ANTICIPATOR: A Medical Expert System Implemented by Prolog/KR

MICHIO KIMURA*, TERUO KOYAMA**,
SHIGEKOTO KAIHARA*** and FUMITO TSUCHIYA****

The authors have made a medical expert system ANTICIPATOR (ANTIbiotics Counsellor for Infectious PAThogenic ORganisms), which counsels antibiotic medications for microbial infections. It is in operation at Hospital Computer Center, University of Tokyo, and substantially used by human doctors.

The system, including its knowledge sources, is all implemented with a programming language Prolog/KR, a superset of Prolog, extended to support knowledge representations. Adopting this, ANTICIPATOR has many kinds of concepts and strategies to make itself feasible.

The purpose of this paper is to describe the following items;

*Specifications of the system
*Example of actual usage
*Implementation by Prolog/KR
*Advantages of programming language Prolog for expert systems.

1. Introduction

Recent developments of effective new antibiotics have shown great significance on chemotherapy. An enormous variety of antibiotics have been developed, but excessive use has promoted pathogenic bacteria to acquire new resistances to formerly effective antibiotics. As a result, priscribing suitable antibiotic medication has become quite a complicated job for most doctors who are not specialized in chemotherapy, though use of antibiotic therapy is common to almost all doctors. The authors thought an antibiotic medication counselling system was feasible, and useful, therefore ANTICIPATOR (1) (8) was constructed.

As an expert system for infectious diseases, MYCIN (2) is the first and is well-known. It is a full consultation system which comprises diagnosis and therapy. It covers, however, a limited number of different infections, and is not extensively used as an antibiotic medication counselling system. ANTICIPATOR limits its performance to therapy recommendation based on a limited amount of common practical heuristic knowledge, but can counsel on common microbial infections which appear at internal medicine.

The knowledge based expert system ANTICIPATOR is implemented in the programming language, Prolog/KR. All the different kinds of knowledge, which comprise declarative knowledge, procedural knowledge, and the system itself as meta-knowledge, are described in predicate logic. Pattern matching and backtracking features of the Prolog processor, along with other facilities of Prolog/KR, enabled the pieces of knowledge to be implemented effectively and to be handled easily. Prolog is adopted as a model of kernel language for new generation computers developed for a project carried on by Japan's Institute for New Generation Computer Technology.

Chapter 2 of this paper briefly explains the ANTICIPATOR system profile including its construction concepts and selection strategies. Chapter 3 is an example of the real usage with a recommendation table and an antibiotic profile explanation table. Chapter 4 describes its implementation by Prolog/KR. Adaptability and advantages of Prolog for knowledge based system construction are also clarified.

2. ANTICIPATOR System Profile

Antibiotic medication was chosen for the domain of the expert system for many reasons. An expert system is not practical in the present primitive stages of expert system diffusion, unless it provides benifits and is feasibility. As mentioned in the last chapter, acute craving for computer system assistance was observed in the domain of antibiotic medication. Therefore, authors stated the requirements for the system as follows.

*The system should provide high level consultations. (domain expert level, if possible)
*The system should make consultations based on each personal case profile.
*The system should explain reasons for its selection.
*The system should supply other information concerning the case.
*The system should deal even with intractable cases with limited case profiles.
*The system should have excellent person-machine interfaces.

*Osaka university, Medical School
**Hamamatsu Medical College
***University of Tokyo, Hospital Computer Center
****University of Tokyo, Hospital Pharmacy

To accomplish the requirements above, many facilities are introduced. One of these is a two-dimensional evaluation mechanism of the system. As ANTICIPATOR is an expert system which helps doctors make selections, the authors thought it better to show a number of candidates with suitable prescriptions rather than to indicate only one recommendation selected from among the vast varieties. With two evaluations considered, positive evidences based on sensitivity, pharmacokinetics, etc., and negative evidences such as side effects, the system can distinguish "*one that shows untolerable side effect in spite of great sensitivity*" and "*another which is milder in both senses*". These dilemmas are commonly found in medical decision makings. On the other hand, two-dimension is the current state of the art that current computer devices can easily display. Therefore, the system can present the state nearer to the real problem. And the final selection is entrusted to the user, who will be guided with the explanation facility of the system. The system supplies details of the antibiotic if required, for evaluations based on each personal case profile.

