Computer-aided detection of lesions in digital mammograms using temporal Bayesian classifiers

Research Plan

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24th October 2005

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1 Introduction

1.1 Preface

The intent of this chapter is to provide information about the project that will be performed at the University Medical Center Nijmegen. This plan includes a global description, justification, background knowledge, the chosen research methodology and a global planning with the identified activities that have to be performed.

1.2 Background

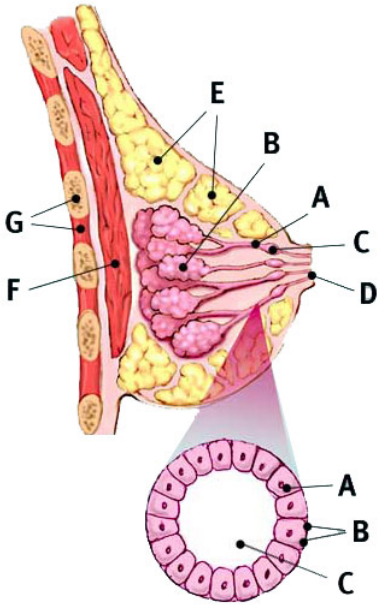
Automated detection of lesions in digital mammograms using Bayesian networks is a masters thesis project and concludes the program Master of Science in Software Construction with a research profile at the Radboud University of Nijmegen. The research will be conducted at the department of Radiology, University Medical Center Nijmegen.

2 Environment

Breast cancer is the most common life-threatening type of cancer affecting women in The Netherlands [27]. About 1 out of each 10 women have to face breast cancer. Men account for less than 1% of diagnosed breast cancers.

2.1 Breast Anatomy

The anatomy of the breast is quite complex, figure 1 shows the most important structures of the breast. To give an understanding of where and how different breast tumors may develop, we will shortly describe the structure of the breast. Each breast contains between 15 and 20 lobes that are connected to the nipple through converging ducts. Each lobule, consists of 10 to 100 terminal duct lobular units where milk is produced. The most common area where breast cancer originates is in the terminal duct lobular unit.



	Breast profile:
A	ducts
B	lobules
C	dilated section of duct
D	nipple
E	fat
F	pectoralis major muscle
G	chest wall/rib cage

	Enlargement:
A	normal duct cells
B	basement membrane
C	lumen (center of duct)

Figure 1: Breast anatomy: image from www.breastcancer.org

2.2 Breast Tumors

We can distinguish three types of breast tumors: benign breast tumors, in situ cancers and invasive cancers.

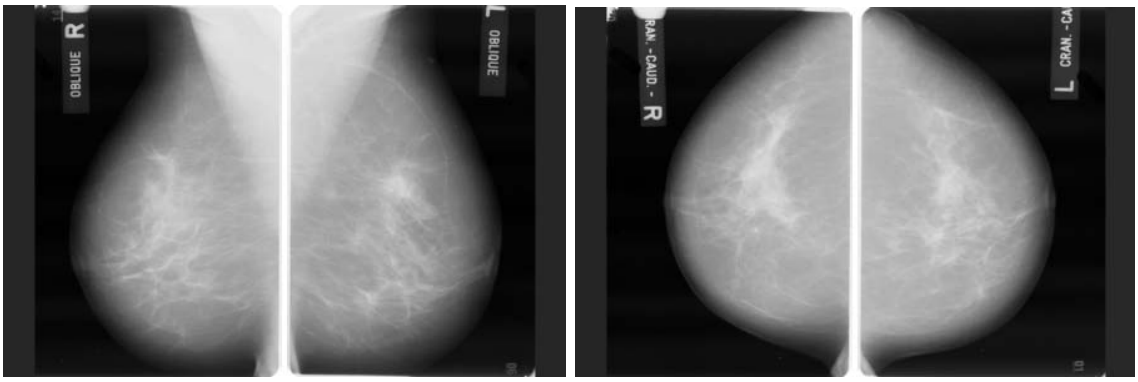
- **Benign breast tumor**: The majority of breast tumors detected by mammography are benign. They are abnormal, non-cancerous growths and cannot spread outside of the breast to other organs. It is however difficult to distinguish certain benign masses from malignant lesions.
- **In situ cancer**: If the tumor has not gone through the basal membrane but is completely contained in the lobule or the ducts the cancer is called *in situ*. It does not spread to the surrounding tissues in the breast or other parts of the body. However, it can develop into a more serious invasive cancer. There are two forms of non-invasive breast cancer: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS is often characterized in mammograms by the presence of micro calcifications. LCIS is more difficult to detect with mammography and is usually being discovered incidentally when taking a biopsy for another abnormality.
- **Invasive cancer**: If the cancer has broken through the basal membrane and spread into the surrounding tissue it is called invasive. The chances on metastases (spreading of cancer from one part of the body to another) increase significantly. The success of the treatment of breast cancer largely depends on the stage of a tumor at the time of detection. There are two features which determine the stage of a tumor: its size and whether metastases have been found in lymph nodes or distant areas. Invasive cancers vary in size from less than 10 mm to over 80 mm in diameter. If the size is smaller than 20 mm and if no metastases are found, chances of successful treatment are high. Therefore, early detection of breast cancer is essential.

