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Development of Graph-Based Algorithm for Differentiating Pathophysiological Conditions

Satoshi IWAI [1,*], Tomohiro MITANI [1], Jin HAYAKAWA [1], Emiko SHINOHARA [2], Takeshi IMAI [3], Yoshimasa KAWAZOE [2], and Kazuhiko OHE [1]

[1] Department of Biomedical Informatics, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan
[2] Department of Artificial Intelligence in Healthcare, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan
[3] Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan
E-mail (*): stihahi@gmail.com

* Author to whom correspondence should be addressed; Tel.: +81-3-5800-6427

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Abstract
Aim: Clinical diagnostic decision support systems, which use pathophysiological information to improve diagnostic accuracy, have historically required knowledge of various relations between pathophysiological states to handle complex cases. Developing a knowledge model centered on pathophysiological functions instead of pathophysiological states may reduce this unwieldiness. *Materials and Methods*: In this study, such a knowledge model is provided by a modified and generalized factor graph, the pathophysiological query (PPQ) graph. A PPQ algorithm that automatically suggests possible pathological conditions of patients in the form of PPQ graphs is also developed. To evaluate the model and the algorithm, a computer software that processes the PPQ algorithm and PPQ graph, which represent the acid-base regulatory functions, was developed. Four case reports were considered, and up to two-time points, used as evaluation data points, were selected for each case. The software was used to obtain the diagnoses suggested by the PPQ model, which were then compared to diagnoses formulated by three physicians. *Results*: The output acquired by the proposed method was in accordance with the diagnosis of the physicians in three out of the five cases. *Conclusion*: The PPQ model may be a valuable diagnostic tool for suggesting differential pathological conditions to physicians in complex cases.

Keywords: Algorithms; Decision Support Techniques; Differential Diagnosis; Knowledge Bases System

Introduction

Diagnostic errors in medicine include both system-related errors and cognitive errors. Mark et al. reported that among 100 cases of assumed diagnostic error involving internists, system-related factors contributed to 65% of the cases and cognitive factors in 74% [1]. A major cognitive error is "premature closure", physicians stop thinking of other possibilities after reaching a preliminary diagnosis[1]. A clinical diagnostic decision support system (CDDSS) is a type of program developed to help physicians diagnose patients; for example, by leading the differential diagnoses[2] and avoiding diagnostic errors.

CDDSSs were actively studied in the 1980s. The majority of systems that were classified as CDDSSs, such as INTERNIST-1 [3], Iliad [4], and DXplain [5], were based on knowledge about relationships between symptoms and diseases. These CDDSSs are conceptual descendants of Gorry's schemata-based heuristic CDSS [6]. INTERNIST-1 [3], which deeply affected these systems, received patient symptoms as input, and listed them according to their confidence values. However, such systems cannot cope with complex cases in which multiple diseases overlap [7]. Another type of CDDSSs used pathophysiological information, enabling them to handle situations with multiple overlapping diseases [7]. Such systems also had the advantage of being able to explain causation between pathophysiological states, allowing physicians to understand the causes of symptoms and signs [8].

Additionally, there is an emerging need to utilize profound knowledge of the underlying pathophysiological concepts for diagnosis in many fields [9,10]. The acid-base electrolyte program (ABEL) was such a system that could output pathophysiological explanations [11]; it expressed the patient's condition by making use of a knowledge base about causal relationships between pathophysiological states. However, in physiologically complex cases, the system required very extensive knowledge about the numerous states that compose such cases. To address this issue, we utilize the knowledge of pathophysiological functions assuming that pathophysiological states can be interpreted as the result of abnormalities. A pathophysiological function model and an algorithm to suggest differential pathological conditions of patients were developed. The aim of this study was to demonstrate the capability of this model and algorithm to explain complex cases.

Materials and Methods

Overview

In this study, a knowledge-based model and an algorithm that identifies differential pathological conditions were proposed. The knowledge-based model is a graphical model that represents pathophysiological functions; it is a subtype of a factor graph with some modifications and restrictions named the pathophysiological query (PPQ) graph. The related PPQ algorithm receives patient information as input and produces a list of possible differential pathological conditions in the form of combinations of abnormal functions. A computer program that implements the PPQ algorithm was developed, and both the PPQ graph and PPQ algorithm were evaluated for complex medical case reports. In the next section, useful terminology regarding the PPQ graph and algorithm is introduced.