Three basic elements, bacteria, diseases, and antibiotics, are all described in hierarchies. Abstract discussions, which are common in biomedical science, can be evolved on abstract elements. Therefore, in ANTICIPATOR, a piece of knowledge such as "*Penicillins are not good for gram-negative bacillus.*" can be handled as it is. This concept is also important in the limitations of searching spaces, and makes ANTICIPATOR work within a tolerable execution time. The implementation of this concept is described in chapter 4.

The knowledge based medical expert system ANTICIPATOR uses many kinds of knowledge, some are basic pharmacological, others are heuristic to be used for intractable cases or high level recommendations. They are categorized as follows.

Declarative knowledge

*Hierarchies of antibiotics, causal bacteria, and microbial infectious diseases.
*Resistance spectrum table described in a matrix of sensitivity for each pair of causal bacteria vs. antibiotics (maybe in abstract form).
*Pharmacokinetics table in a matrix of each antibiotic's pharmacokinetics to each infected organ (maybe in abstract form).
*Causal bacteria appearance probability table by each infectious disease, which is evoked in cases where the causal bacterium is not identified.
*Clinical pharmacological informations for each antibiotic, which are the bases of evaluations of heuristic knowledge below.

Procedural knowledge

*Production rules representing heuristic knowledge which reflects on side-effects, patients' conditions, conventional selections, etc.
*Procedural attachments describing how to acquire the values of case profile factors by the evaluation of production rules.

This knowledge is implemented in a manner which is convenient for human. No redandunt information is used, because it is boring for human to input many-charactered name like *third-generation-cephalospolins* many tims. Therefore, knowledge is implemented in a manner which avoids this above trouble. But this is not the form that the system can handle with good efficiency. In this system, a bootstrapping facility is installed to convert human-convenient-manner to system-handlingmanner. Also installed is a consistency checking facility to detect apparent conflictions.

As mentioned before, there are two scales of evaluation. Positive evaluation is ordinarily based on sensitivity to the causal bacteria and pharmacokinetics to the infected organ. If disk-examination, which tests the sensitivity to actually acquired causal bacteria, is done, the common sensitivity is replaced by the examination result. But when the test shows that none of the antibiotic tested is affective, the common sensitivity revives, from which, of course, antibiotics organically equivalent to the tested ones are eliminated. Semantic categorization of antibiotic is used for this facility. Lack of identification of causal bacteria is redeemed by the *a priori* causal bacteria appearance probability table.

Negative evaluation is all based on production rules of heuristic knowledge. All production rules are evaluated thouroughly beginning from the first one. Rule description ability is so equipped in Prolog that knowledge implementers can easily implement the control strategy of the evaluation sequence of rules using Prolog syntax.

Taking side-effects, patients' conditions, etc., into account, the system categorizes all antibiotics into three classes.
*Nothing warned at all, or only slightly mentioned.
*Inevitable harm may be expected.
*Should not be abused from a public sanitation point of view.

Above two ways are evaluated independently and merged into a two-dimensional evaluation table which can be considered in making the final selection. Each antibiotic profile explanation is available after the total evaluation, as well as the two-dimensional display, that was the bases of the final prescription selection given to the users.

