

# Reasoning Requirements for Diagnosis of Heart Disease

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## Abstract

Over the past dozen years, we have developed the diagnostic capabilities of the Heart Disease Program (HDP). The program has progressed from a logic based model, to a Bayesian probability network (BPN), to a pseudo-Bayesian network with temporal and severity reasoning. The explanations have evolved from graphic causal diagrams to summarized causal outlines of the important diseases and mechanisms. The reasoning and explanation mechanisms evolved as we have identified significant classes of diagnostic situations. Improvements have been made in the input data, in reasoning strategies, and in the explanations. The driving force has been the need to provide clinical distinctions for planning investigation and management strategies.

While the causal probabilistic nature of much of cardiovascular disease fits well into a Bayesian probabilistic framework, closer examination reveals a number of aspects that require other kinds of reasoning. The wide range of times over which disease mechanisms progress requires temporal reasoning that does not fit well in a BPN. The distinct patterns of manifestations, (often labeled as syndromes), associated with different severities of disease runs counter to the independence of effects assumed in a BPN. Similarly, some diseases have multiple distinct types, which may have separate etiologies, with different patterns of manifestations. The constraints and homeostatic mechanisms of hemodynamics can also produce effects poorly modeled by a fixed causal network.

Beyond the generation of appropriate diagnostic hypotheses, there are challenges in gathering data and presenting the results to the physician. For example, making appropriate assumptions about negatives from the case data, summarizing hypotheses to emphasize important diseases and mechanisms, and providing justification and explanation for the physician.

This paper discusses these problems in providing appropriate diagnoses in the heart disease

domain, illustrated with clinical examples. It identifies the requirements for an effective system, and discusses the specific solutions developed for the Heart Disease Program.

**Keywords:** Bayesian probability networks, temporal reasoning, causality, physiologic causality, constraint reasoning, diagnosis, heart disease

## 1 Introduction

The context of this discussion is the development of the Heart Disease Program (HDP)[1, 2, 3]. The HDP is a diagnostic reasoning tool for patients with symptoms suggestive of hemodynamic dysfunction or diseases that could cause hemodynamic dysfunction. (The program also has a component for reasoning about the expected effects of therapy by simulation[4], but this paper will focus on the diagnostic reasoning.) The program allows direct case input from the physician using a series of forms, then generates a differential diagnosis consisting of a small set of hypotheses, each of which is an explanation for the findings entered.

The HDP is a diagnostic program that uses knowledge of the underlying mechanism to reason about diseases — a process often termed “deep reasoning”. In contrast, most of the medical diagnosis programs now working their way into practice, eg, QMR[5, 6] and DXplain[7], only use diseases and findings with measures of association between them. Because they have no model of how the findings interact, their differentials often contain clearly inappropriate diseases. In addition, these differentials are lists of diseases without any indication of how they might account for the patient data. A few programs use physiologic knowledge for diagnosis, e.g., the ABEL[8] program for acid-base and electrolyte disorders operated at several levels of abstraction with varying detail to capture the physiologic interactions. A number of challenging medical domains are similar to the acid-base problem, with intermediate concepts and clinically relevant physiologic knowledge needed to effectively generate and constrain diagnostic analysis. Two programs in cardiology that use physiologic reasoning are the EINTHOVEN arrhythmia analysis system[9] and the DIAVAL program for echocardiography interpretation, reported in this journal[10].

Cardiovascular disorders provide a challenging domain for diagnosis. Over such dimensions as importance, time course, severity, and ease of observation, the diseases display a wide range of characteristics. In addition, the patients often present with more than one interacting pathophysiologic mechanism. The disorders range from acute to chronic. Often the chronic disorders are not correctable, becoming the context in which other disorders manifest themselves. Hence, the patho-

physiologic state may be simple in the patient first exhibiting cardiovascular disease to complex when the disease has progressed and been complicated by additional diseases. The manifestations may be mild and non-specific, such as fatigue or shortness of breath, or they may be the critical signs of shock. Fortunately, the physiology is fairly well understood at the clinical level. That is, we can make reasoned arguments about how the diseases will manifest themselves and how multiple mechanisms will interact with one another. The effort to develop the HDP has given us a wide range of experience in modeling and reasoning about diagnosis in a complex, model rich domain. Other domains where clear pathophysiologic models are developing, such as respiratory disease, neurology, or endocrinology should also benefit from this approach.

The HDP is intended to be a clinical diagnostic tool for the practicing physician — an intellectual sounding board for understanding findings in the challenging patient. As such, it takes the same kind of information about the patient that one would see in the physician’s note, including history, symptoms, physical exam, and laboratory data. Indeed, the discharge summary or clinic letters are often directly transcribable into the input forms. There is no required data, but the program will use whatever is available. It then uses a modified Bayesian probability network modeling the causal pathophysiology of the cardiovascular system to reason about possible explanations for the data. Because the probability network does not conform exactly to the requirements for a BPN, a heuristic algorithm is used to generate diagnostic hypotheses. Each hypothesis provides a complete explanation for the data, within the bounds of the physiologic model. The probabilities of these hypotheses are computed and those above a threshold are ordered as a differential diagnosis. The hypotheses of the differential are then summarized and presented to the user.

Our initial design of the HDP relied on constraints and logical relationships among diseases, physiological states, and findings. These were used to rule out causes and focus the diagnostic effort. It was hoped that such coarse grained diagnosis would be sufficient to direct reasoning about patient management. However, it soon became apparent that uncertainty plays such a large part in the diagnosis and management of cardiovascular disease that the program had to deal with causal probabilities directly.

## 2 Bayesian probability networks

For diagnosis in domains with causal knowledge, the current dominant methodology is Bayesian probability networks (BPN). Examples include MUNIN[11], for electromyographic interpretation, to recent programs on breast cancer diagnosis[12]. A BPN program that has achieved some com-

mercial success is Intellipath, for pathology diagnosis[13, 14]. Several years of research on BPNs has provided sound mathematical underpinnings and efficient algorithms for answering the most common diagnostic questions. The primary advantage of a BPN is the direct representation and reasoning with uncertainties among the domain parameters. In addition, the network structure is a reasonable representation of domain causality. Sometimes however, the dual goals of representing the probability distributions and the understood causality conflict.

