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13. ABSTRACT *(Maximum 200 words)*

This contract aimed at the development of a prototype diagnostic expert system in infectious diseases which might be rare in the United-States but prevalent in foreign countries. The purpose of this work is to demonstrate the feasibility of a prototype which is envisioned to operate in remote places where medical expertise about the rare diseases might be scarce and the handling of cases enhanced with the use of such a diagnostic expert system.

Qfever was selected as the infectious disease agent for studying the feasibility of a prototype diagnostic expert system. The medical expert system used in this project is the Iliad program developed by Applied Informatics and the University of Utah. Iliad's current knowledge base contains over 1,090 diseases and 5,600 disease manifestations across all of the domains of internal medicine. The primary focus of Iliad is to teach and test clinical problem-solving skills and provide a wide range and variety of simulated patient cases.

After completion of this one year project, the Iliad prototype for Q fever is operational and the first performance tests are encouraging.

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A Prototype Diagnostic Expert System in Rare Infectious Diseases Using Iliad and Qfever

Final Report

by
Omar Bouhaddou and Homer Warner Jr.

January 25, 1991

USARIID
Contract # DAAL03-90-C-0001

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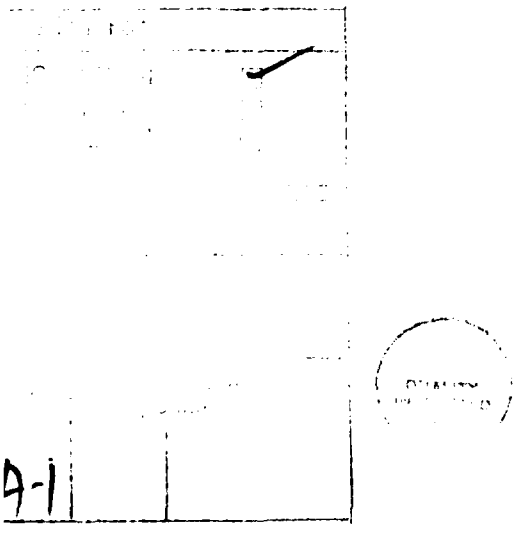

Table of Contents

Introduction

Today, knowledge-based systems constitute a new and exciting way to bring the best of medical knowledge to students, practitioners and patients. Expert systems applications have been implemented in a variety of settings. A few examples of medical expert systems include Iliad, HELP, DXplain, CARE and QMR, PUFF, Oncocyn, etc.(refs). The performance of these systems has been documented in the literature and judged at least as good as that of human experts. However, only a few have made it to the real world and are commercial available.

Today, the field and society at large need to know how artificial intelligence applications and expert systems in particular will make a difference in the real world. Thus, a major issue for developers of expert systems is to investigate practical applications of the technology. One interesting such application constitutes the substance of the collaboration between the USARIID and Applied Informatics. The collaboration aims at the development of a prototype diagnostic expert system in infectious diseases which might be rare in the United-States but prevalent in foreign countries. The purpose of this work is to demonstrate the feasibility of a prototype which is envisioned to operate in remote places where medical expertise about the rare diseases might be scarce and the handling of cases enhanced with the use of such a diagnostic expert system.

Qfever was selected as the infectious disease agent for studying the feasibility of a prototype diagnostic expert system. Qfever is a ricketsiella infectious disease which, although not lethal, causes severe morbidity. The chronic form of the disease may result from the primary infection and lead to cardiac and liver involvement. The medical expert system used in this project is the Iliad program developed by Applied Informatics and the University of Utah. Iliad's current knowledge base contains over 1090 diseases and syndromes across all of the domains of internal medicine. The primary focus of Iliad is to teach and test clinical problem-solving skills and provide a wide range and variety of simulated patient cases.

