Intelligent Information Systems 9999
ISBN 666-666-666, pages 1–10

Application of Dynamic Bayesian Networks to Cervical Cancer Screening

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Abstract

Dynamic Bayesian networks (DBNs) offer a framework for explicit modeling of temporal relationships. They are often used as prognostic tools. In medicine, for example, they can assist planning treatment options or clinical management of patients. They have been also widely applied to genomics and proteomics.

This paper describes the Pittsburgh Cervical Cancer Screening Model (PCCSM), a DBN that combines two sources of knowledge: expert opinion and objective hospital data. The model serves as 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.

1 Introduction

The Pittsburgh Cervical Cancer Screening Model (PCCSM) (Austin *et al.*, 2008a,b) is a dynamic Bayesian network based on two sources of knowledge: expert opinion and objective hospital data. The model serves as a convenient tool for assessing the risk of cervical precancer (CIN2/CIN3/AIS)[1] and invasive cervical cancer over time. These quantitative risk assessments can help to establish the optimal time for follow-up screening and are the first step toward generating individualized reevaluation scheduling. The model also allows for investigating how several variables contribute to a studied outcome, that is, detection of cervical precancer and invasive cervical cancer over time.

The rest of this paper is structured as follows. Section 2 provides a brief review of work focusing on temporal modeling in medicine. Section 3 presents several issues related to cervical cancer screening. Section 4 describes the details of the PCCSM, while Section 5 presents the experimental results of the model. Section 6 discusses selected results.

[1] CIN2-CIN3 are abbreviations for two types of *Cervical Intraepithelial Neoplasia* and AIS stands for *Adenocarcinoma In Situ*.

2 Temporal modeling in medicine

There is a variety of approaches to temporal modeling and reasoning in medicine (see Augusto (2005) and Adlassnig *et al.* (2006) for accessible summaries). These include Markov decision processes, dynamic Bayesian networks, and dynamic influence diagrams. An application of Markov models to medicine was initially proposed by Sonnenberg and Beck (1993). These models have been later used widely in medical decision-analytic and cost-effectiveness models. While Bayesian networks (BNs) (Pearl, 1988) 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. Ground breaking work based on dynamic models in medicine was performed by Harmanec *et al.* (1999), Leong (1998), Xiang and Poh (2002), who, in addition to BNs and DBNs, used successfully a combination of graphical models with Markov chains to address problems in different medical domains, including colorectal cancer management, neurosurgery ICU monitoring, and cleft lip and palate management. There are several applications of dynamic Bayesian networks in medicine. For example, NasoNet, a system for diagnosis and prognosis of nasopharyngeal cancer (Galan *et al.*, 2002), or a DBN for management of patients suffering from a carcinoid tumor (van Gerven *et al.*, 2008). Most recently, dynamic Bayesian networks have been used in genomics and proteomics. For example, in a prediction of protein secondary structure (Yao *et al.*, 2008), modeling peptide fragmentation (Klammer *et al.*, 2008) and cellular systems (Ferrazzi *et al.*, 2006), or in identifying gene regulatory networks from time course microarray data (Zou and Conzen, 2005).

3 Cervical cancer screening

Worldwide, cervical cancer is the fifth most deadly cancer in women worldwide.[2] The widespread 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 cancer in developed countries. Abnormal Pap test result suggests the presence of cervical intraepithelial neoplasia (potentially premalignant changes in the cervix) before a cancer has developed. Pap test allows for an examination and possible preventive treatment. Recommendations for how often a Pap test should be performed vary 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 cervical intraepithelial neoplasia, which can 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 that extracts features from Pap test slides and then based on an

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

artificial neural network predicts the cervical precancerous stage (Mat-Isa *et al.*, 2008). Another tool, developed a decade ago, is the PAPNET system (O'Leary *et al.*, 1998). The PAPNET system is also based on the neural network approach and assists rescreening of Pap test slides to identify cervical abnormalities that were not identified by a manual rescreening.

Cantor *et al.* (2003) 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 (Myers *et al.*, 2000). 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 Siebert *et al.* (2006). 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., (Bidus *et al.*, 2006; Goldie *et al.*, 2004; Kim *et al.*, 2002). Most recently, cost-effectiveness analyses include one more variable: HPV vaccine status, e.g., (Diaz-Sanchis *et al.*, 2008; Goldie *et al.*, 2006; Kim *et al.*, 2008a,b; Stout *et al.*, 2008).

There are many published studies that report risk assessments for cervical precancer and invasive cervical cancer, e.g., (Castle *et al.*, 2007; Khan *et al.*, 2005; Ronco *et al.*, 2006). However, to our knowledge, all of these studies assesses 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.

