APPLICATION OF DYNAMIC BAYESIAN NETWORKS TO RISK ASSESSMENT IN MEDICINE

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Abstract: Dynamic Bayesian networks (DBNs) offer a framework for explicit modeling of temporal relationships, and are useful as both prognostic and diagnostic tools. In medicine, for example, they can assist in planning treatment options or in clinical management of patients. They have been also widely applied to genomics and proteomics.
This paper shows how dynamic Bayesian networks can be used in a risk assessment in medicine and presents an example of an application to cervical cancer screening. The model is a convenient tool for assessing the risk of cervical precancer and invasive cervical cancer over time. These quantitative risk assessments are helpful for establishing the optimal timing of follow-up screening and are the first step toward generating individualized reevaluation scheduling.

Keywords: dynamic Bayesian networks, risk assessment in medicine

1. Introduction

There is a variety of approaches to temporal modeling and reasoning in medicine (see [1] and [2] for accessible summaries). These include hidden Markov models, Markov decision processes, dynamic Bayesian networks, and dynamic influence diagrams. Markov models have been used widely in medical decision-analytic and cost-effectiveness models [25]. Ground breaking work based on dynamic models in medicine was performed by Leong, Harmanec, Xiang, and colleagues [12,16,27], who, in addition to Bayesian networks (BNs) and dynamic Bayesian networks (DBNs), used successfully a combination of graphical models with Markov chains to address different medical problems, including colorectal cancer management, neurosurgery ICU monitoring, and cleft lip and palate management. Several applications of dynamic Bayesian networks have been proposed in medicine. For

Zeszyty Naukowe Politechniki Białostockiej. Informatyka, vol. 5, pp. 35-49, 2010.

example, NasoNet, a system for diagnosis and prognosis of nasopharyngeal cancer [10], or a DBN for management of patients suffering from a carcinoid tumor [26]. More recently, dynamic Bayesian networks have been used in genomics and proteomics, for example, in predicting protein secondary structure [28], modeling peptide fragmentation [15] and cellular systems [9], or in identifying gene regulatory networks from time course microarray data [29].

This paper shows how dynamic Bayesian networks can be applied to risk assessment in medicine. In addition to introducing the formalism to the readers, it describes a real model, based on a DBN, originating from author's work at the University of Pittsburgh [3,4,5]. This model illustrates general principles of building DBN models and applying them to risk assessment in medicine.

The reminder of this paper is structured as follows. Section 1. provides a brief review of work focusing on temporal modeling in medicine. Sections 2. and 3. present the formalism of Bayesian networks and their temporal extension, i.e., dynamic Bayesian networks. Section 4. captures several issues related to cervical cancer screening and describes an example of a risk model based on a dynamic Bayesian network. Sections 5. concludes the paper.

2. Bayesian Networks

Bayesian networks (BNs) [21], also called belief networks or causal networks, are acyclic directed graphs modeling probabilistic influences among variables. The graphical part of a Bayesian network reflects the structure of a modeled problem, while conditional probability distributions quantify local interactions among neighboring variables. Bayesian networks have proven to be powerful tools for modeling complex problems involving uncertain knowledge. They have been practically employed in a variety of fields, including engineering, science, and medicine with some models reaching the size of hundreds or thousands of variables.

Figure 1 captures a simple BN model. This example model includes four risk factors and one effect of breast cancer. Each arc of this graph represents a probabilistic relationship and it is quantified by a conditional probability distribution. For example, the arc between the variables *Family history* and *Breast Cancer* tells that family history of cancer impacts a risk of developing a breast cancer.