The project started in January 1990. Phase 1 of the project describes the diagnostic criteria for Qfever using the literature, expert judgement and real patient cases. Phase 2 tests the performance of the prototype against real as well as simulated cases. Phases 1 and 2 repeat until a reliable performance evolves. Another validation measurement and refinement of the prototype was obtained through face-value evaluation of the medical logic by other experts in the field. Dr. Thomas Marrie from Nova Scotia was involved in critiquing the Qfever disease profiles we developed as well as in the validation study of the prototype based on a relatively large database of Qfever cases (188 cases).

After the one year duration of this work, the Iliad prototype for Q fever is operational and the first performance tests are encouraging. The temporal dimension of Qfever was modelled in Iliad using two clinically significant states of Qfever (i.e., early and late stages). These two states were deemed by medical experts as adequate to represent the different facets of the disease. Furthermore, a link to a database of digitized pictures has strengthened the educational value of the prototype expert system.

In the future, there needs to be further study of the reliability fo the current Qfever prototype. This would involve the abstracting of a large number of cases and a performance judgement of the Iliad prototype by independent experts. Field testing is the next level of testing. This level of evaluation is the study of the impact of Iliad on the judgement of non-expert physicians. Field testing is also useful to collect data about the transferability of the program and the program's performance in different geographical locations. Finally, once

this 'vertical' investigation of the first prototype is achieved with satisfactory results, the knowledge base is expanded to include new disease profiles. The more knowledge the system offers to its users the more useful and reliable the system will be.

Development of a Prototype Diagnostic Expert System in Infectious Diseases

In general, the development a prototype diagnostic expert system starts with the definition of the knowledge domain and the intended audience. Rare infectious diseases is the knowledge of interest and Qfever is the specific agent selected to carry out our study. The task is then to develop a diagnostic model of the Qfever infection combining all available sources of information. The model would be tested in remote areas where Qfever infection is prevalent and the medical staff is not particularly familiar with the pathology.

The knowledge Engineering Environment

The process of knowledge engineering in Iliad refers to the sum of all activities that aim to capture, restructure and validate knowledge in a particular domain in order to build a computer representation of this knowledge for educational, training and testing purposes. In this section, we will give an overview of the different steps involved in the knowledge engineering process which is illustrated by the diagram below and refer to specific chapters in the knowledge engineering handbook for in depth information about each step (see Knowledge Engineering in Iliad: the Development Tools).

