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INKBLOT: A neurological diagnostic decision support system integrating causal and anatomical knowledge

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Abstract

As an initial step in the diagnostic process, human neurologists often use anatomical localization to constrain the set of diagnostic hypotheses deserving further consideration. We describe an automated system, INKBLOT-1, which uses anatomical localization in much the same way as human neurologists. Given a set of manifestations, INKBLOT-1 generates a set of hypothetical localizations relative to a coordinate system of nested cubes and then uses these localization(s) to explain the manifestations. We trace the reasoning mechanism utilized by INKBLOT-1 for a particular set of symptoms and show how INKBLOT-1 is able to generate novel hypotheses that explain the observed manifestations. In doing this, INKBLOT-1 demonstrates capabilities not demonstrated by previously described systems.

Keywords: Neurological diagnosis; Anatomical localization; Model-based diagnosis; Decision support

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1. Introduction

Formulating medical diagnoses is often one of the most difficult tasks which a physician must perform, and the field of neurology in particular presents unique diagnostic challenges. Because of the close association between neurological structure and function, neurologists often must draw upon a detailed knowledge of neuroanatomy to form hypotheses about the spatial localization of lesions as a first step in the diagnostic process. Hypothetical spatial localization(s) in turn constrain the set of diagnostic hypotheses deserving further consideration. This approach presupposes that lesions bearing no spatial proximity to each other are unlikely to be present, so that only diagnostic hypotheses consistent with localized lesions need come under further consideration.

In this paper we describe INKBLOT-1 (Integrated Neurological Knowledge Base and LOcalization Tool), a computer system which utilizes neuroanatomical knowledge in formulating differential diagnoses in the field of neurology. INKBLOT-1 uses the SCAN (Symbolic Coordinate Anatomy for Neurology) neuroanatomical knowledge base which represents the locations of neuroanatomical structures with reference to a hierarchical coordinate system of nested cubes [3]. Mirroring the diagnostic process of human neurologists, INKBLOT-1 first forms hypotheses about the potential coordinates of lesions within the coordinate system and then uses these hypothetical spatial localizations to generate irredundant sets of localized structures, damage to which could explain all observed manifestations.

1.1. Background

We will refer to a system designed to produce a differential diagnosis of neurological problems given a set of observable manifestations as a neurological medical diagnostic decision support (NMDDS) system. The ideal NMDDS system would meet a number of criteria. First, it would be accurate, producing ranked differential diagnoses closely approximating the differential diagnoses of expert clinicians. Second, it would be applicable to a broad domain, potentially covering the entire field of neurology, rather than being limited to a specific sub-domain, for example only to the diagnosis of strokes. Third, it would be able to generate novel diagnostic hypotheses by drawing upon a general knowledge base, rather than being limited to a pre-defined list of diagnoses. Fourth, it would represent causal, probabilistic, and spatial knowledge in a modular format familiar to and comprehensible by human experts, making it easier to refine and extend the system using the knowledge base of human experts. Finally, it would provide output in an easily interpretable format and include an explanation facility.

Researchers have been developing NMDDS systems at least since the early 1970s [1–5,7–9,11–19]. Some of the earlier systems utilizing ad-hoc statistical [14], simple Bayesian [12], or hybrid statistical, model-based approaches [8,9] drew upon shallow knowledge bases and offered limited functionality. One of the first systems utilizing true anatomical knowledge to generate novel diagnoses for visual field defects was limited in its domain and not easily extended [7]. Systems based on

production rules [11,13] and the NEUREX system [19], based on semantic nets, had richer knowledge representation facilities spanning broader domains. However, despite their expressivity these formalisms proved ill-suited to the representation of anatomical knowledge and to probabilistic reasoning. NEUROLOGIST, an NMDDS system [4] making use of a broad knowledge base was unable to produce a ranked differential or to come up with diagnoses other than those pre-programmed. LOCALIZE [5], a system containing an extensive knowledge base of thousands of nervous structures and their interconnections was limited to the peripheral nervous system, and another system using a Bayesian network to integrate knowledge of network structure with probabilistic knowledge was limited to just a few muscle groups [1]. The use of parsimonious covering theory to find minimal covering sets has also been explored, although the particular system described in Tuhrim et al., was limited to the domain of diagnosis of strokes [15,16]. More recent efforts have also explored the use of neural nets [17], which may in some cases be able to learn patterns of manifestations and diagnoses but which do not contain embedded symbolic knowledge.

