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Original Article

Detecting community structure of common syndromes in heart system based on complex networks

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Abstract: Objective: To explore the community structure of common syndromes in heart system. Methods: Modified community detection algorithm was proposed and automated community structure analysis of medical data of heart syndromes from 1741 cases was performed. Results: Six communities corresponding to 4 basic syndromes consisting of heart fire hyperactivity syndrome, mind confusion by phlegm syndrome, heart yin asthenia syndrome and heart yang asthenia syndrome and 2 complex syndromes comprising heart qi-blood asthenia syndrome and heart-brain obstruction syndrome were divided by the community detection algorithm. Conclusion: Community detection algorithm realizes the extraction and identification of disease-location and disease-character characteristics of common syndromes in heart system, so as to provide evidence for analyzing basic syndromes in heart system and summarizing the relationship between disease locations and disease characters as well as the degree of correlation.

Keywords: Complex network, community detection, basic syndromes in heart system, standardization of disease and syndrome, symptom characteristics

Introduction

Syndrome differentiation and treatment is the special feature of traditional Chinese medicine (TCM) [1]. Syndrome differentiation is the premise for legislation, prescription and medication [2]. The accuracy of syndrome differentiation directly influences the clinical outcomes [3]. Numerous methods for syndrome differentiation have been proposed by doctors of all dynasties, such as syndrome differentiation of six meridians, syndrome differentiation of eight principals, syndrome differentiation of wei, qi, ying and blood, syndrome differentiation of three energizers, and syndrome differentiation of viscera, etc [4, 5]. These methods intertwine, overlap and supplement mutually, and jointly guide the TCM clinical practices [6]. How to find out the rationales and rules of syndrome differentiation from large amount of clinical data in order to provide reference and basis for the standardization of disease syndromes has been one of the key points in studies on TCM syndrome differentiation.

TCM electronic medical record (EMR) has been extensively applied in clinical practices, and clinical information has been transformed from paper manuscripts into structural data along with the development of hospital informatization [7]. Liu Bao-yan, believed that data-oriented paradigm was the only way for the development of TCM clinical scientific research [2]. Therefore, this paper tried to form data-supported standardization and definitions of various TCM syndromes by excavating the distribution of symptom characteristics of common syndromes in heart system from TCM clinical data using community detection algorithm, so as to provide reference for studies on visceral syndrome differentiation in this big data era.

Current status of community detection

Community detection is a method for detecting community structure in complex networks. Lots of community detection algorithms have been proposed specific to different types of large-size complex networks [8], modularity optimization-based algorithm [9], hierarchical clustering algorithm [10], and Girvan-Newman (GN) splitting algorithm [11], etc. Currently, complex networks have become a hot topic in scientific studies. Community detection algorithm has been used to analyze the regularity of Chinese medicine application for hepatitis cirrhosis by Li Xin et al. [12], and to analyze the distribution mode of four-examination information based on complex network technique in patients with coronary heart disease (CHD) by Shi Qi, et al. [13].

This study, based on the community detection algorithm principles combined with the characteristics of TCM data, proposed modified TCM Unfolding algorithm by modifying modularity algorithm on the basis of Fast Unfolding algorithm and studied the community detection of disease-location and disease-character characteristics of basic syndromes in heart system.

Materials and methods

Data source

The data form January of 2017 to June of 2018 were collected from EMR in Record Room of Jiangsu Province Hospital of TCM. The study has been approved by the ethics committee of the hospital. The subjects and their family members all signed the informed consent.

Inclusion criteria

There was no limitation in gender and age.

Diagnosis: TCM diagnosis included palpitation, chest Bi syndrome, heart Bi syndrome, heart edema, sleeplessness, manic-depressive psychosis, epilepsy, dementia, Jue syndrome, amnesia, sweating syndrome, and stranguria, etc. Western medicine diagnosis contained CHD, rheumatic heart disease, arrhythmia, chronic congestive heart failure, cardiogenic stroke, myocardiopathy, cardiac neurosis, etc. Meanwhile, numerous diseases from systems like nerve system, psychological system, endocrine system, urinary system and digestive system were also covered, such as cerebral infection lesion, cerebrovascular events, schizophrenia, insomnia, depression, and urinary tract infection, etc.