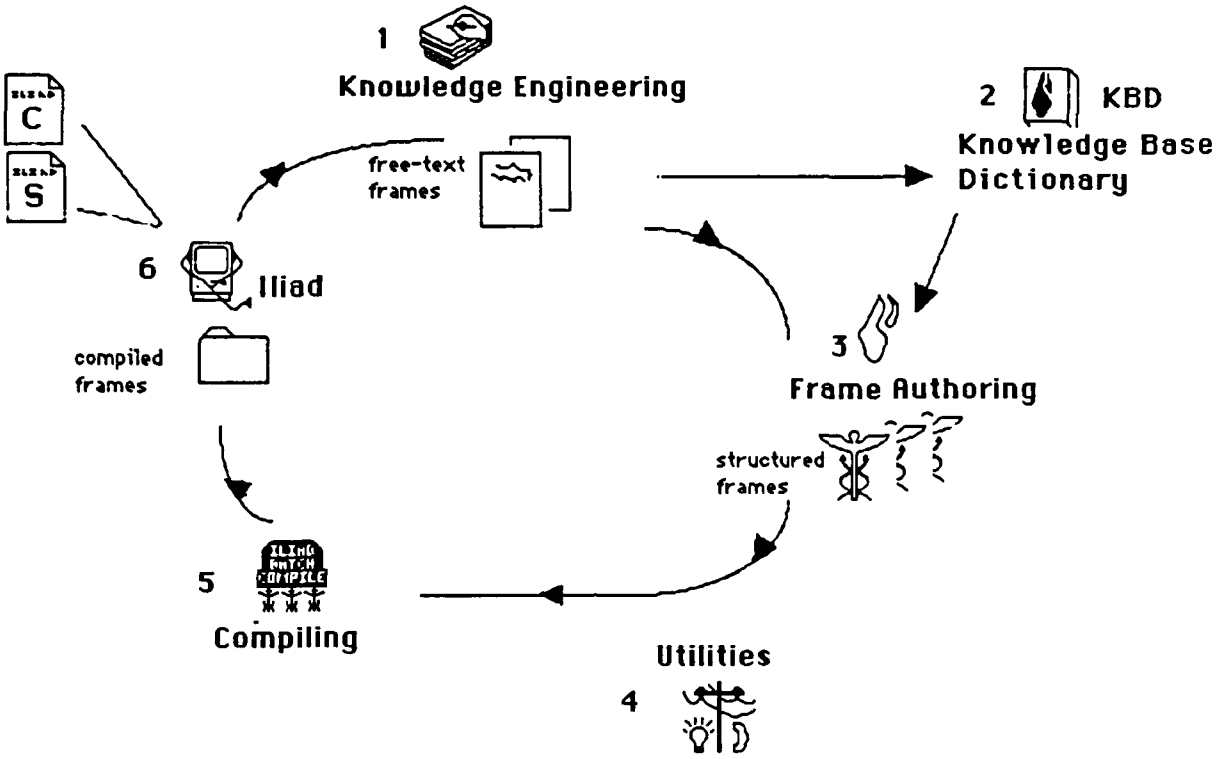

Figure 1: The knowledge engineering process in Iliad

The first step in knowledge engineering is the acquisition of knowledge from human experts. Knowledge is acquired through formal interview techniques with a medical domain expert which is facilitated by a knowledge engineering using computerized support tools in a quiet, comfortable setting.

Step 2, in the knowledge engineering process, is to match the free text terminology used during the frame development effort to coded vocabulary terms in the Knowledge Base Dictionary (KBD).

Once all the terms used in a knowledge frame have been defined in the KBD , the Frame Author program is used to create Iliad frames (step 3). The Frame Author converts the free text fo knowledge to a structured form in which every item is an item previously defined in the KBD.

The frames assembled with the Frame Author program are then checked before they can be compiled to run with Iliad. This is done in step 4 using the IliadUtilities program.

Once the pre-compilation checks have cleared, the BatchCompiler is used to compile the frames into the "Iliad files" folder (step 5).

Running Iliad to test the performance of the frames is the next step (step 6) in the knowledge engineering cycle. The knowledge engineering process cycles with many revisions to the knowledge base taking place before a reliable performance of the system evolves.

The Qfever Prototype

Qfever is the infectious disease agent selected to study the feasibility of a diagnostic expert system that will support military medical staff in remote areas. Qfever is a relatively rare disease in the US, but outbreaks have been reported all around the world. Serology testing (ELISA test) allows for the identification of offending agent: ricketsiella Coxiella Burnetii. The infectious condition, when recognized, has been treated with appropriate dosages of tetracyclin. However, the disease presentation is not very specific and is often confused with other pathologies (e.g., atypical pneumonia) and left untreated. A fraction of the acute Qfever infections develop into chronic Qfever with liver, and heart involvement.

Coxiella Burnetii is an aerosol and is thought to constitute a potential bacteriological weapon. However, in most cases, the infection was traced to animal carriers who do not suffer from any consequences. Specifically, Coxiella Burnetii can be contracted from animal's placenta, thus more prevalent in farmers, slaughter house personel, and infectious diseases laboratory personel.

The development of three major frames for Qfever: Qfever, (Early Stage), Qfever (Late Stage) and Blood Culture Negative Endocarditis were considered by experts in the domain to adequately cover the relevant distinction between the different phases of the disease. Appendix A includes the disease profiles of these three frames and the related intermediate disease-syndromes.

Temporal Aspects

The temporal aspect of an expert system refers to a set of capabilities that helps the system recognize and take advantage of time-oriented clinical events, such as the first value of a laboratory test, the value of a test after or before the occurrence of another event, and the identification of trends. This set of capabilities may help the expert system deal with disease stages and severities.

