Prognosis of High-Grade Carcinoid Tumor Patients using Dynamic Limited-Memory Influence Diagrams*

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Abstract

Dynamic limited-memory influence diagrams (DLIMIDs) have been developed as a framework for decision-making under uncertainty over time. We show that DLIMIDs constructed from two-stage temporal LIMIDs can represent infinite-horizon decision processes. Given a treatment strategy supplied by the physician, DLIMIDs may be used as prognostic models. The theory is applied to determine the prognosis of patients that suffer from an aggressive type of neuroendocrine tumor.

1 Introduction

An important task in medicine is making an accurate prognosis for a particular patient given the patient's history. Accurate prognosis facilitates patient feedback and allows the physician to adjust the treatment strategy but is non-trivial in a world that is characterized by change and uncertainty. In our research, we have been engaged in the construction of a prognostic model for high-grade carcinoid tumors of the midgut, which are an aggressive type of neuroendocrine tumor [Modlin *et al.*, 2005]. The model has been constructed in collaboration with an expert physician of the Netherlands Cancer Institute (NKI).

The aim of this paper is to show how prognostic models may be constructed using an approach that is based on *limited-memory influence diagrams* (LIMIDs) [Lauritzen and Nilsson, 2001]. We extend the definition of LIMIDs to *dynamic* LIMIDs, which explicitly take time into account. We show that dynamic LIMIDs allow the handling of infinite-horizon and partially observable Markov decision processes (POMDPs) [Aström, 1965] whenever they are representable as a so-called *two-stage temporal* LIMID (2TLIMID). Infinite-horizon POMDPs cannot be dealt with using standard (limited-memory) influence diagrams, and contrary to POMDPs, the 2TLIMID representation makes explicit a factorization of the state-space that is defined by the variables in the domain[1]. This is advantageous, from a computational point of view, since it allows for more efficient inference algorithms, and also from a representational point of view, since it allows us to describe the model in terms of the relations that hold between domain variables (see e.g. [Peek, 1999]). Given the strategy of a decision maker, a 2TLIMID can be transformed into a two-stage temporal Bayes network [Dean and Kanazawa, 1989], and prognosis then proceeds by means of probabilistic inference using this Bayesian network.

In contrast to classical approaches to prognosis, such as Cox's proportional hazard model [Cox, 1972], we take a *model-based* approach that aims to represent as accurately as possible the causal relations that hold between domain variables. It has been argued that models which capture cause-effect relationships are more meaningful, accessible and reliable than models which capture empirical associations [Druzdzel, 1997]. Causal models are also richer in representational power than non-causal models, since they allow for reasoning under interventions [Pearl, 2000]. In the context of decision support in medicine, causal models have several advantages. They allow for capturing expert knowledge, which is a valuable commodity in itself, and are more easily modified when new knowledge becomes available (i.e. they are less *brittle* than models based on empirical associations). Furthermore, they facilitate the explanation of drawn conclusions, which may increase the acceptance of decision-support systems in medicine [Teach and Shortliffe, 1984; Lacave and Díez, 2002]. However, building causal models often proves to be non-trivial, as it is difficult to elicit the needed qualitative and quantitative knowledge.

We proceed as follows. Section 2 describes required preliminaries. Dynamic LIMIDs and 2TLIMIDs are introduced in Section 3. Section 4 presents a formalization of prognosis, where we use 2TLIMIDs to represent prognostic models. Section 5 describes the prognostic model for high-grade carcinoids as an illustration of the theory. Section 6 describes some results concerning prognostic model performance. The paper is concluded in Section 7.