Others: The medical data were complete, including patients' basic information, disease names, symptom description, tongue pictures, pulse conditions, modern examination indicators, and clinical treatment and outcomes, etc.

Exclusion criteria

Syndromes with less description of clinical manifestations and lacking of clearly described syndromes were excluded from this study.

Data processing

Normalization of terms: Scientific Research Questionnaire on Disease Syndromes of Heart System [18] was established by our group who have managed and normalized the disease syndromes of heart system. The symptoms, signs as well as tongue and pulse conditions in medical documents were managed specifically, e.g., chest oppression was divided into chest distress, short breath and weak breath were divided into shortness of breath, mild springy pulse and slightly springy pulse were divided into springy pulse, etc. In addition, TCM experts were invited to conduct syndrome differentiation to the medical cases based on visceral syndrome differentiation, and syndrome differentiation results were recorded.

Data input: Each symptom was labelled by one binary bit. The corresponding binary bit was recorded as 1 if the symptom was found, otherwise as 0. All medical record data were input into Microsoft Excel, and were verified and reviewed for multiple times to ensure the data accuracy. It is measured by statistics including kappa, and the inter- or intra-class correlation coefficient.

Broadly speaking, is the degree to which a measure assesses what it is intended to measure, and types of validity include face validity (the degree to which users or experts perceive that a measure is assessing what it is intended to measure), content validity (the extent to which a measure accurately and comprehensively measures what it is intended to measure), and construct validity (the degree to which an instrument accurately measures a nonphysical attribute or construct such as depression or anxiety, which is itself a means of summarizing or explaining different aspects of the entity being measured). Variability usually refers to the distribution of values associated with an outcome measure in the population of interest, with a broader distribution or range of values said to show more variability.

Analysis and excavation: Data were analyzed using TCM Unfolding algorithm, the community detection of symptoms in different basic syn-

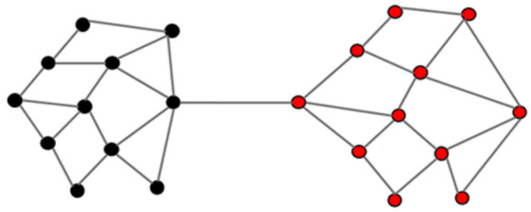

Figure 1. Schematic diagram of communities in networks.

dromes was viewed, and then corresponding network diagrams were drawn by the software gephi (2010, French, University of Technology of Compiègne).

TCM Unfolding, a community detection algorithm

Related definition

Networks: N (networks) is considered as a two-tuples consisting of both node set denoted by V=[1] and edge set denoted by E=[14] corresponding to the nodes in V. Set N=(V, E). The networks in which nodes v_i (a, b) and v_j (b, a) share the same edge are considered as undirected networks, otherwise as directed networks. Networks in which each edge is endowed with corresponding weight are considered as weighted networks, otherwise as unweighted networks. In this study, undirected weighted networks were selected as the study subjects.

Community: In complex networks, the nodes form the structure of the whole network through the connection of edges. Some of these nodes are densely connected while others are lesser connected. The nodes that are densely connected form a community. In **Figure 1**, the network is classified into two communities labeled by black and red respectively. Obviously, the internal connection is dense in both communities, but the connection between two communities is lesser. How to detect above communities is termed as community detection issue.

Modularity: The concept of modularity has been introduced by Newman et al. [15], and modularity is used to assess the advantages and disadvantages of community detection. Simply speaking, nodes that are densely connected are divided into one community, which will lead to increase of modularity value. Ultimately, the division of the maximal modularity is considered as the optimal community detection.