A natural way to incorporate temporal aspects into a decision support module is to tie the module to a live clinical database. The knowledge base could then be 'time-driven' as well as 'data-driven'.

Because Iliad is not tied to real-time patient database, the only way to a model a disease over time is to build a frame for each significant phase of the diagnostic process. Thus, in the Qfever example, domain experts have judged that a good approximation of the disease process is accomplished with two frames: one for the early or acute phase, and one for the late or chronic phase.

Video Link

Any disease or finding name in the Iliad knowledge base dictionary can be linked to available digitized pictures. At any point during a consultation session with Iliad, the user can access the pictorial representations to learn more about the diagnostic criteria or patient finding.

Iliad will append a "(p)" at the end of the text of a term to indicate the term has one or more pictures linked to it. Wherever a dictionary term appears in Iliad, as a patient finding or a workup suggestion, the user can select the term and activate the 'Video' command within the 'Browse' menu. Each picture comes with text describing the content of the picture. The textual description of a picture can include references to other pictures within the picture database, in which case, the name of the picture referenced is in bold.

Double clicking on the bold name will display the referenced picture in a 'Hyperpicture' fashion.

To access digitized pictures within Iliad, the knowledge engineer creates textual descriptions of the pictures and links each picture to one or more Iliad dictionary codes that they illustrate.

The hardware requirements for linking Iliad to digitized pictures are the same as for running Iliad plus a color monitor (e.g., MacII, MacSI) for adequate picture quality. A manual exists with instructions on how to create and link digitized pictures to Iliad (see Linking Digitized Pictures to Iliad).

Transferability

The term transferability in this context refers to the ability of the system's knowledge base to perform reliably in different geographical locations. Iliad's probabilistic knowledge representation models are particularly adaptable for reflecting geographical specificities. Indeed, the Bayesian model used by Iliad includes the a priori of a disease or of a diagnostic finding in its calculations. These frequencies can be estimated from a sample of the local population. Furthermore, Iliad allows for a site specific file where disease prevalences are stored and local knowledge is preserved.

Iliad's knowledge base development approach assumes there will only be one central site for maintaining the master knowledge base with each user site adding disease prevalence information. The central site will integrate feedback from all users into the master knowledge base file. Also, there are tools for producing and maintaining different versions of the expert system in multiple languages (e.g, French, English).

Testing the Qfever Prototype

Testing of a diagnostic expert system encompasses process and outcome performance measures. These performance measures will validate the reliability of the knowledge base as well as the impact of the expert system on the outcome of the practice of its intended users.

This contract work did not include any study of outcome measures. The performance of the knowledge base was measured in several steps. First, a face-value evaluation of the disease descriptions was done by another infectious disease specialist (Dr. Thomas Marrie from Victoria General Hospital in Nova Scotia). Then, Dr. Larry Reimer from the University of Utah Medical Center, developer of the original infectious disease profiles, tested the behavior of the system using textbook examples, case reports in the literature and the simulation mode of Iliad. The simulation mode in Iliad allows for the generation of realistic patient cases from a disease profile. Generating patient cases from the expert system's knowledge base has been compared to the "Turing" test for medical expert system.

Finally, we are currently in the process of testing the performance of the system on 188 Qfever cases from Nova Scotia collected by Dr. Marrie. Tools for transferring data

from the large Nova Scotia database have been developed to facilitate the performance study of the prototype against real cases

Prospects for the Future

The validation of the Qfever prototype against a large set of patient cases should enhance the reliability of the knowledge base. Another extension of this project would involve field testing the prototype in different geographical locations. To facilitate the transferability of the program, we added to the Iliad program the possibility to modify the content of the knowledge base to reflect geographical prevalence of disease. Finally, parallel efforts to the validation studies should aim to expand the knowledge base to include other rare infectious diseases. This would make interaction with the expert system more valuable. The personel of USARIID has been introduced to Iliad knowledge engineering techniques and familiarized with the knowledge development tools in order to facilitate the ongoing efforts of knowledge development and validation.

