Quantification of propensity for differential diagnosis by denotational semantics

Logic Formalisms for the probabilistic model

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Abstract:

We report the design of logic formalisms for simplification of computations involved in belief network representation of Quick Medical Reference-Decision Theoretic (QMR-DT) diagnostic support tool. We quantified the features using denotational semantics. "Propensity for differential diagnosis' is defined as the ratio of sums of quantities of features shared by a group of diseases and their incidence in a given disease. We suggest that Ramsey's theorem is a definition for differential diagnosis. Simple Bayesian probabilistic method is used for testing the logic formalisms in our knowledge base. Several published reports on missed diagnosis give posterior probabilities of presumptive and missed diagnoses. Results derived from logic based and simple probabilistic model suggest that 'propensity for differential diagnosis ' concept can reduce the complexity involved in the computations of probabilistic belief networks of diagnostic systems.

Key words: Diagnosis, expert systems, denotational semantics, belief networks, and probabilistic inference.

Introduction:

Probabilistic models based on Bayesian belief networks have made important contributions to the computation of the medical diagnostic process [1,2]. However, several problems like computability, complexity of inference algorithms still remain. Application of Bayes' rule to probabilistic inference on belief networks is NP-hard. We realize the conceptual lacunae involved in the organization of medical knowledge. For example, we do not have any adequate definition for a differential diagnosis and causes of a disease are often confused with it. As a result diagnosis is often delayed or made only at autopsy. We have independently constructed logic formalisms developed by Ledley and Lusted in their classic paper four decades ago [3] with an intention that these formalisms may simplify the existing probabilistic models [1,2]. For example, Ramsey's theorem can be a definition for differential diagnosis [4]. Here, we report that principles of denotational semantics can be useful for quantification of clinical features. A new diagnostic concept namely 'propensity for differential diagnosis (N_D) is defined to accurately quantify any feature given disease.

Development of these logic formalisms involved implicitly the principles of probabilistic belief networks. For example, disease-to-disease links are derived in a two-dimensional belief network for finding the N_D value of a given disease. Feature-to feature links are also involved in the development of the new model and are exemplified in the Results section. We perceive the limitations of belief networks in earlier models [5,6] and the present one and propose the development of three-dimensional belief network as an ideal computer aided diagnostic system. It involves application of the model on all diseases and all features available in our knowledge base. Towards this aim we tested the model initially on a single disease which involved study of 26 other diseases for calculation of the N_D values. We found posterior probabilities of a disease for a given set of observed findings using equations derived from the probabilistic models [1,2]. We also tested the model on 9 published reports on missed diagnosis, which involved study of 104 other diseases. Results of these studies seem to be clinically sound.

The assumptions of the probabilistic model: marginal independence of diseases, conditional independence of findings and causal independence, are included in the present model. It refines the probabilities of frequencies of features in QMR-DT model. Binary disease and feature assumption is also included in it and is specifically utilized for deriving the probability of a disease for any given set of features. Historical findings, age, gender are not included in it since we can implement these simply after evaluating the posterior probabilities of disease entities. Since the present model assumes the presence of all possible diseases and their features in the knowledge base, calculations involving the leak probabilities are not included. Prior probabilities of diseases are

also not included in it since we cannot correctly ascertain these. For example, bronchial asthma admissions in NCHS database may not reflect the real incidence of the disease since only some of these patients at any time need to be admitted. Moreover, it was found that QMR-DT model is insensitive to uniform prior probabilities and weight of evidence in diagnostic cases predominate the prior probabilities of diseases in deriving posterior probabilities of diseases [2]. We show that the assumptions made in the logic model can reduce the complexity of computations involved in the probabilistic model and remain diagnostically correct.

2. The propensity for differential diagnosis model:

2.1 Denotational semantics for frequencies of features:

Quantification of features using denotational semantics involves the following assumptions: the import value of observing an event itself is greater than that of observing the effect of an event. The import value of observing the effect of an event is greater than that of observing the remote effects of an event. If the event is disease D ,'and its effects are the features, (1) feature f is a direct consequence of disease D and is irrefutable, or (2) feature f is caused by a mechanism of D or (3) feature f is least defined in terms of D. Frequency of f of disease in the first case is high, moderate in the second case and low in the third case. These represent three types of denotational semantics namely, consequence based, operational and fix-point [7]. Each describes a relationship between a feature and a disease. The following functions of features are considered for denotational semantics: pathology, pathophysiology, etiology, organ involvement, biochemical abnormality, enzymatic defect, pathognomonic sign or result, rarity, pathogenesis, direct and indirect consequences of pathogenesis, single disease having several distinct disease entities and iatrogenic effects. Variations of age, gender, genetic and geographical nature may be considered individually and separately and hence are not considered for quantification. We describe these expressions in the following examples, which are common to the probabilistic model.