In summary, no methodology and/or implementation has yet proven entirely successful in meeting the goal of developing an NMDDS system which generates accurate differential diagnoses under general conditions over a broad domain. We believe the INKBLOT-1 system can address some of the shortcomings of these previously described systems.

1.2. INKBLOT-1

Given a set of neurological manifestations, INKBLOT-1 returns a ranked list of hypotheses in the form of groups of localized structures which explain all the observed manifestations. INKBLOT-1 has been implemented in Common LISP. In the following section we will describe the SCAN knowledge base and the localization and hypothesis generation algorithms utilized by INKBLOT-1. To illustrate the operation of INKBLOT-1 we will use the example of a patient presenting with the symptoms of achromatopia (loss of color vision) and decreased level of consciousness. These symptoms are not typical of any particular common neurological condition, but as we shall see INKBLOT-1 is able to reason from first anatomical principles to form hypotheses about the potential neurological basis of the observed manifestations.

1.3. SCAN

The neuroanatomical knowledge base used by INKBLOT-1 is adapted from SCAN, a representation of neuroanatomical knowledge which represents the spatial orientations of neuroanatomical structures using a coordinate system of nested cubes [3]. By using this coordinate system, SCAN represents spatial relationships among neuroanatomical structures without needing to explicitly assert each relationship, just as a map represents spatial relationships between streets in a city without needing to explicitly specify that 'Main St. crosses Oak St.' for every pair

of streets. By comparison to a standard Cartesian coordinate system, the nested coordinate system is more compact, since facts only need to be represented about the largest cubes of which they are true, and more tractable, since computational operations can often be performed on a relatively small number of large cubes rather than on each of the smallest cubes.

The top level cube in the SCAN coordinate system represents a physical space 3 meters on an edge, and is represented by the symbol BX. Each cube is divided into 27 smaller cubes, represented by symbols formed by appending the letters A–Z or the punctuation mark @ to the name of the symbol of the parent cube. These symbols were chosen for convenience in the implementation language and have no other significance. Along with each cube is stored a list of anatomical structures contained or partially contained within that cube. As an example, the cube BXL contains the head and roughly 20 important tracts. The smallest cubes are 3 mm on an edge. As an example, the cube BXLL@WP contains portions of the frontal bone and integument. There are a total of 8896 non-empty cubes defined in the database. If a structure is contained within every sub-cube of a larger cube then it need only appear as being contained within the larger cube. For a given structure, if we were to imagine the cubes of various sizes listed as containing that structure displayed in three dimensions we would have an approximate three-dimensional representation of the structure, limited in resolution only by the edge length of the smallest cubes. Given such a representation of each structure it should be possible to answer any questions which can be answered by referring to a three-dimensional model or drawing of the structures.

In addition, SCAN contains a list of neurological manifestations and for a number of these it contains logical 'causal clauses' specifying which structures or combinations of structures could, if damaged, cause the manifestation. Fig. 1 shows the causal clauses associated with the particular manifestations we shall consider in our example, achromatopia and decreased level of consciousness.

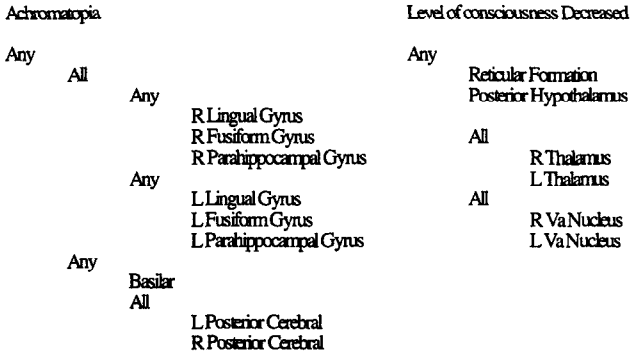

Fig. 1. Causal clauses from the SCAN knowledge base indicating the combinations of structures damage to which can result in achromatopia or decreased level of consciousness. The terms 'Any' and 'All' correspond to logical 'or' and 'and,' respectively. The terms 'Basilar' and 'L and R Posterior Cerebral' refer to arteries.

```
function MINIMAL-CUBES (manifestations) returns a set of coordinate boxes

    inputs: manifestations, a set of manifestations
    outputs: a set of coordinate boxes, representing potential localizations

    goal ← conjunction of the causal clauses of every manifestation in manifestations
    candidates ← top level box
    minimal-boxes ← ∅
    loop do
        if candidates empty then
            return minimal-boxes
        else
        consider ← POP(candidates)
        children ← CHILDREN-OF(consider)
        do loop
            child ← POP(children)
            if SATISFIES(STRUCTURES-IN(child), goal) then
                candidates ← PUSH(child, candidates)
        end
        if no children were pushed onto candidates then
            minimal-boxes ← PUSH(consider, minimal-boxes)
    end
```

