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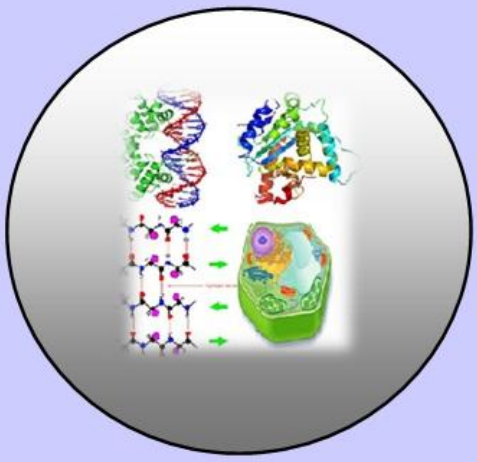
ISSN 2319-3077 Online/Electronic
ISSN 0970-4973 Print

Journal Impact Factor: 4.275
Global Impact factor of Journal: 0.876
Scientific Journals Impact Factor: 3.285
InfoBase Impact Factor: 3.66
Index Copernicus International Value
IC Value of Journal 47.86 Poland, Europe

J. Biol. Chem. Research
Volume 33 (2) 2016 Pages No. 964-971



Journal of Biological and Chemical Research

An International Peer Reviewed / Referred Journal of Life Sciences and Chemistry

Indexed, Abstracted and Cited in various International and National Scientific Databases

Published by Society for Advancement of Sciences®

J. Biol. Chem. Research. Vol. 33, No. 2: 964-971, 2016
(An International Peer Reviewed / Refereed Journal of Life Sciences and Chemistry)
Ms 33/2/185/2016

ISSN 0970-4973 (Print)
ISSN 2319-3077 (Online/Electronic)

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REVIEW ARTICLE

Received: 28/11/2016 **Revised: 29/12/2016** **Accepted: 30/12/2016**

A Dynamic Model of Patient's Conditions Influenced by the Applied Treatment Alternatives

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ABSTRACT

Choosing a suitable drug or combination of drugs is always a difficult task for medical practitioners. In many cases it is challenging and controversial process. **There involve many factors in choosing a proper treatment. We *developed a general user interfaced algorithm in the form of time dependent dynamic model which includes various qualities/properties of drugs/treatment. The model comprises drug applicability with intensity of disease after integrating the patient data (medical history, family history, signs, and symptoms).***
Keywords: Dynamic Model, Drugs, Algorithm, Disease and Patient Data.

INTRODUCTION

There involve many factors in choosing a proper treatment. Once someone have selected the appropriate medicine, the choice of the appropriate doses and the administration in the proper interval is important for the most successful use of the drug.

After studying various research papers on drug qualities and discussions with medical practitioners, there comes to be various qualities and properties of medicinal drugs which a medical practitioner have in his mind when he prescribes the particular drug or combination of drugs.

On the basis of available literature, we can compile various drug qualities. Many of them can be measured quantitatively, but the actual nature of each drug quality is subjective and a fuzzy scale is much better for their measurement. When evaluating new treatments in clinical researches, it is useful to consider the effects of such qualities jointly. The remarkable qualities of medicinal drugs can be measured on a fuzzy scale with range 0 to 1, where 0 represents the worst and 1 represents the best.

THE DYNAMIC MODEL

The Drug Effect Vector

Let for a particular disease, the available treatment alternatives are

M_α ($\alpha = 1, 2, ..., m$) ……(1)

Where *m* (The number of available treatment alternatives) is depend on the particular disease. It should be noted that M_α is either a drug molecule (Rx) or a combination of drug molecules or a procedure to treat.

Now, $M_\alpha = M_\alpha \left(X_1, X_2, ... \right)$ ……(2)

That is, all M_α's are the functions of drug effect variables X_1, X_2,…

Where X_1 is the variable associated with drug efficacy, X_2 is the variable associated with safety profile, and so on.

Therefore X_j (j = 1,2,…) represents the j^{th} quality of the drug.