Nodes in Pathophysiological Query Graphs

Like any factor graph, the PPQ graph contains two types of nodes: variable nodes and factor nodes. It is a bipartite graph, which means that every edge in the graph connects nodes of a different type. **Variable nodes** are associated with patient data such as pH or pCO_2 (restricted in the present study to three discrete values). Two types of factor nodes are defined: functional factor nodes and definitive factor nodes, both expressing the relationships between values of neighboring variable nodes. **Functional factor nodes** are associated with functions in the body and take two states: normal and abnormal. For example, when the function of the respiratory center is normal, if the level of pO_2 drops, the ventilation volume increases to keep the level of pO_2. Contrarily, when the function is abnormal, the ventilation volume does not change, or it decreases. As such, the state of a functional factor node depends on the states of those variable nodes joined to it by the edges; the precise rule governing this is shown explicitly in the PPQ graph "interpretation table". The direction of the edge between a functional factor node and each of its neighbor variables gives information about causality; these directions constitute the static knowledge that is embedded in the PPQ graph. **Definitive factor nodes** have two states, 1 or 0, depending on whether they represent a possible combination of values of the variable nodes to which edges join them. This can be shown explicitly in the form of a "restriction table," the entries of which are combinations of neighbor states for which the definitive factor node takes the value 1. Some example tables for a small graph are shown in Table . The

knowledge in a PPQ graph is composed of the graph structure and the values of the factor nodes of both types.

Table 1. Restriction table of the definitive factor nodes: Restriction table of "pH Def"

	Metabolic effects	Respiratory effects	pH
1	alkalosis	Alkalosis	alkalemia
2	alkalosis	Normal	alkalemia
3	alkalosis	Acidosis	alkalemia
4	alkalosis	Acidosis	normal
5	alkalosis	Acidosis	acidemia
6	normal	Alkalosis	alkalemia
7	normal	Normal	normal
8	normal	Acidosis	acidemia
9	acidosis	Alkalosis	alkalemia
10	acidosis	Alkalosis	normal
11	acidosis	Alkalosis	acidemia
12	acidosis	Normal	acidemia
13	acidosis	Acidosis	acidemia

Terminology for Pathophysiological Query graphs

A variable state set is defined as a subset of the values of the variable nodes in a PPQ graph. As variable nodes are associated with patient data, the variable state set represents the state of a particular patient. In order to explain how the PPQ algorithm works, the term **complete variable state set** is introduced, which includes the value for every variable node in a PPQ graph.

Interpretation graph is a term related to the whole graph state: the interpretation graph holds information about the states of all functional factor nodes as well as variable nodes.

Pathophysiological Query Algorithm

The PPQ algorithm receives partial information about patients in the form of a variable state as input set and has as outputs a list of possible interpretation graphs. In the context of CDDSS, the algorithm outputs differential pathological conditions in the form of interpretation graphs. The PPQ algorithm is composed of three steps:

1. From the input variable state set, list all possible complete variable state sets.
2. From the list produced in Step 1, generate all possible interpretation graphs.
3. Sort the interpretation graphs in ascending order of a number of functional factor nodes that are interpreted as abnormal.

The operation of the algorithm implementing a simple PPQ graph that represents the knowledge of the acid-base regulatory function [12] is illustrated in the next section.

Operation of the Pathophysiological Query Algorithm

Figure 1 shows an example PPQ graph that represents the knowledge of the acid-base regulatory function. There are three variable nodes: "pH," "respiratory effects," and "metabolic effects." The node "pH" has three states: "acidemia," "normal," and "alkalemia." The "respiratory effects" and "metabolic effects" nodes have three states each: "acidosis," "normal," and "alkalosis." There are two functional factor nodes ("respiratory Func" and "metabolic Func") and one definitive factor

node ("pH Def") in this PPQ graph (Figure 1). Tables 1 and 2 correspond to the interpretation table and restriction table of the graph, respectively.

