Physica A 460 (2016) 152–161

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Complex network model of the *Treatise on Cold Damage Disorders*

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HIGHLIGHTS

- Symptoms, formulae, herbal drugs, and their relationships in the *Treatise on Cold Damage Disorders* are described and analyzed based on complex network.
- Topological attributes analysis suggested some prescription laws that could be validated in clinical trials.
- The transitions among diseases were explored by analyzing the strengths of the relationship between six channel subnets.

ARTICLE INFO

Article history:
Received 6 August 2015
Received in revised form 12 December 2015
Available online 8 April 2016

Keywords:
Channel
Complex network
Network topological analysis
Treatise on Cold Damage Disorders

ABSTRACT

Investigating the underlying principles of the *Treatise on Cold Damage Disorder* is meaningful and interesting. In this study, we investigated the symptoms, herbal formulae, herbal drugs, and their relationships in this treatise based on a multi-subnet composited complex network model (MCCN). Syndrome subnets were constructed for the symptoms and a formula subnet for herbal drugs. By subnet compounding using MCCN, a composited network was obtained that described the treatment relationships between syndromes and formulae. The results obtained by topological analysis suggested some prescription laws that could be validated in clinics. After subnet reduction using the MCCN, six channel (*Tai-yang*, *Yang-ming*, *Shao-yang*, *Tai-yin*, *Shao-yin*, and *Jue-yin*) subnets were obtained. By analyzing the strengths of the relationships among these six channel subnets, we found that the *Tai-yang* channel and *Yang-ming* channel were related most strongly with each other, and we found symptoms that implied pathogen movements and transformations among the six channels. This study could help therapists to obtain a deeper understanding of this ancient treatise.

1. Introduction

The *Treatise on Cold Damage Disorders* (*Shan-han Lun*) written by Zhang Zhong-jing is an ancient Chinese medical treatise, which describes the treatment of cold damage, its variants, and related complications [1–4]. This treatise suggests that diseases caused by cold or wind stroke invade the body through the pores in the skin. In recent decades, the effectiveness of many herbal formulae from *Shang-han Lun* has been validated in molecular biology studies and they have been used widely as complementary medical therapies. For example, the integrated use of formulae from the treatise with modern medicine has proved effective in treating severe acute respiratory syndrome [5]. A study of *Sinisan* from the treatise demonstrated

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http://dx.doi.org/10.1016/j.physa.2016.03.115
0378-4371/

its therapeutic effect on chronic restraint stress [6]. The benefit of a *Wumei* pill treatment for typhoid ascariasis was also confirmed [7]. Xiao-chai-hu-tang was studied [8,9] for the treatment of liver injury and chronic pancreatitis. Clinical practice data for *Shang-han Lun* formula prescriptions in Taiwan were also analyzed [10].

However, the underlying principles of this treatise are not understood clearly. Thus, quantitative analyses of the symptoms and their corresponding herbal prescriptions could help practitioners to find the treatment codes that are hidden inside this treatise. There are 381 sections in the treatise, where syndromes and prescriptions are described in most sections. For example, in section 13, a group of symptoms comprising headache, stiff neck, chills, fever, and floating pulse constitute one syndrome. A group of compatible herbs called the *Gui-zhi* formula, which contains *Ramulus Cinnamomi*, *peony root*, *prepared licorice root*, *fresh ginger*, and *Chinese dates*, are prescribed for this syndrome. It is obvious that there are two types of entities (symptoms and formulae) and three types of relationships (treatment relationships between syndromes and formulas, syndrome relationships between symptoms, and compatibility relationships between herbs) in this treatise. Analyzing these entities and their relationships may provide us with a new way of exploring this treatise.