The relationships among the concepts in the domain are represented as an acyclic directed graph of probabilistic links. The probability of a node in the graph is a function of the states of the nodes on incoming links to that node. The fundamental assumption of a BPN is that the probability of an effect is only dependent on the state of the immediate causes. This independence assumption is the source of power of the paradigm, making the computation of such things as the most likely state of the network tractable even in fairly large networks.

A node can have a small number of states and the probability of the each state can be determined by any function of the inputs that produces a valid probability distribution over the states. Most commonly, the nodes are binary and the probability is computed using the “noisy-OR” assumption. That is, if a node C has two causes A and B with  $p(C|A) = a$  and  $p(C|B) = b$  then  $p(C|A\&B) = 1 - (1 - a)(1 - b) = a + b - ab$ . This generalizes to any number of inputs. This assumption is essentially that the inputs make independent contributions to the node. It greatly reduces the number of probabilities that must be determined.

The requirement for an acyclic network is a result of the mathematical formalism. Without that, the probability calculations become inconsistent. For example, consider the simple example in figure 1. The probabilities in the right column are computed locally, just using the truth of the incoming node and the “noisy-OR” assumption. Unfortunately, the sum of the probabilities of the possible states is 1.0625, rather than one.

One source of computational complexity in a BPN is undirected loops. That is, places where the network splits and rejoins (eg, the right diagram in figure 2). Algorithms for BPNs are necessarily exponential as a result of such occurrences [15]. However, the best algorithms are efficient enough to handle networks with a dozen or more such loops. A second source of complexity is nodes with more than two values. Each such occurrence multiplies the amount of computation required.

The challenge in developing a BPN for diagnosis is to represent the knowledge of the domain in a network and keep it computationally tractable.

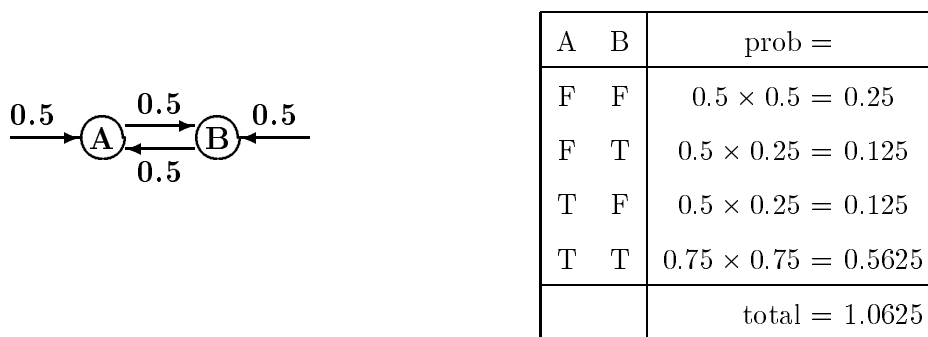


Figure 1: Probabilities in a Cycle

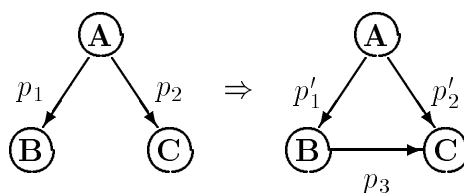


Figure 2: Representing Probability Distributions

### 3 Requirements for diagnostic reasoning

#### 3.1 Modeling a probability distribution

The first challenge is to represent the domain knowledge in a probabilistic formalism. One clash between the BPN formalism and practicality is the distribution of the effects of a node. When developing an expert system for medical diagnosis, data on the frequency of findings and combinations of findings with a disease state, are commonly available since that is the natural organization of medicine. In contrast, while the combining function for the causes of a node can be arbitrary, the BPN assumes that the probability of an effect is independent of the existence of other effects from that node, unless there is an explicit link between the effects. If there are  $n$  possible effects of a node, there are  $2^n$  possible combinations of those effects, for which the only constraint is that their probabilities have to sum to one. For example in figure 2, if A causes B and C, there are only two probabilities to represent the three independent combinations of effects (eg,  $B \& C$ ,  $\neg B \& C$ , and  $B \& \neg C$ , since  $\neg B \& \neg C$  must be one minus the others). Thus, the only way to capture distributions that do not meet the independence criteria is to represent a dependence between B and C, as shown on the right. This adds a loop to the network and the added computational complexity. If it is assumed that the two causes combine as the “noisy-OR” function then this representation is only

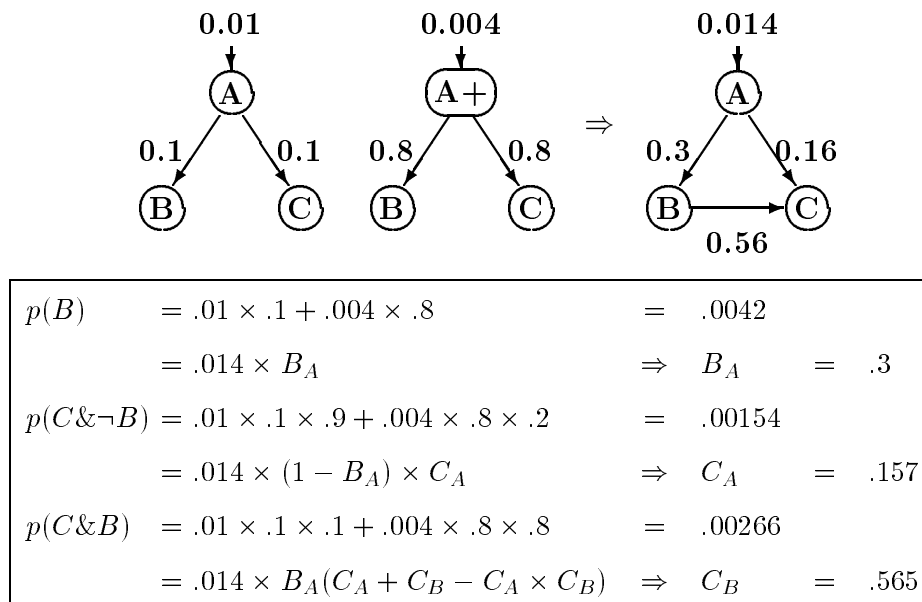


Figure 3: Representing Probability Distributions

sufficient if the distribution is such that  $p(B \& C)p(\neg B \& \neg C) > p(\neg B \& C)p(B \& \neg C)$ .