3. Examples

At first, ANTICIPATOR can be evoked by only one TSS command from the TSS toplevel. The Lisp processor, the Prolog processor, and the system itself are all loaded with only one "≫ANTI" command. This command also ignites the first procedure to be executed.

```
>>anti

 ---------- ANTICIPATOR SYSTEM ----------

What do you want to do?
Valid replies --> NEW-CASE, QUIT, USER-PROFILE.(HELP for details)
-:new-case


Focusing on the INFECTIOUS-DISEASE


To which the INFECTIOUS-DISEASE belongs?

  0 : Unknown (No further classification can be issued.)
  1 : GENERAL
  2 : RESPIRATORY-SYSTEM
  3 : RENAL-SYSTEM
  4 : INTESTINE
  5 : HEPATIC-BILIARY-SYSTEM


 Valid answers --> 0 thru 5 of integers, LIST, REVERT, and others(HELP for details).
-:3


To which the INFECTIOUS-DISEASE belongs?

  0 : Unknown (No further classification can be issued.)
  1 : SIMPLE-URINARY-SYSTEM
  2 : COMPLICATED-URINARY-SYSTEM


 Valid answers --> 0 thru 2 of integers, LIST, REVERT, and others(HELP for details).
-:2


To which the INFECTIOUS-DISEASE belongs?

  0 : Unknown (No further classification can be issued.)
  1 : CHRONIC-PYELONEPHRITIS
  2 : CHRONIC-CYSTITIS
  3 : PROSTATIS
  4 : EPIDIDYMITIS
  5 : GONORRHEAL-URETHRITIS


 Valid answers --> 0 thru 5 of integers, LIST, REVERT, and others(HELP for details).
-:1


Focusing on the CAUSAL-BACTERIUM


To which the CAUSAL-BACTERIUM belongs?

  0 : Unknown (No further classification can be issued.)
  1 : GRAM-POSITIVE-COCCUS
  2 : GRAM-POSITIVE-BACILLUS
  3 : GRAM-NEGATIVE-COCCUS
  4 : GRAM-NEGATIVE-BACILLUS
  5 : MISCELLENEOUS


 Valid answers --> 0 thru 5 of integers, LIST, REVERT, and others(HELP for details).
-:0
```

Fig. 1. Initial evocation and questions about the infectious disease the patient is suffering and the causal bacterium.

```
If any of the followins orsans is in trouble, please note.

 1 : HEPATIC-SYSTEM
 2 : RENAL-SYSTEM
 3 : DIGESTIVE-SYSTEM

Enter 1 thru 3 of inteaers.(maybe multiple)(U for Unknown, N for Not-applicable)
-:2


The severity of the renal insufficiency?

 1 : SLIGHT
 2 : MODERATE
 3 : SEVERE

Enter one of inteaers between 1 and 3.(U for Unknown)
-:3
```

Fig. 2 Questions about patient's profile. Sequence of these questions are evoked by demand-driven evaluation.

```
--------------
Recommendation
--------------

------- PROBABILITY-SELECTION-BY-STATISTICS -------


   RECOMMENDED    ATTENTION-REQUIRED       SPECIALITIES
-----------------------------------------------------------

- - - - - - - - - - - - - - - - - - - - - - - - - - - - -> * * * * *
                  MCR  TOB  AMK  GM
                  SISO
- - - - - - - - - - - - - - - - - - - - - - - - - - - - -> * * * *
                                    CPZ
PIPC
                                    LMOX CZX  CTX  CMX
- - - - - - - - - - - - - - - - - - - - - - - - - - - - -> * * *
FOM
CTM
CMZ
                                    CFS
- - - - - - - - - - - - - - - - - - - - - - - - - - - - -> * *
```

Fig. 3 Recommendation table.

At the first toplevel of ANTICIPATOR, "NEW-CASE" is entered to evoke a new case counselling.

Surveyed is a case of chronic pyelonephritis, without causal bacteria identification and disk examination, with severe renal insufficiency. The first three questions are to designate the infectious disease that the patient is suffering. Inquiries go further according to the hierarchy of infectious diseases. The next question is to designate the causal bacteria. Though causal bacteria are also represented in a hierarchy like that of infectious diseases, inquiry stops with one question answered "0", standing for "No further classification can be issued."

Following questions are for the personal case profiles of the patients. They are all evoked through evaluation of production rules.

A recommendation table is displayed next. In this case, a causal bacteria probability table is evoked. As to efficiency, aminoglycosides (MCR, TOB, . . .) are the best. Broken line delimiters shows the significant difference between the followers and number of stars shows the level of recommendation. But they have renal toxity, then they are stated in the middle column (ATTENTION-REQUIRED). Among antibiotics without renal toxity, PIPC is recommended. CPZ, LMOX, . . . are specialities which should not be abused. Their inferiority to aminoglycosides in efficiency is signified. The final selection among them is entrusted to the user. For the guidance of the selection, EXPLAIN command is used to show explanations on GM, PIPC, LMOX. The product follows on the display and may be used as evidences for the final selection. It includes sensitivity (described in "three pluses", "two pluses", "one plus", and "minus") to each causal bacterium with probability percentage, drug concentration level to the targeted organ, medication route ("I" stands for Injection), and warnings for each antibiotic considered for the patient.