Each drug property X_j (j=1,2,…) is a fuzzy variable having values in the range $\left[X_j^l, X_j^u \right]$ with some associated membership function x_j of the form

$$\left[X_j^l, X_j^u \right] \xrightarrow{x_j} [0,1] \quad \text{……(3)}$$

If the variable X_j has the lowest value X_j^l in the range, it means that its membership function x_j has the value 0 (zero). On the other hand if the variable X_j has the highest value X_j^u in the range, it means that its membership function x_j has the value 1 (one). For all the other values of X_j the membership function x_j has a value between 0 and 1. The basic assumption for all the drug qualities is that it can be scaled into worst to best range. That is X_j has value X_j^l as 'worst' and value X_j^u as 'best' with corresponding value x_j between 0 and 1.

For example consider the variable X_1, the efficacy of the drug. It has the values in the range $\left[X_1^l, X_1^u \right]$ with associated (real valued) membership function x_1, where X_j^l means nil efficacy with $x_1 = 0$ and X_j^u means perfect efficacy with $x_1 = 1$.

All the above drug properties can be represented by a fuzzy vector

$$M_\alpha = \left[X_1 \;\; X_2 \;\; ... \;\; X_{14} \right]^{\mathrm{T}}$$

We called the vector $M_\alpha = \left[X_1 \;\; X_2 \;\; ... \;\; X_{14} \right]^{\mathrm{T}}$ the Effect Vector.

Further treatments effects are related with disease/patient properties say duration, intensity or complications. The disease properties are again fuzzy variables, and can have the values for example as High, Low, Normal, Very Low, Very High and so on.

Disease/Patient Properties versus Treatment Effects

On the basis of literature, disease/patient properties for a particular disease α may be categorized into two parts.

a.) Disease/patient properties those are treatment independent, say patient age/gender, duration of disease, complications present, previous histories, family history etc. Let we denote it by $I_1, I_2, ..., I_p$.'s , the *p* fuzzy variables and can be modified using expert (doctor's) interventions, in the sense that experts can decide which variable are included for α.

An example is the study by Yuequan et.al [1] on prognostic factors and family history for survival of esophageal squamous cell carcinoma patients after surgery suggested that Family history of esophageal cancer is an important prognostic factor that surgeons should take into consideration when selecting a treatment method.

Another example is the study of Ralevski et.al. [2] on analgesic effects of ethanol. In this study they concluded that neuroticism and family history of alcoholism both influence the analgesic response of alcohol.

After finalizing $I_k^{'s};\ k = 1, 2, ..., p$'s for a particular disease, the real condition of the disease in a particular patient is represented by the vector

$I = [I_1, I_2, ..., I_p]^T$ ……(4)

With corresponding membership vector

$i = [i_1, i_2, ..., i_p]^T$ ……(5)

$i_k \in [0,1];\ k = 1, 2, ..., p$

Where we can say

$i_k \to 1,$ for a better condition

and

$i_k \to 0,$ for a worst condition

It should be noted that if i_k is some patient characteristics say age or gender then we called it 'worst' if it is a high risk group (having higher probability) for the disease say older age or 'male' (say for hemophilia).

These properties are essential to make initial steps to take decision about treatment. So we called *I* as Information Vector. For the information vector, there exists a one way relation between *I* and the treatment properties.

i.e. $I_k \to X_i$, for some *i*; *i* =1,2,…,14; *k* =1,2,...,*p*

Since both sides of the relations are the fuzzy variables, therefore these relations can be evaluated using fuzzy rules. One good technique is to show the relation between I_p and X_i by a matrix of the form

$$\begin{array}{c} \\ i_1 \\ i_2 \\ . \\ i_p \end{array} \begin{array}{c} \begin{array}{cccc} x_1 & x_2 & ... & x_{14} \end{array} \\ \begin{bmatrix} \alpha_{11} & \alpha_{12} & ... & \alpha_{1,14} \\ \alpha_{21} & \alpha_{22} & ... & \alpha_{2,14} \\ . & . & ... & . \\ \alpha_{p1} & \alpha_{p1} & ... & \alpha_{p,14} \end{bmatrix} \end{array}$$

We called it the Information Matrix $A_{p\times 14}$. The basic assumption here making for the information matrix is that the relationship between the information variable and the drug quality variable is a constant positive value for each combination of information-drug quality variables.