2.3 Breast Cancer Screening

[23, 28] show that breast screening programs in the Netherlands and Sweden are an effective way to reduce mortality from breast cancer.

Mammography is the technique of choice to detect breast cancer and it's based on the difference in absorption of X-rays between the various tissue components of the breast such as fat, tumor tissue and calcifications. If mammography is not sufficient, other techniques can be used such as ultra sonography and MRI, but this project will focus on mammography only. Mammography has high sensitivity and specificity, even small tumors and micro calcifications can be detected on mammograms. The projection of the breast can be made from different angles. The two most common projections are medio-lateral oblique and cranio-caudal, as shown in figure 2. The advantage of the medio-lateral oblique projection is that almost the whole breast is visible, often including lymph nodes. Part of the pectoral muscle will be shown in upper part of the image, which

is superimposed over a portion of the breast. The cranio-caudal view is taken from above, resulting in an image that sometimes does not show the area close to the chest wall.



(a) Medio-lateral oblique (b) Cranio-caudal

Figure 2: The two most common projections of the breast

The two most important signs of breast cancer that can be seen on a mammogram are focal masses and micro-calcifications. Other signs are architectural distortions and asymmetric breast tissue. In this project we are mainly interested in focal masses. When a mass is present in a breast, a radiologist will estimate its malignancy by looking at the appearance of the lesion and the surrounding tissue. The most important sign of malignancy is the presence of spiculation (spiky lines radiating in all directions from a central region extending into surrounding tissue). Also the borders of a mass may give additional information about the nature of the mass. Benign masses have sharp, circumscribed borders where malignant masses have slightly jagged or spiculated borders.

2.4 Computer Aided Detection

Although a lot of attention has been directed at technical quality assurance to guarantee optimal mammographic image quality, the quality of mammographic interpretation seems to be the weakest link in the proces. Several review studies have revealed that observer errors are frequent in breast cancer screening [13]. Sometimes the radiologist is not aware of the abnormality or misinterprets the significance of an abnormality. It is estimated that 20% - 30% of the cancers could be detected in an earlier screening without an unacceptable increase in the recall rate (i.e., the rate at which mammographically screened women are recalled for additional assessment) [14, 4].

Screening for breast cancer is a difficult task, especially due to the high amount of normal cases: less than 1% of the screened women has breast cancer. To help radiologists in detecting signs of cancer, software has been developed for marking suspicious areas on mammograms. By using computer aided detection (CAD) software the number of errors

might decrease, both false negatives (malignant cases that were not recalled) and false positives (cases that are recalled unnecessarily).