3. Dynamic Bayesian Networks

Dynamic Bayesian networks (DBNs) are a temporal extension of Bayesian networks that allows to model dynamic processes. The hidden Markov model [22] is considered

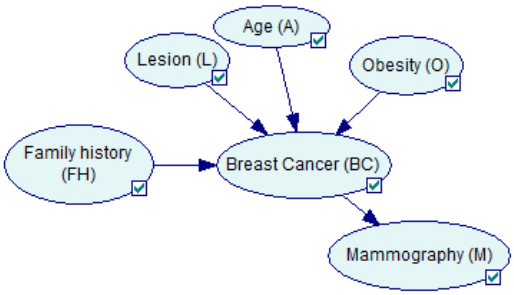

Fig. 1. Example of a BN model

to be the simplest dynamic Bayesian network. While Bayesian networks (BNs) have been used as modeling tools for over two decades, their temporal extension, dynamic Bayesian networks, found their way into medical modeling only in the last decade. Figure 2 captures an example of a dynamic Bayesian network model, an extension of the model presented in Figure 1. The graphical structure of the DBN model is similar to its static version, although there are additional arcs that quantify temporal relationships between neighboring variables.

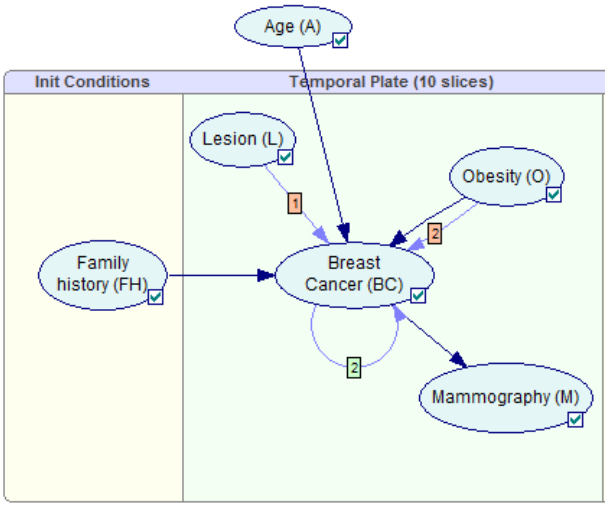

Fig. 2. Example of a DBN model

3.1 Temporal aspects of a DBN model

The dynamic arcs included in the example model, presented in Figure 2, represent changes over time among the variables. The single digit numbers on the arcs denote the temporal delay of influence. An arc labeled as *1* between the variables *Lesion (L)* and *Breast Cancer (BC)*, for example, denotes an influence that takes one time step, while an arc labeled as *2* between the variables *Obesity (O)* and *Breast cancer (BC)* denotes an influence that takes two time steps. Effectively, the model encodes the following conditional distribution over the variable *Breast Cancer (BC)*:

$$P(BC_t|A,FH,O_t,L_{t-1},O_{t-2},BC_{t-2}). \tag{1}$$

In other words, conditional probability distribution for *Breast Cancer (BC)* depends on a patient *Age (A)*, *Family history (FH)*, and a current status of the variable *Obesity (O)*. Furthermore, it depends on *Lesion (L)* result in previous time step and *Obesity* result recorded two time steps ago. Finally, it also depends on *Breast Cancer* result two time steps ago. The time step that is chosen for a dynamic Bayesian model varies on a modeled problem. In this example it could be a time interval used in screening for a breast cancer.

Age (A)	yes						
Obesity (O)	yes						
Lesion (L) [t-1]	present				absent		
Obesity (O) [t-2]	yes		no		yes		n
(Self) [t-2]	yes	no	yes	no	yes	no	yes
yes	0.1	0.08	0.02	0.01	0.1	0.08	0.02
no	0.9	0.92	0.98	0.99	0.9	0.92	0.98

Fig. 3. Fragment of a conditional probability table for the variable *Breast Cancer*

Since there are three types of arcs coming into the variable *Breast Cancer* (i.e., regular arcs representing static relationships between the variables and two types of temporal arcs with labels *1* and *2*), there are three different conditional probability tables that quantify the variable *Breast Cancer*. Equations 2, 3, and 4 correspond respectively to these three conditional probability tables (i.e., regular arcs: time step $t = 0$, temporal arcs labeled as *1*: time step $t = 1$, and temporal arcs labeled as *2*: time step $t = 2$):

$$P(BC_{t=0}|A,FH,O_{t=0}) \tag{2}$$

$$P(BC_{t=1}|A,O_{t=1},L_{t=0}) \tag{3}$$

$$P(BC_{t=2}|A, O_{t=2}, L_{t=1}, O_{t=0}, BC_{t=0}). \tag{4}$$

Figure 3 shows a fragment of the conditional probability table for the variable *Breast Cancer* for time step $t = 2$ (see also Equation 4). In this case a conditional probability distribution for *Breast Cancer* depends on the variables: *Age*, *Obesity*, and *Lesion* in previous time step $t = 1$. Furthermore, this conditional probability distribution depends on the variables *Obesity* and *Breast Cancer* in time step $t = 0$.