2 Preliminaries

Bayesian networks [Pearl, 1988] provide for a compact factorization of a joint probability distribution of a set of random variables by exploiting the notion of *conditional independence*. One way to represent conditional independence is by means of an acyclic directed graph (ADG) G whose nodes $V(G)$ correspond to random variables $\mathbf{X}$ and

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[1]Much recent POMDP research has been concerned with taking advantage of such factorizations [Boutilier *et al.*, 1996a].

the absence of arcs from the set of arcs $A(G)$ represents conditional independence. Due to this one-to-one correspondence we will use nodes $v \in V(G)$ and random variables $X \in \mathbf{X}$ interchangeably. A *Bayesian network* (BN) is then defined as a pair $\mathcal{B} = (G, P)$, such that the joint probability distribution P is factorized according to G:

$$P(\mathbf{X}) = \prod_{X \in \mathbf{X}} P(X \mid \pi_G(X))$$

where $\pi_G(X)$ denotes the *parents* of $X : \{X' \mid (X', X) \in A(G)\}$. We also say that X is the *child* of some $X' \in \pi(X)$ where we drop the subscript G when clear from context. In this paper, we say that a (random) variable X takes values x from a set Ω_X and use $\mathbf{x}$ to denote an element in $\Omega_{\mathbf{X}} = \times_{X \in \mathbf{X}} \Omega_X$ for a set $\mathbf{X}$ of (random) variables.

Limited-memory influence diagrams are models for decision-making under uncertainty [Lauritzen and Nilsson, 2001]. They generalize standard influence-diagrams (IDs) by relaxing the *no-forgetting* assumption [Howard and Matheson, 1984]. This assumption states that, given a total ordering of the decisions, the information known when making decision D is also available when making decision D', if D precedes D' in the ordering. A *limited-memory influence diagram* (LIMID) is defined as a tuple $\mathcal{L} = (\mathbf{C}, \mathbf{D}, \mathbf{U}, G, P)$. Here, $\mathbf{C}$ is a set of *chance variables* (graphically depicted by circles), which are random variables as in a Bayesian network that represent the stochastic component of the model. $\mathbf{D}$ is a set of *decision variables* (graphically depicted by squares), which take on a value from a set of choices Ω_D that represent the decisions that may be externally manipulated by a decision maker. $\mathbf{U}$ is a set of *utility functions* (graphically depicted by diamonds), which represent the utility of being in a certain state as defined by configurations of chance and decision variables. G is an ADG, where nodes $V(G)$ correspond to $\mathbf{C} \cup \mathbf{D} \cup \mathbf{U}$. Again, due to this correspondence, we will use nodes in $V(G)$ and corresponding elements in $\mathbf{C} \cup \mathbf{D} \cup \mathbf{U}$ interchangeably. P is a family of probability distributions that specifies for each configuration $\mathbf{d} \in \Omega_{\mathbf{D}}$ a distribution:

$$P(\mathbf{C} \colon \mathbf{d}) = \prod_{C \in \mathbf{C}} P(C \mid \pi(C))$$

that represents the distribution over $\mathbf{C}$ when the decision maker has set $\mathbf{D} = \mathbf{d}$ [Cowell *et al.*, 1999]. Hence, $\mathbf{C}$ is not conditioned on $\mathbf{D}$, but rather parameterized by $\mathbf{D}$.

The meaning of an arc $(X, Y) \in A(G)$ is determined by the type of Y. If $Y \in \mathbf{C}$ then the conditional probability distribution associated with Y is conditioned by X, as in a Bayesian network. If $Y \in \mathbf{D}$ then the state of X is available to the decision maker prior to deciding upon Y. If $Y \in \mathbf{U}$ then X takes part in the specification of the utility function Y such that $Y \colon \Omega_{\pi(Y)} \to \mathbb{R}$. Utility nodes cannot have children and the joint utility function $\mathcal{U}$ is assumed to be additively decomposable such that $\mathcal{U} = \sum_{U \in \mathbf{U}} U$.

In contrast to standard influence diagrams, the order in which decisions are made in a LIMID should only be compatible with the partial order induced by G, and making a decision D is based solely on its direct parents $\pi(D)$. A *stochastic policy* for decisions $D \in \mathbf{D}$ is defined as a distribution $P_D(D \mid \pi(D))$ that maps configurations of $\pi(D)$ to a distribution over alternatives for D. If P_D is degenerate (i.e. consisting of ones and zeros only) then we say that the policy is deterministic. Let $\mathbf{V}$ denote $\mathbf{C} \cup \mathbf{D}$. A *strategy* is a set of policies $\Delta = \{P_D \colon D \in \mathbf{D}\}$ which induces the following joint distribution over the variables in $\mathbf{V}$:

$$P_\Delta(\mathbf{V}) = P(\mathbf{C} \colon \mathbf{D}) \prod_{D \in \mathbf{D}} P_D(D \mid \pi(D)).$$

Using this distribution we can compute the expected utility of a strategy Δ as

$$E_\Delta(\mathcal{U}) = \sum_{\mathbf{v}} P_\Delta(\mathbf{v}) \mathcal{U}(\mathbf{v}).$$

The aim of any rational decision maker is then to maximize the expected utility by finding the optimal strategy $\arg\max_\Delta E_\Delta(\mathcal{U})$.