The most commonly used CAD systems detect mass lesions and micro calcifications by analyzing a single view of the breast. Most of the CAD programs have a two step procedure to accomplish this. The first step detects suspicious locations inside the breast area. In the second step these locations are segmented into regions and several features are calculated for each region. These features are being used to determine whether a lesion is benign or malignant. They are also used to eliminate false positive detections.

We can distinguish between two kinds of features that are being calculated for each region. The first kind of features describe the general characteristics of lesions such as size, shape and texture. The second kind of features are more specific characteristics such as the degree of spiculation and the presence of focal mass.

More advanced CAD systems which currently are under development, are incorporating information to detect temporal changes in masses. They make use of multiple views of the breast and/or views from consecutive screening rounds for modeling the tumor behavior over time because benign masses tend to change slowly, but malignant masses may change considerably. Such a CAD system has been developed at the UMCN and combines single view and temporal features into a single malignancy score using a Support Vector Machine classifier.

2.5 Dataset

Within the UMCN there are huge quantities of clinical data available. The digitized mammograms that are going to be used in this project are obtained from the Dutch Breast Cancer Screening Program. In this program two mammographic views were obtained in the initial screening: medio-lateral oblique (MLO) and cranio caudal (CC). At subsequent screenings only a MLO was obtained, unless there was an indication that CC views could be beneficial.

For every digitized mammogram, a certain number of suspected regions have been indicated. For every region, specific features such as size, shape and spiculation have been calculated and a classifier that indicates whether the region is a tumor or not. The number of features differs per case: some cases have prior mammograms while others do not, some cases have lesions visible in two views and others in only one. Therefore multiple classifiers have to be constructed. We will use this kind of datasets for the construction of learning and evaluating Bayesian networks.

Many consider Bayesian networks appropriate intuitive tools for incorporating the quantitative and statistical information sufficiently available in medicine [10]. One of the advantages of Bayesian networks compared to Support Vector Machine classifiers or Neural Networks is that Bayesian networks are white box models. They give insight into the probabilities that have been assigned.

Much emphasis has already been put on building Bayesian networks based on medical expert knowledge [7, 1, 11, 12, 20, 21]. However building such networks by hand is very time consuming. With the availability of huge data sets, automatic learning of Bayesian networks becomes interesting [2, 5, 6, 15, 26].

Previous research has shown that naive Bayesian classifiers often outperform more sophisticated network structures as well as other types of classifiers [8]. Additionally, [9] shows that tree-augmented Bayesian networks (TANs), which incorporate extra dependencies among features in the form of a tree structure, often outperform naive Bayesian classifiers. [19] also confirms that using expert causal domain knowledge to add dependencies to the model may improve the Bayesian classifier performance. Additional benefits of using medical knowledge in learning Bayesian networks are that restrictions can be put on the topology of the network such that it can be learned in polynomial time. Without restrictions, the Bayesian-network topology space is super-exponentially large. Finally, [19] shows that adding dependence information can make the classifier more faithful with respect to the data, which is still a weak aspect of current classifiers.

3 Project Objectives

The aim of this project is to increase the quality and efficiency of computer aided detection methods (CAD) used in breast cancer screening programs by means of Bayesian networks or classifiers.

In order to achieve this goal we set the following objectives:

Develop a novel classification technique using Bayesian networks or Bayesian classifiers such that:

- The temporal pattern in the sequence of mammograms is captured by temporal classifiers
- The number of false positive detections is kept to a minimum
- It allows the handling of missing data and uncertainties
- The resulting classifiers are faithful with respect to the data i.e., the dependences and independences of the data are represented correctly
- Medical background knowledge of the breast cancer domain is incorporated

To achieve this objective, several activities have to be conducted:

- Literature study Bayesian networks
- Literature study existing features and classifiers
- Writing research plan
- Inventarisation and selection of suitable BN software
- Literature study on BN learning
- Implementing and testing BN learning algorithms (iterative process)
- Literature study on relevant clinical knowledge
- Construction of BN which integrates clinical background knowledge
- Testing and evaluating model with test data
- Comparing performance with existing techniques using FROC analysis
- Writing master thesis

4 Justification

4.1 Social Relevance

Breast cancer is the most common life-threatening type of cancer affecting women in The Netherlands [27]. The risk of death from breast cancer has dropped significantly since the introduction of mammography screening [28, 23]. Using recent data it is estimated that due to screening, breast cancer mortality has decreased by 800 cases per year in the Netherlands.