4 Pittsburgh Cervical Cancer Screening Model

The Pittsburgh Cervical Cancer Screening Model (PCCSM) is a dynamic Bayesian network that consists of 19 variables including cytological and histopathological data, and hrHPV DNA 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, and recently included HPV vaccine status. The PCCSM serves as a convenient tool for assessing a 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. 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.

4.1 Model structure

The model consists of cytological (*Pap test* result), histopathological (results of biopsies and surgical procedures), and hrHPV DNA variables. It also includes findings representing patient history, such as *History of infections*, *History of cancer*, *History of contraception*, *History of Pap abnormalities*, and *Menstrual history*. It also includes demographical information, *Age* and *Race*. We based the structure of our model on expert knowledge, textbook, and the data, i.e., some of the relationships (arcs in the graph) were learned from the data available to us.

We assumed in our model that a patient was suffering in the past from only one infection. The reason for this is that 98% of all cases in the database were single-infection cases. The model includes eight different types of infections. We applied a similar assumption to the variables *History of cancer* and *History of contraception*. There are eight different cancers and six different types of contraception included in the model. There are four variables related to the *Pap test*. For example, the variable *Adequacy* represents adequacy of a *Pap test* and takes the following four values: *Satisfactory* (assigned for vaginal *Pap tests*), *Satisfactory EC*, *Satisfactory No EC TZ*, and *Unsatisfactory*. The variable *Pap test type* indicates the type of a *Pap test* that was performed and has three states: *Conventional Pap*, *Liquid-based Pap (TP)*, and *Liquid-based Pap (TP) imaged*. We show a simplified structure of the model in Figure 1.

4.2 Temporal aspects of the model

The dynamic arcs included in the model represent changes over time among the variables *Age*, HPV *test* and *Cervix*. The single digit numbers on the arcs denote the temporal delay of influence. An arc labeled as $\boxed{1}$ between the variables HPV *test* and *Cervix*, for example, denotes an influence that takes one time step, while an arc labeled as $\boxed{2}$ between the variables HPV *test* and *Cervix* denotes an influence that takes two time steps. Effectively, the model encodes the following conditional distribution over the variable *Cervix*:

$$\Pr(Cervix_t|Age_t, HPV_t, HPV_{t-1}, HPV_{t-2}, Cervix_{t-1}, Cervix_{t-2}) \qquad (1)$$

The time step that we have chosen for our model was one year. This is also a consequence of cervical cancer screening guidelines in the US, which advise a Pap test (often combined with performing the HPV test) to be performed once a year.

4.3 The numerical parameters

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 (with five months of data excluded for testing). The data were collected at Magee-Womens Hospital of the University of Pittsburgh Medical Center. Majority of the performed Pap tests (96%) were coming from ThinPrep Imaging System: (TIS)-Imaged. Around 10% of the cytology cases were followed by a histopathological and surgical procedure (42,814 data entries) while around 19% of all cytological data entries

were associated with a high risk Hpv DNA test result (75,301 hrHpv DNA test results). Some of the patient cases were additionally described by patient history data, such as history of infections, history of cancer, history of contraception, history of abnormal cytology, and menstrual history (depending on the variable, these data were available for around 2%-30% of all cytology entries). Each patient case was described by two demographic variables: age and race.

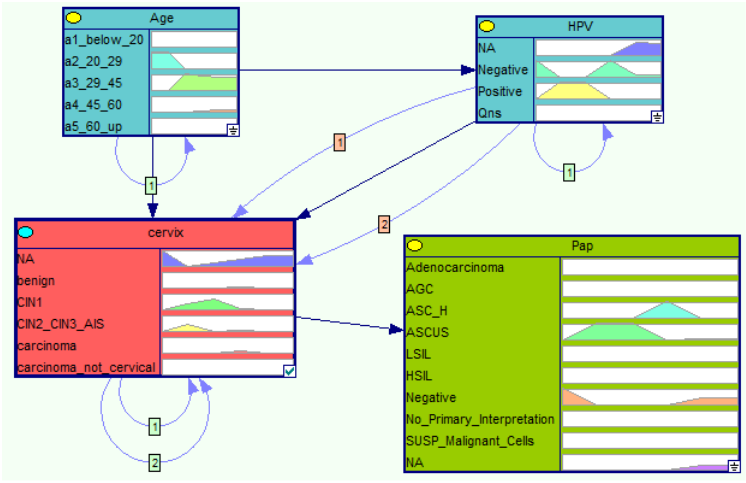

Figure 1: A simplified version of the PCCSM Model

4.4 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. Modeling with Bayesian networks facilitates this task and allows for representing missing values as an additional state. We investigated the consequences of this approach in an earlier paper Oniśko *et al.* (2002). Furthermore, reasoning algorithms for Bayesian networks do not require complete information on a patient case.