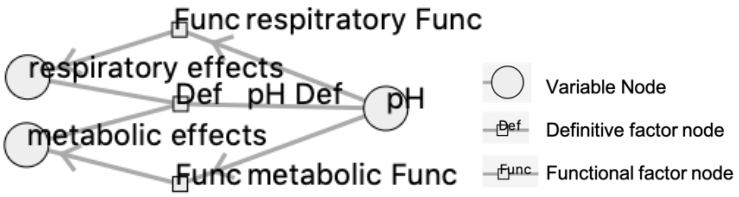

Figure 1. Simple PPQ graph representing the acid-base regulatory function. The large circles are variable nodes; the small squares are functional or definitive factor nodes. PPQ, Pathophysiological Query; Func and Def stands for functional factor node and definitive factor node, respectively.

Table 2. Interpretation table of the functional factor nodes

Interpretation table of "metabolic Func"

pH	→	**metabolic effects**	**interpretation**
alkalemia		acidosis	normal
acidosis		alkalosis	normal
normal		normal	normal
other			abnormal

Interpretation table of "respiratory Func"

pH	→	**respiratory effects**	**interpretation**
alkalemia		acidosis	normal
acidosis		alkalosis	normal
normal		normal	normal
other			abnormal

As an example, we applied the PPQ algorithm to a simple variable state set for which the value of the pH variable is "acidemia." The process steps are as follows.

1. List all possible complete variable state sets. As the variable nodes "metabolic effects" and "respiratory effects" can each take three different values, there are nine possible complete variable sets (Table 1).

Table 1. All possible full variable sets

G1

variable node	**state**
pH	acidemia
respiratory effects	acidosis
metabolic effects	acidosis

G2

variable node	**State**
pH	acidemia
respiratory effects	alkalosis
metabolic effects	Acidosis

G3

variable node	**state**
pH	acidemia
respiratory effects	acidosis
metabolic effects	alkalosis

G4

variable node	**state**
pH	acidemia
respiratory effects	normal
metabolic effects	acidosis

G5

variable node	**State**
pH	acidemia
respiratory effects	Acidosis
metabolic effects	Normal

G6

variable node	**state**
pH	acidemia
respiratory effects	normal
metabolic effects	normal

G7

variable node	**state**
pH	acidemia
respiratory effects	normal
metabolic effects	alkalosis

G8

variable node	**State**
pH	acidemia
respiratory effects	alkalosis
metabolic effects	normal

G9

variable node	**state**
pH	acidemia
respiratory effects	alkalosis
metabolic effects	alkalosis

2. Generate all possible interpretation graphs. According to rows 5, 8, 11, 12, and 13 of the restriction table (Table), the possible complete variable sets are G1 to G5. After selecting the possible complete variable sets, add the interpretation of every functional factor node, referring to the interpretation table (Table). This results in the five interpretation graphs described in Table 2.

Table 2. All possible interpretation graphs

G1

nodes	state
pH	acidemia
respiratory effects	acidosis
metabolic effects	acidosis
respiratory effects Func	abnormal
metabolic effects Func	abnormal

G2

nodes	state
pH	acidemia
respiratory effects	alkalosis
metabolic effects	acidosis
respiratory effects Func	normal
metabolic effects Func	abnormal

G3

nodes	state
pH	acidemia
respiratory effects	acidosis
metabolic effects	alkalosis
respiratory effects Func	abnormal
metabolic effects Func	normal

G4

nodes	state
pH	acidemia
respiratory effects	normal
metabolic effects	acidosis
respiratory effects Func	abnormal
metabolic effects Func	abnormal

G5

nodes	state
pH	acidemia
respiratory effects	acidosis
metabolic effects	normal
respiratory effects Func	abnormal
metabolic effects Func	abnormal

3. Sort the interpretation graphs in ascending order of the number of functional factor nodes interpreted as abnormal. G2 and G3 each have one abnormal functional factor node, while G1, G4, and G5 each have two. As a result, the PPQ algorithm sorts them into two groups: a low-abnormality group (G2, G3) and a high-abnormality group (G1, G4, G5). That means that if a patient is in a condition of acidemia followed by either respiratory acidosis or metabolic acidosis, and the counterpart system is alkalosis to alleviate the change, then the level of abnormality is low (G2 and G3). If, however, both systems are normal or acidotic despite the acidemia, (G1, G4 and G5), the level of abnormality is high. In G2, the single abnormality is metabolic, while in G3 it is respiratory. The other cases involve both metabolic and respiratory abnormalities. Figure 2 serves as an output example, showing the graphical representation of G2.