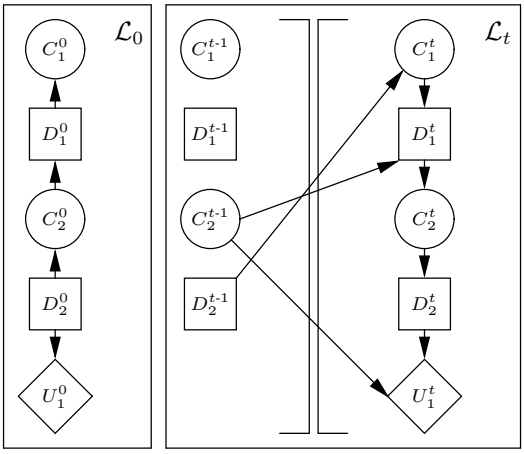

Figure 1: Structure of a 2TLIMID.

3 Dynamic LIMIDs

In this section we demonstrate how to use dynamic LIMIDs that are constructed by means of a structure that we term a *two-stage temporal LIMID* (2TLIMID). When dealing with time, we use $\mathbf{T} \subseteq \mathbb{N}$ to represent a set of time points, which we normally assume to be an interval $\{u \mid t \leq u \leq t', \{t, u, t'\} \subset \mathbb{N}\}$, also written as $t : t'$. We assume that chance variables, decision variables and utility functions are indexed by a superscript $t \in \mathbf{T}$, and use $\mathbf{C^T}$, $\mathbf{D^T}$ and $\mathbf{U^T}$ to denote all chance variables, decision variables and utility functions at times $t \in \mathbf{T}$, where we abbreviate $\mathbf{C^T} \cup \mathbf{D^T}$ with $\mathbf{V^T}$. If $\mathbf{T} = 0 : n$, where $n \in \{1, 2, \ldots\}$ is the *horizon*, then we suppress $\mathbf{T}$ altogether, and we suppress indices for individual chance variables, decision variables and utility functions when clear from context.

3.1 Constructing Dynamic LIMIDs

A *dynamic LIMID* (DLIMID) is simply defined as a LIMID $(\mathbf{C}, \mathbf{D}, \mathbf{U}, G, P)$ such that for all pairs of variables $X^t, Y^u \in \mathbf{V} \cup \mathbf{U}$ it holds that if $t < u$ then Y^u cannot precede X^t in the partial ordering that is induced by G. If the first-order Markov assumption holds that the future is conditionally independent of the past given the present, then we can define a DLIMID in terms of a two-stage temporal LIMID (Fig. 1).

Definition 3.1. *A* two-stage temporal LIMID *(*2TLIMID*) is a pair* $(\mathcal{L}_0, \mathcal{L}_t)$ *with* prior model $\mathcal{L}_0 = (\mathbf{C}^0, \mathbf{D}^0, \mathbf{U}^0, G^0, P^0)$ *and* transition model $\mathcal{L}_t = (\mathbf{C}^{t-1:t}, \mathbf{D}^{t-1:t}, \mathbf{U}^t, G, P)$ *such that chance and decision variables* V_i^{t-1} *in* $\mathbf{V}^{t-1}$ *have no parents.*

The prior model is used to represent the initial distribution $P^0(\mathbf{C}^0 : \mathbf{D}^0)$ and utility functions $U \in \mathbf{U}^0$. The transition model is not yet bound to any specific t, but if bound to some $t \in 1 : n$, then it is used to represent the conditional distribution $P(\mathbf{C}^t : \mathbf{D}^{t-1:t})$ and utility functions $U \in \mathbf{U}^t$ where both G and P do not depend on t. We define the *interface* of the transition model as the set $\mathbf{I}^t \subseteq \mathbf{V}^{t-1}$ such that $(V_i^{t-1}, V_j^t) \in A(G) \Leftrightarrow V_i^{t-1} \in \mathbf{I}^t$.

