# Representing Knowledge of Multiple Disorders by Object-Oriented Bayesian Networks

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**Abstract.** Multimorbidity in the elderly is becoming a significant health-care problem of the modern, western society. Unfortunately, medical knowledge whether contained in clinical guidelines or medical textbooks, is mostly organized around single disorders, rendering it unlikely that the elderly patient with multiple disorders receives appropriate treatment. In the research described in this paper, we use an object-oriented representation formalism to get a grip on the clinical knowledge contained in multiple clinical guidelines, with the aim of obtaining insight into the nature of the interaction between the various aspects of the conditions. As an experiment, we analyzed clinical guidelines on dementia and hypertension and developed an object-oriented probabilistic representation formalism that allowed us to represent such knowledge. We conclude that the object-oriented probabilistic representations offer a promising method for making steps ahead in this area.

**Keywords:** Object-oriented Bayesian networks, Multinets, Comorbidity, Disease modeling.

## 1 Introduction

Recent epidemiological research in the Netherlands indicates that more than two third of all patients older than 65 years have two or more chronic disorders at the same time; this is referred to as the problem of *comorbidity* or *multimorbidity*. The difference between the terms 'comorbidity' and 'multimorbidity' is that the former considers multiple disorders from the viewpoint of one, possibly most significant disorder, whereas the latter takes all disorders to be equally important. Although both terms occur in the medical literature, there is a growing preference for use of the term 'multimorbidity'. The Netherlands is similar to other western countries in that health-care funding is under increasing pressure due to the increasing size of the population of the elderly. However, it is not only the increasing size of the problem that worries policymakers. Another, possibly more significant, problem is that medical knowledge is organized around single disorders. If a patient has multiple disorders, this knowledge may no longer be fully applicable [1]. Thus, there are no guarantees that elderly patients receive appropriate treatment for their disorders, a conclusion that is hardly acceptable

given that the health-care field is increasingly expected to take the delivery of quality care seriously. At the moment there is no easy solution to the sketched problem of multimorbidity, as clinical practice guidelines are mostly concerned with the diagnosis and treatment of single disorders.

The question that drove the research discussed in this paper was, therefore, whether the exploitation of methods from probabilistic graphical models would allow obtaining more insight into the multimorbidity problem of clinical guidelines. Probabilistic graphical models support modeling knowledge of the interaction between multiple diseases, both in terms of manifestations and treatment actions and their effects, and also support the modeling of the temporal aspects of clinical guidelines. Thus, an analysis of a clinical guideline using probabilistic graphical models could, in principle, shed light on potential interactions. In particular object-oriented Bayesian networks (OOBNs) [3] offer suitable methods to carry out such an analysis.

For the research, we selected the guidelines on dementia and hypertension, common disorders in the elderly which share certain pathophysiology. By modeling central aspects of the guidelines as a network there should be a possibility to link them together. For establishing a diagnosis a static model often suffices, whereas modeling prognosis and treatment effects require a temporal dimension.

The paper is organized as follows. In Section 2 we present reduced models for both hypertension and dementia derived from clinical guidelines, and discuss the main interactions between them. We demonstrate in Section 3 how the knowledge of multiple disorders can be modeled in the framework of object-oriented Bayesian networks, based on the work of Koller and Pfeffer [3]. Furthermore, we introduce two extensions of OOBNs, i.e., qualitative OOBNs and dynamic OOBNs, to describe simultaneous and temporal interactions of comorbidity or multimorbidity. Thus, we conclude that object-oriented probabilistic graphical representations offer a suitable means for shedding light on the problem of multimorbidity. Further conclusions and future work are discussed in Section 4.

## 2 Medical Background

### 2.1 Clinical Guidelines

Clinical guidelines provide recommendations to physicians and patients, mostly about the management of one disease, and are developed by basing recommendations as much as possible on scientific evidence. European guidelines on hypertension [4] and dementia [7] were analyzed with the aim of constructing causal models that could be used as a start for detecting interactions.