With more than two effects, it may be necessary to add all possible acyclic links between effects to capture the probability distribution. Besides the additional computational burden imposed by such a network, the additional links do not have the same meaning for the user as the intended causal links. In most instances it is better to compromise and keep the model simple at the cost of some deviation from observed probabilities. If the probability data is derived from the literature, only a few probabilities of combinations of findings may be available. A large database of cases may provide accurate probabilities, however the data should be a representative sample of the patient population. Even when the probabilities of combinations of findings can be determined within narrow variance, if they differ from the probabilities implied by independence, the diagnostic implications need to be weighed against the additional computational burden.

Often the probability of findings is dependent on the severity of the disease. If the disease is mild there is a low probability of findings, but if the disease is severe, findings are common. If the node representing the disease is binary, the only way to provide appropriate probabilities is to add dependencies among the findings. For example, consider the mild and severe forms of disease A in figure 3. Let A+ be 0.4 times as likely as A. This could be represented as a single node as in the right part of figure 3. (The representation must be asymmetric to avoid a cycle between B and C.) The required probabilities to maintain the same distribution are shown on the right and are computed as shown. The probability of 0.56 on the connecting link would indicate

a stronger association between the findings than with the cause, even though this is an artifact of the severity manifestation. The more natural representation is to give the disease node multiple values representing the possible severities of the disease. Then the structure maintains the intended causality and conveys information that may be useful in managing the patient.

The distribution requirement for the “noisy-OR” function in this context translates into the requirement that all of the probabilities have to increase or stay the same as the severity increases. This is normally true, but there are a number of nodes in the HDP in which a few finding probabilities decrease. For example, in aortic stenosis there is almost always a murmur. However, when the lesion is severe enough to lower cardiac output, the murmur often becomes inaudible and the diagnosis may be missed. This is important because the AS is a correctable condition which left untreated will in time be fatal. This is the kind of situation in which HDP is most needed.

In implementing HDP, we found that the most natural divisions of severities are the points at which new manifestations are possible, that is, where the manifestations are qualitatively different. For example, the node for aortic stenosis has four severities. Mild AS only causes murmurs and appears on the more sensitive tests (eg, echocardiography or catheterization). The second severity causes left ventricular (LV) hypertrophy. The third severity causes limitations to cardiac output (decreased exercise response), high filling pressure, or angina. The most severe form causes a weakened ventricle and all of the sequelae of dilated cardiomyopathy.

This is a very different definition of severity from that traditionally used, which focuses on measured valve areas, but it serves a different purpose. That is, to provide a division of the model that simplifies the data and the reasoning. The division by manifestation enables identifying the severity from clinical findings without requiring more extensive testing. This makes it easier to classify cases for knowledge acquisition and also allows pruning of the problem space during diagnostic reasoning. Thus, the HDP makes an initial pass through the input data and eliminating many more severe states of diseases by the absence of the discriminating manifestations. This significantly speeds the reasoning. The qualitative severities are consistent with the observation that the structure of the network is more important to accurate diagnosis than the actual probabilities, although the probabilities do make a difference[16].

### 3.2 Modeling disease types

The heart disease domain has several diseases with more than one distinct type. For example, a primary aortic regurgitation (AR) can have different etiologies. To keep the model simple HDP

includes five valvular disease etiologies covering the most distinct patterns, each with some unique findings. For example, degenerative AR may have calcification or other evidence of the degenerative process. Rheumatic AR may have a history of rheumatic fever. The most important aspect of the different etiologies of valvular disease is that they provide appropriate probabilities for multiple valvular lesions, since multiple lesions are common and the combinations of lesions are characteristic of the different etiologies.

Besides the different types representing the etiology of primary valvular disease, AR itself has different types, depending on whether the problem is at the root (dilatation of the aortic root) or valve (leaflet damage), characterized by distinct findings. Some AR is caused by acute processes and this is further distinguished. Acute AR is always secondary, either to a failed valve replacement, endocarditis, or aortic dissection. Thus, if the AR was absent a month ago and is present now, the diagnosis immediately focuses on endocarditis or aortic dissection.

The disease type provides a template to represent diagnostically important qualitative distinctions as well. This provides one mechanism for representing disease patterns. Since physicians tend to describe diagnosis and to learn in terms of disease patterns, it is useful to capture expertise in the model presented in similar patterns. The diagnosis explanation can then follow a similar process to present the results. Patterns do not fit well with the BPN methodology, since all of the knowledge in the network is local to each node. The HDP makes use of the type information as properties on the links in the model with probabilities dependent on them. In this way, the patterns may be embedded in the model, coordinating probabilities as well as the pattern recognition in a completed hypothesis.

### **3.3 Modeling temporal relations**

The main source of problems with the BPN methodology is the need for reasoning about time in the domain. There are a number of ways in which problems arise. First, if time is required to produce an effect, the cause must have existed long enough. For example, an acute MI often causes pulmonary congestion and pulmonary congestion occasionally causes pleural effusion, however, it takes days or weeks to produce the pleural effusion. Therefore, an acute MI could not explain a pleural effusion discovered on the same day. The second problem is the wide range of time scales over which the changes in heart disease take place. Thus, the findings provided by auscultation (the heart sounds) reflect the immediate. The findings of pulmonary congestion take a few hours; pedal edema takes days; ventricular hypertrophy, months; and usually valvular stenosis takes years. The



third problem is the need for multiple instances of some nodes to explain the findings. An example is aortic regurgitation (AR) leading to a valve replacement and the replacement failing and causing an acute type of aortic regurgitation. The earlier AR would be responsible for the evidence of LV hypertrophy still on the electrocardiogram and the acute AR would be responsible for the murmur and a number of other findings. (Our approach to temporal reasoning is discussed in detail in [3].)