In 2006, Newman proposed following formula (1) specific to modularity denoted by Q in his paper [16]:

$$Q = \frac{1}{2m}\sum_{i,j}\left(A_{i,j} - \frac{k_i k_j}{2m}\right)\delta(C_i, C_j) \tag{1}$$

In the formula, the sum of all weights in the networks is denoted by $m = \frac{1}{2}\sum_{i,j} A_{i,j}$ in which $A_{i,j}$ represents the weight between nodes i and j. $k_i = \sum_j A_{i,j}$ is the weight of all edges connected with node i, and is the community where node i is detected. $\delta(c_i, c_j)$=1 in case nodes i and j are detected in one community, otherwise it is zero (0). Although Newman proposed that modularity had limit of resolution as a measurement for community detection in his paper, i.e., small communities could not be detected in large-size networks, it had no influence on this study where communities mainly focused on the distribution of syndromes after network division and no tiny-size communities were found.

Modified modularity: According to formula (1), modularity Q is actually the difference between the ratio of edges that connect the internal vertexes of community structure in given networks and the expected value of the ratio of edges that randomly connect the two nodes in the same community structure. In other words, as to two random nodes in the same community, it is reasonable to divide them into one community if their actual weights are higher than the expected weights in random networks emerging under random combination of all edges, which will make contribution to the modularity. Conversely, they will make consumption to the modularity if their actual weights are lower than the expected weights in random networks.

The modularity formula was modified as follow based on above logic and the sample data in this study:

$$Q = \frac{1}{2m}\sum_{i,j}\left(A_{i,j} - \frac{k_i k_j}{2m}\right)f(i,j)\delta(C_i, C_j) \tag{2}$$

$f(i,j)$ denote the frequencies of combinations of nodes I and j in sample data, which will advantageously increase the occurring frequencies of contribution and consumption in samples, so that the modularity will be more sensitive to the edges that have greater influ-

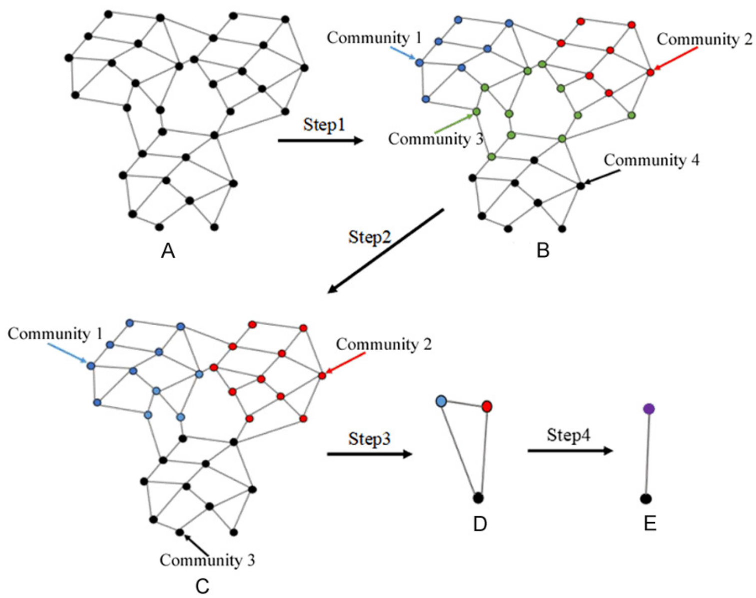

Figure 2. TCM Unfolding workflow.

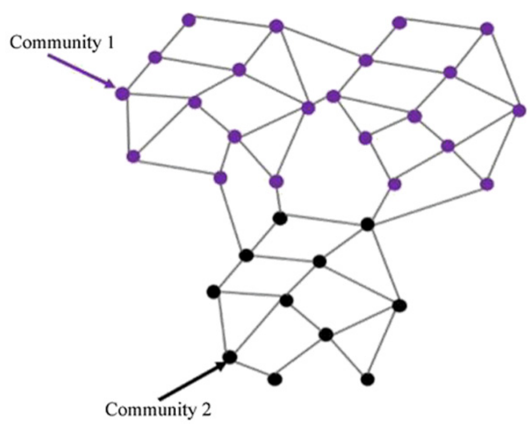

Figure 3. Schematic diagram of the optimal community detection results.

ence in samples. The more reasonable the division of important edges is, the larger the contribution becomes, otherwise the larger the consumption. The division of core nodes in networks will be more accurate and the community detection results will be more reasonable so that the iterated results can maximally increase the modularity in networks after the formula is substituted into the algorithm.