Given a horizon n, we may *unroll* a 2TLIMID for n *time-slices* in order to obtain a DLIMID such that we obtain the following joint distribution:

$$P(\mathbf{C}, \mathbf{D}) = P^0(\mathbf{C}^0 : \mathbf{D}^0) \prod_{t=1}^{n} P(\mathbf{C}^t : \mathbf{D}^{t-1:t}). \quad (1)$$

Let $\Delta^t = \{P_D(D \mid \pi_G(D)) \mid D \in \mathbf{D}^t\}$ be the strategy for time t and $\Delta = \Delta^0 \cup \cdots \cup \Delta^n$. Given a strategy Δ^0, $\mathcal{L}_0$ defines the following distribution over variables in $\mathbf{V}^0$:

$$P_{\Delta^0}(\mathbf{V}^0) = P^0(\mathbf{C}^0 : \mathbf{D}^0) \prod_{D \in \mathbf{D}^0} P_D(D \mid \pi_{G^0}(D)).$$

Likewise, given a strategy Δ^t with $t > 0$, $\mathcal{L}_t$ defines the following conditional distribution over variables in $\mathbf{V}^t$:

$$P_{\Delta^t}(\mathbf{V}^t \mid \mathbf{V}^{t\text{-}1}) = P(\mathbf{C}^t : \mathbf{D}^{t:t-1}) \prod_{D \in \mathbf{D}^t} P_D(D \mid \pi_G(D)).$$

Combining these equations, given a horizon n and strategy Δ, a 2TLIMID induces the following distribution over variables in $\mathbf{V}$:

$$P_\Delta(\mathbf{V}) = P_{\Delta^0}(\mathbf{V}^0) \prod_{t=1}^{n} P_{\Delta^t}(\mathbf{V}^t \mid \mathbf{I}^t). \quad (2)$$

Let $\mathcal{U}^0(\mathbf{V}^0) = \sum_{U \in \mathbf{U}^0} U(\pi_{G^0}(U))$ stand for the joint utility for $t = 0$ and let $\mathcal{U}^t(\mathbf{V}^{t-1:t}) = \sum_{U \in \mathbf{U}^t} U(\pi_G(U))$ denote the joint utility for time-slice $t > 0$. We redefine the joint utility function for a dynamic LIMID as

$$\mathcal{U}(\mathbf{V}) = \mathcal{U}^0(\mathbf{V}^0) + \sum_{t=1}^{n} \gamma^t \mathcal{U}^t(\mathbf{V}^{t-1:t})$$

where γ, with $0 \leq \gamma < 1$, is a *discount factor*, representing the notion that early rewards are worth more than the same rewards earned later in time.

3.2 Representing Observed History

It is clear from Eq. 1 that DLIMIDs constructed from a 2TLIMID take into account *at most* all chance and decision variables in two subsequent time-slices, since $\pi(D_i^0) \subseteq \mathbf{V}^0$ and $\pi(D_i^t) \subseteq \mathbf{V}^{t-1:t}$. Observations made earlier in time are not taken into account and as a result, states that are qualitatively different can appear the same to the decision maker, leading to suboptimal policies. This phenomenon is known as *perceptual aliasing* [Whitehead and Ballard, 1991]. In this paper we use *memory variables* to take into account (part of) the observed history $\mathbf{v}'$ with $\mathbf{V}' \subseteq \mathbf{V}^{0:c}$ and current time c, as depicted in Fig. 2.

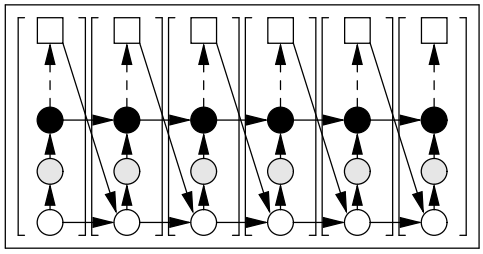

Figure 2: Dealing with perceptual aliasing by introducing memory variables (black circles). Memory variables are used instead of associated observed variables (shaded circles) as the informational predecessor for a decision variable (squares).