3.2 Unrolled DBN model

Figure 4 captures three unrolled time steps of the DBN model presented in Figure 2. Four out of six variables are repeated in each time step, i.e., *Lesion*, *Obesity*, *Breast Cancer*, *Mammography*. The variable *Family history* is not repeated since it was modeled only as an initial condition and it is not changing over time. Another variable that is not repeated is *Age*, although, it impacts the variable *Breast Cancer* in each time step.

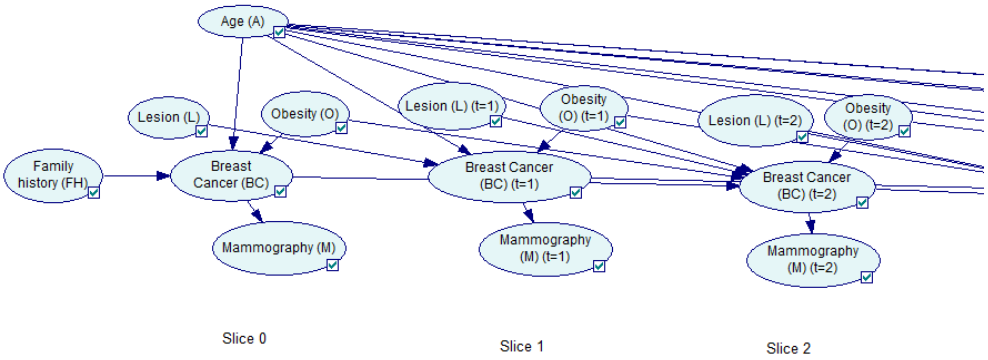

Fig. 4. Unrolled DBN model for the first 3 time steps

3.3 Dynamic evidence

Evidence can be observed for any time step implemented in the model. Figure 5 shows dynamic evidence for the variable *Mammography*. The model has 10 time steps (see Figure 2), therefore, there is a possibility of observing this variable for 10 different time steps. At time step *0* the result of the variable *Mammography* has been

observed normal, at time step *1* normal, there is no observation at time step *2* and an abnormal mammography was observed at time step *3*.

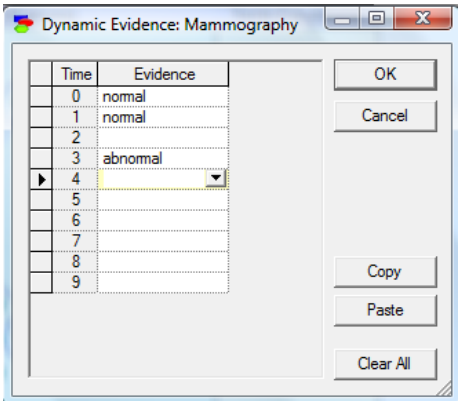

Fig. 5. Entering dynamic evidence for the variable *Mammography*

3.4 Risk assessment

Given observed dynamic evidence, the model can derive the probability distribution over a variable in question (in this case, the variable *Breast Cancer*). For example, the model will calculate the following probability:

$$P(BC(present)|E), \tag{5}$$

where

$$E = A(55), O_t(present), L_{t-1}(present), M_{t-1}(abnormal). \tag{6}$$

In this case, the model calculates a risk of developing a breast cancer for a 55 old, obese woman with a lesion and an abnormal mammography result in a previous time step. Figure 6 shows the probability of developing a breast cancer given this dynamic evidence, i.e., $P(BC(present)|E)$. This plot shows the risk of developing breast cancer over 10 time steps. It can be used to estimate the optimal time for follow-up medical tests and procedures.