The problem of effects requiring time means that physiologic states such as pulmonary congestion cannot be represented by a single node in a traditional BPN because the truth of the state is insufficient information to determine the probability of effects. That is, pulmonary congestion caused by an acute MI has different effects from pulmonary congestion caused by dilated cardiomyopathy. In some form, it is necessary to know whether the state has been true long enough to produce the effect. This breaks the fundamental assumption of the BPN that the truth of a node only depends on the state of the immediate causes.

In several domains, the problem of temporal reasoning has been handled by replicating the causal network for a number of time slices and using the BPN to reason about the transitions as well as the causality[17]. This approach means that the size of the network is multiplied by the number of time slices. With a large network of diseases, states, and findings, the computational costs rapidly get out of hand. An improvement in this approach is to only replicate the model for those time periods that matter[18]. By extending this approach, one could imagine replicating those parts of the model having different time scales with time slices of appropriate sizes. Even assuming that such an approach would work, the number of different time scales that matter in the cardiovascular domain would imply many replications of most parts of the model, making the approach just not feasible. The approach in the HDP is to carry the temporal information as properties on the instantiation of the network used in reasoning. The deduced time intervals propagate through the network constraining all effects below the node. Thus, the time constraints on the MI apply not only to the pulmonary congestion it causes but also to the effects of the pulmonary congestion. Since this temporal constraint is quite different from the probability constraints imposed by the BPN, it is a powerful tool in directing the hypothesis generation.

The problem of multiple instances of a node only happens in a few situations in the heart disease domain, but they led to a significant number of incorrect diagnoses before temporal reasoning was added to the program[20]. Most of the cardiovascular diseases either cause permanent dysfunction, so once they are present, they remain (eg, dilated cardiomyopathy), or have a specific time course and afterward are irrelevant to future diagnoses. Diseases that are chronic but completely cor-

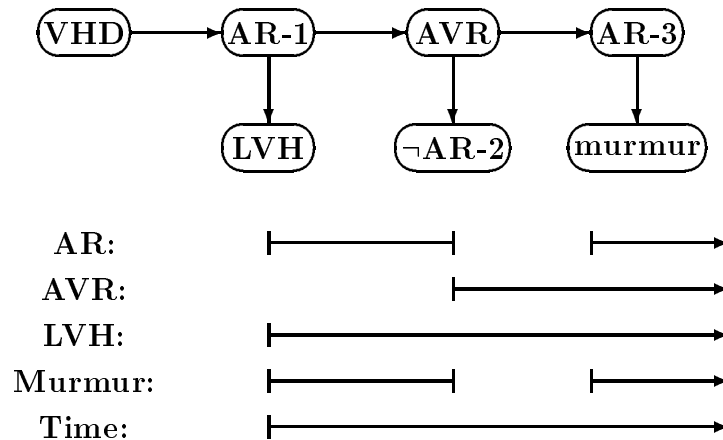


Figure 4: Representing Recurrence of a Disease

rectable are also irrelevant after they have been corrected. The problem for reasoning arises when there are diseases whose findings remain after the disease has ended and the disease may recur with new findings. The prime examples are valvular disease, but diseases like endocarditis also exhibit the same challenge for reasoning. Myocardial infarction also recurs with both acute and chronic findings, but the disease profiles in the acute, subacute, and chronic phases are so different that in the HDP they are modeled as three different diseases.

A situation like the recurrence of AR is handled in the HDP by generating two instances of the AR node in the hypothesis as shown in figure 4. The valvular heart disease (VHD) over many years causes the initial AR (AR-1), which causes LV hypertrophy (LVH). The aortic valve replacement (AVR) corrects the AR with a probability of 1.0 at the time it was done. Thus, AR-1 ends at that time and there is an instance of AR being false that begins at that time. Meanwhile, the LVH continues for an indefinite period of time. With some time delay, the AVR causes acute AR (AR-3), which ends the period of AR being false and causes the murmur. The explicit representation of these relationships in the network allows the HDP to make appropriate attribution of the findings and ensure the temporal consistency of the hypotheses it generates.

### 3.4 Causality in feedback systems

Modeling causal relations with a BPN, one assumes that each cause-effect relationship is directly and effectively represented by a probability. Many of the parameters of the cardiovascular system are part of a large feedback system that is continuously seeking a stable state. Perturbations to the system cause changes in the stable state that are reflected as changes in one or more parameters.

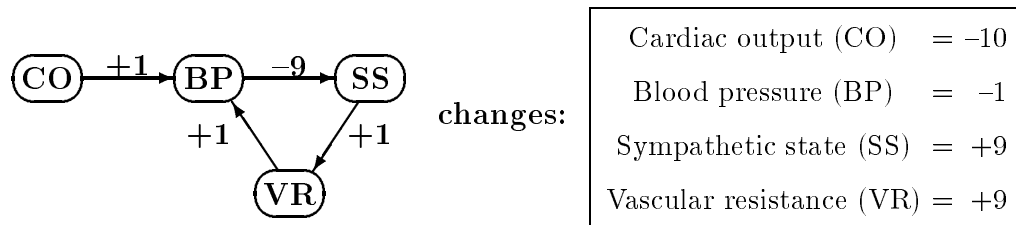


Figure 5: Parameter Gains and Resulting Changes with Feedback

For example, if there is a reduction in the pumping strength of the left ventricle, it is only a few beats before the balance of blood volumes between left and right sides is changed to reflect the new situation. As a result, the cardiac output would decrease and the left atrial pressure (the filling pressure for the left ventricle) would increase. To include such changes in a BPN, the most useful way to model the relationships in such a system is to use the network to represent the qualitative aggregate results of this behavior. Thus, one would have a link from low pumping strength to the final low cardiac output and to high left atrial pressure (LAP), since that is the result of the feedback process, even though every part of the hemodynamic system is involved.

