Journal of Traditional Chinese Medical Sciences (2016) 3, 37—40

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In silico method for studying property combination of traditional Chinese herbs

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Received 25 February 2016; accepted 1 July 2016
Available online 7 July 2016

KEYWORDS
Traditional Chinese medicine;
Herbal property combination;
Prescription compatibility;
Bipartite graph;
Greedy algorithm

Abstract *Objective:* This paper discusses the composition of prescription qualitative, quantitative design principles and methods based on herbal property combination, describing the method application in new prescription design.
Method: Qualitative property-combination pattern (PP) calculation was based on bipartite graphing and performing a greedy algorithm which was designed to optimize obtaining a new herbal prescription. Quantitative PP calculation was based on the qualitative computation. To calculate the Euclidean distance for the PP of the new prescription, an optimized algorithm for solving the unknown minimum Euclidean distance was used with, the new weighted proportions. Finally, non-linear optimization software was used to find the minimum Euclidean distance.
Results: Using the PP of classic prescription Large Yin-Nourishing Pill, applying quantitative PP calculation a new prescription was created. Mathematical algorithms based on property combinations of traditional Chinese herbs can be applied to identify compatibility and synergies of herbs within prescriptions, especially classic formulas.
Conclusion: In silico methods can then be used to create new prescriptions or modify existing ones depending on need. This type of automated approach may increase efficiency in designing new drugs based on Chinese herbs.

Introduction

In traditional Chinese medicine (TCM), the characteristics, or properties, of an herb determine its actions (mechanisms) and clinical application. The major categories of herbal properties are: four natures, five tastes, channels entered, direction of action, and toxicity. Modern research has allowed for scientific understanding of the properties of

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Peer review under responsibility of Beijing University of Chinese Medicine.

http://dx.doi.org/10.1016/j.jtcms.2016.07.004

herbs, and is elucidating the mechanisms of the properties and their clinical applications. For example, Liang et al used integrative bioinformatics analysis to determine the chemical components of hot and cold property herbs.[1]

While there is an abundance of TCM research on herbal properties, it has been difficult to translate the results into clinical applications and new drugs. Therefore, applying computational methods may be an efficient approach toward amalgamating the essence of the various herbal properties into utilitarian value. In our previous studies, we used in silico methods to explore herbal property combination as applied to medicinal-efficacy correlation,[2,3] compatibility principles for combining herbs,[4] and formulation principles of herbal prescriptions.[5] In this study, we continue our investigation by applying software-based technology to combine the core herbal properties of the four natures, five tastes, and channels entered to establish a medicinal-efficacy correlation.

Methods

Concepts of property combination and property-combination pattern

In this study, property combination (PC) is a concept that includes the nature, taste, and channel entered of an herb, which helps in the study of synergy among other herbs in a prescription.[6] Property-combination pattern (PP) refers to multiple property combinations of herbs with the same or similar efficacy recurring in a prescription.[5]

Qualitative and quantitative computation of property-combination pattern

Qualitative computation

In mathematics, a bipartite graph is a special graph that can display the relationship between two sets of objects when the characteristic between the sets of objects needs to be known. The uniqueness of a bipartite graph is that there is no connection among objects in the same set. A greedy algorithm is a mathematical problem-solving approach that finds the optimal solution for each step of a complex process, without reconsidering the choices.

Thus, in this study, qualitative PP calculation was based on bipartite graphing[7] and performing a greedy algorithm,[8] which was designed to optimize obtaining a new herbal prescription. The PP of a classic TCM prescription served as a template, and application of bipartite graphing and greedy algorithm construction were then used to generate the new PP.

A bipartite graph was created by assigning herbs and PCs to respective sets A and B to reveal the relationship between each herb and its PCs. For example, Fig. 1 shows a set of Chinese herbs (A) and a set of PCs (B) that represent a binary coverage. This process aims to find the fewest herbs in set A that can cover the PCs in set B.

The greedy algorithm would then be applied with each step seeking the optimal solution. Again, using Fig. 1 as the example, herb 3 would be selected because it is associated with the three PCs cold-bitter-stomach, cold-bitter-bladder, and cold-bitter-liver. However, herb 3 is not associated with the PCs of warm-sour-spleen and warm-sour-stomach, whereas herb 1 is. Herb 2 is associated with two of the same PCs that are associated with herb 3, that is, cold-bitter-bladder and cold-bitter-stomach. For this reason, herb 2 is eliminated from consideration. Thus, herb 1 is chosen as the target herb and based on the greedy algorithm, herbs 1 and 3 are associated with all PCs without any overlap of coverage (Fig. 1).

Quantitative computation

Quantitative PP calculation was based on the qualitative computation. To calculate the Euclidean distance for the PP of the new prescription, an optimized algorithm for solving the unknown minimum Euclidean distance was used with the new weighted proportions. Finally, non-linear optimization software was used to find the minimum Euclidean distance.

The new prescription was calculated as follows:

A classic formula, F, contains n herbs, set of f_{ij} using PC "j" of herb "i" in prescription F, $i = 1, 2, 3\ldots n$; $j = 1, 2, 3\ldots m$ (m represents PCs in the classic recipe),

$$fij = \begin{cases} 1 & i \ \ contains \ \ j \\ 0 & i \ \ contains \ \ no \ j \end{cases}$$

$i = 1, 2, 3\ldots n$, $j = 1, 2, 3\ldots m$.

The prescription's jth PC can be expressed as

$$F_j = (x_1 \quad x_2 \quad \cdots \quad x_n)(f_{11} \quad f_{21} \quad \cdots \quad f_{n1})^T$$

where F_j is the jth combination of prescription PC, $j = 1, 2, 3\ldots m$; and x_i represents the weight percentage of the herb "i" in the prescription, $i = 1, 2, 3\ldots n$.

The PC of n herbs in the prescription constitutes an m-dimensional matrix, that is PC matrix Y,

$$Y = \begin{pmatrix} f_{11} & f_{12} & \cdots & f_{1m} \\ f_{21} & f_{22} & \cdots & f_{2m} \\ \cdots & \cdots & \cdots & \cdots \\ f_{n1} & f_{n2} & \cdots & f_{nm} \end{pmatrix}$$

$X = (x_1 \quad x_2 \quad \cdots \quad x_n)$ as the percentage of the amount of drug matrix.

The PP of the classic prescription can be expressed as F:

$$F = (F_1 \quad F_2 \quad \cdots \quad F_m) = (x_1 \quad x_2 \quad \cdots \quad x_n) \begin{pmatrix} f_{11} & f_{12} & \cdots & f_{1m} \\ f_{21} & f_{22} & \cdots & f_{2m} \\ \cdots & \cdots & \cdots & \cdots \\ f_{n1} & f_{n2} & \cdots & f_{nm} \end{pmatrix} = X \cdot Y$$

The PC m in the calculation method of the PP of the classic prescription was used according to the number of PCs in the classic formula PC.

New prescription design based on PP

Qualitative design

Herb-PC data was converted into binary variables, in which an herb that is of a given PC was assigned 1, and one that is not of a given PC was assigned 0 (Table 1). Using MATLAB programming (Math Works, Natick, MA, USA) and the greedy