A Cognitive Model for Forecasting Progress of Multiple Disorders with Time Relationship

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Abstract

Many diseases cause other diseases with strength of influences and time intervals. Prognostic and therapeutic assessments are the important part of clinical medicine as well as diagnostic assessments. In cases where a patient already has manifestations of multiple disorders (complications), progress forecasting and therapy decision by physicians without support tools are very difficult: physicians often say that "Once complications set in, the patient may die."

Treating complications are difficult tasks for physicians, because they have to consider all of the complexities, possibilities and interactions between the diseases. The prediction of multiple disorders has many bundles that arise from such time-dependent interrelationships between diseases and nonlinear progress.

This paper proposes a model based on time-dependent influences, which appropriately describes the progress of multiple disorders, and gives some modifications for applying this model to medical domains; time-dependent influence matrix, manifestation vector, therapy efficacy matrix, S-shaped curve approximation, definitions of which are provided. This research proposes an algorithm for forecasting the state of each disease on the time horizon and for evaluation of therapy alternatives with not toy example, but real patient history of multiple disorders.

I. Introduction

The large amount of existing medical knowledge, and the rapid growth of that knowledge during the last quarter of this century, have resulted in a situation where most physicians find it increasingly difficult to assimilate all of the information which would be useful in making optimal clinical judgments. Unfortunately under normal circumstances, the biomedical scientist is not solely interested in the mathematical model of a physiological system under healthy or orthological conditions.

While specialization provides a partial solution to this problem, the rapid evolution of technology and clinical research makes it difficult for even the specialist to keep up. This problem extended across all aspects of medical decision making from diagnosis to patient management. For at least 25 years now the idea has been advanced that *C*omputer-assisted *M*edical *D*ecision making (CMD) systems might provide a solution to many of the problems created by this information explosion. The motivations for attempts to understand and assist the process of clinical decision making have been numerous [1].

Clinicians often encounter challenging cases that involve patients with several diseases that interact with one another. For example, nearly 40% of the patients that undergo EMG (electromyography) examination have two or more diagnoses [3]. A multiple disorder, or complication, is a mixture of symptoms and diseases in one patient. A multiple disorder is the complicated and difficult problem that faces clinicians.

To diagnose multiple disorders causal modeling has improved the physicians' ability to make diagnoses by considering both intermediate pathologic states and disease manifestations [5,6]. Patient *S*pecific *M*odels (PSM) can generate coherent descriptions of disease findings in patients through causal reasoning [7]. The ability to diagnose multiple interacting disorders and explain them in a coherent causal framework has only partially been achieved in medical expert systems. However, *A*rtificial *I*ntelligence in *M*edicine (AIM) systems have not been able to explain the collection of pathophysiologic states and findings when several interacting diseases are present. The problem of correctly diagnosing, treating, and forecasting multiple disease entities in a single patient is a difficult problem facing AIM systems.

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II. Multiple disorders

A multiple disorder, so called complication, is a mixture of symptoms and diseases in one patient. A complication is a new illness, or a new development of an illness caused by another disease, that makes treatment more difficult. Most physicians use unstructured inductive or deductive logic individually to make diagnosis and prognosis of multiple disorders. This process requires much medical knowledge and complex inference, so the accuracy and reliability of the clinical work mainly varies with physician's experiences. But physicians currently do not have any decision supports to forecast the progress of complications and to select the optimal therapy for multiple disorders. There are some mathematical difficulties when deriving the model equations from biomedical phenomena. A further difficulty in describing physiological systems mathematically is due to the well-known fact that the vast majority of physiological processes implies wide-range, intrinsic nonlinearities, that cannot be approximately determined by linearities. The ability to diagnose and explain multiple disorders requires a detailed examination of the interactions between disease entities in the knowledge base. With few exceptions, most probability-based knowledge base assume that diseases are mutually exclusive and all features are independent for a given disease [17]. Belief networks improved an this limitation in probabilistic reasoning but do not provide for a simple way to generate convincing explanations [18]. Manifestations of each disease in a multiple disorder are neither mutually complementary or exclusive and all features are independent for a given disease. A disease has many manifestations and then a manifestation may be induced by two or more diseases.

The stage of a disease are divided as shown in Figure 1. Although the divisions between these stages are not always apparent, most individuals follow the general pattern [19].