The diagnostic processes are supported by indicating relevant symptoms, risk factors, signs obtained by physical examination and laboratory investigations to decrease the uncertainty in the diagnosis. Guidelines on hypertension now emphasize that the diagnosis and management of hypertension should be related to the quantification of total cardiovascular risk. The co-presence of a metabolic syndrome worsens the prognosis and common causalities of hypertension are

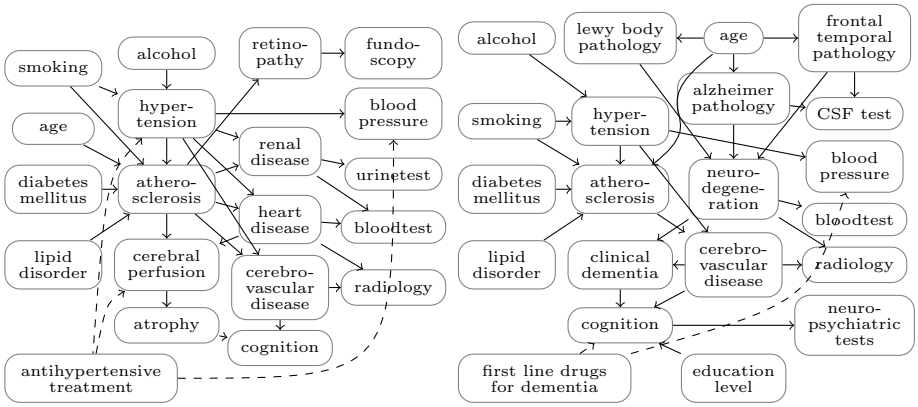


**Fig. 1.** Simplified graphical models of hypertension (left) and dementia (right), extracted from the respective clinical guidelines.

cerebral vascular disease, heart disease, renal disease and retinopathy. In the absence of specific neuro-pathological confirmation, the etiological diagnosis of a dementia syndrome can only be made in terms of probability. The diagnosis can be supported by medical history and comorbidity, neuro-physical examination, assessment of neuro-psychological functioning, blood tests, neuro-imaging, and cerebrospinal fluid analysis. Each of these so called biomarkers relates with a certain probability to a stage of the disease [2] and helps differentiating between the different types of dementia. Treatments are supported by providing advice through a stepwise approach with regular control of the patient's symptoms and signs, until a proper balance in the patient's condition is achieved.

We represent this knowledge in simplified graphical models due to space consideration (see Figure 1). Most of vertices are derived from guidelines, but some of the pathophysiological processes (atherosclerosis and neurodegeneration) and some interactions (therapeutic side effects) are derived from other medical knowledge such as scientific medical journals. To represent an associations between vertices, we draw an arc from the vertex of causality to the vertex of effect. The arcs in Figure 1 represent causalities between patient characteristics, pathophysiology and diagnostic processes, as where the dotted arcs represent effects of treatments.

### 2.2 The Complexity of Modeling Multiple Disorders

In case of the elderly, the physician often deals with multimorbidity, and then several guidelines need to be applied. Eventually this can lead to conflicts, e.g. treatment of one disease can reduce the efficacy of a treatment of another disease or worsen its outcome. In particular, there can be interactions between drugs. Treatment should focus on a common pathways rather than administering drugs for symptom relief of the diseases separately, since many side effects of drug treatment can blur out the total picture.

| Interactive variable(s) | Type of action | Effect on |
|---|---|---|
| Hypertension | influence | Dementia |
| Antihypertensive treatment | influence | Brain Perfusion |
| Metabolic syndrome + hypertension | synergy | Dementia |
| Cholinesterase inhibitors + antihypertensive drugs | synergy | Blood pressure |
| NMDA-antagonist + antihypertensive drugs | synergy | Blood pressure |

**Table 1.** Interactions between hypertension and dementia.

Three major problems occur when modeling multiple disorders. Firstly, some symptoms, signs, risk factors, pathophysiology, and so on, may be present in more than one disorder. For example, hypertension and dementia share common risk factors such as alcohol use, smoking, diabetes mellitus and lipid disorders. Secondly, the influence of pathophysiology changes over time. For example, hypertension is probably a midlife risk factor for dementia, initiating or advancing the onset in late life, whereas it is probably a protective factor by maintaining a high perfusion of the brain [6]. Finally, there can be interactions between different models, e.g. drugs for treating dementia have an effect on the blood pressure and may conflict with antihypertensive treatment.