2.1.1 Consequence based semantics:

Bronchial adenocarcinoma can have a bronchoscopic endobronchial biopsy as adenocarcinoma. This feature belongs to consequence based semantics. A CT scan of this patient may also suggest bronchogenic carcinoma. Both these features belong to consequence based semantics and have different import values. The biopsy finding has a higher frequency (=4) than the CT scan report frequency (=3). Consequence based semantics is denoted by:

$$\{ X/ \text{ disease } (Y) \models \text{ entity } (X) \} \qquad (1)$$

Where $X= X_1$ or X_2 whose values are 4 and 3 respectively. $\models$ = Semantic consequence.

2.1.2. Operational semantics:

Feature, 'blood streaked sputum' in a bronchial adenocarcinoma patient belongs to operational semantics [7]. This semantic is based on SLD resolution (linear, definite, selection) which uses negative clause queries with definite clause programs. Some selection rule is applied to each resolution step in order to select a particular literal to resolve upon the input clause or an earlier resolvent. If our input clause is 'bronchial adenocarcinoma' and a query is '? friability' meaning cancerous tissues are usually friable, we can resolve 'bleeding'. Similarly, the query '?mucous' upon the centre clause 'bleeding' would resolve the 'blood streaked sputum'. It sugests the pathophysiological effect of bronchial adenocarcinoma in producing the feature 'blood streaked sputum'. Operational semantic is denoted:

$$\{ X/ \text{ disease } (Y) \cup \{ ? \text{ feature } (X) \} \vdash ? \text{ feature } (X,Y,Z) \rightarrow ? \text{ feature-or-effect } (X,Y) \,\&\, ! \; Z=Y \rightarrow ? X$$

$$\text{is a feature of } Y \,\&\, Z = Y \rightarrow \square \; \} = \{ X/ \text{ feature } (X) \; \varepsilon \; \{ \text{disease } (Y), \text{feature } (X) \} \} \qquad (2)$$

Where $X= X_3$ whose value is 2. ! = cut, used for pruning the search process, Z= pathophysiological effect, $\cup$ = resolution, $\vdash$ = syntactic consequence, $\square$ = resolved, ε = set member.

A simplified explanation of this denotation using the previous example is as follows: to solve the 'blood streaked sputum' problem using SLD, we query the possibility of generation of feature 'blood streaked sputum' from the

disease ' bronchial adenocarcinoma' by ' ? feature (X,Y,Z)'. In the next step, the pathophysiological effect of the tumor involves release of friable cancerous tissue into the bronchial tract resulting in bleeding and as well as reflex mucous production. This resolves the 'blood streaked sputum' for bronchial tumor. Similarly, 'muscle weakness' and 'constipation' problem can be resolved for 'primary hyperparathyroidism'. Thus, application of the denotation using SLD can facilitate a deeper pathophysiological understanding of the features that are produced by a mechanism of a disease. This formalism is similar to belief networks and implicitly suggests the conditional independence of findings given a disease. Assuming the possibility of another disease 'pulmonary tuberculosis', the 'blood streaked sputum' problem can generate the same pathophysiological effects. This explains the causal independence described in the probabilistic model and is similar to the noisy-OR- gate interaction between two diseases. Since the import value of observing an event itself is greater than that of observing the effect of an event, features belonging to operational semantics have a lower frequency (=2) than the features of consequence based semantics.

2.1.3. Fix-point semantics:

Feature 'clubbing' of fingers in a bronchial adenocarcinoma belongs to fix point semantics [7]. It describes the least defined relationships of findings, their pathophysiological effects and the disease possibilities. Logical understanding of fix-point semantics involves a lattice of uncertain pathophysiological effects that are indirectly related to the findings given a disease. It involves a partially ordered set whose least upper bound (lub) is an indirect pathophysiological effect causing features of constitutional or common nature. Fix-point semantics is expressed:

{ X/ feature (X) ε lub { indirect effects (features of common nature) / indirect effects Y } } = { X /

feature (X) ε pathophysiology of (cause of disease) } (3)

Where $X = X_4$ whose value is 1.

2.2. Propensity for differential diagnosis:

Quantification of features based on denotational semantics is similar to the QMR frequencies. Expressions for each semantic clearly aid in the accurate quantification of feature given disease. However, sometimes there may be difficulties in the identification of frequencies. If quantification of feature by logic formalism is difficult, probabilistic incidence of the feature is taken into consideration. Because of these problems the mapping between QMR frequencies and probabilities may not be ideal. To improve these quantities, we developed a new diagnostic concept known as 'propensity for differential diagnosis'.