New diagnosis methods based on Bayesian reasoning developed in this project may lead to higher sensitivity and earlier detection of lesions which is essential for increasing the effectiveness of mammography screening and consequently a further reduction of breast cancer mortality.

4.2 Scientific Relevance

Improving the accurate classification of diseased versus non diseased screenings is one of the ongoing challenges in the world of medical informatics. Also the use of Bayesian classifiers in detecting malignancies, taking the temporal behavior of lesions in consideration, will support the interpretation process of mammograms by radiologists.

5 Background Material

5.1 Bayesian Networks and Bayesian Classifiers

Bayesian networks are examples of so-called probabilistic graphical models. Bayesian networks are directed acyclic graphs where each node represent a random variable and the edges represent conditional independence assumptions [18, 22]. In essence, they provide a compact representation of joint probability distributions for a given domain. Directed edges impose an order on the pair of nodes that they link. The edges go from a parent node to a child node which intuitively indicates that the parent directly influences the child, and that these influences are quantified by conditional probabilities.

To fully capture this joint probability distribution, in addition to the graph structure it is necessary to specify the parameters of the model. For a Bayesian Network, one must specify the Conditional Probability Distribution at each node. If the variables are discrete, this can be represented as a Conditional Probability Table, which lists the probability that the child node takes on each of its different values for each combination of values of its parents.

Consider the following very well known example from [17], who introduced a fictitious ex-

pert system representing the diagnosis of a patient presenting to a chest clinic, having just come back from a trip to Asia and showing dyspnoea (shortness of breath). The doctor considers that possible causes are tuberculosis, lung cancer and bronchitis, including the possibility that none of them or more than one of them is the cause for dyspnoea. Additional relevant information include whether the patient has recently visited Asia (where tuberculosis is more prevalent) and whether or not the patient is a smoker (which increases the chances of lung cancer and bronchitis). A positive x-ray would indicate either tuberculosis or lung cancer. A graphical model for the underlying process is shown in the Figure 3.

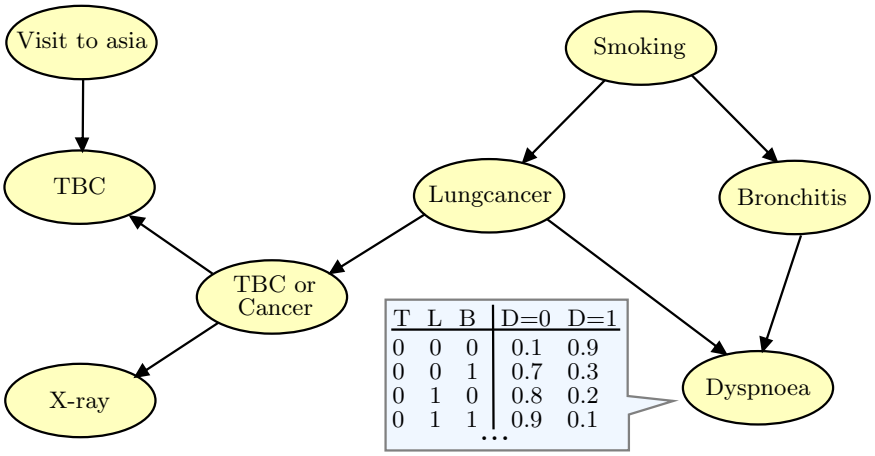


Figure 3: An example Bayesian network 'Asia'

Each node in a Bayesian network has an associated conditional probability table, of which one is shown partially to the left of node Dyspnoea.