Complex networks are a powerful tools for understanding the complex relationships among units, where they have been used to explore complex relationships in the diagnosis of syndromes and knowledge discovery for determining the compatibility of drugs [11–15]. In general, herbs or symptoms are regarded as nodes. Edges are defined as relationships between nodes, such as compatibility relationships between herbs, co-occurrence relationships between symptoms, or more complex relationships obtained by data mining methods [16]. Constructing homogeneous Traditional Chinese Medicine (TCM) networks containing one type of node is a popular approach. However, in [17], a heterogeneous TCM network was studied with multiple types of nodes, including herbs, biomolecules, and syndrome. Our study was inspired by [17], but our approach differs from their method because we used a multi-subnet composited complex network model (MCCN), which is a generalized complex network model for describing different types of entities and multiple types of relationships between the entities [18,19], to describe syndrome relationships between symptoms, compatibility relationships between herbs, and treatment relationships between syndromes and formulas. We investigated the topological characteristics of a composited network with multiple types of nodes and edges based on the degree of given relationships and the clustering coefficients of given relationships.

Another interesting subject is six-channel transmission. In this treatise, the progress of a disease is classified as *Tai-yang*, *Yang-ming*, *Shao-yang*, *Tai-yin*, *Shao-yin*, or *Jue-yin*, which represent six different developmental stages of a disease. The three *yang* channels are located in the exterior parts of the body, whereas the three *yin* channels are found in the interior parts. Cold or wind stroke invasion will damage the three *yang* channels first. If the disease progresses or it is mistreated, the disease's symptoms will develop throughout the interior *yin* channels. For example, a sick man may have syndromes in the *Tai-yang* channel, such as headache, stiff neck, chills, fever, and a floating pulse, so the *Guizhi* formula may be prescribed. However, if the man is mistreated and he has *Yang-ming* syndromes, such as constipation, perspiration with fear of heat but no fear of cold and huge pulse, then this means that the disease has progressed to the *Yang-ming* stage. The mechanism of six-channel transmission is rather complex, so we tried to identify symptoms that imply the movement of a pathogen among the six channels. By dynamic reorganization of the MCCN, we obtained six channel subnets (*Tai-Yang*, *Yang-Ming*, *Shao-Yang*, *Tai-Yin*, *Shao-Yin*, and *Jue-Yin*). After determining the strengths of the relationships between the subnets, we analyzed the relationships among the six channel subnets to find symptoms that implied the movement or transformation of pathogens.

The remainder of this paper is organized as follows. Section 2 introduces the MCCN model and the MCCN measures. Section 3 describes the data source used in this study and its preprocessing. In Section 4, we present the MCCN model of *Shang-han Lun* and the results of the analysis. We give our conclusions in Section 5.

2. MCCN

MCCN [18,19] is a generalized complex network model for describing a complex system that involves multiple types of entities and relationships. The classic complex network for describing one type of entity and their single type of relationship is a special case of the MCCN. The dynamic reorganization of an MCCN provides two ways of analyzing networks: compounding (combining subnets into a "bigger' one) and reducing (obtaining a "smaller' network from a "bigger" one).

In Fig. 1, there are six entities and each is regarded as a node, which can be homogeneous or heterogeneous. There are three types of relationships between nodes. Subnet G_1 has relationships between v_1, v_2, v_3, v_4, v_5, and v_6. The second relationships between nodes v_1, v_2, v_4, v_5, and v_6 are illustrated in subnet G_2. The third relationships among nodes v_1, v_2, v_4, and v_6 are shown in subnet G_3. Given a compounding mapping, a composited network G will be generated. The compounding mapping indicates how the nodes and edges in G are generated. In Fig. 1(d), the nodes of G are assigned as the union set of the nodes of G_i and G_j, and the edges in G are also the union set of the edges of G_i and G_j. The weight of an edge in G indicates the number of subnets to which the edge belongs. The weight of an edge indicates a compounding relationship between nodes. When the weight equals 1, this means that there is only one type of relationship between the nodes. Given a reducing mapping, such as an edge weight of 3, a reducing network G' will be obtained, as shown in Fig. 1(e). Each pair of nodes in G' has three types of relationships.

Next, we define the MCCN measures used for quantifying different types of relationships in the composited network. These measures were inspired by classical and frequently used measures, such as the degree and clustering coefficient. However, we aimed to describe different types of relationships among nodes, so we propose degree and clustering