A common disease has common features, which are shared by many diseases whereas a rare disease has unusual features shared by few diseases. Every disease is unique for its features and their import values. We assert that every disease has a finite number of features and are shared by n number of other diseases. We study by selecting a disease and its features and quantify them as described. The sum of these quantities is equivalent to $N_{max.}$ For example, if a disease has 30 features and their quantities showed that 4 belonged to the frequency 4, 3 belonged to the frequency 3, 10 belonged to the frequency 2 and rest to the frequency 1 then the N_{max} is equivalent to 58. If the differential diagnosis includes n number of diseases, they share the features. Each disease sharing a common feature will have different frequency depending on their pathophysiology and consequent denotational semantic. We realized the problem of correctly identifying the differential diagnosis given a disease in the absence of a formal definition. We looked for logic formalisms that may be useful in this regard and identified Ramsey's theorem as a possibility [4]. We developed a two-dimensional belief network for quantification of features shared by diseases given differential diagnosis. The sum of these quantities derived similarly to N_{max} is equivalent to N_{smt}. Propensity for differential diagnosis is expressed:

$$N_D = \frac{N_{smt}}{N_{max} \times n} \qquad (4)$$

N_D value denotes a relation of the disease in differential diagnosis context and is a constant for the given disease. Any disease characteristics are dependent on their constituent features. The features in a clinical context are quantified and hence the sum of their quantities is an expression of their nature. N_{max} and N_{smt} mutually oppose in a differential diagnosis context. The value of N_{max} ascertains the probability of a disease to be the diagnosis whereas N_{smt} verifies the probability of other diseases in the differential diagnosis to be the diagnosis.

The ultimate diagnosis depends on the ratio of N_{smt} and N_{max} values. If N_{smt} and N_{max} are constant the N_D is indirectly proportional to n ($N_D \propto 1/n$). A common disease has common features that are shared by many diseases and hence their n value is high. In contrast a rare disease may have unusual features which are not shared by many diseases and hence their n, N_{smt} are low and N_{max} are high. If N_D determines the propensity of any feature to take part in a diagnosis then N_D X Nr (Nr = frequency) should reflect this. In other words N_D should be smaller for a rare disease (since frequency of feature given disease is not related to the frequencies of the same feature given other diseases). Given that high N_{max} and low N_{smt} are features of rare diseases, $N_D \propto N_{smt}/ N_{max}$. Since $N_D \propto 1 / n$, $N_D = N_{smt} / n$ X N_{max}.

N_D represents the propensity of any disease to take part in a differential diagnosis and is a numerical representation of commonality of clinical data between a given disease and other diseases. N_D varies according to N_{max} and N_{smt}. Since the variables have finite values N_D may be unique for a given disease. If n is constant and N_{smt} is high (N_{max} low) N_D will be high and if N_{smt} is low (N_{max} high) N_D will be low. If N_{smt} and N_{max} are constant and n is high, N_D will be low and if n is low N_D will be high. If the frequency Ns represents the propensity of any feature to take part in the diagnosis of a given disease, Ns is expressed:

$$Ns = N_D \text{ X } Nr \qquad (5)$$

Higher the Ns value greater the significance of the feature and lower the Ns value lower its significance. Ns, is a logically accurate quantification of features given disease.

2.3. Logic formalisms for the probabilistic model:

As mentioned earlier Nr values (4,3,2,1) are similar to QMR frequencies. The probabilistic model assumes a symmetrical distribution in each of the intervals to generate the mapping of P (f^+/only di^+). The present model differs significantly on this assumption. We propose that Ns values represent the logically accurate probabilities of features given disease. Therefore,

$$Ns = P(f^+ / \text{only } di^+) \qquad (6)$$

The set of findings that are absent F^- include those that are unobserved [1]. Logic formalisms cannot quantify P (f^- / only di^+) and hence are not included in the probabilistic equations. It is not incompatible with causal independence to assume that a given set of features found could all together, caused by a single disease. By extension of the intuition behind equations (2,3 and 5) of the probabilistic model [1] we derive:

$$P(F^+ / \text{only } di^+) = 1 - \prod_{f \varepsilon F^+} 1 - P(f^+ / \text{only } di^+) \qquad (7)$$

Finally, we derive the posterior probability of a given disease by using the equation (12) in the model:

$$P(\text{only } di^+ / F, \mu) = \frac{P(F^+ / \text{only } di^+)}{\sum_{n=1}^{n} P(F^+ / \text{only } di^+)} \qquad (8)$$

Where n= number of diseases in the differential diagnosis, μ is the assumption that diseases are mutually exclusive.