5 Results

We have initially analyzed 45,930 patients with cytology testing during a time period of five months (April through August 2008). Their age ranged from 12 to 95 years ($\mu = 42.17$, $\sigma = 15.71$). We have entered cytology data for these patients into the model, along with patient history findings and available hrHpv DNA test results. Given the observed patient data, the model assessed the risk of precancer and cervical cancer for each patient.

5.1 Temporal beliefs

The PCCSM generates risk assessments for cervical precancer and invasive cervical cancer over time. Figure 2 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 HPV test results, respectively).

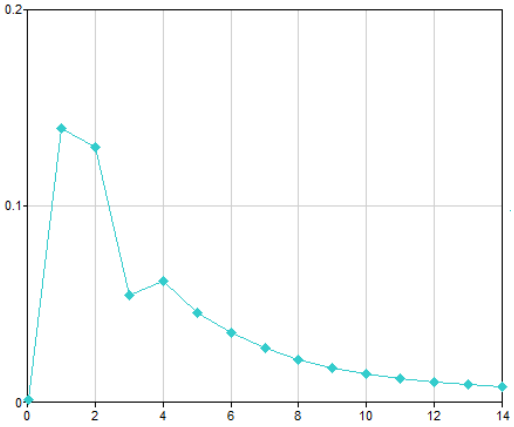

FIGURE 2: Temporal beliefs: Risk assessments for cervical precancer over 15 years.

5.2 Analysis of patient history records

Another goal of the PCCSM was an analysis of the impact of various history events on the quantitative risk of cervical precancer and cancer. A dynamic model allows one to enter all available history events into the patient case (so far, our data consist of records collected during the last four years). Based on these history entries, the model assesses the quantitative risk of cervical precancer and invasive cervical cancer over time (Figure 3).

5.3 Validation

In our validation and testing efforts, we focused on individual patient cases. We have verified that the model's predictions in individual selected patient cases corresponded to pathologist expert intuition. With the expected increase in the number of observations per patient, we plan to perform a formal validation and calibration of the model.

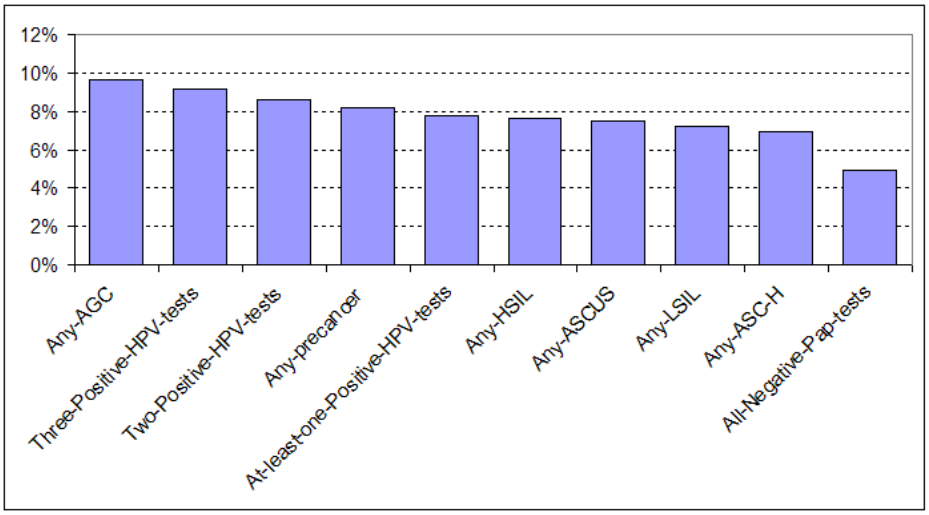

FIGURE 3: Risk assessments for precancer and cervical cancer for patients suffering currently from ASCUS HPV(+) for various history records.

6 Conclusions

The PCCSM model allows for computing quantitative risk estimates of how several variables contribute to a studied outcome, that is, detection of cervical precancer and invasive cervical cancer. The model identifies groups of patients that are at higher risk of developing cervical precancer and cervical cancer. These quantitative risk assessments can be used as a quality control tool and as an aid in clinical follow-up.

Acknowledgments

We would like to thank Karen Lassige for her invaluable help in retrieving the data from the hospital database. Thank to Nancy Mauser for her expertise in data interpretation and Jonee Matsko for identification of CIN2/3, AIS, and cancer cytology-histology correlates.

This work was supported by the Air Force Office of Scientific Research grant FA9550-06-1-0243 and by Intel Research.

The model was 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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