Such an approach has problems. Consider the relationships among parameters illustrated on the left in figure 5. A decrease in cardiac output (CO) directly causes a decrease in blood pressure (BP), which causes a strong increase in the sympathetic stimulation (SS), causing an increase in the vascular resistance (VR). The increased vascular resistance counteracts the decrease in cardiac output to bring the blood pressure back up — a typical negative feedback system. For illustration, the numbers on the links are gains. That is, a decrease of 1 (normalized unit) in the BP would directly cause an increase of 9 units in the SS. Thus, if the cardiac output were decreased by 10 (normalized units), the final stable state would be the changes in the table on the right in the figure. Since the gains sum, the decrease of 10 in the CO plus the increase of 9 in VR results in a decrease of only 1 in the BP and the changes are consistent.

The blood pressure only decreases by one because the increase in VR adjusts for the rest of the decrease in cardiac output. Because of the high gain in this negative feedback, the change in blood pressure is probably undetectable. The natural way to represent the aggregate causality among the qualitative states is shown in the top of figure 6. This summarization of the causality is adequate unless there is some other process involved that prevents the VR from changing, a vasodilator therapy, for example. In that case, the feedback mechanism is blocked and the blood pressure does fall significantly. Then the causality is that in the bottom of the figure. Unfortunately, this is a

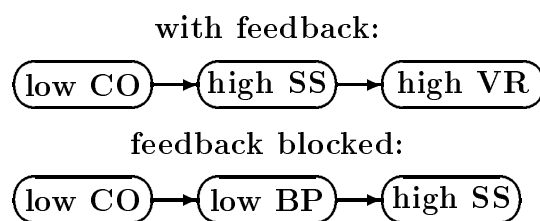


Figure 6: Representing Results of Feedback as Causality

change in the structure of the network and not just an addition to it.

In general, this is a situation for which a fixed acyclic network does not adequately represent all of the possible causal relationships. That is, it is possible to show feedback circuits that would require several different networks in different situations to cover the possible dynamics. In a practical network, however, it is usually possible to determine an architecture that accounts for the situations that arise in practice. There are also ways of working around the problems. In the example, one might model two severities of low BP, the lesser one undetectable and include the low BP in the causal chain. This approach is taken in the HDP to account for the effect of low CO over a period of days on blood volume and manifestations such as pedal edema, since when the pedal edema is observed, there may not be any measurable decrease in the CO. Still, determining an architecture that accounts for the many distinct abnormalities of physiology in the determinants and interactions of the CO on the left and right sides of the heart has been a significant challenge in the development of the HDP.

A practical goal for the BPN representing a feedback circuit is that the architecture is consistent with the causal intuitions of physicians. Even though all of the nodes change together, we usually think of them as a single chain of causality. This chain must support the possible pathophysiologic variants. The usual heuristic is that the causality is represented in the direction of the blood flow. There are exceptions, such as the usual view that low CO causes high LAP.

In situations like a BPN representing a feedback circuit, the meaning and determination of the probabilities is a problem. If the feedback circuit is an accurate model of physical reality, then all the changes actually take place — there is no uncertainty. Therefore, the probability represents the frequency that a change within a qualitative range (e.g., low CO) produces a change that falls within the qualitative range of the effect parameter. This probability depends on the joint distributions of all of the parameters involved in the feedback. For example, the probability that

low CO causes high LAP depends not only on the distribution of COs considered low, but also on the distribution of the other parameters in the feedback circuit when the CO is low. Thus, having an equation that relates the parameters is insufficient information to determine the probabilities. Still, the equations do provide additional information that may aid the diagnostic reasoning. In the HDP, such quantitative constraints are used whenever there is enough information in the input to force the value of an additional parameter. For example, the CO, BP, and right atrial pressure would be used to infer the vascular resistance, which would then be used as evidence for causes of the corresponding qualitative state of the vascular resistance. In a domain as physiologically rich as heart disease, these constraints frequently provide additional leverage for the diagnosis.

### 3.5 Forward cycles in the network

The final issue of representation is the existence of cycles in the domain. That is, situations where the natural causal representation leads to forward cycles like that shown in figure 1. This was the first problem that drove the HDP to a pseudo-BPN. There are three kinds of situations that lead to cycles in the network. The first is events whose consequences increase the probability of those events recurring in the future. For example, a pulmonary embolism can increase the resistance through the lungs, which may decrease cardiac output. Low cardiac output is one of the primary causes of a pulmonary embolism. Thus, the patient is at greater risk of pulmonary embolism in the future (not to mention the other predisposing factors for pulmonary embolism). The pattern that emerges in the individual is an increased probability of the disease once the patient has a past incidence of the event. It is particularly important to reason appropriately about pulmonary embolism because it is a common, often underdiagnosed, treatable cause of hospitalization.

The second kind of cycle is the true positive feedback. Cardiogenic shock is an example. Once the patient starts experiencing a drop in cardiac output such that oxygen delivery is compromised, the function of the ventricle is reduced, causing a further decrease in the cardiac output. Thus, the patient is in a downward spiral which requires immediate aggressive intervention to stop. The third kind of cycle is one with more than one starting point but the effects do not further aggravate the causes (at least noticeably). A typical example is hypertension and renal insufficiency. Either can cause the other.

In the HDP the approach we have taken is to represent the cycles in the model, but not to allow cycles in the hypotheses the program generates. This alleviates problems such as trying to separate the causality between hypertension and renal insufficiency. The program picks the causality that is

consistent with the available evidence and maximizes the probability of the hypothesis. The problem of recurrences of pulmonary embolism require multiple instances of the pulmonary embolism node, with sequential time intervals. This is handled by instantiating the node as needed (in the same way that AR corrected then recurring is handled). The positive feedback cycles are handled by representing the current state of the cycle. That is, the initial cause for the poor ventricular function is the only cause in the hypothesis. The poor ventricular function accounts for the low cardiac output and low oxygen delivery. For the positive feedback cycles in the heart disease domain, this is adequate because these are situations too acute for the HDP to be of much practical benefit. What is being sacrificed is the ability to have an explicit representation of the dynamic behavior. That is, to represent the fact that the cardiac output or blood pressure is dropping as evidence of the positive feedback cycle. It is still possible to analyze the hypothesis and identify the potential for positive feedback by identifying those places in the hypothesis with a causal link in the knowledge base that would create a cycle. This is an important ability because it means that the program can alert the physician to the dangerous possibility of rapid disease progression in situations that might lead to flash pulmonary edema, cardiogenic shock, or other catastrophic events.