2.4. Logic formalisms Vs probabilistic models:

Disease-to-disease links are implicitly built in the 'propensity for differential diagnosis' system. This permits the computations of posterior probabilities that are similar to the result of tabular Bayes ' (TB). Hence, iterative tabular Bayes' (ITB) computations are not needed to arrive at a 'heuristic importance step'. A given feature caused by several diseases. Any set of features found can have few commonly shared diseases. The posterior probabilities of the commonly shared diseases of the features present, computed by logic formalism would be higher than the rest. The definition of 'propensity for differential diagnosis' involves similar computations of disease-to-disease links as described in ITB. Thus logic formalism makes ITB redundant. Logic formalism asserts the importance of diagnosis given features found in a simplified manner.

Logic formalism using N_D values for quantification of features implicitly consider its given diseases. Therefore, if both 'decreased hepatic arterial vascularity' and 'increased prothrombin time' are found in a patient the posterior probability of cirrhosis would be much higher than the posterior probability for any single finding. It suggests that our model implicitly consider the binary diseases and findings. Propensity for differential diagnosis also implies the causal independence. The quantification of any given feature depends on its frequency given disease and the N_D value of the disease. Hence, 'positive Guaiac test' have different quantities for different diseases causing it, Moreover, in logic formalism the causal independence assumption is equally accurate in cases where diseases operate through a common pathway to cause a finding.

Probabilistic models based on Bayesian' belief networks use stochastic simulation algorithms based on likelihood-weighting [8]. However, these are only approximation-algorithms, used because of the general problem of probabilistic inference on belief networks, which is NP - hard. Central to this is the key issue of generalizing the tabular Bayes' rule. The basic difference between the Bayes' rule under the assumptions of single disease hypothesis and conditional independence of findings and its generalization to allow the diagnostic hypothesis to contain any subset of diseases in the knowledge base is the summations in its numerator and denominator. Although this generalization is consistent with the QMR - DT model, it is not consistent with the logic model. The assumptions made in the use of probabilities do not belong to the realm of medical diagnosis, but rather in statistics [3]. Propensity for differential diagnosis limits the disease hypothesis to a specific subset of diseases in the knowledge base. This is defined by finding their N_D values. The concept of generalizing a disease hypothesis to include the probabilities of all diseases seems contrary to the reality. An expert may readily diagnose a disease given findings without the knowledge of many diseases in the knowledge base. Moreover, finding propensity for differential diagnosis of any given disease seems not only similar to the expert's diagnostic process but also much simpler than the generalized Bayes' rule or simulation algorithms [8]. In other words combination of N_D values and tabular Bayes' rule may be sufficient for computation of posterior probability of any disease. The reason for computability problems and complexity of inference algorithms is reliance of the probabilistic model on concepts like noisy - OR gate, likelihood weighting simulation or Markov blanket scoring. Application of Bayes' probabilistic inference on belief networks is NP - hard. Development of logic formalisms like 'propensity for differential diagnosis' would simplify the probabilistic belief networks of diagnostic - decision tools.

2.5. Ramsey's theorem is a definition for differential diagnosis:

Propensity for differential diagnosis is directly proportional to the number of diseases taking part in a differential diagnosis. We felt the need for a formal definition of differential diagnosis. Here I propose that Ramsey's theorem is a mathematical definition for differential diagnosis [4]. Ramsey's theorem has two parts: infinitary and finitary. Here we will deal with the second part only. It is defined as follows: if r, s and n are positive integers and n >= r then there exists a positive integer m >= n such that no matter how the size r subsets of { 0,1,…,m-1 } are divided into s mutually exclusive classes, there is a large subset Y of { 0,1, …, m-1 } of size at least n such that all size r subsets of Y belong to the same one of the s classes. For the clinical situation m =features of a disease, n= systemic or organ effects, r= pathophysiological basis and s= diseases considered for differential diagnosis. It is assumed that this interpretation satisfies the condition: m>=n >= r. Ramsey's theorem suggests that a group of diseases having similar pathophysiological basis may also have similar features and systemic or organ effects. Specifically it allows us to consider a group of diseases as a differential diagnosis for any given features. Adaptation of Ramsey's theorem aids in emphasis the role of pathophysiology and its systemic or organ effects. These effects can be derived from r number of pathophysiological effects. A group of competing diagnosis of a presumptive differential diagnosis are compared each with the given m, n and r. A unique s number of diseases that can best compete with the given m, n and r are selected as definitive differential diagnosis.