List of Scientific Personnel that Participated in the development of the Qfever Prototype Expert System

Omar Bouhaddou, PhD
Senior knowledge engineer at Applied Informatics
Homer R. Warner, Jr.
principal investigator and president of Applied of Informatics
Homer R. Warner, MD, PhD
professeur, chaiman of the department of medical informatics and knowledge engineer on the Iliad project
Dean K Sorenson, PhD
biochemist and knowledge engineer on the Iliad project
Stan Altman, MD
hematologist and knowledge engineer on the Iliad project
Larry Reimer, MD
infectious diseases specialist and knowledge engineer on the Iliad project
Thomas Marrie, MD
infectious diseases specialist and consultant on the Qfever prototype
Tim Cannon
primary contact at the USARIID
Glen Higbee
principal investigator at the USARIID

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3. Clark et al. Q Fever in California. Arch Int. Med. 88:155,1951

4. Field et al. Detection of C.burnetii. Journal of Infectious Diseases 148:477-487,1983

5. Safety and Immunogenecity of Q fever vaccin.reference from Tim cannon

6. Powell OW. Liver involvement in Q fever. Australasian Annals of Medicine 1961;10:52-9.

7. Dr. Stan Altman (Hematologist expert working on the Iliad project at the University of Utah)

8. Dr. Thomas Marrie (Infectious Diseases expert working in Nova Scotia)

9. Dr. Larry Reimer (Infectious Diseases expert working on the Iliad project at the University of Utah)

10. Raoult et al. "Chronic Q ffever: diagnosis and follow up", Ann New York Academy of sciences, 51-60

11. TS Marrie "A comparison of Qfever endocarditis with native valve endocarditis", Ann. New York Academy of sciences, 61-67

12. Iliad references (see Appendix B)

Appendix A: QFEVER DISEASE PROFILES

A few guidelines on how to read the disease descriptions below:
1. The disease name appears at the top
2. the a priori represents the prevalence of the disease in the hospital (our hospitals)
3. the findings are either direct observations (e.g., historical, physical examinations, laboratory results) or a group of findings described in a sperate frame and indicated by an '@' sign.
4. sensitivity is the true positive rate = the fraction of patients **with** the disease that have with the finding.
5. 1 - specificity is the false positive rate = the fraction of patients **without** the disease that have with the finding.

Disease name: Q fever (early stage)
A priori = .00003

findings:	sensitivity	1-specificity
a. Temperature		
>38 and < 40 C	.95	.15
>= 40 C (104)	.52 (1)	.01
b. @Atypical_Pneumonia	.51(5)	.015
(7)		
or		
@Non-specific symptoms of Q fever	.90	.20
d. Hx of headache at retrobulbar area	.30 (3,10)	.01
or		
Hx of headache	.90 (2)	.15
or		
Hx of headache [with a specific quality] which is severe and frontal	.25	.03
e. Sex, male	.85	.57
g. Coxiella Burnetii ELISA is positive >= 7 days of onset of symptoms	.50 (4)	.01
or		
Coxiella Burnetii ELISA is positive 4 fold rise >= 7 days of onset of symptoms	.50 (4)	.001
or		
Immunofluorescence shows Coxiella Burnetii antibody >= 15 days of onset of symptoms	.95 (4)	.01
or		
Immunofluorescence shows Coxiella Burnetii antibody 4 fold rise >= 15 days of onset of symptoms	.90 (4)	.001
or		
Complement fixation test shows >= 4 fold rise in phase II antibody titer to C. Burnetii >= 7 days of onset of symptoms	.90 (2,3,4)	.001
or		
Complement fixation test shows phase II antibody titer > 1:128 to C. Burnetii >= 7 days of onset of symptoms	.95 (2)	.001
g. Hx of contact with cattle, sheep, goats	.70	.02
or		
Hx of contact with sheep placenta	.50	.001
or		
Hx of work in animal research facility housing sheep	.20	.01
or		
Hx of contact with cats	.50	.40
h. @Abnormal liver functions criteria for Q fever	.65	.05
or		
PE shows hepatomegaly	.43(1,3,5,6)	.06
or		
Liver tenderness	.11(6)	.03
(9)		
or		
PE shows splenomegaly	.10(10)	.01