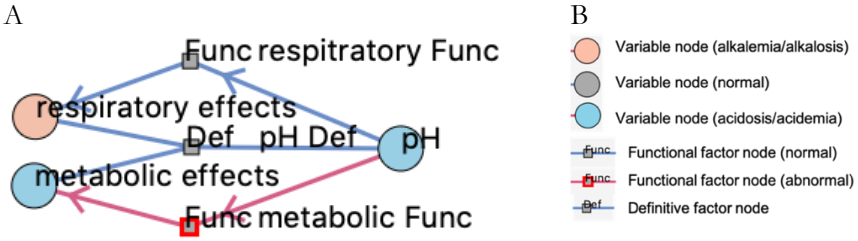

Figure 2. (A) Graphical representation of the interpretation of graph G2. (B) Legend of interpretation graph

Experimental Evaluation: Settings

The PPQ algorithm was evaluated following four steps. First, a PPQ graph for a field of acid-base regulatory functions was developed. Second, four case reports with detailed descriptions focused on the acid-base disturbance of patients were selected. After that, for each case, up to two evaluation data points (total of five points) were selected. Third, practicing physicians made the interpretation graphs for each data point; these were taken as gold-standards. Finally, a computer software to

implement the PPQ algorithm (Figure 4) was developed, and the rank of the gold-standards were searched within the lists of interpretation graphs generated by the software.

First Step: Development of the Pathophysiological Query Graph

The PPQ graph of acid-base regulatory functions is developed using information from a standard pathophysiology textbook [13] (Figure 3). The graph is composed of 11 functional factor nodes, 5 definitive factor nodes, and 17 variable nodes.

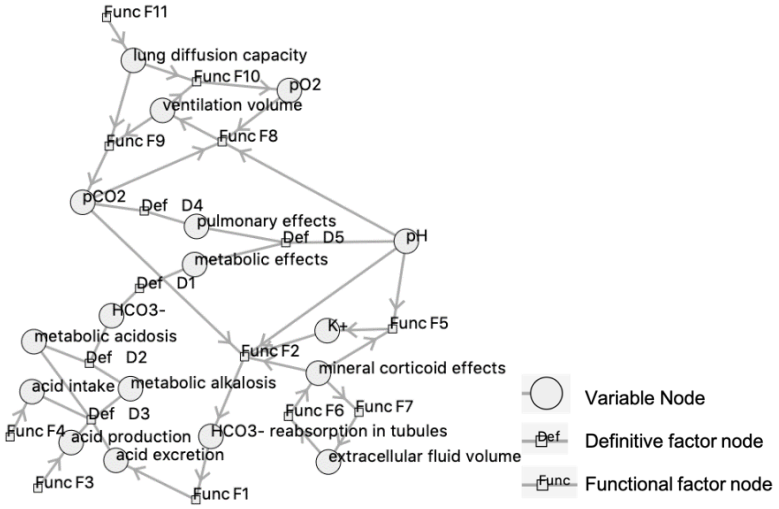

Figure 3. PPQ graph of acid-base regulatory functions. PPQ, Pathophysiological Query

Second Step: Selecting Case Reports and Data Points

The search was done in PubMed for four major acid-base disturbances: respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis. One case report for each type of disturbance was selected. After selecting the case reports, one or two evaluation data points were selected for each case report. Five data points were selected (Table 3, Table 4).

Table 3. Selected case reports for each acid-base disturbance

Case Report #	Description
Case 1	Respiratory alkalosis due to hyperventilation after kidney transplant surgery[14]
Case 2	Metabolic acidosis caused by inhalation of formic acid accompanied by carbon monoxide intoxication[15]
Case 3	Metabolic alkalosis due to intake of anti-diuretics and licorice [16]
Case 4	Respiratory acidosis accompanied by idiopathic interstitial pneumonia [17]

Table 4. Case reports and data points

Case report	Target time point	Datapoint code
Case 1: respiratory alkalosis	1 day after surgery	Point 1
Case 2: metabolic acidosis	On admission	Point 2
Case 3: metabolic alkalosis	On admission	Point 3
Case 4: respiratory acidosis	On admission	Point 4-1
	Repeated arterial blood gas analysis	Point 4-2

After selecting the data points, initial variable state sets were extracted from laboratory data written in case reports for each data points. These variable state sets were validated by physicians.