III. Model and algorithm

3.1. Definitions

Medical knowledge for explaining influences between diseases is represented in a map which is composed of *nodes* and *arcs*, and the former are diseases or symptoms and the latter are influences between nodes. A double-lined node is a disease (or symptom) which is treatable by treatment.

A disease is different from a symptom in that a symptom is the sign of the existence of something bad or changes in the body that indicates an illness.

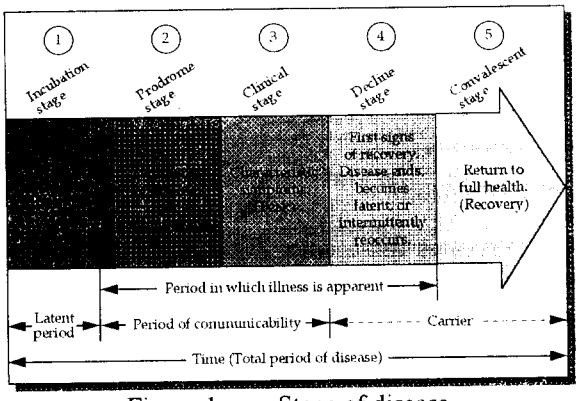

Figure 1 Stage of disease

You can say that a disease is determined by symptoms. Therefore, a symptom in a map can be untreatable (uncontrollable). Every node has a numeric value which explains the seriousness which is determined by laboratory tests.

The map is a directed graph $G = (X, M, I, T)$ consisting of a finite set X of N nodes (diseases and symptoms), $X = \{i\}_{i=1}^{N}$, a set M of manifestation values m_i, $M = \{m_i\}_{i=1}^{N}$, a set I of arcs (influences) i_{ij}, $I = \{i_{ij}\}_{i,j=1}^{N}$, and a set T of therapy efficacy arcs t_{ij}, $T = \{t_{ij}\}_{i,j=1}^{N}$, where $i, j \in X$ and $I \subseteq X \times X$.

Each m_i has the lower bound and upper bound, normal range of the parameter value of disease i, then the disease is classified into an abnormal state ,where $m_i \notin [m_i^L, m_i^U]$.

Each arc i_{ij} of the map has two kinds of relative causalities: the *strength* $s_{ij} \in [s_L, s_U]$ and the *duration* $d_{ij} \in [d_L, d_U]$, where s_L and s_U are the lower bound and upper bound of the strength for making the problem more realistic. The duration holds the same idea with the strength. An arc i_{ii} is the recursive arc which means the increasing (or decreasing) percents of the parameter value of node i when the patient has only disease i.

Each arc t_{ij} of the map also has two kinds of relative treatment characteristics: the *therapy strength* (efficacy) ts_{ij} and the *therapy duration* td_{ij}, where $i = j$, so the matrix T is a diagonal matrix with t_{ii} on the diagonal. An arc t_{ii} is the recursive arc which means the increasing (or decreasing) percentages of the parameter value of node i after therapy is done.

As described above, we deal with time lags on not continuos but discrete space. The d_{ij} is a value in a finite set Ω of M-many values. $\Omega = \{d_{ij}\}_{i=1}^{M}$. For example, if the duration (time lag) involved before an influence from node i has an effect on node j, $d(i \rightarrow j) = 5$ days, then we can assign $d_{ij} = 5$. After the first time lag the influence from node i to node j is assigned as $s_{ij}' = s_{ij}/d_{ij}$ by influence strength translation. Thus, it has a different duration on each arc i_{ij}. An arc from node i to node j has two values that physicians know or can estimate. One is the strength and the other is the duration. If disease i affects disease j directly, we put an arc from node i to node j (i.e. $i \rightarrow j$). If disease i in abnormal state causes an increase of the parameter value of disease j, then the arc has a plus (positive) sign (i.e. if abnormal $i \rightarrow m_j \uparrow$, then $i \rightarrow s\,j$, where $s > 0$ is the strength or intensity of the causal relationship). If disease i in abnormal state causes a decrease in the parameter value of disease j, then the arc has a minus (negative) sign (i.e. if abnormal $i \rightarrow m_j \downarrow$, then $i \rightarrow s\,j$, where $s < 0$).