If we learn the fact that a patient is a smoker, we will adjust our beliefs regarding lung cancer and bronchitis (i.e., the risks have increased). However, our beliefs regarding tuberculosis will be unchanged, because tuberculosis is conditionally independent of smoking given the empty set of variables. A positive X-ray result will affect our beliefs regarding tuberculosis and lung cancer, but not our beliefs regarding bronchitis (i.e., `bronchitis` is conditionally independent of `X-ray` given `smoking`). However, had we also known that the patient suffers from shortness-of-breath, the X-ray result would also have affected our beliefs regarding bronchitis (i.e., `bronchitis` is not conditionally independent of `X-ray` given `smoking` and `dyspnoea`).

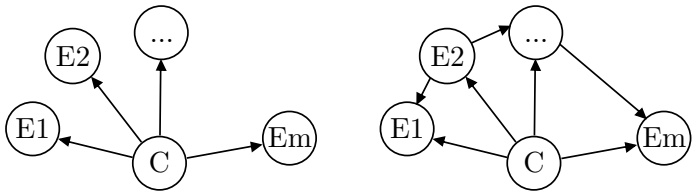


Figure 4: (a) Naive Bayesian network and (b) tree-augmented Bayesian network

The directed acyclic graph of a Bayesian network can have an arbitrarily complex topology. However, for classification purposes, often networks of limited topology are being used. Bayesian networks conforming to the topology of Figure 4 correspond to the situation where a distinction is made between *evidence variables* E_i and a *class variable* C. The evidence variables describe the characteristics of the instances to be classified and they are assumed to be conditionally independent given the class variable.

The class value is determined by assigning the evidence variable to the class whose function is maximal. If E is the evidence, and $f_i(E)$ is the discriminant function corresponding to the ith class, the chosen class C_k is the one for which:

$\forall_i \, f_i(E) > f_i(E) \quad$ where $i \neq k$

Even with such strong simplifying assumptions, [8] shows that such naive Bayesian classifiers yield surprisingly powerful classifiers. In a tree-augmented Bayesian network (Figure 4(b)), where arcs are allowed between evidence variables as long as they form a tree, [9] shows that this network again outperforms the naive Bayesian network (Figure 4(a)). To conclude, there are more extensions possible, one of them is a forest-augmented Bayesian network (FAN) where arcs are allowed between evidence variables as long as they form a forest of trees.

Although the variables in a Bayesian network are often assumed to be discrete, a network may also include continuous variables that adopt a value from a range of real values [16]. Generally, the conditional probability distributions for such continuous variables are assumed to be Gaussian, or normal, distributions. These distributions then are specified in terms of a limited number of parameters, such as their means and variance.

Many of the Bayesian networks developed in the medical environment have been constructed by hand, based on medical background knowledge. Much help is needed of medical experts to manual construct a Bayesian network and turns out to be very time consuming in practice. With the increasing availability of clinical data, machine learning will be a more feasible method for developing a Bayesian network. However, to increase the performance of the network, medical background knowledge of the breast cancer domain should be incorporated if it's available.

5.2 Influence Diagrams

The Bayesian network formalism provides only for probabilistic reasoning. For making therapeutic decisions, certain extensions are required as offered, among others, by an influence diagram. An influence diagram [25] can be seen as a Bayesian network extended with decision and utility nodes and provides a simple notation for creating intuitive decision models.

More formally, an influence diagram is a directed acyclic graph that consists of three types of nodes:

1. *Chance nodes*, usually represented as circles, represent random variables that cannot be controlled directly but are relevant to the decision problem. Conditional probability distributions are assigned to these nodes, identical to those used in Bayesian networks.

2. *Decision nodes*, usually represented as rectangles, represent possible choices available to the decision maker that can be controlled directly.

3. *Utility nodes*, usually represented as diamonds, represent utility specifying the desirability of the consequences. The utility of each of the possible combinations of outcomes of their parent nodes will be evaluated.

There are also different types of arcs in an influence diagram. The arcs between chance nodes represent probabilistic dependences similar to the arcs in a Bayesian network. The arcs between a chance and a decision node represent the variables that will be known at the moment of the decision. The arcs from chance nodes into the utility node represent which variables participate in the calculation of the desirability [20, 3, 24].