The fuzzy values of drug qualities will be changed on disease conditions or states of the disease. Assuming that old drug qualities and disease influenced drug quality changes are additive in nature, a new membership function for drug qualities is evaluated by the formula

$$\begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{\text{improved by } I} = \begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{\text{General}} + \begin{bmatrix} \alpha_{11} & \alpha_{12} & \ldots & \alpha_{1,14} \\ \alpha_{21} & \alpha_{22} & \ldots & \alpha_{2,14} \\ . & . & \ldots & . \\ \alpha_{p1} & \alpha_{p2} & \ldots & \alpha_{p,14} \end{bmatrix}^T \begin{bmatrix} i_1 - 0.5 \\ i_2 - 0.5 \\ . \\ i_p - 0.5 \end{bmatrix} \quad \ldots\ldots(6)$$

or in usual notations

$$X_{\text{improved by } I} = X_{\text{General}} + A^{\mathrm{T}} I - A^{\mathrm{T}} I_{0.5} \quad \ldots\ldots(7)$$

Where $I_{0.5}{}^{\mathrm{T}} = \begin{bmatrix} 0.5 & 0.5 & \ldots & 0.5 \end{bmatrix}$

subject to :

$x_j > 1 \Rightarrow x_j = 1$

and

$x_j < 0 \Rightarrow x_j = 0 \;;\; j = 1,2,\ldots,14$

It should be noted that

X_{General} are the observed qualities of the drug at $I = I_{0.5}$

b.) Disease properties those are treatment dependent, say intensity of disease, health recovery or complications initiated during treatment. We called these properties 'conditions'. Let we denote the 'conditions' by $D_1, D_2, \ldots, D_q$.

For example in a study by Budzynski et.al. [3] in patients with coronary artery disease, it is shown that double dose of omeprazole significantly decreased symptoms severity in 35% of patients with coronary artery disease, as well as frequency of some electrocardiographic signs of myocardial ischaemia during stress test.

After finalizing $D_k{}^{'s};\ k = 1,2,\ldots,q$'s for a particular disease, the real condition of the disease in a particular patient is represented by the fuzzy vector called 'condition vector'

$D = [D_1, D_2, \ldots, D_q]^{\mathrm{T}}$ ……(8)

With corresponding membership vector

$d = [d_1, d_2, \ldots, d_p]^{\mathrm{T}}$ ……(9)

$d_k \in [0,1];\ k = 1,2,\ldots,q$

Without loss of generality, we can write

$d_k \to 1,$ if condition improves

and

$d_k \to 0,$ if condition worsen

For these properties there exists a two way relation between disease property and the treatment property

i.e. $D_k \square X_i$, for some *i*; *i* =1,2,…,14; *k* =1,2,...,*q*

Since both sides of the relations are the fuzzy variables, therefore these relations can be evaluated using fuzzy rules.

D_k'*s* are the fuzzy variables and modifiable using expert (doctor's) interventions, in the sense that experts can decide which variable are included for α and what are the values (in the fuzzy sense) of those variables in a particular condition.

The mathematical representation of $D_k \square X_i$ is more difficult than the representation of $I_k \to X_i$, because every side is influenced by the other side simultaneously. A time dependent dynamic model is useful for representing such relation. Let *T* be the time set with starting time 0 and then 1, 2, 3...,*t*,*t*+1,... and so on. Let the fuzzy interactions between disease properties (conditions) and drug/treatment qualities are represented by the matrix

$$\begin{array}{c} \\ d_1 \\ d_2 \\ . \\ d_q \end{array} \begin{array}{c} \begin{array}{cccc} x_1 & x_2 & ... & x_{14} \end{array} \\ \begin{bmatrix} \beta_{11} & \beta_{12} & ... & \beta_{1,14} \\ \beta_{21} & \beta_{22} & ... & \beta_{2,14} \\ . & . & ... & . \\ \beta_{q1} & \beta_{q1} & ... & \beta_{q,14} \end{bmatrix} \end{array}$$

We called it the Condition Matrix $B_{q\times 14}$. The basic assumption here making for the condition matrix is that the relationship between the condition variable and the drug quality variable is a constant value for each combination of condition-drug quality variables. However in general case it may be variable.

