Harvard-MIT Division of Health Sciences and Technology
HST.947: Medical Artificial Intelligence
Prof. Peter Szolovits
Prof. Lucila Ohno-Machado

Potential Use of a Causal Bayesian Network to Support Both Clinical and Pathophysiology Tutoring in an Intelligent Tutoring System for Anemias

Michael D. Blechner
Final Project for HST.947
May 17, 2005

Background & Problem Definition

Medical education in the United States is under increasing strain due to a number of influences. This paper will briefly describe some of the challenges in modern medical education and propose a potential, partial solution using artificial intelligence techniques to design intelligent tutoring software.

The first 1½ or 2 years of training in most U.S. and Canadian medical schools focuses on building an understanding of the pathophysiologic mechanisms of common diseases. An assumption exists that students will retain this knowledge and have the ability to recall and apply it in real clinical settings. However, some evidence from the cognitive science and education literature call such assumptions into question[1, 2]. Such studies suggest that the recall of pathophysiology knowledge obtained from didactic lectures is poor in clinical situations. Although many medical schools have made efforts to move away from didactic lectures and teach pathophysiology in settings that are more representative of clinical practice (i.e., problem-based learning), the majority of pathophysiology is still taught in a didactic manner.

The need to recall and apply relevant pathophysiology knowledge in the clinical setting has been clearly documented. Experts use knowledge of pathophysiology to reason about difficult cases or cases outside of their domain of expertise[3]. Trainees make use of such knowledge more regularly until more "compiled" knowledge structures emerge (illness scripts, etc)[2]. Unfortunately, effective reasoning in both situations is compromised by the limited ability to recall such knowledge.

The effective selection and interpretation of laboratory tests is critical to the diagnostic process. Many laboratory tests are dynamic measurements with complex behavior. Consequently, test selection and interpretation often requires detailed knowledge of relevant pathophysiology. One illustrative example is serum ferritin. Ferritin is used in conjunction with measurements of serum iron and transferrin to assess iron status in anemic patients. Most medical students know that the most common cause of a microcytic anemia is iron deficiency and that iron status is assessed by the above labs. Most students also know that ferritin levels are low in iron deficiency. However, few students know what ferritin is and why it is low in iron deficiency. Many practicing physicians do not know that a normal or even elevated ferritin level is consistent with iron deficiency and many who know this fact have no idea why it is the case. Although pathophysiologic knowledge is often required for the correct interpretation of lab values, laboratory medicine is learned in a mostly ad hoc fashion, typically during clinical rotations. The previously discussed difficulty recalling pathophysiology knowledge in the clinical setting, potentially impairs the learning and practice of good laboratory utilization.

In addition to the described disconnect between clinical and pathophysiology education and knowledge, there is a similar disconnect between declarative knowledge and procedural knowledge. *Procedural* in this setting refers to the process of applying declarative knowledge, not to performing medical procedures. For example, students may know that serum iron, ferritin and transferrin provide detailed assessment of iron status. However, this declarative knowledge does not necessarily translate into ordering iron studies in the appropriate clinical situation. Learning the procedural complement to declarative knowledge often requires a real or simulate clinical encounter.

Solution

One potential, albeit theoretical, solution to these problems would be a case-based teaching program capable of uniting clinical and pathophysiology training. By teaching pathophysiology within a realistic and relevant clinical setting, such a program could enhance recall of pathophysiology in clinical settings.

Cases that focus on the laboratory workup of diseases would specifically help ground knowledge of lab studies in the underlying pathophysiology while simultaneously adding lab studies to a student's clinical repertoire. In addition, such a program would enable students to develop the associated procedural knowledge. The remainder of this paper provides a description and discussion of a theoretical program covering the sub-domain of anemias.

The interface for such a program provides the user with some initial presenting information including a hematocrit or hemoglobin establishing the diagnosis of anemia. The student works through a case in a relatively unconstrained fashion by performing the following actions; (1)adding diagnostic hypotheses to a differential diagnosis list, (2) supporting hypotheses by associating each hypothesis with the relevant case data, (3) testing hypotheses by ordering additional lab studies in the context of a particular hypothesis, (4) making diagnoses by selecting from the current hypothesis list. Tutoring of clinical knowledge takes the form of guidance through the clinical workup provided by feedback and limited Socratic dialogue generated in response to user actions. Physiology tutoring takes the form of physiologically detailed feedback in response to user actions as well as exercises in which the user would build causal maps of the underlying physiology.

The knowledge requirements of such a system are not trivial. For clinical tutoring, the system must be able to take the current case data, i.e., the information available to the student, and determine all reasonable hypotheses, supportive data-hypothesis associations, labs studies for each hypothesis and any diagnoses. In addition, the system must be capable of generating useful feedback and Socratic dialogue. For physiologic tutoring, the system must have a representation of the causal relationships that make up the related pathophysiology of anemias. In order to generate physiologically detailed feedback associated with user actions, this knowledge must be closely linked to the clinical knowledge.