Figure 5 shows a basic example of an influence diagram [25]. In this decision problem, a decision maker is trying to decide whether to bring an umbrella on a trip. The decision maker has heard the weather forecast and has seen the current local weather state by looking out of his window. The problem here is that neither source of information is flawless: the weather forecast has limited predictive ability, and the local weather may not predict if the weather will stay the same over the course of the trip. If it rains, the decision maker would prefer to have the umbrella for preventing getting wet. On the other hand, the decision maker doesn't prefer to drag along an umbrella on a sunny day. The goal of the influence diagram modeling is to choose the decision alternative that will lead to the highest expected utility. In order to compute the solution, for each sequence of decisions, the consequences are weighted with the probabilities of these consequences will occur.

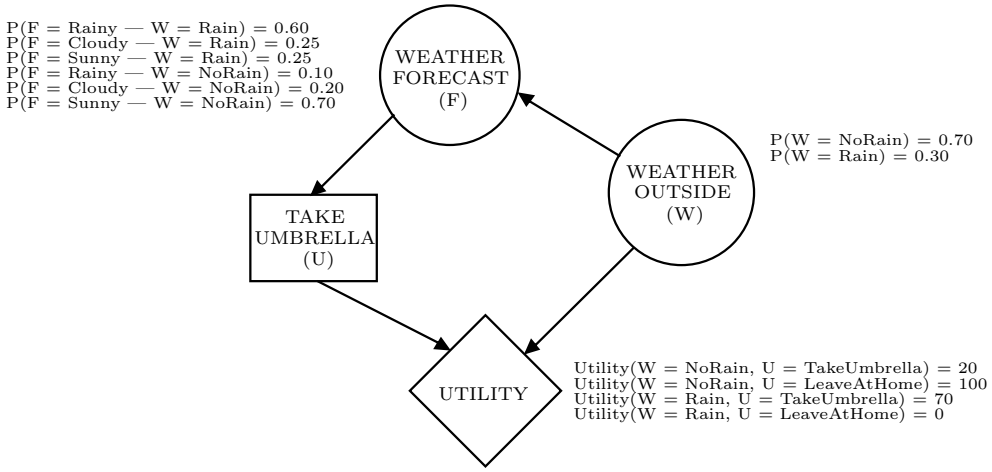


Figure 5: An example of an influence diagram 'Umbrella'

6 Research Methodology

6.1 Machine Learning

Manually constructing a Bayesian network turns out to be very time consuming in practice, therefore several techniques have been developed for automatically learning Bayesian networks from clinical data. Learning a Bayesian networks consists of two tasks, namely learning the *structure* (i.e., identifying the topology of the network) and learning the *parameters* (i.e., determining the conditional probability distributions). Because the number of possible Bayesian network structures is exponentially large, it is necessary to use heuristic methods to construct a Bayesian network automatically using medical data. There are several existing learning algorithms available for Bayesian networks that offer a good starting point [6, 5, 15].

Besides fully automatic learning, fragments of causal background knowledge will be used to guide the learning process. The causal background knowledge can be provided by the Radiology department as it already has a lot of experience in building classifiers for this problem domain.

6.2 Classification

Multiple classifiers have to be constructed as the number of features differs per case. Some cases have prior mammograms while others do not. Some cases have lesions visible in two views and others in only one. Additionally, background knowledge can be used to construct additional classifiers.

6.3 Comparison

The performance of the developed Bayesian networks will be measured by using cross-validation where a set of available feature measurements and output classifier is divided into two parts: one part for training and one part for testing. In this way several different Bayesian networks, all trained on the training set, can be compared on the test set. This is the basic form of cross-validation. A variation is the leave-one-out method, where one case is taken out for testing and the rest of the data is used to learn the Bayesian network. Futhermore, the results will be compared to existing classification techniques such as Support Vector Machines and Neural Networks by using the FROC analysis method.