Workflow of community detection algorithm

This algorithm is a modularity-based community detection algorithm in which constant iteration is started from initialized community detection results, different community detection methods are attempted, and modularity is calculated and compared until the modularity no long increases.

More intuitively, taking the network in **Figure 2A** for example, the algorithm can be divided into following steps [17]:

(1) Network initialization: Divide each node in the networks into a single community, as shown in **Figure 2B**. (2) Iteration algorithm: Try to divide each node into the community where its neighboring nodes can be detected, and calculate the modularity Q_{n+1} at this time. Compare Q_{n+1} and modularity Q_n before this division, thus obtaining ΔQ. Accept this division if ΔQ is positive, otherwise refuse it. Repeat above process until modularity Q no longer increases. The iteration results are shown in **Figure 2C**. (3) Network reconstitution: Condense the nodes in one community into one node and calculate the weights of corresponding edges based on current community detection conditions. The reconstitution is shown in **Figure 2D**. (4) Repeat step (2) and (3) successively until this network no longer changes. The iteration results are shown in **Figure 2E**. (5) Recover the clustered community to obtain the optimal community detection result, as shown in **Figure 3**.

Results and analysis

General data conditions

Medical records of disease syndromes of heart system were collected from 1741 cases, which involved 125 symptoms and 8 basic syndromes. The data distribution conditions are shown in **Table 1**.

Community detection conditions

Syndromes, symptoms and frequencies were input into TCM Unfolding algorithm which found 6 community structures (**Figure 4**) in the automatically constructed complex networks. The corresponding symptom communities are shown as follows (the numerical values in the bracket denote the node degrees):

Table 1. Medical data distribution conditions

No.	Basic syndromes	Frequency	High-frequency symptoms (the top 10)	Western medicine diagnosis	No.	Frequency
1	Heart qi asthenia syndrome	621	Palpitation, chest distress, thin pulse, white coat, thin coat, fatigue, stringy pulse, chest distress and pain, insomnia, spiritlessness	All kinds of heart diseases	2	600
5	Heart blood stagnation syndrome	548	Chest distress; white coat, palpitation, greasy coat, red tongue, thin pulse, fatigue, purple dark, insomnia, vertigo	Coronary heart disease, angina pectoris or myocardial infarction	4	550
3	Heart yin asthenia syndrome	184	Chest distress, palpitation, thin coat, thin pulse, red tongue, stringy pulse, fatigue, insomnia, white coat, spiritlessness	Heart disease, arrhythmia for various reasons	2	170
4	Heart yang asthenia syndrome	121	Palpitation, chest distress, white coat, greasy coat, asthma, fatigue, edema of lower limbs, insomnia, chest distress and pain, anorexia	Coronary heart disease, pulmonary heart disease, etc.	5	130
7	Mind confusion by phlegm syndrome	112	Greasy coat, stringy pulse, red tongue, yellow coat, vertigo, palpitation, smooth pulse, spiritlessness, fatigue, chest distress	Found in neurological disorders such as neurosis and anxiety, menopausal syndrome, depression, Madness	7	92
2	Heart blood asthenia syndrome	70	Thin coat, thin pulse, white coat, palpitation, fatigue, insomnia, vertigo, spiritlessness, light red, stringy pulse	Arrhythmia, anemia, neurasthenia, etc.	4	75
6	Heart fire hyperactivity syndrome	53	Red tongue, stringy pulse, yellow coat, insomnia, palpitation, rapid pulse, spiritlessness, fatigue, smooth pulse, anorexia	Arrhythmia, myocardial ischemia, heart failure neurasthenia etc.	5	60
8	Brain collateral obstruction syndrome	32	Greasy coat, thin coat, red tongue, purple dark, yellow coat, thin pulse, spiritlessness, fatigue, stabbing pain in head, vertigo	Cerebral infarction	7	64