Note that if we represent the full observed history, inference becomes intractable for long histories since the states of a memory variable $M \in \mathbf{C}$ associated with a variable $V \in \mathbf{V}$ are given by Ω_M^n, where $\Omega_M^{j+1} = \Omega_M^j \cup (\Omega_M^j \times \Omega_V)$ and $\Omega_M^0 = \Omega_V$. However, by restricting the length of the observed history and/or by using *aggregation* techniques [Boutilier *et al.*, 1996a] that group states which are indistinguishable from the point of view of the decision maker, we can both use the limited-memory assumption of LIMIDs and deal with perceptual aliasing[2]. Examples of variables that fulfill the role of memory variable are BMDHIST and TREATHIST in Fig. 3, which maintain information regarding complications and previous treatments respectively. An additional advantage of the use of memory variables is the fact that we retain the first-order Markov assumption. Due to this property DLIMIDs can take benefit from efficient algorithms for probabilistic inference.

3.3 Inference using 2TLIMIDs

To perform inference with a LIMID $\mathcal{L} = (\mathbf{C}, \mathbf{D}, \mathbf{U}, G, P)$ given a strategy Δ, we convert $\mathcal{L}$ into a Bayesian network $\mathcal{B} = (G', P')$ that is subsequently used for inference purposes. As has been remarked, a strategy Δ induces a distribution over variables $\mathbf{V}$ (viz. Eq. 2). Hence, given Δ, we may convert decision variables D into random variables X_D with parents $\pi_G(D)$ such that

$$P'(X_D \mid \pi_{G'}(X_D)) = P_D(D \mid \pi_G(D)).$$

Additionally, it is possible to convert utility functions U into random variables X_U. Let $\pi_{G'}(X_U) = \pi_G(U)$ where $\Omega_{X_U} = \{0, 1\}$. We associate $P'(X_U \mid \pi(X_U))$ with X_U by means of a transformation

$$P'(X_U = 1 \mid \mathbf{x}') = \frac{U(\mathbf{x}') - \min_{\mathbf{x}} U(\mathbf{x})}{\max_{\mathbf{x}} U(\mathbf{x}) - \min_{\mathbf{x}} U(\mathbf{x})}$$

with $\mathbf{x}, \mathbf{x}' \in \Omega_{\pi(U)}$, as defined in [Cooper, 1988]. We use $B(\mathcal{L}, \Delta)$ to denote this transformation. If the strategy is stationary for each time-slice $t \in \{1, \ldots, n\}$ then we can apply the transformation to a 2TLIMID $(\mathcal{L}_0, \mathcal{L}_t)$, to obtain a so-called *two-stage temporal Bayes network*

[2] In the context of POMDPs, methods that rely on the use of a finite history are common [Aberdeen, 2003].