All together there is a need for a model-based approach that can deal with complex structures, time evolution and probabilistic interactions. Therefore, we employ qualitative and dynamic OOBNs as possible solutions for the above-mentioned problems. OOBNs allow one modularize the representation of relevant medical knowledge. Interactions between variables can be represented using qualitative probabilistic networks, QPNs for short [8]. Interactions are cause-effect influences or synergies. An influence exists when the presence of a certain value of a variable makes the presence of a certain value of another variable more or less likely. In case of a synergy the presence of certain values of two variables makes a certain variable of a third variable more or less likely. Table 1 shows some possible influences and synergies between hypertension and dementia.

## 3 Dynamic Qualitative Object-Oriented Bayesian Networks

In this section, the basics of employing object orientation for building Bayesian network models are briefly described and illustrated by means of examples from dementia and hypertension.

### 3.1 Clinical Bayesian Networks

Bayesian networks are looked upon as an effective framework for knowledge representation and reasoning under uncertainty [5]. Formally, a *Bayesian network*, or BN, is a tuple $\mathcal{B} = (G, X, P)$, where

- $G = (V, E)$ is a directed acyclic graph (DAG) with a set of vertices $V$ and an edge relation $E \subseteq V \times V$;

– $X$ denotes a set of variables, where each vertex $v \in V$ corresponds one-to-one to a variable $X_v$ in $X$, with the variable taking on values from its domain;
– The joint probability distribution $P$ of $X$ is defined such that all independences that can be derived from the DAG $G$ using *d-separation* are obeyed by $P$ [5].

A *clinical* Bayesian network represents the probabilistic relationships between diseases, symptoms, signs and interventions, such as tests and treatments. The formalism quite naturally allows for representing the uncertainties involved in these relationships. To develop methods for identifying disease interactions, and possibly conflicting clinical interventions, from combining clinical guideline BN translations, we need to be able to handle very complex models. Object-oriented Bayesian networks [3], OOBNs for short, allow us to easily construct large and complex models by exploiting ideas from object orientation in the construction process.

### 3.2 Object-Oriented Bayesian Networks

In order to model a probabilistic network for multiple diseases by combining the corresponding Bayesian networks, we need to study the relations between the networks. Often we can find vertices representing same variables in different probabilistic graphs for disorders. Those variables describe normally the same object. Basically, OOBNs allow us to define probabilistic models over multiple objects. Therefore we introduce an approach based on the theory of OOBNs from Koller and Pfeffer [3] in this section.

**Object.** An *object* in OOBNs is any entity composed of *input attributes* $A_I$ and *value attributes* $A_V$, where input attributes are parameters to the object. Value attributes are divided into *encapsulated attributes* $A_E$ and *output attributes* $A_O$, which are part of the specification of the object itself. For instance, the attributes Age, Gender and Lifestyle of a patient could act as input attributes for a value attribute Disease, while the encapsulated attribute Pathophysiology together with the output attributes Symptom and Sign describe Disease itself. The encapsulated attributes are d-separated from the rest of the network by the inputs and outputs of the object. There are two types of objects. A *simple object* is composed of a set of input attributes $A_I$ and a single output attribute $a_O$ of basic types, e.g., Boolean, Integer, etc. A *complex object* is composed of input attributes $A_I$ of basic or structured types, encapsulated attributes $A_E$ and output attributes $A_O$ which are themselves objects.