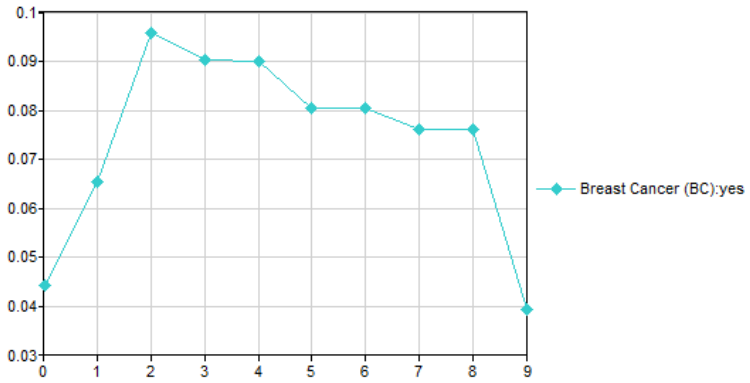

Fig. 6. Risk of a breast cancer over time

3.5 Challenges

The most challenging task in building a dynamic model are missing data, since often there is no complete follow-up of a patient case. A patient may show up for a test and then skip a year or never come back. There are several ways of dealing with this problem, one of which is representing missing values as an additional state [20]. Reasoning algorithms for Bayesian networks do not require complete information on a patient case. This means that the posterior probability distribution over a variable in question can be derived given any subset of possible observations.

4. Cervical Cancer Screening

DBNs are especially suitable for modeling screening data where there are temporal dependencies among variables. In this section, I will present an example of a medical problem, cervical cancer screening, in which DBNs have proven invaluable.

4.1 The problem of cervical cancer

Cervical cancer is the fifth most deadly cancer in women worldwide.[1] The introduction of the Papanicolaou test (also called PAP smear or PAP test) for cervical cancer screening has dramatically reduced the incidence and mortality of cervical

[1] World Health Organization, Fact sheet No. 297, Cancer, February 2006 (http://www.who.int/mediacentre/factsheets/fs297/en/index.html

cancer. Abnormal PAP test result suggests the presence of potentially premalignant or malignant changes in the cervix. PAP test allows for an examination and possible preventive treatment. Recommendations for how often a PAP test should be performed vary, depending on a screening program, between once a year and once every five years. The most important risk factor in the development of cervical cancer is infection with a high-risk strain of human papillomavirus (hrHPV). The virus works by triggering alterations in the cells of the cervix, which can lead further to the development of precancer, which can further result in cancer.

There have been several computer-based tools implemented to assist cervical cancer screening, diagnosis, and treatment decisions. These tools include computer-based systems to assist cytotechnologists and cytopathologists in the interpretation of PAP test slides. For example, an automated cervical precancerous diagnostic system extracts features from PAP test slides and then based on an artificial neural network predicts the cervical precancerous stage [17]. Another tool, developed a decade ago, is the PAPNET system [19]. The PAPNET system is also based on the neural network approach and assists rescreening of PAP test slides in order to identify cervical abnormalities that were not identified by a manual rescreening.

Cantor et al. [7] presented several decision-analytic and cost-effectiveness models that could be applied to guide cervical cancer screening, diagnosis, and treatment decisions. One of the decision-analytic models was a Markov model for the natural history of HPV infection and cervical carcinogenesis [18]. The model assesses life-time risk of cervical cancer as well as approximates the age-specific incidence of cervical cancer. Similar model was built for the German population [24]. The model was a Markov model for evaluating a life-time risk and life-time mortality of cervical cancer. Another group of tools for cervical cancer screening are cost-effectiveness models. Most of these cost-effectiveness models refer to investigation of an optimal scenario for cervical cancer screening based on two tests: PAP test and testing for the presence of hrHPV, e.g., [6,11,14].

There are many published studies that report risk assessments for cervical precancer and invasive cervical cancer, e.g., [8,13,23]. All these approaches have a major weakness, i.e., to my knowledge, all of these studies assess the risk based on the current state of a patient and do not include any history record. Many of these studies are based on cross-sectional data or on data coming from clinical trials. The strength of graphical models, such as DBNs is that they can easily combine information originating from history records and other sources.