An arc is classified to two kind of influences. One is the influence arc from disease i to disease j (i_{ij}), and the other is the therapy efficacy (t_{ii}). When the therapy on specific disease i is performed, the recursive arc i_{ii} will be cut and the therapy efficacy arc t_{ii} is added into the map as the recursive arc of disease i.

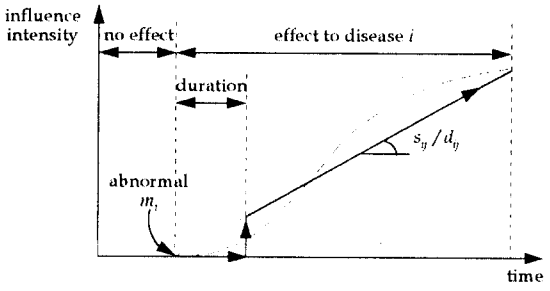

Figure 2 Approximation of influences' change curve from i to j

3.2. Assumptions

As described above, actual clinical manifestations, influences from a disease to another disease (s), and responses to certain treatments are understood to be *S-shaped* curve. This makes the biomedical problem more complicated when applying mathematical modeling because the estimation of progress is very difficult to calculate. The approximation in the change of influence intensity from disease i to disease j according to time horizon is proposed to make the problem easier to deal with.

With only two information (s_{ij} and d_{ij}) about the influences, the explanation for the change in influences can be reasonably forecast by this approximation work (see Figure 2).

When m_i falls into the abnormal range, the effect from disease i to disease j starts. The human body has compensatory mechanisms against agents, so the influence intensity in the incipient stage is not significant.

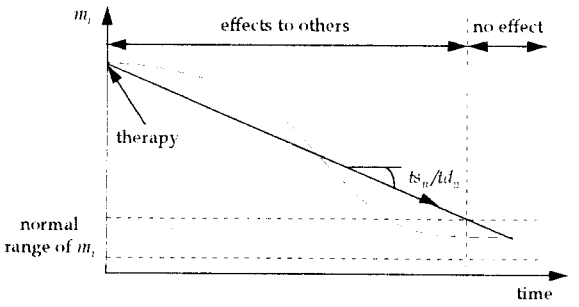

Figure 3 Approximation of therapy efficacy's change curve

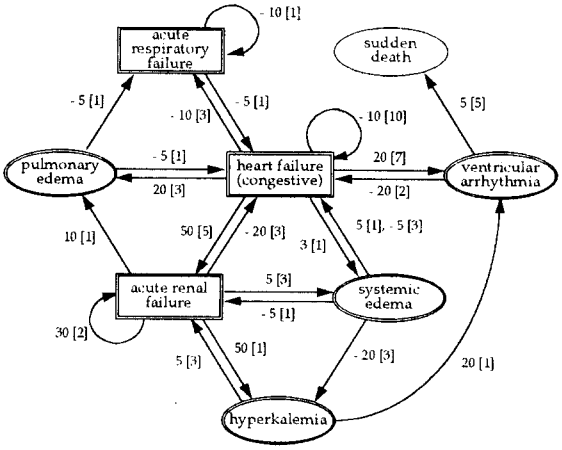

Figure 4 A map of the example (Congestive heart failure)

The approximation about the therapy efficacy change is shown in Figure 3. The therapy efficacy hold the same idea with the effects, but it has influence to m_i without delay. The recursive arc is also approximated like as the efficacy. So the recursive arcs and therapy efficacy arcs are linear influence.

When a patient with one (or more) disease (s) consults with a physician, the physician performs laboratory tests to determine if the disease (s) is in the abnormal state (s) or not and to determine the seriousness about that disease (s). If the parameters

of some diseases are ascertained to be in abnormal range by laboratory tests on suspicious diseases, the diseases float above the therapy surface with the arcs that represent the influences from diseases in the abnormal state to other diseases. A disease under the therapy surface is one in which the parameter value falls into the normal range in initial time or after therapy.