## 4 Requirements for input

The goal for the HDP in gathering the case data is to enable the user to unambiguously specify anything that would make a difference in the diagnosis.

The input is more complex than for most expert systems primarily because the HDP needs to do temporal reasoning. The temporal information may be simple, such as the time of a test or event — a single time point. However symptoms, such as chest pain, dyspnea, or fatigue have time intervals during which they have occurred, as well as properties such as length of individual occurrences, frequency, changes, and associations with other symptoms or events. The most challenging findings are murmurs. There can be multiple murmurs, each with a primary and secondary locations, loudness, frequency, and occasionally changes with particular maneuvers. Every property of a finding may provide an important clue in a particular situation but none is always important or even available. So many possible features means a fixed input menu list would be overwhelming. Another problem is the large number of tests that are occasionally available and pertinent. Costly tests such as an echocardiogram or catheterization have many possible findings that can clarify the diagnosis. Even an old test may provide important evidence for ruling in or out chronic pathophysiologic states. Thus, it is necessary to guide the input process and only ask for details

as needed. This is a challenge for a Web interface because HTML forms are fixed. Java applets improve the situation, but not without effort.

The large number of possible inputs is not as problematic for the physician as it might seem, since only a fraction of the data will be available for a patient. Furthermore, users only enter the information they think might be relevant. As a result, physicians rarely enter negative findings. However, the negatives are very important to focus the diagnostic search. Thus, the program needs a good model for inferring negatives from the positive findings. The basic strategy is to assume complete information within what reasonably could have been observed in any category in which the user has specified something. For example, if the user gives information about auscultation (eg, a loud S1), it is assumed that other auscultation information was negative (ie, no murmurs).

There are many situations where this assumption of complete information is unreasonable. In particular, one finding might cover or obscure another. To handle such situations, HDP has rules for deciding which findings are unknown rather than false. For example, if the patient has postural syncope, syncope at rest is false, but if there is syncope at rest, postural syncope and syncope on exertion are considered unknown. In addition, the program assumes that a few important findings, such as chest pain, would be mentioned if they were present.

This mechanism for reasoning about unspecified findings usually provides a reasonable set of negative findings for the program. The most common failing is when the user tries to probe the HDP with “what if” questions or if recorded data includes partial information about a test result. For example, if the user enters a number of findings consistent with mitral stenosis and includes a normal ejection fraction on echocardiogram, the program is likely not to hypothesize mitral stenosis because the expectation that the mitral stenosis would have been present on the echocardiogram is so high that it overwhelms most positive physical examination evidence. Our human ability to make deductions from partial information is so natural that we often do not realize we are doing it. This problem is part of a larger issue of how to handle data in conflict. If the conflict is definite, the HDP identifies the conflict as an error, makes an assumption about what to believe (generally believing an abnormal finding over a normal one) and continues with the analysis. If the conflict is only partial (eg, the common explanations for a finding are ruled out by other evidence), the program continues with the analysis. This occasionally leads to obscure hypotheses, such as diagnosing coronary spasm instead of coronary artery disease to account for unstable angina because in entering catheterization results the user did not enter findings about the coronary arteries, which the HDP then assumed were clear. (We now allow different kinds of

catheterization to be entered.) Another strategy might be to use any instance in which the common explanations of findings have been ruled out as an indication that the absence of those common explanations needs to be indicated to the user and explained.

While developing the HDP we have considered a number of mechanisms for entering uncertain data. One could include a measure of belief with any data item that was uncertain. However, physicians are not used to doing that explicitly and there are few studies of the consistency or meaning of such information. Thus, we assume the physician will follow the old advice to be sure of your data and state what you are sure of. On the other hand, it may be appropriate to provide information on the circumstances of some findings. For example, auscultation in a noisy environment, such as the emergency room, might mean that many of the items not reported are unknown rather than false. This is information that is clearly used by physicians but is difficult to quantify. One instance in which we have a category for poor data is the echocardiogram. Because poor quality results may convey some useful data and not be repeated, we allow the user to indicate that it is a suboptimal study.

Another aspect of the data that is difficult to quantify is the effect of expertise on the accuracy and thoroughness of the data. From our discussions with physicians it is clear that most general internists would not recognize an M-shaped jugular pulse, while most cardiologists would. Similarly, on auscultation the ability to discriminate between an S3 and an opening snap varies with experience. This is an important distinction because an S3 almost rules out mitral stenosis while an opening snap is a fairly specific finding for mitral stenosis.

When physicians consider data, they also factor in the source. Positive physical findings by a cardiologist may overrule a poor quality echocardiogram or a good echocardiogram may overrule auscultation findings reported by an intern. Since the HDP does not have access to the additional information necessary to make these determinations, it is all the more important for the program to explain the basis for the conclusions it draws.

## 5 Requirements for explanation

Given the patient data and ability to reason, the program needs to provide the user with a diagnostic analysis of the case useful in managing the patient. The analysis should be supported in ways that convince the physician of its correctness.

The first question is, what should be in the diagnosis? An appropriate diagnosis includes not only the most likely hypothesis, but also a differential of other hypotheses with significant likelihood.