**Object-oriented Bayesian network fragment.** In order to model uncertainty about the possible values of an object, the object is associated with a probabilistic model. A *stochastic function* can be associated with an object and defines a distribution of the possible values of this object for each assignment of values to the object's inputs. In general, complex models often involve many similar objects or attributes of objects, whose stochastic functions are essentially

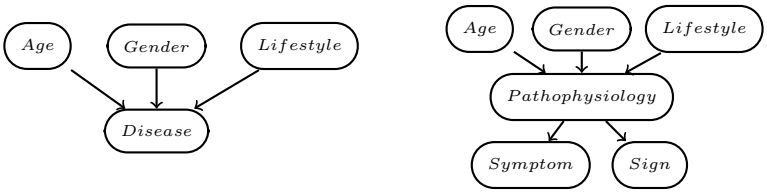


**Fig. 2.** A DAG of OONF Patient (left) and a DAG of OONF Disease (right).

identical. Thus, we use the notation of a class in order to use generic stochastic functions multiple times in defining similar objects.

A stochastic function is described by using recursive composition of *object-oriented Bayesian network fragments* (OONFs). An OONF of a set of input attributes $A_I$ and a set of value attributes $A_V = A_E \cup A_O$ is a stochastic function over a DAG $G = (V, E)$ where the set of vertices $V$ corresponds one-to-one to each element in the set of the attributes of OONF. For each value attribute $a_V \in A_V$, every parent of $a_V$ is annotated with at least one input $a_I \in A_I$. Let $a_O(\mathcal{O})$ denote an output attribute of object $\mathcal{O}$ and $\mathcal{O}.\rho$ denote an attribute chain of $\mathcal{O}$, each input attribute $a_I \in A_I$ has the same type with the output attribute $a_O(\pi(a_I).\rho)$, where $\pi(a_I)$ denotes the set of parents of $a_I$ in the DAG. An OONF over a simple object is a *simple OONF*.

To establish a probabilistic model representing uncertain knowledge of multimorbidity, we organize objects extracted from clinical guidelines for certain diseases. Patient and Medical Facility are considered as common objects in the clinical guidelines of disorders. A class Patient defines complex objects, which contain attributes Name, Address and Age etc. Figure 2 shows DAGs of the OONF for Patient and for Disease, where Disease -a complex object itself- is the value attribute of Patient. Therefore an OONF of Disease is defined inside the OONF of Patient with inputs Age, Gender, and Lifestyle. Since many common attributes of Patient, e.g., Name, Address, have no direct influence on diseases, they are not considered as inputs of the attribute Disease.

We can define the classes of common objects in the clinical guidelines with an object-oriented language, which together with the corresponding stochastic function define OONFs. As a subclass of Person, for instance, class Patient inherits its attributes from its superclass Person. Diseases are defined by each individual class which contains an encapsulated attribute Pathophysiology and output attributes Symptom and Sign. The relevant attributes for class Medical Facility and their relations are displayed in Figure 3.

**Object-oriented Bayesian network.** Up to this point we showed how to define a class for each individual object. The relations and interactions among objects are represented by an abstract object, or a *situation object* as it is called. An *object-oriented Bayesian network* (OOBN) is a single situation object without input, whose probabilistic properties are defined by an associated OONF.

An OOBN describing medical interventions consists of classes Patient, Medical Facility and the situation object Medical Treatment with an associated OONF. Figure 3 shows the constructed OOBN model for medical treatment. The *dotted lines* represent relations between attributes inside a class, and the *arcs* describe the probability dependency of the associated OONF between classes.

**Inference in object-oriented Bayesian networks.** The key to effective inference in OOBNs is the observation that complex objects are only used to group simple objects together into coherent units. A Bayesian network $\mathcal{B}$ of an OOBN contains a set of attributes for each simple object defined by the OOBN. The structure of a *multiply sectioned Bayesian network* (MSBN) [9] is a multiply sectioned DAG (MSDAG) with a hypertree organization, where each set of shared variables between subsets are d-sepset. Given such a BN $\mathcal{B}$, we can construct an MSBN which contains subnets for each object in the OOBN. Koller and Pfeffer [3] proved that a Bayesian network $\mathcal{B}$ constructed from an OOBN is an MSBN of hypertree structures. In a hypertree MSBN, all the message can be passed in the probabilistic inference process along the paths of the tree.