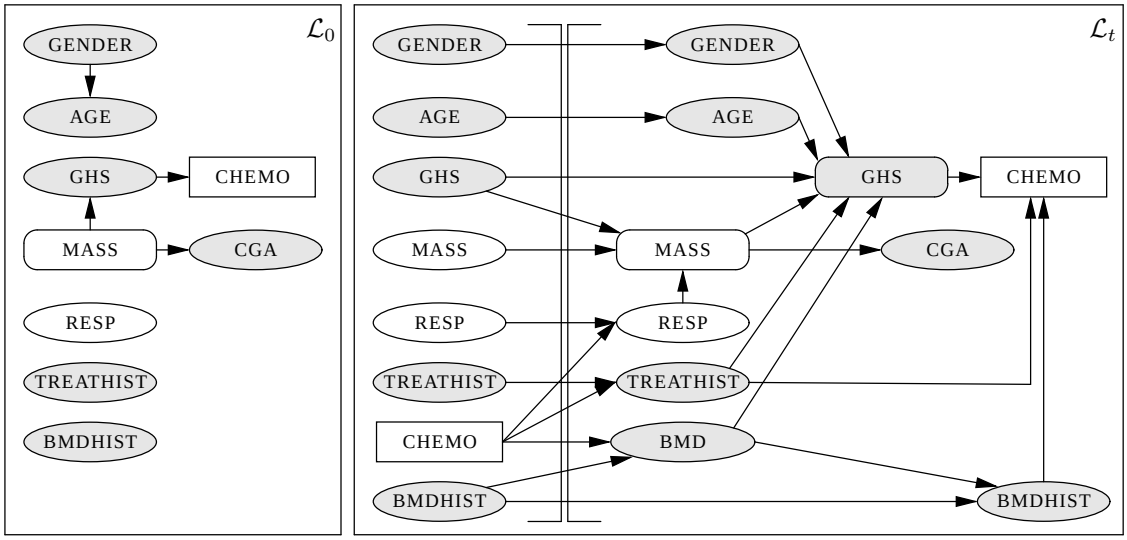

Figure 3: The prognostic model, where shaded nodes are observed and rounded rectangles denote internal structure.

(TBN) $(\mathcal{B}_0, \mathcal{B}_t)$ that is often used to construct a *dynamic Bayesian network* or DBN [Dean and Kanazawa, 1989; Boutilier *et al.*, 1996a; Peek, 1999]. For online inference, efficient algorithms exist that exploit the structure of a 2TBN. In our work, we have used the *interface algorithm* [Murphy, 2002], which allows for online filtering, where the space and time taken to compute $P(\mathbf{X}^t \mid \mathbf{X}^{t-1})$ is independent of the number of time-slices.

4 Prognosis with 2TLIMIDs

Informally, we interpret prognosis as *the prediction of the future status of the patient given the patient history, conditional on a treatment strategy*. This is a non-trivial task since the physician often has incomplete information upon which to base treatment and treatment itself can have uncertain effects. Let $\mathbf{C}$ and $\mathbf{D}$ be sets of chance and decision variables respectively. Let $\mathbf{o}^{0:c}$ with $\mathbf{O}^t \subseteq \mathbf{C}^t$, $t \in 0:c$, represent the observed evidence until the *current time* c and let n denote the horizon. We use the *query variable* $Q \subseteq \mathbf{C} \cup \mathbf{D}$ to denote the variable of interest, and define prognosis given a 2TLIMID as follows:

Definition 4.1. *A* prognosis *for a query variable Q and a horizon n is a conditional probability distribution $P_\Delta(Q^{c:n} \mid \mathbf{o}^{0:c})$ over $Q^{c:n}$.*

In order to compute $P_\Delta(Q^{c:n} \mid \mathbf{o}^{0:c})$, we assume that the prognostic model is defined by $\big((\mathcal{L}_0, \mathcal{L}_t), (\Delta^0, \Delta^t)\big)$, where $(\mathcal{L}_0, \mathcal{L}_t)$ is a 2TLIMID and (Δ^0, Δ^t) is a pair of strategies. Prognosis then proceeds as follows:

1. Define $\big((\mathcal{L}_0, \mathcal{L}_t), (\Delta^0, \Delta^t)\big)$.
2. Create $(\mathcal{B}_0, \mathcal{B}_t) = \big(B(\mathcal{L}_0, \Delta^0), B(\mathcal{L}_t, \Delta^t)\big)$.
3. Recursively compute $P_\Delta(Q^{c:n} \mid \mathbf{o}^{0:c})$ using $(\mathcal{B}_0, \mathcal{B}_t)$.

Although the processes we consider in medicine are finite since they are bounded by patient's life-span, we describe them as infinite-horizon processes where the process has some probability of terminating at each time-slice. In computing the prognosis however we assume that the horizon n is finite. In the next section we develop the actual model for prognosis of high-grade carcinoid tumor patients using the theory developed so far.

5 The High-Grade Carcinoid Model

A carcinoid tumor is a type of neuroendocrine tumor that is predominantly found in the midgut and is normally characterized by the production of excessive amounts of biochemically active substances, such as serotonin [Modlin *et al.*, 2005]. In a small minority of cases, tumors are of high-grade histology which, although biochemically much less active than low-grade carcinoids, show much more rapid tumor progression. Therefore, aggressive chemotherapy in the form of an etoposide and cisplatin-containing scheme is the only treatment option [Moertel *et al.*, 1991]. In this section we develop the prognostic model for high-grade carcinoid tumors, consisting of a 2TLIMID $(\mathcal{L}_0, \mathcal{L}_t)$ and a strategy (Δ^0, Δ^t), supplied by the physician. Patients are admitted to the hospital at the initial time $t = 0$. Each time-slice represents the patient status at three-month intervals since patients return for follow-up every three months. Since the aim is not to improve upon the provided strategy, we omit utility nodes from the discussion.