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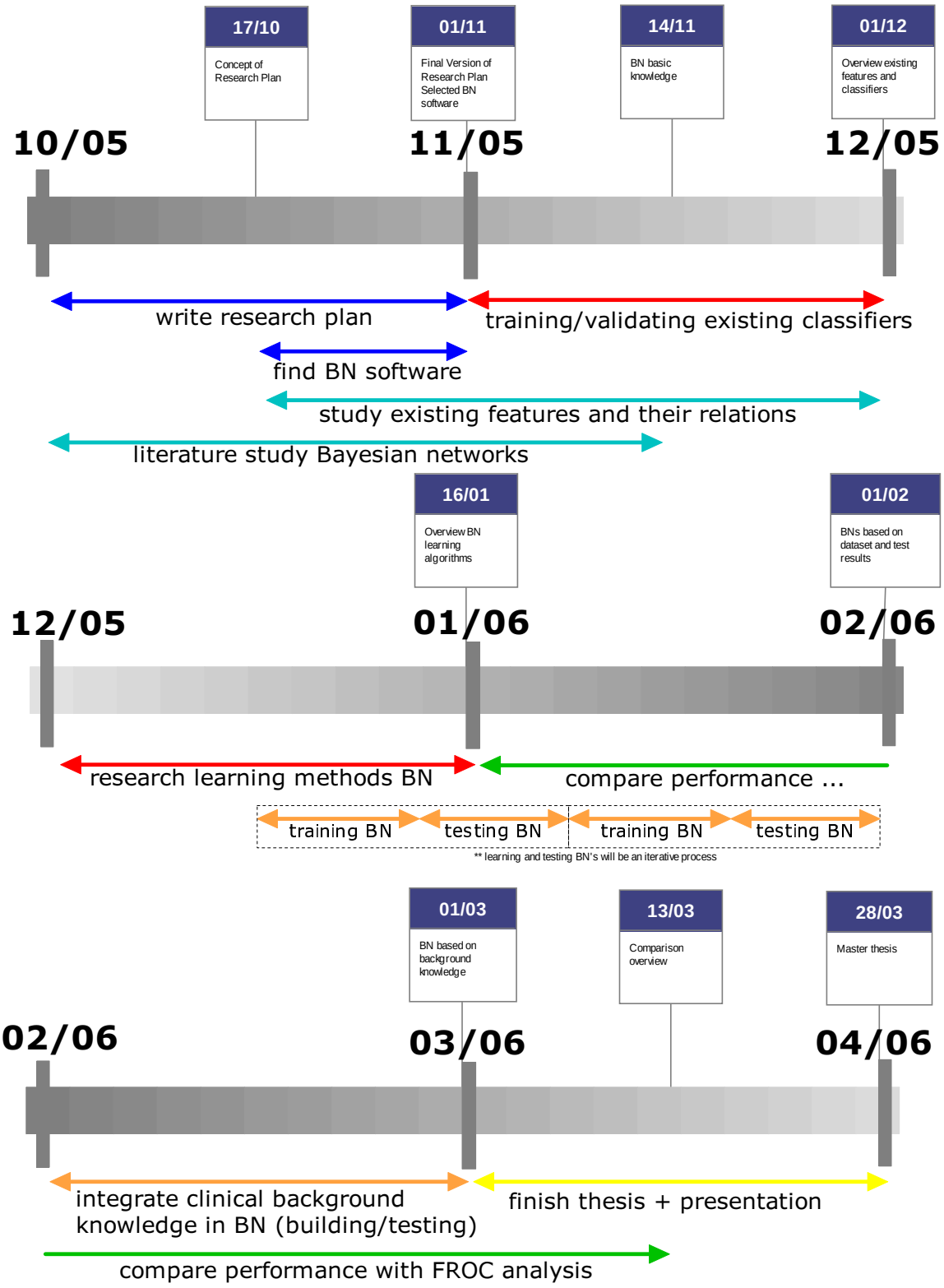
8 Global Planning



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