Community 1: Yellow coat (30), rapid pulse (15), dysphoria (7), red urine (6), fever (5), dry mouth and throat (3), red complexion (2), sores in mouth (1), and dry coat (1). Community 2: Greasy coat (66), smooth pulse (35), dysphoria (12), epilepsy (9), thick coat (8), gurgling with sputum in throat (4), depressive psychosis (3), unsmooth speech (3), shortness tongue (2), and manic psychosis (1). Community 3: Red tongue (84), insomnia (69), thirsty with desire of drinking water (29), scanty coat (29), chest dull pain (12), crackles tongue (12), expectoration (11), night sweat (7), dry tongue with less fluid (6), dysphoria with feverish sensation in chest, palms and soles (4), hot eyes (2), thin tongue (2), absence of coat (2), red tongue tip (1), and curdy coat (1). Community 4: Asthma (47), edema of lower limbs (33), cough (25), unavailability of lying on back (21), deep pulse (18), irregular pulse (16), aversion to cold (12), white sputum (11), teeth prints tongue (10), systemic edema (7), suffocation of heart and chest (7), edema of face (4), white complexion (3), sallow complexion (3), diarrhea (3), and retarded pulse (2). Community 5: Thin coat (430), chest distress (361), palpitation (373), thin pulse (335), fatigue (301), spiritlessness (243), anorexia (174), shortness of breath (121), aggravation after movement (85), spontaneous perspiration (51), weak pulse (57), slow pulse (48), light white tongue (48), plump tongue (28), abdominal distension (25), emaciation (17), dreaminess (20), chest pulling pain (6), weak breath and laziness to speak (8), tender tongue (4), and severe palpitation (2). Community 6: Chest distress and pain (209), purple dark tongue (178), vertigo (158), dizziness (97), stabbing pain in head (80), nausea and vomiting