The qualitative structure of the 2TLIMID that resulted from our modeling efforts is depicted in Fig. 3. The patient's *general health status* (GHS) is of central importance. In oncology, one way to represent the general health status is by means of the *performance status* [Oken *et al.*, 1982]. We define $\Omega_{\text{GHS}} = \{0, \ldots, 5\}$ where $\text{GHS} = 0$ stands for normal health status, $\text{GHS} = 1$ stands for mild complaints, $\text{GHS} = 2$ stands for impaired age-appropriate activity, $\text{GHS} = 3$ stands for confinement to bed for more than 50% of the time, $\text{GHS} = 4$ stands for intensive care and $\text{GHS} = 5$ stands for patient death. The general health status depends on patient properties such as AGE, GENDER and current general health status. Furthermore, GHS is influenced by the tumor mass (MASS) and the treatment policy

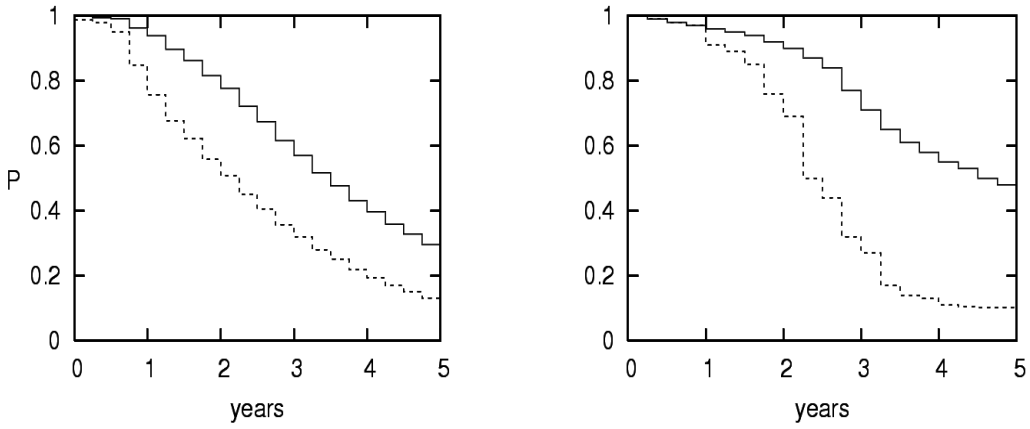

Figure 4: Kaplan-Meier curve, showing the cumulative probability of survival for patients A (dashed line) and B (solid line) over a five year period, as predicted by the model (left), and the physician (right).

that is adopted. Chemotherapy (CHEMO), with $\Omega_{\text{CHEMO}} = \{\textit{none}, \textit{reduced}, \textit{standard}\}$, is the only available treatment, where a reduced dose is at 75% of the standard dose. Chemotherapy can have both positive and negative effects on general health status; positive due to reductions in tumor mass, and negative due to severe bone-marrow depression (BMD) and damage associated with prolonged chemotherapy. We use BMDHIST, with $\Omega_{\text{BMDHIST}} = \{\textit{no-bmd}, \textit{bmd}\}$, as a memory variable to represent whether or not the patient has experienced BMD in the past. Severe BMD is assumed to be fully observable since patients are always tested for it. We use TREATHIST, with $\Omega_{\text{TREATHIST}} = \{0, 1, 2, 3\}$, as a memory variable to represent the patient's relevant treatment history, such that $\text{TREATHIST} = i$ represents continued chemotherapy over the past $3 \cdot i$ months. Reductions in tumor mass due to chemotherapy are often described in terms of tumor response (RESP).