Since there are few certainties in medicine, the patient may not have the “most likely” disease. Furthermore, the diagnosis is just the first step in managing the patient. Indeed, an important function of the diagnosis is to guide further investigation in the refinement of the diagnosis. Thus, the physician needs to know what possible diagnoses, especially treatable ones, should be considered. Since the purpose is to alert the physician to important possible diseases, the differential need only include those alternate hypotheses that differ from the best hypothesis in clinically significant ways. The HDP accomplishes this by only including hypotheses that differ in a disease state of diagnostic significance. It is possible to imagine situations in which finer grain alternatives would be useful, such as possible complicating mechanisms that might have therapeutic implications.

The second task is to present the differential to the user. There are a number of possible strategies one might pursue. The approach for BPNs suggested by Suermondt[21] and more recently modified by Haddawy et.al.[22], assumes that there is a single disease node that is the focus of the diagnosis. Their approach is to identify the findings that have the greatest influence on the probability of that node, either by sensitivity analysis in the fully specified network or by comparing the contribution of each finding in the absence of other findings. The causal pathways from the node to the most influential findings are then used as the explanation of the diagnosis. This approach is inappropriate for the HDP because the hypothesis is not just one node, rather it is an instantiation of a subset of the network representing a complete explanation of the findings. Determining a complete explanation is important in cardiology as well as other domains in which there are chronic diseases because the primary disease may not be the clinically important part of the hypothesis. Often the primary disease is already known and uncorrectable and the important question is what new treatable complications are causing the patient to be decompensated.

Thus, the approach taken by the HDP is to consider the differential as a set of possible complete and consistent explanations. As mentioned in the earlier section we have added a number of properties to the nodes, so in fact, the internal representation of the hypothesis contains considerable detail. Each of the instances of nodes in a hypothesis includes the temporal intervals, severity, and disease type properties. In many cases there are multiple instances representing the progression of the disease over time. For example, there might have been echocardiographic evidence of mild AS two years ago and findings indicative of more severe AS now. This would be represented by an instance of mild AS covering the time two years ago and extending into the past and sometime prior to now. The second instance of more severe AS would follow the mild AS and extend into the future. In this way, the program is able to maintain the temporal consistency and consistency

of findings of the disease at different severities.

Given the amount of detail in hypotheses, we have chosen to explain the differential in two steps. First, to explain the best hypothesis and then to give an outline of the rest of the hypotheses. In this way the user is given the program's best estimate of how the findings fit together and an overview of the possibilities that should be considered or ruled out. Another possible strategy would be to abstract from the set of hypotheses in the differential one or more general hypotheses that are noncommittal in areas where the hypotheses give alternative causes. For example, if all of the differential hypotheses have dilated cardiomyopathy but they explain it variously as of hypertensive, ischemic, or idiopathic (primary) origin, the general hypothesis would just refer to it as dilated cardiomyopathy of unknown origin.

Since the best hypothesis is a large causal network supported by positive and negative findings, the challenge is to explain it succinctly. In a typical hypothesis a causal chain from disease to finding may include as many as ten intermediate nodes representing the mechanisms leading to the finding. While a detailed explanation is useful for understanding the basis of the conclusions, the complexity and prevalence of concepts relating mechanism tends to obscure the more important messages of the hypothesis.

## 5.1 Summarization

To handle the problem of explaining a hypothesis, we have developed a technique for summarization that eliminates the nodes relating mechanism, combines nodes into recognized syndromes, and eliminates much of the detail of time and type.

The nodes representing mechanism are eliminated by merging them into the most closely associated important node and using only the links needed to establish the structure of the diagnosis. Mechanisms are recognized by labels supplied in the knowledge base. For example, low blood volume is labeled as the mechanism through which dehydration causes its effects. If a hypothesis had the causal link from dehydration to low blood volume, the summary would only have dehydration with causal links to any effects of either dehydration or low blood volume. Sometimes the effect node needs to replace the mechanism node. For example, acute myocardial ischemia is labeled as the mechanism for its effects: acute MI and unstable angina. If the hypothesis has acute MI, summarization eliminates the acute myocardial ischemia and only the acute MI node remains. Other effects of acute myocardial ischemia are attributed to the cause of the ischemia (eg, coronary artery disease), since they are not effects of the MI.

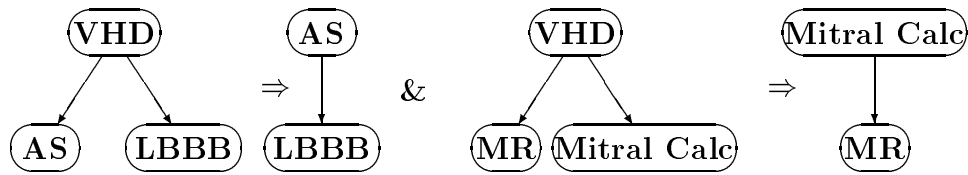


Figure 7: Summarization by Incorporating Mechanism

Unfortunately, when a number of nodes are collapsed into one, the appropriate action varies with the circumstances. Eliminating the valvular heart disease (VHD) node as the mechanism for valvular disease in cases from our previous evaluation[2] illustrates the range of possibilities for handling effects. VHD is a covering node that is instantiated as the appropriate type of primary valvular disease (rheumatic, degenerative, etc.) when there is adequate evidence.

In one case where the VHD included left bundle branch block (LBBB) and aortic stenosis (AS), the summary absorbed the mechanism, VHD, into the AS, and left LBBB as a separate entity. In another case, the VHD was manifest as both mitral annular calcification and mitral regurgitation (MR) with the summary separating them. The more appropriate summarizations are in figure 7. The difference in these two situations is that the LBBB does not influence the AS and to a large extent the AS causes the LBBB. Thus, the AS can substitute for the VHD in causing the LBBB. In the second situation, the mitral calcification is seen as at least worsening the MR and can substitute for the degenerative process that is the VHD. Thus, this additional causal information needs to be in the knowledge base to make the appropriate summarization decision.