Fig. 2. Pseudocode for the INKBLOT-1 localization algorithm. The output represents potential localizations relative to the hierarchical coordinate system.

For example, decreased consciousness can be caused by damage to the reticular formation, the posterior hypothalamus, both the left and right thalamus, or both the left and right Va nuclei, and similarly for achromatopia. In making a diagnosis, our task is to identify a subset of these structures sufficient to explain both manifestations. One hypothesis might assume damage to all of these structures, which would certainly explain the positive manifestations. However, such a hypothesis would be highly unlikely because it would assume damage to large sections of the nervous system. Our goal is to find a subset of the structures which not only explain the manifestations but are also as localized as possible.

1.4. INKBLOT-1 inference algorithm

1.4.1. Localization algorithm

Just as human neurologists first attempt to form hypotheses about the spatial localization of neurological lesions before proceeding to consider individual structures, INKBLOT-1 first attempts to localize lesions to individual cube(s) within the SCAN coordinate system. Pseudocode for the localization algorithm is provided in Fig. 2. In this pseudocode, POP removes the first element from its argument and returns the element, PUSH returns the result of adding its first argument to the end of its second argument, CHILDREN-OF returns the sub-cubes within a given cube, STRUCTURES-IN returns the structures within a given cube, and SATISFIES returns true if the variables in its first argument satisfy the clause in its second argument.

Briefly, as can be seen from this pseudocode, MINIMAL-CUBES narrows its focus to successively smaller cubes until it finds that it cannot narrow its focus any further and still explain the observed manifestations. A given cube is included in the

output if and only if it both contains structures sufficient to explain all observed manifestations without considering structures not contained within the cube and contains no sub-cube(s) which individually contains structures sufficient to explain the manifestations. The hierarchical structure of the SCAN coordinate system allows this successive focusing to be computationally efficient. This algorithm is not unlike algorithms described in Genesereth [6] and Mozetic [10] for the diagnosis of faulty electrical components, although in this case a spatial hierarchy takes the place of a functional hierarchy. Each of the cubes returned represents a potential localization to be used in generating diagnostic hypotheses in the form of sets of structures which could be damaged.

In practice, when run with the given manifestations achromatopia and decreased level of consciousness this function returns {BXLLL BXLLMIM BXLLMIN BXLLMJO BXLLML}, reflecting five potential localizations of varying specificity.

It should be noted that this localization algorithm does not allow for the possibility of complex localizations involving multiple boxes. Consideration of localizations involving multiple boxes could be implemented by pushing onto the queue not only individual sub-boxes but, under certain conditions, pairs or larger sets of sub-boxes, although such a modification would add considerably to computational requirements of the algorithm. For example, if all pairs of sub-boxes were considered instead of only individual boxes this would increase the time complexity by a factor equal to the branching factor of the coordinate system, 27 in the case of SCAN. We hope to address both of these limitations in the INKBLOT-2 system, a planned successor to INKBLOT-1.

1.4.2. Hypothesis generation algorithm

After a set of localizations has been generated by the localization algorithm, it is the job of the hypothesis generation algorithm to take these localizations and generate sets of structures contained within the localized regions and explaining the observed manifestations. Pseudocode for the hypothesis generation algorithm is provided in Fig. 3.

In this pseudocode, the function POWER-SET returns the power set of its argument, STRUCTURES-REFERENCED returns the set of structures referenced by the causal clause in its argument, and the other functions are as previously described. Given the list of potential localizations generated by MINIMAL-CUBES, the MINIMAL-HYPOTHESES function iterates over each localization to generate a set of sets of specific structures contained within the localized regions and explaining the observed manifestations. For each localization, the power set of the intersection of the set of structures associated with the manifestations and the set of structures contained within the single cube is generated. Each member of the power set is tested to determine whether it explains the manifestations. This yields a set of hypotheses, each of which is a set of localized structures sufficient to explain the manifestations observed.