The amount of tumor mass can be estimated by measuring the plasma *chromogranin A* level (CGA) since it is strongly correlated with tumor burden [Nobels *et al.*, 1998]. Since CGA levels are always measured we need not include the decision variable whether or not to determine CGA levels (i.e., the associated policy is *blind*). Severe bone-marrow depression may cause patient death due to associated sepsis and/or internal bleeding [Moertel *et al.*, 1991]. AGE and GENDER are risk factors that may lead to patient death due to causes other than the disease. MASS and GHS in Fig. 3 are compact representations of a Bayesian network fragment. This representation has the advantage of preventing unnecessary clutter in the graphical representation of a Bayesian network and provides a way to represent *context-specific independence* [Boutilier *et al.*, 1996b]. Due to space restrictions, we will not discuss the internal structure of these fragments.

To complete the model, we have to choose a treatment strategy and assess the probabilities that parameterize the model. We mention only the chosen treatment strategy. In $\mathcal{L}_0$, $\pi(\text{CHEMO}^0) = \{\text{GHS}^0\}$, whereas in $\mathcal{L}_t$, $\pi(\text{CHEMO}^t) = \{\text{TREATHIST}^t, \text{BMD}^t, \text{GHS}^t\}$. The policy for chemotherapy in Δ^0 is to apply standard chemotherapy only if the general health status is good enough ($\text{GHS}^0 \leq 3$); otherwise no chemotherapy is applied. The policy used in Δ^t is as follows:

$$(\text{TREATHIST}^t = 0 \wedge \text{GHS}^t \leq 3 \wedge \text{BMDHIST}^t = x) \vee$$
$$(\text{TREATHIST}^t = 1 \wedge \text{GHS}^t < 3 \wedge \text{BMDHIST}^t = x)$$
$$\rightarrow \text{CHEMO}^t = y$$

where $x = \textit{no-bmd} \Leftrightarrow y = \textit{standard}$ and $x = \textit{bmd} \Leftrightarrow y = \textit{reduced}$. In all other cases, we do not give chemotherapy.

6 Experimental Results

In this section we use the prognostic model to answer the following query:

> *What is the probability of patient survival over the next five years?*

We assume that the current time $c = 0$ and compare the prognosis for the following two patients. Patient A is a 75 year old male of poor general health status ($\text{GHS}^0 = 2$) and an initially extreme CGA level. Patient B is a 50 year old female of average general health status ($\text{GHS}^0 = 0$) and an initially elevated CGA level.

In order to compute the probability of patient survival (Q) over the next five years, we assume that $Q \in \mathbf{C}$ with $\Omega_Q = \{\textit{alive}, \textit{dead}\}$, where GHS is a parent of Q, such that $P(Q^t = alive \mid \text{GHS}^t = x)$ is one if $x \neq 5$ and zero otherwise for $0 \leq t \leq n$. We have compared the prognosis made by the model with the prognosis made by the physician, as is shown in Fig. 5.

The physician felt that model predictions where somewhat too positive for patient A, whereas they where somewhat too negative for patient B. Of course, it is difficult to decide how the model would perform in clinical practice, since the physician's opinion is not necessarily the gold standard with which to compare performance. Furthermore, according to the physician, the predictions made by the model do make sense from a qualitative point of view in that it reflects a much worse prognosis for patient A than for patient B. The evaluation and possible calibration of the model in a clinical setting deserves further attention.

7 Conclusion

We have defined DLIMIDs constructed from 2TLIMIDs as a framework for decision-making under uncertainty and used them as the basis for a prognostic model for high-grade carcinoid patients. Although the repetitive structure of a 2TLIMID has been used implicitly in [Lauritzen and Nilsson, 2001], the explicit use of a 2TLIMID and its transformation to a 2TBN allows for the representation of infinite-horizon POMDPs. This benefit comes at the expense of using policies that may suffer from perceptual aliasing. This is resolved by means of memory variables which represent the observed history that is considered relevant by the physician. This approach is particularly useful whenever the policy depends on a small subset of the observed history, as is for instance dictated by a treatment protocol. In general, we would also like to use 2TLIMIDs in order to improve strategies for infinite-horizon partially-observable Markov decision processes, which is a research topic we are currently pursuing. The advocated model-based approach allows for a computationally efficient prognostic model that facilitates interpretation by the physician, while the experimental results demonstrate the feasibility of our approach to prognosis in medicine.

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