Bayesian Network as the Knowledge Representation

Like virtually all areas in medicine, the workup of an anemia contains elements of uncertainty. Uncertainty in the laboratory workup of anemias is due to multiple interpretations of certain findings in the absence of other clarifying data, variability in the presence of certain findings for a given disease, and a variable degree of reliability in the testing method. Although the educational setting may allow for simplification of the domain, clinical teaching must address this uncertainty. A Bayesian causal network has the potential to support both clinical and pathophysiology tutoring as defined above as well as address issues of uncertainty in clinical medicine. The proposed BN contains input nodes corresponding to data elements typically considered in the workup of anemias. However, the pedagogic goals of the system would likely obviate the need to represent all of these data elements in the model. For example, although various potential findings in the history and physical exam (pica, pale conjunctiva) would undoubtedly contribute to an anemia workup if present, such data need not be in the model if none of the cases report these findings. Figure #1 depicts an example network covering only microcytic anemias. All data nodes contain the prefix "DATA_". The granularity of discritization for continuous variables will be determined by the underlying pathophysiologic mechanisms and the pedagogic goals. For example, most clinicians know of the conceptual division of MCV (mean corpuscular volume, i.e., average red blood cell size) into low, normal and high corresponding to an MCV < 80, 80-100 and > 100 respectively. However, this level of detail will not allow the system to explain the likely physiologic mechanisms for an MCV of 62 seen in a case of beta thalassemia trait.

In order to determine diagnosis probabilities, the model contains nodes for the diagnoses in the domain. All diagnosis nodes depicted in the figures are prefixed with "DX_". Mutually exclusive diagnoses can be represented as categories within a single node. A patient cannot have both beta thalassemia trait and beta thalassemia major for example. In addition, pedagogic goals may enable further consolidation of otherwise unique nodes. For example, if none of the teaching cases will have concurrent beta and alpha thalassemia, these diagnoses can be consolidated into the same node (Figure 1). However, this does not prevent the student from considering this combination and an additional set of rules residing outside of the BN may be required to provide appropriate feedback should a student try to diagnose both alpha and beta thalassemia. The system must to be able to represent multiple concurrent diagnoses (iron deficiency and anemia of chronic disease for example). These diagnoses must be represented as distinct nodes. Each mutually

exclusive diagnostic group can either be set to one of a number of possible positive settings or false indicating that none of the diagnoses in the node are present.

In some cases, a more severe case of a particular diagnosis will activate different pathophysiologic mechanisms. To support this, diagnoses typically rendered in a binary fashion (present or absent) may be represented in varying severity. These "diagnoses" are mutually exclusive and would therefore be grouped in a single node. An example using iron deficiency anemia is illustrated in Figure 1.

In order to serve as a diagnostic model, links representing causal connections are placed between the diagnosis nodes and the appropriate data nodes. Since all diagnoses cause a decreased hemoglobin, all diagnosis nodes would be linked to the hemoglobin node. However, only beta thalassemia trait causes a change in HbA2 levels. Therefore, the other diagnostic nodes would not connect to the HbA2 node. Since the beta thalassemia diagnosis is embedded in a general thalassemia node (Figure 1), this causal connection would be represented in the conditional probability table of the HbA2 node (Figure 2). Additional causal links are placed between data nodes when appropriate. For example, an increase in the RBC count will result in an increase in the hemoglobin level if all other variables remain unchanged.

Additional nodes representing the steps in a causal chain of pathophysiology are inserted between diagnosis and data nodes that are causally linked. These elements provide the detailed representation of the underlying pathophysiology required for tutoring. All pathophysiology nodes depicted in the figures are prefixed with "M_" for mechanism.

Anemia subtypes are notoriously poorly documented in the clinical record. In addition, the diagnostic workup varies widely between different subtypes of anemias. As a result, detailed and complete data from cases of anemia are not available. Therefore, the conditional probabilities for this model must be based largely on expert opinion. The pathophysiology mechanism nodes do not represent measurable data points and therefore these conditional probability tables must also be constructed based on expert opinion. The physiologic nodes are associated with uncertainty in many cases and thus cannot be represented as simple causal nodes. Uncertainty stems both from our limited understanding of pathophysiologic mechanisms and from the variability manifest by many medical conditions. However, it is important to note that the model need only produce accurate results and appropriate feedback for cases in the teaching set.

The Model in Action

Recall that the system must be capable of determining; (1) the reasonable hypotheses, (2) supportive data-hypothesis associations, (3) lab studies for each hypothesis and (4) diagnoses from the current case data. The program can use the BN to determine the set of reasonable diagnostic hypotheses by instantiating nodes using the current case data, and returning an ordered list of diagnoses whose probability is above some predetermined cutoff.