IV. Example - A Set of Congestive Heart Failure and the Others

Congestive heart failure is considered to be the condition in which an abnormality of cardiac function is responsible for the inability of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues (see Figure 4). Heart failure induces the elevation of venous pressure and volume retention, as a result, systemic edema is developed. It also elevates intrapulmonary pressure and results in fluid retention in the lungs which cause the pulmonary edema and acute respiratory failure in severe cases. A series of adaptive mechanisms aid heart faced with increased hemodynamic burden. These mechanisms include: (1) the Frank-Starling law operating through increased in loading to heart; (2) the development of myocardial hypertrophy; (3) redistribution of a subnormal cardiac output; and (4) neurohumoral adjustment which maintains cardiac output. These compensatory mechanisms also have harmful effect to the failing heart, for example, neurohumoral mechanism results in fluid retention and systemic edema, and because of Frank-Starling law the heart become more dilated which precipitates fatal ventricular arrhythmia and aggravates heart failure. During heart failure, systemic and renal blood flows are compromised, so acute renal failure (prerenal azotemia) is usually present. With renal failure hyperkalemia is induced which is one of the important causes of sudden-death-inducing ventricular arrhythmia. If systemic edema is tended to treat, we must consider beneficial and harmful effect of volume retention. The parameters and therapy efficacy are shown in Table 1 and Table 2.

Diseases (or symptoms)	Parameters	Normal	Crucial
Acute respiratory failure	PaO_2	> 95 mmHg	< 60 mmHg
Pulmonary edema	Severity	-, ±, +, ++, +++	+++
Heart failure	Ejection fraction	55~65%	< 25%
Ventricular arrhythmia	Grade	0, I, II, III, IV	IV
Acute renal failure	Creatinine (in serum)	< 1.5 mg/dl	> 8.0 mg/dl
Hyperkalemia	K^+ concentration (in serum)	3.5~5.5 mEq/dl	> 7.0 mEq/dl
Systemic edema	Δ Body weight	change %	individual

Table 1 Parameters of the example

V. Experiment

A 20-year-old male patient entered *S*eoul *N*ational *U*niversity *H*ospital (SNUH), complaining of dyspnea when he exercised. He was treated in the ICU, because his manifestations were so serious. The laboratory tests on respiratory failure and heart failure proved that the two diseases were abnormal. The tests on a set of abnormal diseases, renal failure, and hyperkalemia were performed on day 1.

Disease (symptom)	Therapy	Efficacy
Acute respiratory failure	Oxygen therapy &/or mechanical ventilation	20 [1]
Pulmonary edema	Diuretics	-25 [2]
Heart failure	Inotropic agent (cardiac glycoside)	20 [2]
Ventricular arrhythmia	Anti-arrhythmic agent	- 25 [3]
Acute renal failure	Hemodialysis	- 30 [2]
Hyperkalemia	Glucose & insulin, hydration	-10 [1]
Systemic edema	Diuretics	-20 [1]

Table 2 Therapy efficacies of the example

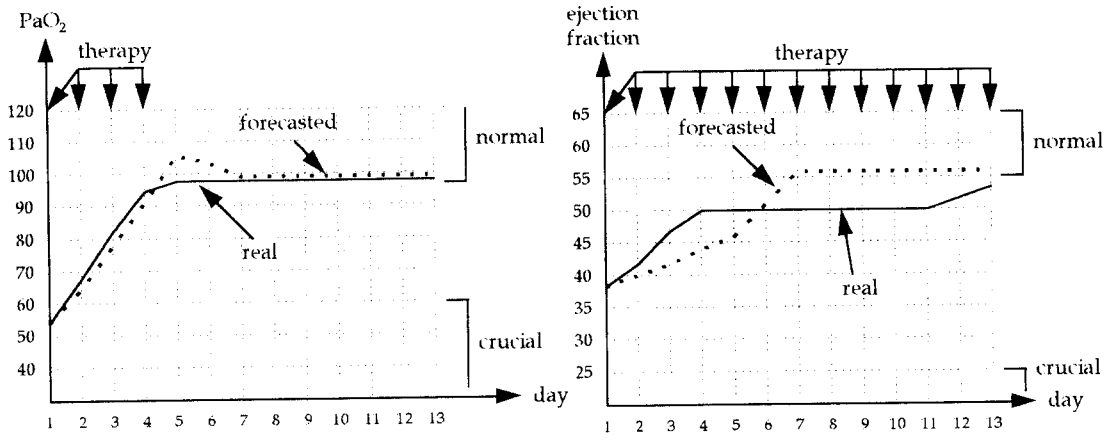

Figure 5 Progress of respiratory failure and heart failure

day 4, day 11, and day 13 after entering the hospital. The real manifestation vectors and estimated manifestation vectors on the time horizon (from day 1 to day 13) are shown in Table 3 and the graphs of the progress of the disease are shown in Figure 5 and 6. Details in procedures and illustrative explanations have been omitted. The treatments for respiratory failure and heart failure began on day 1 as did the mechanical ventilation for respiratory failure and the inotropic agent dosage for heart failure. But therapy for respiratory failure stopped on the day 5 because PaO_2 climbed into the normal range.