2.6 Evaluation of diagnostic performance:

We have studied 'hemolytic jaundice' to test the model described [9,10]. Its differential diagnosis: cholestatic jaundice, viral hepatitis, cirrhosis and congenital hyperbilirubinemias. For deriving the N_D values 21diseases are considered. The N_{max}, N_{smt} , N_D and n values are calculated as described. A test is performed for a few features to find the posterior probabilities of the disease. These probabilities would indicate the diagnostic possibility of a disease and hence the validity of the model. As a comparison, the posterior probabilities of these diseases given same features are calculated using equations (7) and (8). This is performed by assuming $X_1 = 0.985$, $X_2=0.800$, $X_3=0.500$ and $X_4 = 0.200$, where X_1, X_2 , X_3 and X_4 are as described and their corresponding values indicate probabilities of QMR frequencies [1].

We assumed that if propensity for differential diagnosis is a true diagnostic system, it should be a solution for missed diagnosis. For this possibility, we studied several published case reports on missed diagnosis [11-16]. N_D values of presumptive and missed diagnosis of published case reports are calculated as described. We performed a comparison of this study with the probabilistic model as described. Confirmatory results for the missed diagnosis are excluded from quantification. Features having same pathophysiological basis, for example, pain and its radiation or tenderness considered as a single entity.

3. Results:

A test of this model is performed using features of hemolytic jaundice [9,10], namely, jaundice, clubbing, anemia, raised unconjugated bilirubin, hepatomegaly and splenomegaly. The n, N_{max}, N_{smt} and N_D values for hemolytic jaundice and its differential diagnosis are given in appendix. As a comparison, posterior probabilities of hemolytic jaundice and its differential diagnosis for the same features are found by probabilistic method. These values for the logic based model and the probability model given in parenthesis are as follows: hemolytic jaundice 0.233 (0.203), cholestatic jaundice 0.182 (0.197), viral hepatitis 0.214 (0.199), cirrhosis 0.233 (0.203) and congenital hyperbilirubinemia 0.138 (0.198). The values for hemolytic jaundice 0.232655 (0.2024665) are slightly lower than those for cirrhosis 0.2327947 (0.2024535) for the logic based model. The values for viral hepatitis are higher than the values for congenital hyperbilirubinemias. These values for probabilistic model show small difference between viral hepatitis and congenital hyperbilirubinemias and the same for cirrhosis is smaller than hemolytic jaundice. This suggests that logic based model is more accurate than the probabilistic model in suggesting the posterior probabilities for hemolytic jaundice and its differential diagnosis. This suggestion is based on the assumption that any congenital disease may be rarer than a commonly infective disease.

To test the possibility of propensity for differential diagnosis as a solution for missed diagnosis, we studied several published reports. The n, N_{max}, N_{smt} and N_D values of these diseases are given in appendix. The posterior probabilities of these diseases are calculated as described and given in table 1. These values show that logic based model predicted the diagnosis in 5 out of 9 cases, probabilistic model correctly predicted the diagnosis in 1 out of 9 cases. Both predicted correctly the diagnosis in 2 cases and both failed to diagnose correctly in 1 case. These results confirm the earlier finding that logic based model may be more accurate than the probabilistic model. Limitations of these observations are discussed.

The similarities of the posterior probabilities of diseases given findings shown in table 1 suggest that logic based formalism has similar and comparable conceptual basis to that of the probabilistic model. These results are elaborated for various diseases here. Chest pain due to spontaneous rupture of esophagus (Boerhave's syndrome) can be confused with pneumonia, perforated ulcer, pulmonary infarction and aortic dissection [11]. Its feature representation leads to a 'tradition of misdiagnosis'. Patients are considered to have a 'medical' problem and surgeons are the most likely to make the diagnosis. It is noteworthy that neither of the models able to predict the correct diagnosis. Logic based model diagnose another surgical condition, perforated ulcer whereas the probabilistic model diagnose a medical condition, pneumonia. Because of the rules for selecting the features mentioned confirmatory finding 'surgical emphysema right side of the neck' and features 'pain radiating to inter scapular area' or 'epigastric tenderness are not considered. The features considered are: (1).'severe lower thoracic epigastric pain' common for all the diseases, (2).'decreased breath sounds at right base' for Boerhave's syndrome, pneumonia and pulmonary infarction (3), pulse 120/mt is considered for pneumonia, (4) 'right sided hydro pneumothorax on chest radiogram' for Boerhave's syndrome and (5) 'nausea and vomiting' for aortic dissection.