The current findings that support a given hypothesis can be defined as data elements whose removal significantly decreases the probability of the diagnostic hypothesis. However, as a diagnosis' probability approaches 100%, the removal of supporting data element may not result in a significant decline in probability. Alternatively, supportive data can be determined by comparing the parameter's value in the current case with the probability of finding that value if the hypothesis is instantiated in the model. This approach is independent of other current findings in the case.

Determining which lab tests are likely to have significant impact on a hypothesis' probability can be achieved by independently instantiating each remaining test node with the finding that is most likely, given the current case findings. Reasonable lab studies are those that result in a significant change in the diagnostic probability of the hypothesis. In general terms, a reasonable lab test is one that has a relatively large impact on the hypothesis' probability at relatively low financial and health risk cost. The elements of cost, either financial or otherwise, are not represented in a standard Bayesian network but could be included using influence diagrams or decision networks.

Feedback concerning any student action can be generated by following the causal paths between the appropriate diagnostic nodes and the data nodes. Figure 3 shows the causal path used to generate a critique of a "mild-to-moderate iron deficiency" hypothesis given a mild anemia, markedly depressed MCV (< 65), normal RDW (< 13) and an increased RBC count. Generating easily readable and natural sounding text from these nodes is a non-trivial issue that has not be addressed in the current work. Figure 4 depicts the paths used to explain why a very low MCV is supportive evidence of beta thalassemia.

Unfortunately, a Bayesian network approach has limitations. As discussed and addressed by Long[4], temporal effects on pathophysiologic causal pathways can be very difficult to model using a Bayesian network. This can be illustrated by considering how a BN model based on the above description would handle a case of recently treated, but not fully resolved, iron deficiency. In this scenario the serum iron will be normal but many of the abnormalities in RBC indices may not have resolved. Again, we only have to worry about those scenarios which will be present in our teaching cases. A more substantial problem is the inability of a BN to contain loops. An illustrative example is the relationship between serum iron and ferritin in iron deficiency anemia (IDA) and in the anemia of chronic disease (ACD). In IDA, a decrease in serum iron leaves insufficient serum iron for macrophages to store resulting in a decreased amount of ferritin within macrophages. Since the source of serum ferritin is macrophage ferritin, IDA causes a decreased serum ferritin. In ACD, on the other hand, inflammatory cytokines cause macrophages to store more iron than usual resulting in increased cellular and serum ferritin and decreased serum iron. A BN cannot easily represent the relationship between serum iron and ferritin for both conditions since this would result in ACD first causing an increased ferritin (iron sequestration) leading to a decreased serum iron which would then cause a decreased cellular ferritin due to inadequate iron for storage. Such paradoxes can be addressed in a BN but only at the cost of a more complex network.

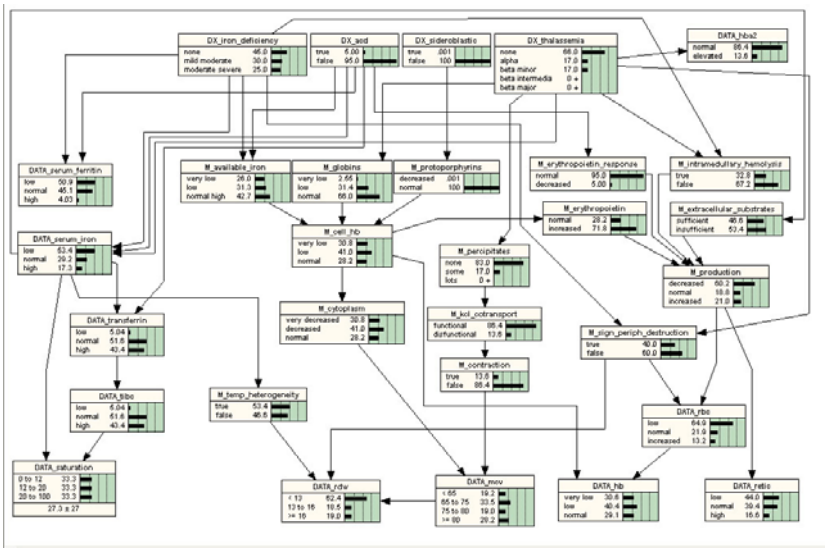

Figure 1 – Example of uninstantiated network covering only microcytic anemias.

DX_thalassemia	normal	elevated
none	100.00	0.000
alpha	100.00	0.000
beta minor	20.000	80.000
beta intermedia	0.000	100.00
beta major	0.000	100.00

Figure 2 – Conditional probability table for the Hemoglobin A2 node (DATA_hba2) showing that only beta thalassemia minor (trait) is ever associated with an elevated HbA2.