The Iterative Dynamic Model

Now an iterative dynamic model for representing the above relation is given by

$$\begin{bmatrix} d_1 \\ d_2 \\ . \\ d_q \end{bmatrix}_{T=t} = \begin{bmatrix} d_1 \\ d_2 \\ . \\ d_q \end{bmatrix}_{T=t-1} + \begin{bmatrix} \beta_{11} & \beta_{12} & ... & \beta_{1,14} \\ \beta_{21} & \beta_{22} & ... & \beta_{2,14} \\ . & . & ... & . \\ \beta_{q1} & \beta_{q2} & ... & \beta_{q,14} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{T=t-1} + \begin{bmatrix} d_1^{(n)} \\ d_2^{(n)} \\ . \\ d_q^{(n)} \end{bmatrix}_{T=t} \quad \text{……(10)}$$

or in usual notations

$$D_{(t)} = D_{(t-1)} + BX_{(t-1)} + D_t^{(n)} \quad \text{……(11)}$$

subject to :

$$d_i > 1 \Rightarrow d_i = 1$$

and

$$d_i < 0 \Rightarrow d_i = 0 \;\; ; i = 1,2,...,q$$

and $D_t^{(n)} = \left[d_1^{(n)}, d_2^{(n)}, ... \right]_t^T$ is representing the variations due to natural forces in the conditions of disease/patient without any drug intervention. Natural forces can either of the positive nature that improves patient condition or of the negative nature that worsen the patient condition.

For example body's immunity, capacity of self healing etc are the positive natural forces, as we know a great degree the body has the capacity to heal itself. On the other side multiplication of harmful microorganisms or growth of harmful tissues are the negative natural forces. Diseases arise and develop from either genetic abnormalities, detrimental environmental factors (poor diet, infectious organisms, or toxins), or a combination of these so all these are considered to be the negative forces.

And also $d_k^{(n)} \in [-1,1]$

$d_k^{(n)} \to 1,$ if condition improves naturally

and

$d_k^{(n)} \to -1,$ if condition worsen naturally

and obviously

$d_k^{(n)} \to 0,$ if condition is stable naturally

{What we observe is not nature itself, but nature exposed to our method of questioning. Natural science, does not simply describe and explain nature; it is part of the interplay between nature and ourselves.

—Werner Heisenberg, Physics and Philosophy, 1958}

and at *T*=*t*, the required drug qualities at the current situation are given by

$$\begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{T=t} = \begin{bmatrix} \gamma_{11} & \gamma_{12} & \cdots & \gamma_{1q} \\ \gamma_{21} & \gamma_{22} & \cdots & \gamma_{2q} \\ . & . & \cdots & . \\ \gamma_{14,1} & \gamma_{14,2} & \cdots & \gamma_{14,q} \end{bmatrix} \begin{bmatrix} d_1 \\ d_2 \\ . \\ d_q \end{bmatrix}_{T=t} \quad \text{……(12)}$$

or in usual notations

$$X_{(t)} = GD_{(t)} \quad \text{……(13)}$$

We called $G_{14\times q}$ the Improvement Matrix, because it shows the improvement or modifications in the qualities of drug treatment based on the present conditions.

And we can easily say that

$$\begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{T=0} = \begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{\text{Improved by } I} \quad \text{……(14)}$$

These are the initial conditions or point of beginning for the dynamic model.