Acute mesenteric ischemia can be confused with acute pancreatitis due to perforated viscous [12]. For the reasons mentioned earlier, the finding 'raised serum amylase levels' are not considered for acute pancreatitis or for acute mesenteric ischemia. Posterior probability results for these diseases show that logic based model correctly diagnosed whereas the probabilistic model could not correctly diagnose. The features considered are: (1).'generalised abdominal tenderness and vomiting (for both diseases), (2) 'colicky abdominal pain and leucocyte count 25.1 X 10^9/L (For mesenteric ischemia) and (3) ' nausea and sinus tachycardia 110/mt' (for acute pancreatitis) [12].

Acute mesenteric infarction can also be confused with acute myocardial infarction [12]. Key to early diagnosis is a high index of suspicion of acute mesenteric ischemia. At present (1993) there is no reliable laboratory indicator of intestinal ischemia [12]. Both logic based and probabilistic models correctly predicted the diagnosis. The features considered are: (1) 'colicky abdominal pain, vomiting (both diseases), (2) WBC count 15.4 x 10^9 /L (acute mesenteric ischemia), (3)'nausea'(myocardial infarction).

Costovertebral joint dysfunction can be misdiagnosed for pulmonary infarction [13]. Atypical thoracic pain could be responsible for inappropriate, repetitive, potentially dangerous and costly investigative procedures. Logic based model could accurately diagnose costovertebral joint dysfunction whereas the probabilistic model failed to diagnose the disease. The features considered are: for both diseases, (1)'severe left basithoracic pain' and (2) the 'pain increased with breathing movements'.

Caroli's disease can be misdiagnosed as hydatid cysts [14]. Logic based model correctly diagnosed Caroli's disease whereas probabilistic model diagnosed the hydatid cyst disease. The features considered are: for both the diseases: (1) 'right upper 1/4 abdominal pain',(2) 'hepatomegaly' and (3) 'ultrascan liver cysts'. Contrary to expectations, a congenital disease has a higher probability than an infective disease using logic model. However, the posterior probability values (0.516 and 0.486) differ marginally although significantly.

Gliomatosis cerebrii can be misdiagnosed as benign intracranial hypertension [15]. The logic based model correctly diagnosed Gliomatosis cerebrii whereas the probabilistic model diagnosed the same as benign intracranial hypertension. The features considered are : (1)'papilledema' and (2)'rised intracranial pressure'(for both diseases),(3) 'obesity' (for benign intracranial hypertension) and 'blood glucose 10.9 mmol /L' (for gliomatosis cerebrii).

Myocardial infarction can be misdiagnosed as otitis media when atypically presenting with ear pain [16]. Both logic based and probabilistic models correctly diagnosed the myocardial infarction. The features considered for the study are 'sweating and pallor (for both otitis media and myocardial infarction),'severe aching pain in ear' (for otitis media) and 'nausea, PR 100/mt, BP 140/90 mm Hg' (for myocardial infarction).

ANCA associated vasculitis can be misdiagnosed as polymyalgia rheumatica [17]. The probabilistic model correctly diagnosed the ANCA vasculitis whereas the logic based model diagnosed the same as polymyalgia rheumatica. The features taken into consideration for the study are: (1) 'polyarthropathy and raised ESR' (for both diseases), (2) 'shortness of breath', weight loss, microcytic anemia, hematuria, proteinuria and granular casts in urine (for ANCA - associated vasculitis)[17].

Churg-Strauss syndrome can be misdiagnosed as congestive cardiomyopathy [18]. Logic based model correctly diagnosed Churg-Strauss disease whereas probabilistic model diagnosed congestive cardiomyopathy. Features taken into consideration for the study are : 'dyspnea' (for both diseases), 'pericardial effusion on CT' (Churg-Strauss syndrome) and 'cardiomegaly on CT' and 'congestive cardiomegaly on echocardiography' (congestive cardiomyopathy) [18].

Mitral valve prolapse associated with occult aortic coarctation can be diagnosed as only mitral valve prolapse [19]. Although the presentation of aortic coarctation may be atypical or obscured by other conditions, it can always be diagnosed if upper and lower limb blood pressures are compared. This patient underwent valvuloplasty, which did not improve the cardiac failure. The patient had a heart transplant but died. Post-mortem examination revealed an occult aortic coarctation. In this case leg blood pressures are not made. However, he had a bicuspid aortic valve, which may suggest a coarctation [19]. This is an example for two diseases in a given patient. Both logic based and probabilistic models show similar posterior probabilities for both the diseases. The features considered for the study include: 'central chest pain and palpitations' (for mitral valve prolapse),'left ventricular hypertrophy on ECG and bicuspid aortic valve on echocardiography' (for occult aortic coarctation) [19]. Since both the diseases have similar posterior probabilities and significantly these features are not shared between the two diseases, both diseases must coexist in the patient. This is an example for feature-to-feature links in a patient having more than one disease.