### 3.3 Representing Interactions of Multiple Disorders

Based on the clinical guidelines, the framework of OOBNs for representation and reasoning comorbidity or multimorbidity under uncertainty is introduced in the previous section. With summarizing the work of Koller [3] we demonstrated the implementation of their theory in our study case and yielded an abstract model to link the Bayesian networks of hypertension and dementia. Nevertheless, the (both simultaneous and temporal) interactions between multiple diseases are not displayed intuitively in the OOBN model. Therefore we extend our model in the framework of qualitative OOBNs with the theory of *qualitative probabilistic network* (QPN) [8] to represent simultaneous interactions in an OOBN, and in the framework of dynamic OOBNs to represent temporal interactions of diseases between OOBNs.

```
Class definitions of Person and Patient:

Class Person is                      Class Patient is
 Superclass nil;                      Superclass Person;
 Name: String;                        Physiology:{
 Address: String;                      Medical Record:{diabetes mellitus,
 Age: Integer;                                        dyslipidemia,etc};
 Gender:{male,female};                 Family History:{hypertension,
 Education:{high,average,low};                        dementia,etc};};
 Lifestyle:{smoker,alcoholic,etc};   Disease: {Class Hypertension;
End                                             Class Dementia; etc};
                                     End
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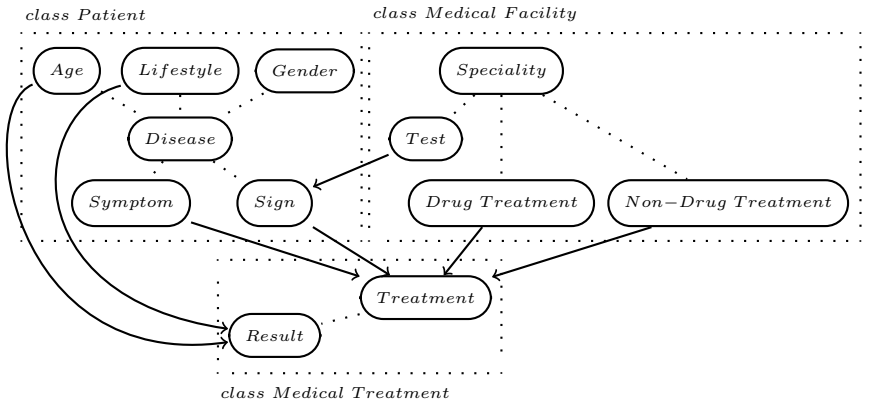


**Fig. 3.** An OOBN model of medical treatment.

**Qualitative object-oriented Bayesian network.** A *qualitative OOBN* is an extension of OOBNs by adding qualitative influences and synergies between objects and attributes from different probabilistic models. A *qualitative influence* expresses how the value of one variable influences the probability of observing values of another variable. A *additive synergy* expresses how the interaction between two variables influences the probability of observing the values of the third variable. A *product synergy* expresses how upon observation of a common child of two vertices, observing the value of one parent influences the probability of observing a value of the other parent. For instance, both antihypertensive treatment and first line drugs for dementia (cholinesterase inhibitors) negatively influences the blood pressure (by decreasing it), which is an important determinant in both disease models. A additive synergy expresses how the interaction between the treatment for hypertension and for dementia influences the probability of observing the values of blood pressure. Using both treatments together, the decreasing effects on the blood pressure add up, making the chance of a low blood pressure (and so hypotension) much more likely, and thus form a negative additive synergy on a high blood pressure. Figure 4 shows the negative additive synergy between these two treatments.

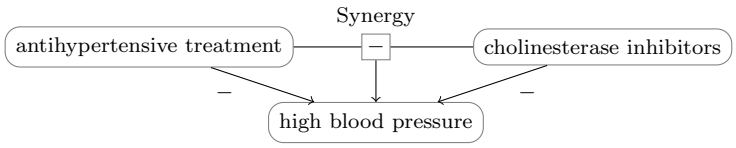


**Fig. 4.** Negative additive synergy between antihypertensive treatment and first line drugs for dementia.

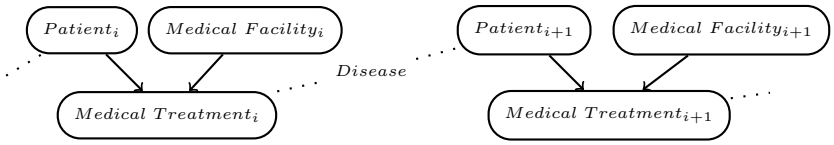