Third Step: Definition of the Gold-Standards

Three physicians were recruited from the Division of Nephrology and Endocrinology, The University of Tokyo. Their medical experience varied from 7 years to 16 years, while they all held General Internal Medicine Specialist certificates. For each data point, the physicians read the case reports and made interpretation graphs by themselves. Afterward, the physicians discussed the cases among themselves until they agreed on one interpretation graph for each data point. These were adopted as the gold-standards.

Fourth Step: Comparing the Output of the Software and Gold-Standards

A comparison was conducted between the gold-standard interpretation graphs and the ones produced by the developed evaluation software (Figure 4). Whether the software output contained the gold-standard graph or not was evaluated.

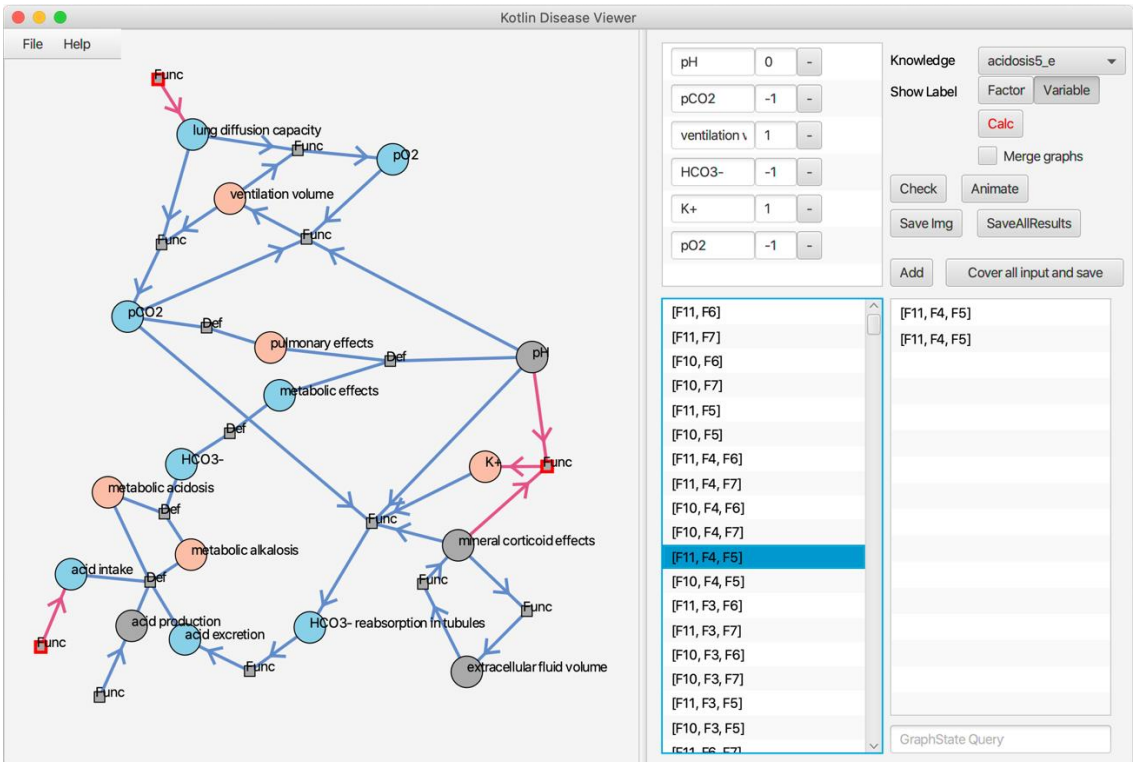

Figure 4. Screenshot of the evaluation software, which accepts input of patient information in the form of value lists of variable nodes, generates interpretation graphs and visualizes them one by one. The program was written in the Kotlin language, using the JavaFX library for the graphical user interface

Results and Discussion

Table 5 indicates whether the gold-standards were contained in the computer output and the ranks of gold-standards among the output graphs. For three out of the five data points, the gold-standard interpretation graphs were contained in the software output. However, the gold-standard interpretation graphs were not contained in the output of the software for data points 1 and 3. The

interpretation graphs were ranked in ascending order according to the number of abnormal functional factor nodes.

Table 5. Ranking of gold-standard interpretation graphs among output lists. Not applicable (NA): the gold-standard graph was not included in the output.