4.2 The Pittsburgh Cervical Cancer Screening Model

The risk model presented in this paper is called *Pittsburgh Cervical Cancer Screening Model (*PCCSM). The model was built in Pittsburgh (Pennsylvania, USA) and the data that quantified it, reflect greater Pittsburgh population. The model is a dynamic Bayesian network that consists of 19 variables including cytological and histopathological data, and hrHPV test results. It also includes patient history data, such as history of infections, history of cancer, history of contraception, history of abnormal cytology, menstrual history, and demographics, i.e., age and race. One of the unique features of the PCCSM is the fact that risk assessments are generated not only based on a current state of a patient case, but also on a history record. Another advantage of the model is its sound quantification. All numerical parameters of the model were assessed based on a hospital data set coming from one population of patients. The model was parametrized by means of data collected during four years (2005-2008) and consisting of 393,531 patient records with PAP test result. The data were collected at Magee-Womens Hospital of the University of Pittsburgh Medical Center. More details on the model can be found in [5].

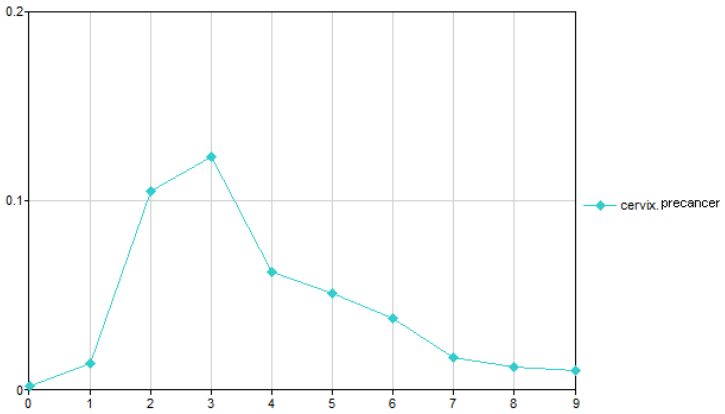

Fig. 7. Temporal beliefs

The PCCSM generates risk assessments for cervical precancer and invasive cervical cancer over time. Figure 7 captures quantitative risk assessments of precancer over the time period of 15 years for a single example patient case. It shows that this patient will run the highest risk of cervical precancer between the first and third year after the initial test. The dip in the third year is due to a delay in the effect of an

hrHPV virus infection. This risk will decrease after the fourth year. The reason for this shape of the curve were abnormal observations for *t=1* and *t=2* (abnormal PAP test results and positive hrHPV test results, respectively).

The PCCSM model allowed for identifying those risk categories that are crucial for follow-up planning, e.g., patients that are at higher risk for cervical cancer should be screened more often than patients that are at lower risk. Figure 8 presents risk assessments generated by the PCCSM model and stratified by the outputs of two variables: PAP and HPV tests. The chart captures average two years risk assessments for over 40,000 patient cases tested with the PCCSM model. It is evident from Figure 8 that a combination of *HSIL+* PAP test result with a positive HPV test result indicated the highest risk group for cervical precancer and cervical cancer. On the other hand a positive HPV test result does not by itself put a patient in a high risk group if the PAP test result is negative.

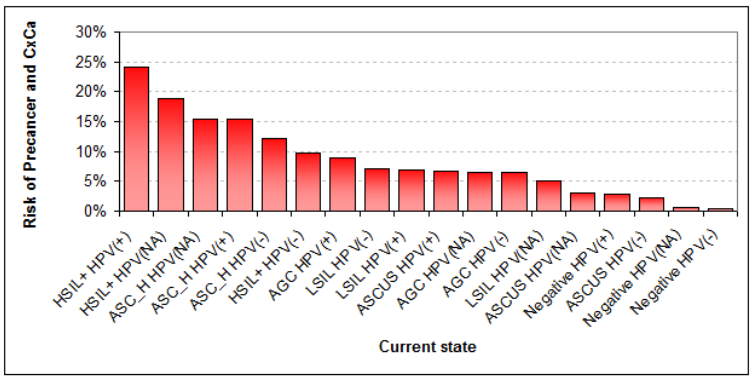

Fig. 8. PCCSM risk assessments for cervical precancer and cervical cancer (CxCa) stratified by the outputs of PAP and HPV test results

The PCCSM model allows for individualized management of patients and computes patient-specific risk based on the patients characteristics, history data, and test results. Figure 9 captures the PCCSM risk assessments given different patient history record. For example, a patient with all negative PAP test results in the past (last bar on the chart) is at different risk category than a patient having at least one *ASCUS* result (one of the abnormal PAP test results) in the past (the category *Any-ASCUS*). From the chart we can see that a risk assessment for the latter category doubles.