**Fig. 5.** A fragment of dynamic OOBN model with situation object Medical Treatment.

**Dynamic object-oriented Bayesian network model.** Since both hypertension and its treatment influence the onset and cause of dementia in the future, the consideration of time is therefore mandatory, i.e., it is not sufficient to model a static OOBN to deal with the problem of multimorbidity. For an elderly patient with hypertension for instance, often the cause of hypertension and the medical treatment for this disease can affect the probability of dementia in the future. In order to work with domains that evolve with time, we need a model for each unit of time. Dynamic models consider the cases that an event can cause another event in the future. A *time slice* is a local model, i.e., an OOBN in our representation formalism. The time slices are connected through temporal links to create a full model, i.e., a dynamic OOBN. A *dynamic OOBN* model is a repetitive temporal OOBN model, if the structures of the time slices together with conditional probabilities are identical and the temporal links are the same.

We illustrate this approach by discussing a dynamic OOBN model of medical interventions for dementia and hypertension. The OOBN we defined in the previous section can be considered as a local model in the dynamic OOBN. A time unit is determined by the period of treatment rather than a point in time. The dynamic link between the local models contains the complex attribute Disease. The values of Disease of treatment's result are the output values of the local model at current time, and are considered as the values of the Disease of Patient at the begin of the next time unit. The temporal links in Figure 5 are represented by dotted lines between local models. In a dynamic OOBN for hypertension and dementia, we can see the conflicts of medical interventions, e.g., antihypertensive treatment at time unit $i$ changes the risk of dementia at time unit $i+1$. Vice versa, drugs for dementia alter antihypertensive treatment. Thus, conflicting medical interventions of multiple disorders can be represented in the dynamic model, and allow medical doctors to detect the future consequences of the current treatments in advance.

## 4 Discussion

The only way to make progress in the management of multiple disorders in elderly patients to guarantee the quality of the delivered care is, to offer means to pinpoint interactions between the various disorders and their management. Although clinical guidelines are mostly organized around single disorders, they can still be used as a starting point for such identification.

In this paper we provided a framework for modeling the essential disease knowledge from the guidelines using OOBNs. We showed that the models representing knowledge of clinical guidelines can be effectively linked together using OOBNs, yielding a tool for determining shared risks and pathophysiology. In addition, by adding qualitative influences and synergies the simultaneous interactions of multiple disorders can be represented in qualitative OOBN models. And by exploiting the temporal dimension offered by dynamic OOBNs, which allows monitoring disease progression and effects of therapeutic choices, it is possible to capture interactions in both from a temporal point of view.

Nevertheless, we did not provide the actual probabilistic parameters of the constructed qualitative and dynamic OOBNs. On one hand future work will focus on quantification of probabilities by adding known probabilistic evidence from scientific research and learning probabilities from patient datasets. Eventually, interactions between diseases will inherit probabilistic evidence from several pathways changing probabilities downwards to prognosis and therapeutic choices. On the other hand we will extend the formal definitions of qualitative influences and synergies in the framework of object-orientation, with a temporal dimension, to provide a formalism for modeling interactions of multiple disorders in terms of time. Following the identification of such interactions, disease management can be adjusted where probabilities deviate significant comparing to a single guideline.

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