With the success of these principles we are encouraged to apply them on a large scale. Presently we are involved in the development of a knowledge base. Initially we are interested in collection of the features of various diseases from text sources. For practical purposes we limit each finding to the interest of a physician. For example, there may be several electrocardiographic findings, which may suggest angina or myocardial infarction. However, a physician would be interested only to the extent of an ECG finding's import value in regard to a diagnosis. Similarly, several pathological aspects of a biopsy may be of interest, but a summary of these findings only are taken into consideration. A differential diagnosis is worked on the diseases whose features are complete. Ramsey's theorem, is used for pathophysiological and system and organ effects in developing a differential diagnosis. If a disease shares very few or insignificant features with another disease, it is not considered for differential diagnosis. A belief network for features given disease shared by differential diagnosis are constructed whose arcs are represented by the frequency of that feature in the background of a

disease. This tabular form or two-dimensional belief network is being constructed for each disease. Another approach to building the knowledge base is to collect all the possible features and their disease possibilities. For example, we have approximately 4500 features. Some of the differential diagnoses consist of up to fifty or sixty diseases. We have about 3 person-years of work covering about 150 diseases, till date. We are hoping to complete this knowledge base in future and calculate their Ns values.

4. Discussion:

We are introduced to the belief networks much after developing the 'propensity for differential diagnosis' concept. We found that application of simple Bayesian probabilistic theory for logic model gives interesting results. This experience is similar to that of the authors of the probabilistic model [1]. Eighteen years ago we had been working on theoretical structural analysis of three-dimensional structures of proteins. We find analogies between these and the probabilistic belief networks. Short, medium and long range interactions within protein structures are similar to the heirarchial frequencies of features given disease. More recently, we found complex variations of nucleic acid sequences and their various restriction endouclease sites are amenable to a mathematical expression. Simple Bayes' model may be superior to Dempster-Shafer-Barnett and certainty factor models. We thought that a new mathematical theory for evidence in uncertainty can be built by defining the variables and their extent and mode of interactions. Definition of the variables may involve some arbitrarily fixed set or position from which the range of interactions of variables in uncertainty may be estimated. For nucleic acid example, we used the triplet of genetic code (3x3 nucleic acids) in a tabular form as a set retaining the amino-acid code. Similarly, we thought that the uncertainties involved in the diagnosis of features found given disease if expressed mathematically simplify further diagnostic concepts. We report 'propensity for differential diagnosis' which indicates the ratio of common clinical features shared by a group of diseases and their incidence in a given disease. A given disease may be more common than the other diseases and estimating 'propensity for differential diagnosis' is a way of mathematically defining that property. Each feature has a unique Ns value depending upon the disease in which it is taking part. One can resolve difficult cases by using Ns values as a guideline. Possibilities expressed by Bayesian theorem are reflections of truth-values of any sentences. All reasoning has a basis in logic. Hence, the models derived from denotational semantics may be unifying theories of quantification.

The probabilistic model we refer is based on simple Bayesian probabilistic theory and is not the result of simulation algorithms as described in the probabilistic model. Hence, we do not claim any better results than those derived from probabilistic models. We think our model by itself is not complete diagnostic system. Concepts developed here for the logic model if supplemented with the probabilistic model may give useful results. The similarities and the subtle differences in the posterior probabilities of diseases obtained by logic model and the probabilistic model make us believe that our model may be as good as the probabilistic model. Logic based model attains its objective, that is simplification of the computations involved in the probabilistic diagnostic process. The Ns values of logic formalisms are similar to the strengths of causal links of diseases and their manifestations in neural network [20]. Parsimonious covering theory suggests accurate diagnosis when multiple disorders are present simultaneously. The criterion for selecting a solution involves identifying the most probable covers using Bayesian classification. The global Bayesian ' formula for optimal set of disorders is decomposed into local rules for identification of each node to update its activation level [20]. This may be conceptually similar to the 'propensity for differential diagnosis' based on denotational semantics. We propose that the logic formalisms presented here can be applied to the neural networks also. We use MS access to simulate the brain learning systems like pattern-associator, auto associative and competitive networks.