In a third case, the VHD was manifest as both MR and mitral stenosis (MS). The summarization left these as separate entities, but the reviewers preferred maintaining the VHD, which in this case was of rheumatic origin. The summary lost the important information that the MR and MS had a common source. The valvular heart disease could be replaced by more specific labels of rheumatic heart disease or mitral valve disease to provide the connection, but the node is needed. In contrast, in one case there is a causal link from renal insufficiency to hypertension. This causal explanation was the highest probability explanation generated by the program. However, there was no specific support for this relationship among the findings. Since hypertension can also cause renal insufficiency and the high prior probability both are primary, the reviewers would have preferred having no causal connection between them, indicating no commitment. That was also true in a case in which the patient had anemia. While a few of the causes of anemia are in the model, most

are outside the domain of the program and unless there is specific evidence for a causal relation, the summary should not indicate a possible cause. Since the program concentrates on cardiovascular disease, the diseases that are peripheral have only partial lists of causes in the model and the program should be noncommittal about causes.

If there are multiple possible causes for the node, physicians want them included in the summary. For example, ventricular ectopy should be attributed to all of the possible causes in the hypothesis, such as coronary artery disease, hypokalemia, hypoxemia, and cardiac dilatation, rather than just the one or two of these with highest probability. This is useful for creating a management plan for the patient.

Thus, the appropriate summarization preserves the sense of causality, which may require additional information and reasoning. The summarization also needs to keep the causal connections between diseases supported by evidence and discard those only supported by a higher probability. If there are multiple possible causes within the hypothesis, all should be included in the summary.

In addition to removing the mechanisms from the hypotheses, the summarization process includes the recognition of syndromes. The syndromes are combinations of nodes considered as an entity by physicians. For example, congestive failure is the combination of left and right heart failure. In turn, left heart failure consists of high left atrial pressure and pulmonary congestion caused by low cardiac output. Situations that do not match this definition, such as forward failure in which the effects of the low cardiac output are fatigue, peripheral cyanosis, etc., are summarized by the low cardiac output with its effects. Syndromes in the HDP include cor pulmonale, cardiogenic shock, and coronary heart disease.

Another important kind of information to include in the summary is pertinent negatives. There are a couple of kinds of pertinent negatives. First, there are the findings that decrease the likelihood of the generated hypothesis. For example, the hypothesis may include MS on the basis of a number of findings. However, if the auscultation did not find an opening snap, it is worth noting the fact because an opening snap is present in the majority of MS cases. Such negative information gives the physician a more balanced impression of the hypothesis. Some of the negative findings may have been overlooked by the physician. In other cases, the presence of significant negative findings may point to underlying conflicts in the data. In either case the information helps the physician assess the validity of the hypothesis.

Secondly, situations where a common cause for a finding or group of findings is ruled out indicate another kind of pertinent negative. (This is the partial data conflict problem mentioned earlier.)

To determine these pertinent negatives, it is necessary to first determine the common causes of each abnormal finding in the absence of other findings. Of those causes that have strong support from individual findings and do not appear in the differential, determine the negative findings that rule out or significantly decrease their probability. This strategy ignores the possibility that a ruled-out cause may be supported by a pattern of findings and not any single finding, but we have not seen any such examples. It is valuable to point out to the physician such pertinent negatives both to assess the hypotheses and to assess his/her own data.

## 6 Discussion

It is clear that the challenge of diagnostic reasoning in heart disease, as well as many other knowledge rich domains, is multifaceted. While BPNs are a good first pass at capturing the pertinent relationships, they only scratch the surface. To improve the diagnostic capabilities of a program, more of these relationships will have to be used. The HDP has extended the BPN paradigm to incorporate knowledge about temporal characteristics, severities, the patterns of distinct disease types, implications of data entered by the physician, constraints on data relationships, and physician requirements for an appropriate diagnosis.

While not all domains will benefit from all of these additional kinds of knowledge, there are several in which physicians may reason about the underlying physiology in a similar manner, including respiratory disease, neurology, endocrinology, and acid-base and electrolyte disorders. Some domains will require additional kinds of reasoning. Indeed, the requirements of the acid-base domain for quantitative analysis go well beyond that of cardiology. As physiological research produces fruit there will be more domains that require multifaceted reasoning to achieve the necessary leverage to solve the diagnostic problems.

From the perspective of the HDP, there are a number of directions for research in improving the methodology. The development of a knowledge base for a domain as complex as cardiovascular disease is a lengthy and difficult process, prone to error. A number of techniques have been developed recently for generating BPNs from data. A major constraint when the reasoning includes causality and temporal relations is to preserve the causal structure in the model. More recent work is heading in that direction[23]. At present, the most reliable approach is simply to start with a causal structure and use the data to refine the probabilities.

One of the challenges is making sure that the model captures what is known about patterns of disease. Physicians often remember diseases in terms of their typical manifestations, so this

information is relatively easy to elicit from experts or medical texts. Since no current patient data base is large enough to accurately reflect all such patterns, it is necessary to provide additional guidance to make the network incorporate this knowledge. We have used the idea of types of a disease enforced with properties on nodes that adjust the probabilities. This partially addresses the problem, although in a way that is counter to the basic assumptions of a BPN. There are undoubtedly other approaches that would combine the basic insights of frames (a natural way of capturing patterns) and a BPN.

The difference between a physician's reasoning and a probabilistic approach to diagnosis also comes out in the explanation. Physicians tend to think in terms of evidence rather than probabilities. Therefore, they tend to be satisfied with causes that can be "ruled in" or "triggered" by findings and less satisfied with causes based on probabilities. Thus, giving a specific cause for dilated cardiomyopathy just on the basis of the prevalence of ischemic or hypertensive disease is considered inappropriate, but is fine if the patient has some history of angina or high blood pressure. However, there are specific situations in which one should include unsupported causes. These are the treatable diseases that might otherwise go unnoticed, such as pulmonary embolism or endocarditis. Probabilistic approaches have much to offer in such situations, because these are the problems may be overlooked by the physician's approach, particularly with inadequate data.

The HDP is currently undergoing an evaluation that will give us a better understanding of the strengths and limitations of the knowledge base and the mechanisms we have developed for reasoning. To conduct this evaluation, we have developed a Web based interface that will allow physicians with a Web browser[26] and Internet access the ability to run the program[24, 25].

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