ANTICIPATOR also has dosage recommendation subsystem. It shows a recommended dose according to certain formulae. Because of renal insufficiency of the patient, the dose of GM (Gentamicin) must be governed

```
What do you want to do?
Valid replies --> NEW-CASE, CASE-PROFILE, COUNSEL, END, and others.(HELP for details)
-:explain gm pipc lmox

COMPLICATED-URINARY-SYSTEM

                                          GM        PIPC      LMOX
-------------------------------------------------------------------------

PROBABILITY
              P.AERUGINOSA      28.5%    + + +      + +        +
              E.COLI            18.1%    + + +     + + +     + + +
              PROTEUS           15.9%    VARIES    VARIES    VARIES
              SERRATIA          14.3%     + +       + +       + +
              KLEBSIELLA         6.1%    + + +      + +      + + +
              ENTEROBACTER       6.1%     + +       + +      + + +
              CITROBACTER        6.1%     + +       ---      + + +

KINETICS
              RENAL-SYSTEM
                                        + + +     + + +     + + +

MEDICATION ROUTE
                                          I         I         I

********
WARNINGS
********

GM
-------------------------
LEVEL 4 : (as GM)           (CONTRAINDICATION OF RENAL-TOXIC DRUG, DUE TO
                             SEVERE RENAL DISORDER)

LEVEL 2 : (as GM)           (RENAL-DISTURBANCE)

LEVEL 1 : (as GM)           (NERVE-SYSTEM-DISTURBANCE)

PIPC
-------------------------
LEVEL 1 : (as BROAD-SEMISYNTHESIZED-PENICILLINS)
            (MAY CAUSE DIARRHEA BY P.O. MEDICATION.)

LEVEL 1 : (as PENICILLINS)  (DRUG-IRRITATION)

LMOX
-------------------------
LEVEL 5 : (as OXACEPHEM)    (NOT PREFERRED IF ANY OTHER SHOWS ENOUGH EFFICIENCY
                                 (STRONG EFFECT ON INTERNAL BACTERIAL FLORA))

LEVEL 1 : (as CEPHEMS)      (DRUG-IRRITATION)
```

Fig. 4 Explanation table. "COMPLICATED-URINARY-SYSTEM" means this is a table for chronic infection of urinary tract. Sensitivity is shown with symbols "+++" (highly effective) to "---" (no good).

with the level of renal insufficiency. Creatinine clearance value is used to state the level. Then the recommended dose is shown, calculated with the value of creatinine clearance and the weight of the patient.

Moreover, ANTICIPATOR can supply drug information. Information about GM is displayed. The content is not what is represented and used by regular counselling but an approval of Ministry of Public Health and Welfare. In certain items, therefore, inconsistency may be observed. However this facility is also important to acquire users' confidences. ANTICIPATOR's recommendations are always prepared for each personal case profile, while the approval is a general decision. Users are expected to cross-check the ANTICIPATOR's recommendation compared with the general approval.

4. Implementation by Prolog (Prolog/KR)

ANTICIPATOR is implemented by Prolog/KR (3) (4), a superset of Prolog (5) (6) (7), extended to support knowledge representations. Prolog/KR has the abilities

```
What do you want to do?
Valid replies --> NEW-CASE, CASE-PROFILE, COUNSEL, END, and others.(HELP for details)
-:dosage gm


----- DOSAGE RECOMMENDATION SUBSYSTEM -----

GM : AMINOGLYCOSIDES intensive attention must be done

CREATININE-CLEARANCE?

Enter REAL NUMBER more than or equal to 0.(U for Unknown)
-:33


GM : GM dose must be governed according to creatinine clearance

Weight of patient?

Enter REAL NUMBER more than or equal to 0.(U for Unknown)
-:75


      Initial dose : 41.5 mg ( 0.55 mg/kg)
      Maintainance dose : 51.0 mg ( 0.68 mg/kg) (every 8 hours)
```