	Gold-Standard Contained or Not	Number of Abnormal Functional Factor Nodes of Gold-Standard	Rank of Gold-Standard/Total Number of Output Graphs
Data point 1	Not contained	4	NA/26193
Data point 2	Contained	6	969/6071
Data point 3	Not contained	4	NA/30141
Data point 4-1	Contained	3	11/8106
Data point 4-2	Contained	4	165/37727

Figure 5 (A) shows the gold-standard interpretation graph of data point 2, which is contained in the output of the software. In this case, the patient attempted suicide by inhaling carbon monoxide. He mixed formic acid and sulfuric acid to generate carbon monoxide. At data point 2, the patient had lung injury (Func F11) and was hypoxic despite increased ventilation volume (Func F10). According to the physicians, he suffered dehydration (Func F7), acute kidney injury due to exposure to formic acid (Func F2), elevated K^+ due to rhabdomyolysis (Func F5), and increased acid production due to anaerobic metabolism (Func F3). Figure 5 (B) shows the gold-standard interpretation graph of data point 1, which is not contained in the software output. In this case, the patient had undergone a kidney transplant that caused low reabsorption of bicarbonate (Func F2). According to the physicians, he suffered dehydration (Func F7) due to insufficient infusion; he also exhibited decreased acid intake (Func F4) and increased acid production (Func F3) as a result of fasting for the operation.

The study evaluating CDDSS [18] mentioned the importance of including appropriate diagnosis on the output list even if the case was complex with an atypical presentation because true diagnosis might appropriately be ranked fairly low in such cases. Table 5 showed that the PPQ algorithm successfully generated interpretation graphs that were consistent with the diagnosis formulated by physicians for three out of five data points. This suggests that it is possible to differentiate pathophysiological conditions by knowledge of functions using the proposed method despite the complexity of those case.

In previous CDDSSs, such as ABEL [11], representing the state of the patient under complex circumstances required very precise knowledge of abnormalities. For example, in the case of data point 2 described in Table 3 and Table 4, it would be necessary to prepare concrete pathophysiological states, such as "inhalation of acids," "carbon monoxide intoxication," "acute kidney injury," and "dehydration." Subsequently, the causal relationships among those states must be noted. However, in the proposed method, by noting body states as the variable nodes and the pathophysiological functions that cause the interaction between those nodes (see Figure 3), differential pathophysiological conditions are generated.

However, there are two data points (1 and 3) for which the evaluation software failed to produce the gold-standard graphs. Physicians tend to judge abnormality on the basis of the clinical situation, while the PPQ algorithm only generates interpretation graphs that are consistent with the tables of PPQ graphs. In each of these two data points, there was an abnormal combination of variable node values indicating that the functional factor node is abnormal, but the physicians consider it normal. In these instances, the PPQ algorithm indicated a function abnormality, but the physicians regarded it as normal because it did not require clinical intervention. For example, in data point 1, the gold-standard graph nodes "lung diffusion capacity" and "pO_2," took the value "normal", while the node "ventilation volume" took the value "high". The physicians judged Func F10 as normal (Figure 5B)

because they thought it was not an abnormal clinical condition requiring extra intervention. However, the interpretation table of Func F10 indicates that if "lung diffusion capacity" is normal and "ventilation volume" is high, the function is normal only when "pO_2" is high. Therefore, the algorithm generated interpretation graphs in which Func F10 was abnormal. Although the acid-base disturbance is a well-studied area [19], there are many models to understand acid-base, and they are not mutually exclusive [20]. In proposed cases, it may be necessary to incorporate models that consider the clinical situation. The fundamental problem is the difficulty of developing a model that considers all possible constructs.