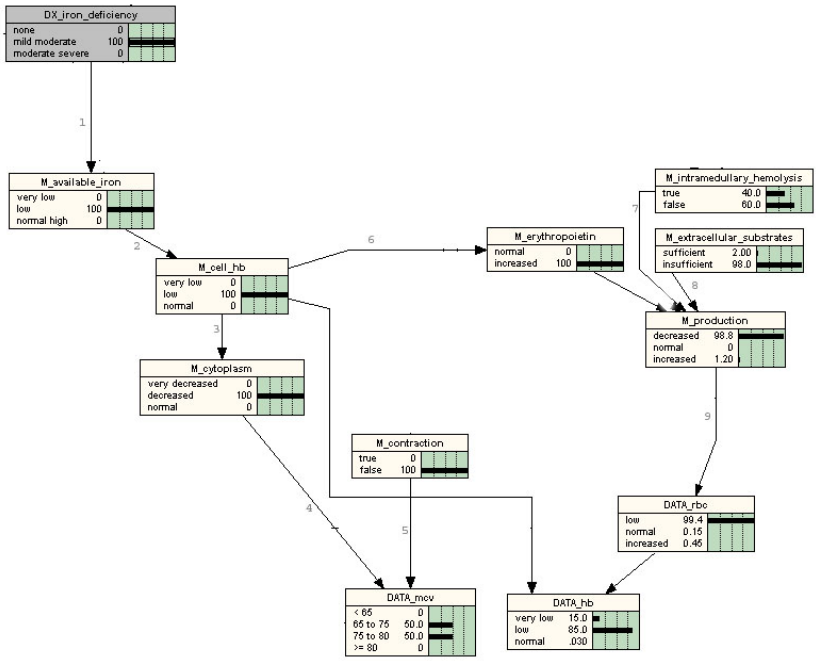

Figure 3 – Pathophysiologic critique of mild-to-moderate iron deficiency with a MCV < 65 and increased RBC count. (1) Iron deficiency results in low available iron, (2) which results in decreased cell hemoglobin production, (3) leading to decreased cytoplasmic volume, and (4) decreased MCV. However, a mild-to-moderate iron deficiency can not account for the MCV of 62 in this case. (5) Such a low MCV could be due to severe iron deficiency or concurrent cell contraction that does not occur in iron deficiency. In addition, the decreased cell hemoglobin results in (6) an increase in erythropoietin, but the (8) insufficient extracellular substrates (iron) for RBC production and the (7) possible component of intramedullary (in the bone marrow) hemolysis would result in a (9) decreased RBC production by the bone marrow and a decreased rather than an increased RBC count.

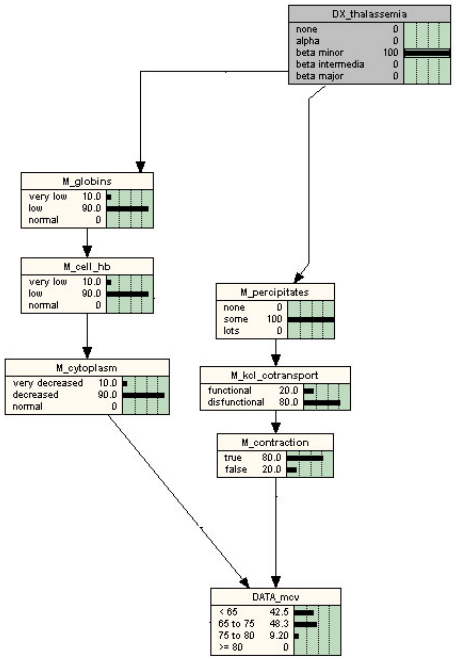

Figure 4 – Paths used to explain why a very low MCV is supportive evidence of beta thalassemia. Beta thalassemia results in (left hand path) decreased beta globin chain synthesis resulting in decreased hemoglobin synthesis, decreased cytoplasmic volume. Beta thalassemia trait also results in unbound alpha chains (node not depicted) which results in precipitates of alpha globin chains which in turn interfere with potassium and chloride exchange and cell dehydration. Together both mechanisms can result in a very low MCV.

1. Singley, M. and J.R. Anderson, *The Transfer of Cognitive Skill*. 1989, Cambridge, MA: Harvard University Press.
2. Schmidt, H.G., *Problem-based learning:rationale and description.* Medical Education, 1983. **17**: p. 11-16.
3. Charlin, B., J. Tardif, and H.P.A. Boshuizen, *Scripts and Medical Diagnostic Knowledge: Theory and Applications for Clinincal Reasoning Instruction and Research.* Academic Medicine, 2000. **75**: p. 182-190.
4. Long, W., *Temporal Reasoning for Diagnosis in a Causal Probabilistic Knowledge Base.* Artificial Intelligence in Medicine, 1996. **8**: p. 193-215.