Fig. 5 Dosage recommendation.

```
What do you want to do?
Valid replies --> NEW-CASE, CASE-PROFILE, COUNSEL, END, and others.(HELP for details)
-:di gm


----- DRUG INFORMATION SUBSYSTEM -----

[Generic Name] Gentamicin

[Abbreviation] GM

[Administration] I.M.

[Product Name] Gentacin(Essex Japan)

[Effective Organisms] Pseudomonas aerusinosa
                      Proteus sp.,
                      Serratia sp.,
                      E.coli,
                      Klebsiella,
                      Entorobacter

[Uses] Sepsis,
       Secondary infections in wounds, burns, after operations,
       Pneumonia,
       Peritonitis,
       Pyelonephritis,
       Cystitis,
       Otitis media

[Dosage] 80-120 mg (children 0.4-0.8 mg/kg) daily in 2-3 devided doses.
         Not usually continued more than 10 days.

What do you want to do?
Valid replies --> NEW-CASE, CASE-PROFILE, COUNSEL, END, and others.(HELP for details)
-:end
```

Fig. 6 Drug information of GM (Gentamicin).

of describing Lisp-like control structure, in order to support procedural knowledge descriptions. In this chapter, utilization of Prolog (and Prolog/KR) for expert system construction, will be described.

ANTICIPATOR can be recognized as a high level knowledge retrieval system with backward chaining production system. Utilizing the pattern matching facility of Prolog, the first half of this system is a forward chaining process of general recommendation. The second half makes recommendations suitable for each personal case profile. This is done by a backward chaining process, on which MYCIN depends on for the whole con-

sultation. This hybrid combination is possible by means of implementing by Prolog (Prolog/KR). With this whole architecture of hybrid combination, this system can easily be applied to other problems, because the inference engine and the knowledge base is totally separated. The primitives for knowledge base system construction extracted from this system are called PROPAGATOR utility (1).

A Horn-clause, which is a basis for prolog programming, can be described as,

P:−Q, R. or P.

The latter, a special case of the former, stands for "P *is true*" as a fragment of a declarative knowledge. As Prolog represents list structures as a pattern, various kinds of declarative knowledge, from a simple one to a complicated-structured one, can be implemented.

Some examples of ANTICIPATOR knowledge in Prolog/KR predicates are as followings.

```
(ASSERT (HIERARCHY-ANTIBIOTICS
   NATURAL-PENICILLINS PCG))
(ASSERT (TOXIC AMINOGLICOSIDES
   HEPATIC))
```

These stand for "*PCG (penicillinG) belongs to a natural penicillin group*", "*Aminoglycosides antibiotics have hepatic toxicity*". These are free-format, and labels, which may be necessary for some other language implementations, are not needed. Owing to the pattern matching feature of Prolog, these pieces of knowledge can be retrieved no matter what factor is a variable, in other words, any factor can be a key to the retrieval.

Using this type of assertion, three basic elements, bacteria, infectious diseases, and antibiotics, are described in hierarchies. Three basic knowledge pieces, sensitivity, pharmacokinetics, and causal bacteria appearance probability, are represented not by merely two-dimensional table, but with the concepts of relations between two of those three hierarchies, *i.e.* sensitivity, being a bactericidal force of antibiotics, is defined between bacteria and antibiotics. Therefore, these three kinds of knowledge in ANTICIPATOR are installed with two term relations between abstract concepts of two hierarchies.

```
(ASSERT (SENSITIVITY GRAM-NEGATIVE-
   BACILLUS NATURAL-PENICILLINS-))
```

This stands for "*Natural penicillins are not effective for gram-negative-bacillus*".

Overloading, inheritance and discussions on abstract level elements can be described, in knowledge bases, using these hierarchies.

The former of the Horn-clauses can be interpreted both as the declarative knowledge, "P *is true when both* Q *and* R *are true*", and as the procedural knowledge, "*To execute* P, *execute* Q *and then* R". To implement different semantics into a monomorph predicate is an important process of programming in Prolog.