Since each localization returned by MINIMAL-CUBES is chosen to contain structures which explain the observed manifestations, it is guaranteed that at least one hypothesis will be generated for each localization in the first loop of

MINI-MAL-HYPOTHESES, namely the element of the power set containing all the structures within the cube. However, it may be that there are smaller sets which explain the manifestations equally well, perhaps even sets containing a single structure. In the second loop of the MINIMAL-HYPOTHESES function, the set of hypotheses generated in the first loop is pruned to eliminate hypotheses which are supersets of other hypotheses. This parsimony criteria eliminates redundant hypotheses, defined as hypotheses containing structures which could be eliminated from the hypothesis without leaving any manifestations unexplained, since if a hypothesis were redundant the subset missing the redundant structure would also be in the set of hypotheses and the redundant hypothesis would be a superset and would therefore be eliminated. While it is possible that a redundant structure is in fact damaged, it would not alter the observations if it were, and consequently the combination of the observations and the causal component of the knowledge base lends no weight to the possibility of damage to a redundant structure.

Note how restricting the hypothesis generation algorithm to consideration of sets of localized structures greatly limits the number of hypotheses generated. If there were n structures implicated by a complicated set of manifestations, consideration of every possible combination would require consideration of 2^n sets, clearly an intractable number for large n. However, if these structures could be grouped by location into m sets of n/m, each consistent with a single localization, the number of hypotheses for consideration would drop to $m \cdot (2^{n/m})$, a potentially much more tractable number.

```
function MINIMAL-HYPOTHESES (manifestations) returns a set of sets of structures

    inputs: manifestations, a set of manifestations
    outputs: a set of sets of structures

    goal ← conjunction of all causal clauses in manifestations
    localizations ← MINIMAL-CUBES(manifestations)
    good-hypotheses ← ∅
    minimal-hypotheses ← ∅

    loop do until localizations empty
        cube ← POP(localizations)
        hypotheses ← POWER-SET (INTERSECTION
                                (STRUCTURES-IN(cube))
                                (STRUCTURES-REFERENCED (goal)))
        loop do until hypotheses empty
            hypothesis ← POP(hypotheses)
            if SATISFIES(hypothesis, goal) then
                good-hypotheses ← PUSH(hypothesis, good-hypotheses)
        end
    end

    loop do until good-hypotheses empty
        hypothesis ← POP(good-hypotheses)
        if hypothesis is not a superset of any member of good-hypotheses then
            minimal-hypotheses ← PUSH(hypothesis, minimal-hypotheses)
    end

    return minimal-hypotheses
```

Fig. 3. Pseudocode for the INKBLOT-1 hypothesis generation algorithm. The first loop generates hypotheses consistent with the localizations and the second loop prunes redundant hypotheses.

```
Formulating differential for (1) ACHROMATOPIA and
                             (2) LEVEL OF CONSCIOUSNESS DECREASED
Score: 1
(BASILAR)

Score: 17
(|R PARAHIPPOCAMPAL GYRUS| |L PARAHIPPOCAMPAL GYRUS| |R THALAMUS| |L THALAMUS|)

Score: 36
(|R LINGUAL GYRUS| |L LINGUAL GYRUS| |R VA NUCLEUS| |L VA NUCLEUS|)

Score: 36
(|R LINGUAL GYRUS| |L LINGUAL GYRUS| |R THALAMUS| |L THALAMUS|)
```

Fig. 4. Sample output of the INKBLOT-1 program. Each set of structures is sufficient to explain the observed manifestations and represents a diagnostic hypothesis sufficient to explain the evidence.

A limitation of this algorithm is that it does not take into account the potential for negative findings. Even if a set of structures is sufficient to explain positive manifestations, we might exclude it if it contains structures damage to which would predict manifestations not observed. Consideration of negative findings could be accommodated by testing each potential hypothesis for consistency with negative findings. In addition, the algorithm as described does not utilize knowledge of network structure, which is particularly important in the peripheral nervous system. Some knowledge of network structure is contained within SCAN, although it is incomplete. It would be conceptually straightforward to modify the SATISFIES function to allow parents of structures to substitute for their children, and the function was originally written to do this, but it was found that searching for potential proximal lesions in this way caused the algorithm to run slowly.

