Time in Clinical Decision Support Systems: Temporal Reasoning in ONCOCIN and ONYX

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Time is an essential part of our environment. We use temporal reasoning to analyze the past for recurring patterns or trends in order to predict and plan for future events. Temporal relationships allow us to understand how events are related and what events are likely to occur in the future. As time proceeds, new information may force a re-evaluation of our expectations made with previous data. This re-evaluation may result in altered plans or predictions based on the new expectations. It is this special property of continual change that makes time an interesting but difficult subject for computer-based modeling.

Time has a prominent role in medical reasoning. Diagnoses are based on the patterns of signs and symptoms that evolve over time. Once a diagnosis emerges, prognostic factors provide insight into possible future clinical events. Management decisions are greatly influenced by the set of expected future gains that may be realized if a treatment option is given. If a patient has received similar treatments in the past, a careful understanding of the subsequent clinical course may change the expected outcomes in a particular patient. For example, if a patient had a serious reaction to a prior administration of the standard therapy, the physician may prefer to either modify the usual treatment or select an alternate treatment to avoid another undesired reaction.

The development of two decision support programs for cancer chemotherapy management at Stanford University has provided an opportunity to investigate the representation and utilization of temporal relationships and reasoning techniques in medical computer-based advice systems. ONCOCIN has been employed in the Stanford Oncology Clinic since 1981 where it provides treatment advice to physicians administering experimental chemotherapy to cancer patients. ONCOCIN's recommendations are based on the therapy guidelines specified in a research protocol document. This document details the order of treatment events, the contents of each treatment episode, and possible adjustments that may occur if specific patient conditions are present. ONYX is a chemotherapy advising system being developed to provide treatment recommendations in clinical situations where the protocol does not provide therapy guidelines. ONYX will develop therapy plans in unusual clinical situations that are not specified in the ONCOCIN protocols. ONCOCIN has had five years of in the clinic experience and relies on a well-structured body of knowledge for reaching conclusions and recommendations. ONYX requires a larger body of medical and oncology knowledge than found in ONCOCIN in order to develop new treatment plans in atypical settings. For example, ONYX will need to encode clinical strategies and basic research concepts to design an optimal therapy recommendation. Therefore, these two systems provide markedly different settings in which to explore approaches to temporal representation and reasoning.

ONCOCIN encodes protocol knowledge using IF-THEN rules. Protocol treatments generally are comprised of repeated cycles of multiple drug combinations. Protocol decisions such as drug dosages are based on the current treatment plan, current patient laboratory and toxicity findings, and pertinent past patient findings. ONCOCIN's major temporal requirements are: (1) the need to know what events have recently transpired and (2) the need to obtain past patient data based on past clinical events. For example, some ONCOCIN rules may apply if the current treatment was initially planned for the previous clinic visit but was delayed due to
some toxicity. Many ONCOCIN rules use past patient values that were obtained during previous treatment cycles. These retrievals are based on past clinical events such as "the previous chemotherapy cycle" rather than elapsed times such as "two weeks ago". ONCOCIN does not depend on trends across multiple values but uses specific values obtained at key points in time. These key values may have a significant impact on an ONCOCIN recommendation especially if a previous value was markedly abnormal. Therefore, the patient's past record can greatly influence the ultimate recommendation generated by ONCOCIN.

We recognized that ONCOCIN's major temporal requirements were for retrieval of patient data based on complex clinical contexts rather than simple calendar dates. Therefore, we implemented a structure called the temporal network that provides a framework to partition the patient record according to the clinical events present at the time of data collection (Fig. 1). Each node in the temporal network marks an interval of time during which a key event was occurring to the patient. These nodes permit the patient data to be aggregated according to intervals of time that have clinical meaning. A temporal query language was developed that permits expressing retrievals in a style similar to the protocol specifications. For example, with the temporal network in Fig. 1, we can request data from the LAST VISIT, or from the PREVIOUS CYCLE of POCC chemotherapy, or from ALL VISITS during ALL CYCLES of VAM chemotherapy. With the creation of the temporal network to organize the database and the temporal query language to exploit this partitioning by clinical events, we have provided new temporal support to meet the informational need of the ONCOCIN knowledge base.

The temporal concepts that need to be represented and manipulated in ONYX will be more extensive than in ONCOCIN. In addition to the structured temporal relationships found in the ONCOCIN temporal network, ONYX must interpret a patient's record for patterns and trends that make this individual unusually difficult to treat with the standard protocol guidelines. For example, a patient with markedly depressed blood counts after each administration of a mildly myelosuppressive drug may represent a person with an unusual sensitivity to this agent. ONYX may use this conclusion to drop the offending drug from new treatment plans. Many agents have slow cumulative toxicities. Detecting these toxic effects may require the comparison of many clinical parameters that are scattered across different periods of time. Therefore, the temporal findings in a patient record comprises an important body of patient-specific information to be used in ONYX.

We have implemented a prototype interpretation program that analyzes an ONCOCIN patient database for recurring patterns or trends over time and creates a machine-readable structure of its interpretation for use by ONYX (Fig. 2). We represented the "expected" clinical course of a "typical" protocol patient as an augmented transition network (ATN) where nodes represent protocol states (Fig. 3). For each patient visit, a particular ATN node contains the range of patient values that are expected for clinical attributes in patients that reach this state in the protocol. Node-specific interpretation routines detected the presence of deviant values, treatment delays or cycle aborts. The ATN findings are analyzed by a second interpretation system that uses a rule-based design to detect abnormal events over time (Fig. 3). For example, trends such as decreasing WBC values or improving clinical status were detected in the second analysis. Abnormal events that recurred in the patient record were also detected by the rules. A machine readable structure was generated that contained the rule conclusions. This structure represents the system's temporal analysis of the patient record. Although this approach can successively capture temporal events not previously detected using ONCOCIN's temporal capabilities, we have found that this design is too rigid for many subtle temporal inter-relationships. In particular, we were unable to incorporate temporal relationships between multiple clinical parameters even when there were known temporal dependencies between the attributes.

From our experience in the ONCOCIN and ONYX projects, we have continued to work on more flexible temporal representation and reasoning schemes that can be used to analyze time-oriented patient data. We believe that this task is important in our domain of medical decision support systems and represents a difficult issue for most current AIM systems.
This patient has received 5 cycles of chemotherapy (CYCLE) and 1 treatment of radiation therapy (XRT) over 7 clinic visits (VISIT). Note that some cycles have subcycles (SUBCYCLE) and some visits have simultaneous chemotherapy and radiation therapy (VISIT.6 and VISIT.7).
The patient was on protocol until 14 December.
Chemotherapy was normal until 3 August.
Low drug dosages of adriamycin were given 3 out of 4 VAM cycles.
Decreasing drug dosages of CCNU started 24 August.
POCC cycles were delayed 2 out of 4 POCC cycles.

Figure 2: Patient Record Interpretation Program
Top is a fragment of an ONCOCIN patient record showing chemotherapy data only. Bottom is a paraphrased output from the interpretation program which can be used by ONYX to alter treatment decisions based on patient events.

Figure 3: Two-Pass Interpretation System Design
The ONCOCIN record is initially analyzed by an ATN on a visit-by visit basis. A second pass by a rule based system performs analysis of temporal aggregates using the ATN conclusions to create the final interpretation.