a priori: about 1 case / year

?confirm this before adding:
cxr of multiple rounded opacities .95 (10) .--

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2. Powell OW. Q fever: clinical features. Australians Annals of Medicine. 9:214, 1960
3. Clark et al. Q Fever in California. Arch Int. Med. 88:155,1951
4. Field et al. Detection of C.burnetii Journal of Infectious Diseases 148:477-487,1983
5. Safety and Immunogenecity of Q fever vaccin.reference from Tim cannon
6. Powell OW. Liver involvement in Q fever. Australasian Annals of Medicine 1961;10:52-8
7. a priori
8. Dr. Reimer
9. Dr. Altman
10. Dr. Thomas Marrie

Abnormal liver function criteria for Q fever

a. SGOT u/mL
b. SGPT u/mL
c. alkaline phosphatase U/L
d. Serum bilirubin mg/100mL

True if: a > 34 or b > 59 or c > 147 or d > 1.0

Non-specific symptoms of Q fever

a. Hx of Abdominal pain
b. Hx of sore eyes
c. Hx of malaise/fatigue
d. Hx of rash
e. Hx of myalgia/weakness
f. Hx of arthralgia
g. Hx of nausea or/and vomiting
h. Hx anorexia
i. Hx of chest pain
j. Hx of chills
k. Hx of cough
l. Hx of weight loss > 5%
m. PE shows clubbing
n. Hx of back pain
o. Hx of headache
p. Hx of diarrhea
q. @Anemia

True if 6 of a-k and 4 of (l-q)

References:
1. Dr. Larry Reimer
2. Raoult et al. "Chronic Q ffever: diagnosis and follow up", Ann. New York Academy of sciences, 51-60
3. TS Marrie "A comparison of Qfever endocarditis with native valve endocarditis", Ann. New York Academy of sciences, 61-67

Disease name: Q fever (late)
A priori = .00001

findings:	sensitivity	1-specificity
a. Hx of Q fever	.80 (1)	.001
or		
Hx of contact with cattle, sheep, goats	.70	.02
or		
Hx of work in animal research facility housing sheep	.20	.005
b. @Fever	.90	.15
or		
@Non-specific symptoms of Q fever	.50	.20
c. Sex, male	.85	.57
e. @Abnormal liver functions criteria for Q fever	.25	.05
or		
PE shows hepatomegaly	.25 (2)	.06
or		
PE shows splenomegaly	.07 (2)	.01
f. Complement fixation test shows phase I antibody titer > 1:128 to C. Burnetii	.99	.001
h. @Culture-negative endocarditis	.95	.0001

References:
1. Dr. Larry Reimer
2. Clarke, (see above references)
3. Dr.Thomas Marrie

a priori: about 1/3 y around here or about 1/100,000

Disease name: Culture-negative endocarditis
A priori = .0001

findings:	sensitivity	1-specificity
a. Heart murmur	.85	.10
or		
definite change in murmur or new murmur	.10	.001
or		
@Aortic insufficency	.15	.0011
or		
@Mitral valve prolapse	.29	.01
or		
Hx of mitral valve prolapse	.25	.03
b. Blood culture positive for bacteria	.0000001	.01
c. vegetations on heart valves (echocardiography)	.50	.02
d. Hx of a heart valve replaced?	.05	.002
or		
Hx of rheumatic fever	.20	.01
e. @Infective embolic phenomena	.50	.001
f. joint pains	.33	.10
g. @Anemia of chronic disease	.80	.07

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1. Dr. Larry Reimer
2. see also infective endocarditis

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LIST OF INVENTIONS:

No inventions were created.