In conclusion, we report a new diagnostic concept 'propensity for differential diagnosis' that can simplify computations of probabilistic models and neural networks. Application of this model to 'hemolytic jaundice' and several missed diagnoses suggest its scope all clinical domains. Results of this study show that the quantitative information used in the model is reliable. We are yet to initiate clinical evaluation of the model.

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Appendix:

N_D : propensity for differential diagnosis. N_{smt}: the sum of quantifications of the features given diseases sharing the features given disease. N_{max}: the sum of quantifications of features given disease. n: number of diseases considered for the given differential diagnosis. These values are calculated for the following diseases for the study and are as follows: (1).Hemolytic jaundice (n=5, N_{max} =101, N_{smt}=127, N_D =0.251). (2). Cholestatic jaundice (n=6, N_{max} =153, N_{smt}=123, N_D =0.134). (3). Viral hepatitis (n=13, N_{max} =117, N_{smt}=307, N_D =0.201), (4). Cirrhosis (n=6, N_{max} =111, N_{smt}=204, N_D =0.306). (5). Congenital hyperbilirubinemia (n=2, N_{max} =73, N_{smt} =15, N_D =0.082). (6). Boerhave's syndrome (n=4, N_{max} =37, N_{smt}=30, N_D =0.202). (7). Pneumonia (n=5, N_{max} =83, N_{smt}=36, N_D =0.087). (8). Perforated ulcer (n=4, N_{max} =32, N_{smt}=45, N_D =0.351). (9). Pulmonary infarction (n=9, N_{max} =70, N_{smt}=54, N_D =0.086). (10). Aortic dissection (n=7, N_{max} =78, N_{smt}=38, N_D =0.07). (11). Churg-Strauss syndrome (n=5, N_{max} =73, N_{smt}=109, N_D =0.299). (12). Congestive cardiomyopathy (n=5, N_{max} =95, N_{smt}=67, N_D =0.141). (13). ANCA associated vasculitis (n=13, N_{max} =142, N_{smt}=201, N_D =0.109). (14). Polymyalgia rheumatica (n=4, N_{max} =24, N_{smt}=34, N_D =0.354). (15). Gliomatosis cerebrii (n=6, N_{max} =82, N_{smt}=237, N_D =0.482). (16). Benign intracranial hypertension (n=2, N_{max} =27, N_{smt}=24, Nd=0.444). (17). Otitis media (n=4, N_{max} =35, N_{smt}=22, N_D =0.157). (18). Myocardial infarction (n=8, N_{max} =80, N_{smt}=69, N_D =0.108). (19). Mitral regurgitation

(n=3, N_{max} =61, N_{smt}=16, N_D =0.087). (20). Occult aortic coarctation (n=4, N_{max}=75, N_{smt}=15, N_D =0.50). (21). Costovertebral joint dysfunction (n=2, N_{max}=31, N_{smt}=5, N_D =0.081). (22). Caroli's disease (n=4, N_{max} =13, N_{smt} =8, N_D =0.154). (23). Hydatid disease (n=3, N_{max} =33, N_{smt}=14, N_D =0.141). (24). Acute mesenteric ischemia (n=2, Nmax=48, smt=9, N_D =0.094). (25). Acute pancreatitis (n=8, Nmax=86, N_{smt}=55, N_D =0.080). (26). Mitral valve prolapse (n=2, Nmax=47, N_{smt}=5, N_D =0.053).

Table 1. Posterior probabilities of missed diagnoses using logic based and probability models.

S. No	Final/presumptive diagnosis	Logic based	Probabilistic	Correct model
1.	ANCA vasculitis Polymyalgia rheumatica	0.482 0.516	0.571 0.429	Probabilistic
2.	Boerhave's syndrome Pneumonia Perforated ulcer Pulmonary infarction Aortic dissection	0.258 0.154 0.365 0.134 0.089	0.210 0.220 0.192 0.216 0.163	Neither
3.	Gliomatosis cerebrii Benign intracranial hypertension	0.539 0.461	0.467 0.533	Logic based
4.	Myocardial infarction Otitis media	0.564 0.436	0.562 0.438	Both
5.	Costovertebral joint dysfunction Pulmonary infarction	0.538 0.462	0.440 0.556	Logic based
6.	Caroli's disease Hydatid disease	0.514 0.486	0.457 0.543	Logic based
7.	Acute mesenteric ischemia Myocardial infarction	0.556 0.444	0.575 0.425	Both
8.	Acute mesenteric ischemia Acute pancreatitis	0.510 0.490	0.496 0.504	Logic based
9.	Churg-Strauss syndrome Congestive cardiomyopathy	0.543 0.457	0.476 0.524	Logic based