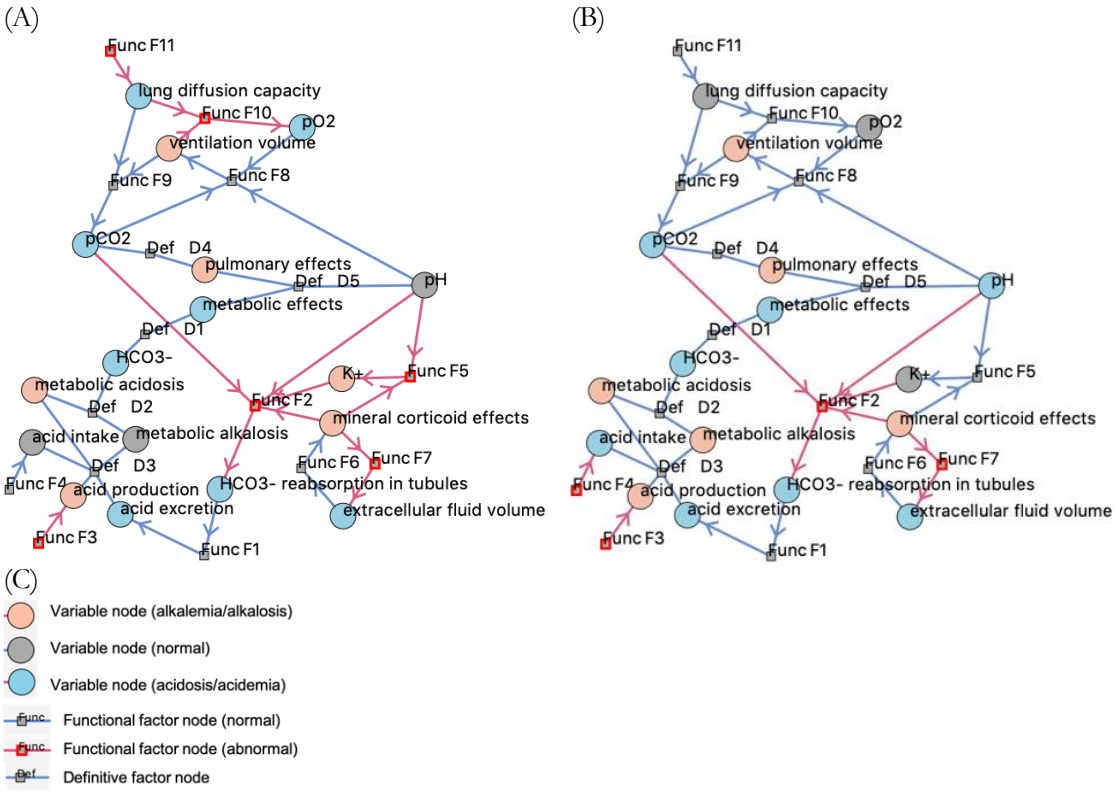

Figure 5. (A) Gold-standard of data point 2, which is included in the output of the software. (B) Gold-standard of data point 1, which is not included in the output of the software. (C) Legend of interpretation graph.

Another problem was the sheer number of graphs generated by the software, which made it difficult to identify the gold-standard graphs. The prolific output, which would cause trouble for physicians seeking differential diagnoses, was caused by the smallness of the input information compared to the complexity of the graph. The output corresponds with the result of a previous study that described the difficulty of ranking correct diagnosis higher in atypical cases [18]. This problem could be ameliorated by improving the user interface. For example, grouping graphs with similar interpretations and displaying them on one simpler graph with fewer nodes might enhance the user experience.

There are some limitations to this method. First, the granularity of the knowledge incorporated in the PPQ graph is arbitrary and needs to be selected according to the use case. Second, the values of variable nodes are discrete. The PPQ graph cannot provide information about degrees of deviation from the normal range in variable nodes. As a result, it fails to describe properly any pathological conditions for which it is the degree rather than the mere presence of deviation from the normal range that is significant. Finally, an evaluation based on only four case reports may not be sufficient to validate the PPQ algorithm. Further investigation is required for accurate validation of this method.

Despite these limitations, the proposed method can suggest differential pathophysiological conditions even if there are few test results. On the contrary, for example, the Stewart equation [21] [21] is an approach for analyzing acid-base disorders, but it cannot list up candidates if there are not enough test results that consist equations. Because the proposed method can list candidates with any number of inputs, if properly implemented, it can dynamically change the list of the candidates as physicians input more detailed information about patients. This may serve physicians in gaining more accurate insights on the pathophysiological diagnosis.

Conclusion

Comparing the expert opinion of three physicians to the candidate diagnosis obtained from the proposed method revealed that the graph-based algorithm can properly represent and differentially diagnose complex cases; past methods had difficulty representing such cases using the knowledge of causal relationships between pathophysiological states. The proposed method may contribute to the development of a CDDSS capable of suggesting differentiated pathological conditions to physicians dealing with complex cases.

List of abbreviations

ABEL: Acid-Base Electrolyte (program)
CDDSS: Clinical Diagnostic Decision Support System
PPQ: Pathophysiological Query

Conflict of Interest

The authors declare that they have no conflict of interest.

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