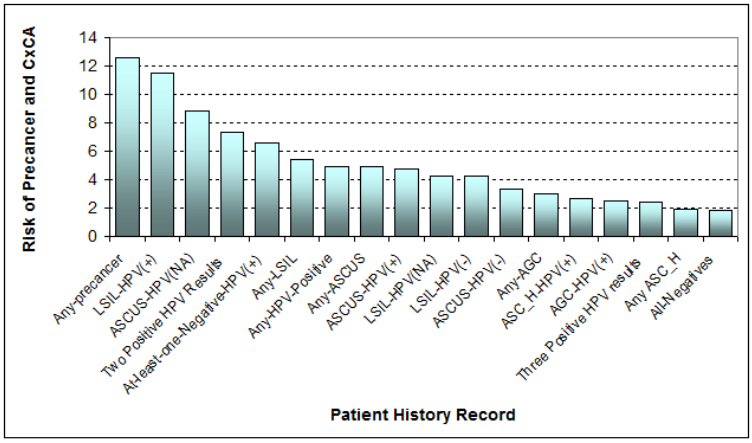

Fig. 9. PCCSM risk assessments for cervical precancer and cervical cancer (CxCa)

The PCCSM model is going to be used in Magee-Womens Hospital in the routine practice of identifying high risk patients. We are in the process of building a web-based graphical interface that will help to interact with the model.

5. Conclusions

Dynamic Bayesian networks are capable to model temporal relationships in medicine. They allow for computing quantitative risk assessments given observed variables. Dynamic Bayesian network models offer looking at risk assessments from different perspectives. They allow to identify groups of patients that are at higher risk of developing a disease. These models generate risk assessments over time. Furthermore, they quantify risk given patient history record. These quantitative risk assessments can be helpful in establishing the optimal timing of follow-up screening and can increase the accuracy of risk estimates. This can have a noticeable effect on the quality of medical care.

Acknowledgments

I would like to thank my collaborators at Magee Womens Hospital, University of Pittsburgh Medical Center: prof. R. Marshall Austin, for his expertise in cytopathology, his invaluable guidance, and his constant support and encouragement, Karen Lassige for her invaluable help in retrieving the data from the hospital database.

The models presented in this paper were created and tested using SMILE, an inference engine, and GeNIe, a development environment for reasoning in graphical probabilistic models, both developed at the Decision Systems Laboratory, University of Pittsburgh and available at http://genie.sis.pitt.edu/.

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ZASTOSOWANIE DYNAMICZNYCH SIECI BAYESOWSKICH W WYZNACZANIU RYZYKA W MEDYCYNIE

Streszczenie Dynamiczne sieci bayesowskie (DBNs) pozwalają na modelowanie zależności czasowych. Modele te są niejednokrotnie używane w prognostyce. Na przykład w medycynie, jako narzędzia do prognozowania czy też planowania terapii. Dynamiczne sieci

bayesowskie są też szeroko stosowane w genomice oraz w proteomice.
Atrykuł ten opisuje, w jaki sposób dynamiczne sieci bayesowskie mogą być zastosowane w wyznaczaniu ryzyka w medycynie. W pracy przedstawiono przykład zastosowania dynamicznych sieci bayesowskich w profilaktyce raka szyjki macicy. Prezentowany model został zbudowany w oparciu o dwa źródła wiedzy: opinie eksperta oraz dane medyczne. Model ten pozwala na wyznaczanie ryzyka zachorowania na raka szyjki macicy. Wartości ryzyka wyznaczane przez model pozwalają na określenie optymalnego czasu wykonania kolejnych badań przesiewowych oraz na zindywidualizowanie procesu profilaktyki.

Słowa kluczowe: dynamiczne sieci bayesowskie, wyznaczanie ryzyka w medycynie