinoid model is able to make highly detailed prognostic predictions and is much more flexible with respect to the integration of patient evidence and the answering of prognostic queries as compared with a proportional hazards model. We firmly believe that these features render DBNs more
suitable as a tool for supporting physicians in difficult patient management tasks than traditional methods. Since the carcinoid model is a prototype, we expect that the prediction of patient survival can benefit from further refinement of the model.

The use of the database of patients with low-grade midgut carcinoid tumors was sometimes problematic as the treatment protocol for carcinoid tumors is still under development. This resulted in the inclusion of sequences of treatments in the database that were impossible according to the model. Furthermore, some treatments that were present in the database are no longer used in clinical practice. For instance, chemotherapy is currently considered to be too aggressive as a treatment option for low-grade carcinoid patients. Also, sometimes the operationalization of variables in the database was not clear, as was the case with mesenterial fibrosis, and abdominal pain. Additionally, Table 4 showed that some risk factors had a positive effect on patient survival in the database. We are convinced that these problems are not unique for this case-study, but rather a property of many clinical databases, which suggests that the validation of prognostic models is preferably done in clinical practice.

Even though the carcinoid model has demonstrated that disease progression for complex domains can be modeled successfully by means of dynamic Bayesian networks, there are also other lessons to be learned from this study. During the development of the structure of the carcinoid model, it was found that, sometimes, the physician had difficulty in determining the causal structure of the domain. At the early stages of modeling, it was clearly hard for the physician to structure the domain, which frequently led to the claim that everything is connected to everything. However, as domain variables became consolidated, the task became easier; especially when pathophysiology was distinguished from the treatment protocol, and modeling focused on individual submodels for the various complications. Another problem that was encountered is that sometimes the physician was unsure of certain interactions. For example, the formation of mesenterial fibrosis is still under debate, thereby making model construction and parameter estimation difficult. In general, carcinoid disease as a whole is still not well-understood and disease progression is subject to much variation, making model construction a difficult task. Also, due to the highly complex pathophysiology of carcinoid tumors, and the large number of treatments that are used, model complexity grew considerably, leading to a long development time.

During the estimation of probabilities, it was found that the physician was not very sure about the point estimates that she provided. Therefore, it might have been advisable to model the physician’s uncertainty explicitly in terms of hyper-parameters, although this would also have increased model complexity considerably. Various kinds of biases have also been observed during the estimation process. For instance, the physician sometimes claimed initially that some events never occur (while in reality they had a small chance of occurring) or always occur (while in reality they had a small chance of not occurring). It seemed to be the case that the physician conditioned her estimates on the average situation, without taking into account. The physician also noticed that she tended to base her estimates more strongly on patients that stood out in one sense or another. These are examples of the availability heuristic [48]. Another observed bias was the recency effect [49], where knowledge about patients that were seen most recently was used disproportionately for belief estimation.

Sometimes, difficulties arose due to the discretization of continuous variables. As a simple example, consider the variable age. Modeling age progression by means of a small probability that patients advance one discrete state at a time (e.g., from 50–60 to 60–70 and from 60–70 to 70–80), leads to the bizarre effect that a very small patient group ends up in much older age groups after a few transitions. Although the expected age is properly modeled, this behavior is clearly undesirable. Two ways to address this problem are to retain the continuous nature of random variables as much as possible or to use holding times in order to model that random variables remain in specific discrete states for a prolonged time. In the latter case, the resulting dynamic Bayesian network can be interpreted as a semi-Markov decision process [50].

Our work has demonstrated that the construction of realistic prognostic models using dynamic Bayesian networks that take causal, temporal, and decision-making characteristics into account, is feasible. We also expect that the quality of (dynamic) Bayesian networks, as used for clinical decision support, is improved by taking into account the considerations that have been presented in this paper. It is our hope that the discussed carcinoid model demonstrates the potential of dynamic Bayesian networks in medicine and guides the future development of prognostic models in medicine.

References