The mean values of forecasting error are 3.01 (mmHg) in repertory failure, 4.52 (%) in heart failure and 0.6 (mEq/dl) in hyperkalemia. According to the estimated progress of the patient the recovery time for heart failure was calculated on day 7, while it is after day 13 in real history. About progress of renal failure, this algorithm estimated that the indirect influences from respiratory failure and heart failure were not arrived at renal failure yet, but these influences slightly increased (0.2 mg/dl) creatinine concentration in serum in real history.

While the real data about hyperkalemia increased, the estimated value of K^+ concentration in serum did not work. One reason for this could be the late admission to hospital and/or the effects from respiratory failure and heart failure have enough time to cause hyperkalemia. Consequently the estimated progress of multiple disorders presented similar behavior with real history, and the model could reflect the trend in multiple disorders.

VI. Conclusions

The major contributions of this research can be summarized as follows:

1. This paper proposed a model which is appropriate to represent biomedical knowledge about time-dependent influences, progress of diseases ,and treatment efficacy. The physicians can learn more detailed and exact knowledge with a map which is made by

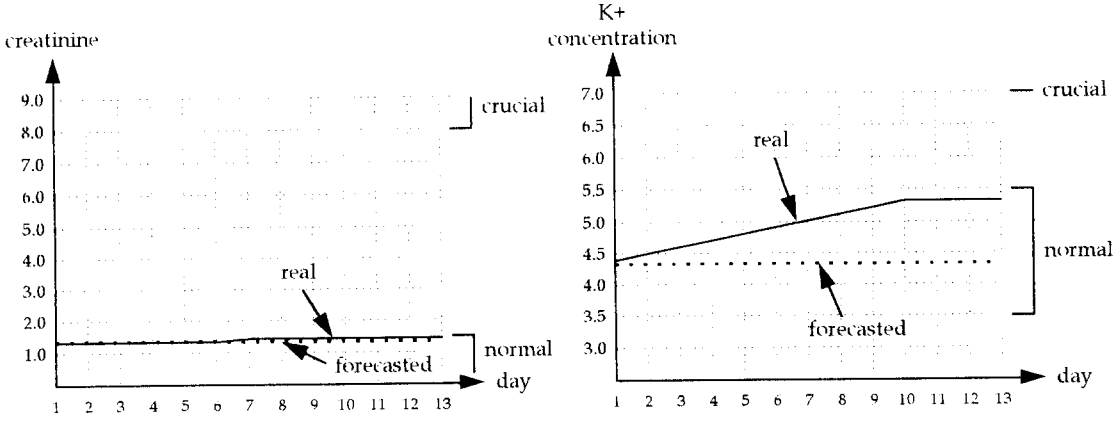

Figure 6 Progress of renal failure and hyperkalemia

more distinguished physicians;

2. This research developed an algorithm to enhance the physicians' ability to assess reasonable forecasting about progress of multiple disorders.

Parameter estimation either to optimize the model behavior by optimizing the parameter sets can be used, or to estimate even those parameters which are not directly measurable that are important for updating in health care units. For example, you can more accurately forecast the progress of diseases in the example by changing the efficacy duration of inotropic agent from 2-day duration to 3-day duration (mean of error with T': 2.94mmHg in PaO_2 and 4.46% in EF).

$$T = [20[1] \quad -25[2] \quad 20[2] \quad -25[3] \quad -30[2] \quad -10[1] \quad -20[1] \quad 0]$$
$$T' = [20[1] \quad -25[2] \quad 20[3'] \quad -25[3] \quad -30[2] \quad -10[1] \quad -20[1] \quad 0]$$

The influence matrix I can become a singular form by adding or deleting some nodes, and then this nonhomogeneous system can be solved with many real data by simple Gaussian elimination. Knowledge about multiple disorders can be achieved by connecting different maps which have the same node, so the model has the ability to grow because it can connect two or more different maps. This connecting work is vital. This model can be further developed and improved with new medical knowledge and techniques.

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