1.4.3. Parsimony metric

Following the generation of hypotheses, an ad-hoc parsimony metric is applied to each hypothesis and the hypotheses are sorted by score. The score assigned by the parsimony metric is equal to the sum of the third power of the level of the smallest coordinate cube containing all the structures assumed by the hypothesis and the second power of one less than the number of structures assumed. The smallest cubes are assigned level 0, so the minimum score is 0 and a smaller score is better, representing a more parsimonious hypothesis. Thus, both highly localized hypotheses and hypotheses containing few structures are favored.

Fig. 4 contains the output produced by INKBLOT-1 for the example we have been considering. It concludes that the most likely explanation is a lesion in the basilar artery, followed by three other less likely hypotheses. Each set of structures within parentheses represents a conjunction of structures all of which would need to be damaged to explain the observed manifestations.

It should be noted that, while this parsimony metric provides a way of ordering hypotheses according to a rough measure of plausibility, it is not based on any formal probability model and the scores produced cannot be interpreted quantitatively. For example, a hypothesis receiving a score of 1 is probably not 17 times as likely as a hypothesis receiving a score of 17. An hypothesis with a lower score than another hypothesis may be more likely, but it is difficult to draw any quantitative conclusions or even to have confidence that hypotheses have been ranked correctly.

We hope to address this limitation in the INKBLOT-2 system, which will use a formal probability model.

In summary, by using localization as a heuristic to limit the search space of possible hypotheses, INKBLOT-1 mimics to some degree the diagnostic process that human neurologists appear to use in formulating neurological differential diagnoses. INKBLOT-1 is potentially able to formulate diagnoses over a broad domain and can easily be extended with new knowledge. INKBLOT-1 does not consider complex localizations involving multiple cubes, negative findings, or efficiently consider network structure, but these features could be addressed given sufficient computational capacity. INKBLOT-1 also does not incorporate a formal probability model or provide explanations for its conclusions. These are more basic limitations which we plan to address in INKBLOT-2.

2. Discussion and conclusions

While the present SCAN knowledge base contains a fairly comprehensive set of over 1000 neuroanatomical structures, it contains relatively few associations between structures and manifestations. Consequently, extensive testing on real clinical cases is not practical at this time. However, as the example we have presented illustrates, INKBLOT-1 is able to perform diagnostic inference from first anatomical principles. In identifying specific sets of structures which explain the presence of the given manifestations, and in ranking these sets of structures, the program produced a result using knowledge present in its own database but not known to the author of the program, who is not an expert in neurology. Based on these results, we believe that by extending the knowledge base available to INKBLOT-1 and by enhancing the inference algorithm, we will be able to develop a system capable of performing more flexible inference over a broader domain.

There are also additional sources of knowledge currently available or likely to become available which could be integrated into a future version of the INKBLOT system, such as the Visible Human data set being developed by the National Library of Medicine. The Visible Human project has sectioned complete male and female cadavers into 1 mm and 0.33 mm sections, respectively, and obtained MRI, CT, and photographic images of each section at a resolution of 0.33 mm in the horizontal and vertical dimensions. Segmentation and classification of this data set, so that each voxel is associated with a named structure in the Unified Medical Language System (UMLS), is currently under way and is expected to be complete within the next 2 years. Once this has been done, the Visible Human data set can be automatically recoded according to a nested cube coordinate system, such as that utilized by SCAN. Because INKBLOT makes use of anatomical knowledge in a modular format, it is our hope that it will be possible to integrate this high quality data set with a future version.

We also hope to utilize the National Library of Medicine's UMLS, a controlled medical vocabulary incorporating many existing medical vocabularies within a single framework. The Metathesaurus draws upon a number of vocabularies with

either specific applicability to neurology and neuroanatomy, such as the Neuronames vocabulary developed at the University of Washington, or incorporation of neurological and neuroanatomical terms, such as the SNOMED vocabulary developed by the College of American Pathologists. The Metathesaurus represents relationships between concepts taken from the source vocabularies, for example parent and child relationships. We hope to make use of these relationships to enhance the completeness of our knowledge base as well as to provide standardization which will enhance the portability and expandability of the system.

In summary, while much development and testing of the INKBLOT system remains to be done before its effectiveness under clinical conditions can be objectively assessed, the results we have obtained thus far lead us to be hopeful these efforts will be successful.

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