As each Lisp function has two aspects, "*value as a result of evaluation*" and "*side effects in through the evaluation*", each Prolog predicate has "*success (and change of environment within the predicate) and failure, as a T-F value of the predicate*" and "*side effects (I/O, or change of environment outside of the predicate) in through the execution of the predicate*". Let Q be a conditional predicate, which takes T-F value with no side effect, and let R be a procedural predicate, then execution of P is similar to an application of a production rule; "*If* Q *is true, then do* R". Therefore, production rules can be implemented as they are, in Prolog predicates.

```
(ASSERT (NEGATIVE-HEURISTIC-RULE)
  (CASE-PROFILE INSUFFICIENCY HEPATIC)
  (FOR-ALL (TOXIC *DRUG HEPATIC)
    (ASSERT (NEGATIVE-SCORE *DRUG 3))))
```

(Note that *DRUG is a variable.)

This stands for a heuristic knowledge, "*If the patient has hepatic insufficiency, state the negative score of all the hepatic toxic antibiotics as 3 (level 3 warning)*".

Predicate CASE-PROFILE, which is supplied by ANTICIPATOR, is used to take T-F value by pattern matching. If the factor has not been defined yet, it evokes a demand driven inquiry, with procedures (where, predicate name in charge, inquiry type, prompting, valid answeres, and significant conditions are defined) stored in knowledge sources.

```
(ASSERT (CASE-PROFILE-ACQUISITION
    INSUFFICIENCY
    MULTIPLE-CHOICE
    "Is there any insufficiency in organs below?"
    (HEPATIC RENAL DIGESTIVE)))
```

(Note that in this case significant conditions is absent)

Unlike Lisp implementation, these procedures need not be "attached" to a node of a hierarchy. They are searched and evoked through pattern matching, whenever necessary.

Together with declarative knowledge, CASE-PROFILE retrieval results are used as bases of conditional evaluation. Rules are all evaluated with pattern matching and backtracking, and all action parts of rules, whose condition part is proven true, are executed.

A production system with pattern matching and backtracking is already installed in the Prolog processor.

Therefore, knowledge sources of expert systems, which comprise procedural knowledge and declarative knowledge, can be easily represented in Prolog predicates.

5. Conclusions

ANTICIPATOR is now in operation at the University of Tokyo Computer Centre with alpha-numeric characters, and the Hospital Computer Center of the University of Tokyo in *Kanji* characters, and is frequently used by medical doctors. The authors conclude that its popularity owes to the following factors.

*Limitations of the domain to rather clarified knowledge.
*Evolvement on where such an expert system was needed.
*Adhesion to feasibility.
*Two-dimensional recommendation which improved person-machine knowledge transformation.
*Adaptability of Prolog/KR in constructing expert systems.

The authors are convinced of the promisingness and the applicability of the concepts, the strategies, and the experiences, which are extracted through the development of ANTICIPATOR, to other knowledge based expert systems.

References

1. KIMURA M. Construction of an Antibiotic Medication Coun-selling System by Means of Knowledge Engineering, METR 83-01, Dept. of Mathematical Engineering, Univ. of Tokyo, 1983.
2. SHORTLIFFE, E. H. Computer-Based Medical Consultations: MYCIN, American Elsevier, 1976.
3. NAKASHIMA H. Prolog/KR User's Manual, METR 82-04, Dept. of Mathematical Engineering, Univ. of tokyo, 1982.
4. NAKASHIMA H. Prolog/KR-Language Features, *Proc. of the lst Int'l. Logic Programming Conference,* 1982.
5. KOWALSKI, R. A. Predicate Logic as Programming Language, *Proc. of IFIP Congress,* 1974.
6. PEREIRA, L. M. et al. User's Guide to DECsystem-10 PROLOG, Dept. of Artificial Intelligence, Edinburgh, 1978.
7. WARREN, D. H. D. et al. Prolog-the Language and its Implementation Compared with Lisp, SIGPLAN/SIGART *Proc. of the Symposium on Artificial Intelligence and Programming Language,* 1977.
8. KIMURA M. et al. Knowledge Based Antibiotic Medication Counselling System ANTICIPATOR and Its implementation by Prolog, *Proc. of MEDINFO 83,* 1983.

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