The performance score of the treatment at time *T* = *t* is given by

$$\begin{bmatrix} d_1^{(t)} \\ d_2^{(t)} \\ . \\ d_q^{(t)} \end{bmatrix} = \begin{bmatrix} d_1 \\ d_2 \\ . \\ d_q \end{bmatrix}_{T=t} - \begin{bmatrix} d_1 \\ d_2 \\ . \\ d_q \end{bmatrix}_{T=t-1} \quad \text{with } d_i^{(t)} < 0 \Rightarrow d_i^{(t)} = 0 \ \ \forall i = 1,2,...,q \quad \text{……(15)}$$

And the Performance Index of the treatment at time *t* is the joint effect of performance scores of all the condition components. We make performance index function $P(t)$, using some suitable fuzzy aggregation operation among $d_1^{(t)}, \ d_2^{(t)}, \ \ldots \ , d_q^{(t)}$ in such a manner that it must be satisfy the following axioms,

Axiom P1. $P\left(d_1^{(t)}, \ d_2^{(t)}, \ \ldots \ , d_q^{(t)}\right) = 0$ if at least one $d_i^{(t)} = 0$

Axiom P2. As any $d_i^{(t)}$ goes to 0, $P(t)$ goes to zero rapidly.

$\left[d_1^{(t)} \quad d_2^{(t)} \quad \ldots \quad d_q^{(t)}\right]^T$ is actually the membership vector of the fuzzy vector $\left[D_1^{(t)} \quad D_2^{(t)} \quad \ldots \quad D_q^{(t)}\right]^T$ called performance of the treatment at time *T* = *t*.

So we can define performance index as the geometric mean of the squares of all the condition changes at *T* = *t*.

i.e. $P(t) = \left(d_1^{(t)} \cdot d_2^{(t)} \cdot \ldots \cdot d_q^{(t)}\right)^{\frac{1}{q}}$ ……(16)

An upward trend in the performance index means condition improves and vice versa.

Another term associated with the performance $D_i^{(t)}; i = 1, 2, \ldots, q$, the performance of the treatment on *i*th condition is Ω_i called the importance of the *i*th condition. Ω_i is also a fuzzy variable with membership function ω_i whose value lies in [0,1]. ω_i has value 1 for the 'most important condition' and value 0 for unimportant condition.

Now let we combine $D_i^{(t)}$ and Ω_i to get new fuzzy variable $Y_i^{(t)}$ (the best values of important conditions at time *T*=*t*) with membership function $y_i^{(t)}$.

A good method for making membership function of $Y_i^{(t)}$ is using the Schweizer and Sklar class of *t*-norms [4], given by

$$y_i^{(t)} = \frac{\omega_i \cdot d_i^{(t)}}{\left[\omega_i^{\,p} + d_i^{(t)p} - \omega_i^{\,p} \cdot d_i^{(t)p}\right]^{\frac{1}{p}}} \qquad \ldots\ldots(17)$$

Where $p > 0$ is the parameter of Schweizer and Sklar class, whose value is chosen for the best performance of the model in real life situations. We call it the 'adjustment parameter'.

and finally, the utility of each treatment M_α at *T*=*t* is given by

$$U_t\left(M_\alpha\right) = \frac{\sum_{i=1}^{q} y_i^{(t)}}{\sum_{i=1}^{q} \omega_i} \qquad \ldots\ldots(18)$$

The term 'utility' for the treatments was used by Thiyagrajan and Selvam [5], though the formula was different.

So at time *T* = *t*, the best chosen treatment is the treatment which has the maximum utility.

CONCLUSIONS

Some general conclusions based on the given model are:

1. Utility of a drug decreases as patient's condition improves. In real life it is true that drug is required only if patient is unable to recover without drug intervention.
2. As patient's condition improves, effect of drug intervention reduces and effect of positive natural forces increases.
3. Drug effects are bidirectional, means its qualities may be reduced after a particular stage of condition improvement. Therefore stopping of treatment at that stage is necessary otherwise negative drug effect will deteriorate patient's condition.

The model can also find whether the improvement in patient's condition is natural or the drug effect involve in improvement of patient condition. The proposed dynamic model has great potential in different disciplines of medicine and health. This model suggests how the effectiveness of treatments can be maximized.

ACKNOWLEDGEMENTS

Author (Z.H. Zaidi) is grateful to Director Era's Medical College, Lucknow, U.P., India for providing all facilities during course of present investigation.

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