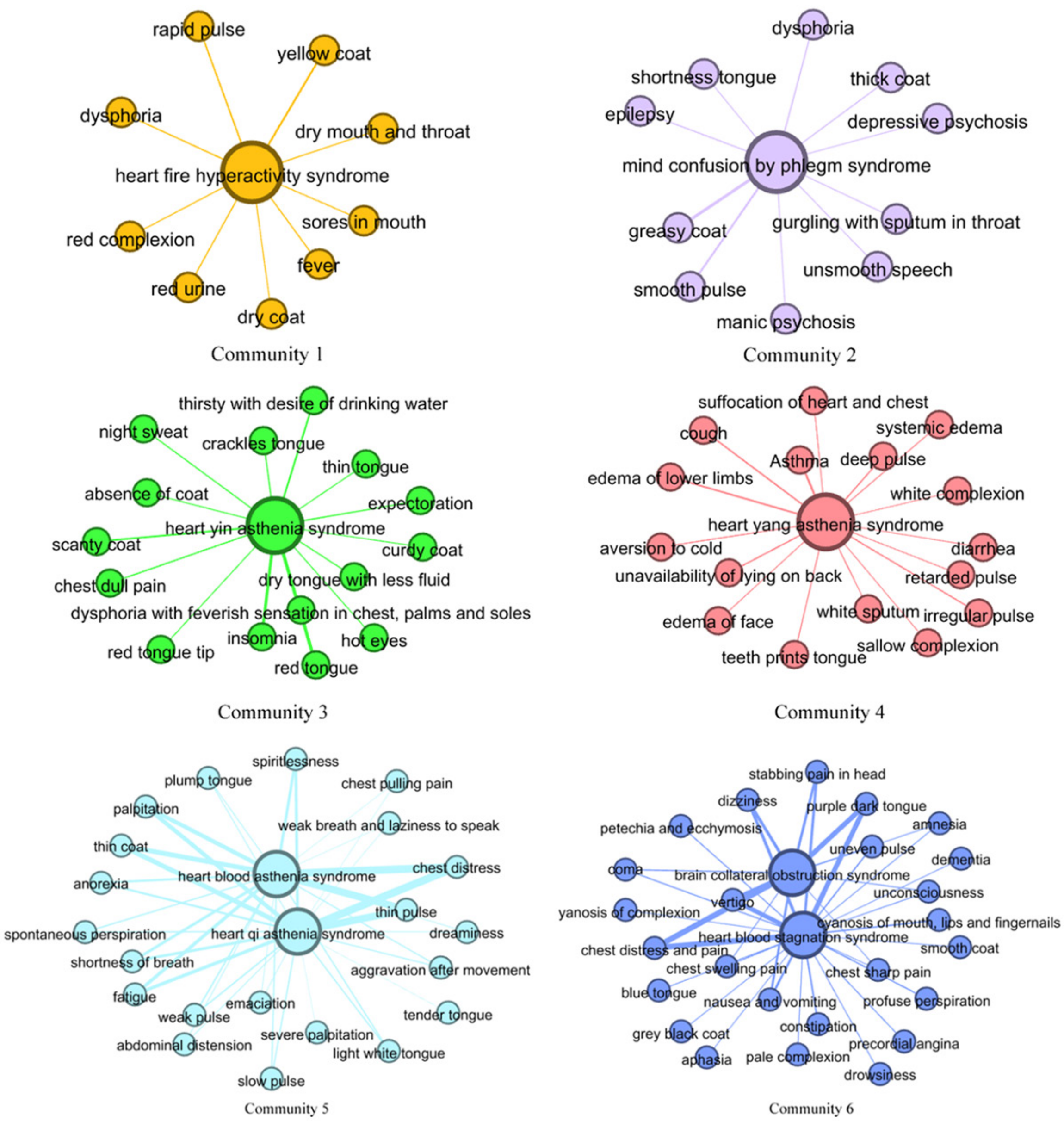

Figure 4. Community structure divided by TCM Unfolding algorithm.

(63), constipation (39), cyanosis of mouth, lips and fingernails (32), uneven pulse (27), profuse perspiration (24), coma (18), petechia and ecchymosis (15), precordial angina (12), unconsciousness (10), blue tongue (9), drowsiness (8), pale complexion (7), chest swelling pain (7), amnesia (7), grey black coat (5), dementia (3), aphasia (3), cyanosis of complexion (2), smooth coat (2), and chest sharp pain (2).

TCM Unfolding algorithm divides communities into 6 types, whereas there are 8 kinds of syndromes in primary data. It found from community results that community 1 responded to Brain collateral obstruction syndrome, while community 2 to Mind confusion by phlegm syndrome, community 3 to Heart yin asthenia syndrome, community 4 to Heart yang asthenia syndrome, community 5 to Heart qi and blood asthenia syndrome (compound syndrome of heart qi asthenia syndrome and heart blood asthenia syndrome) and community 6 to heart-brain obstruction syndrome (compound syndrome of heart blood stagnation syndrome and brain-collateral obstruction syndrome).

Discussion

Qi is the commander of blood and blood is the mother of qi, which indicates that qi and blood exist, produce and influence mutually, thus it is reasonable to divide both qi and blood asthenia syndromes into community 5 [19]. It is recorded in *On Linglan Secret Classics* of *Plain Questions* that the heart is the monarch organ and mainly dominates mind, revealing that both heart and brain belong to heart system in TCM and have close association with each other [20]. Therefore, Zhang Xi-chun, a doctor in late Qing Dynasty, proposed the theory of "heart and brain dominate the mind jointly [21]". When heart blood is obstructed, systematic blood circulation will be unsmooth and stagnated. Head is easily involved by blood stasis as it is the confluent site of all yang meridians and is located the top of human body, which can lead to symptoms like unconsciousness, drowsiness and amnesia [22]. Therefore, dividing both heart blood obstruction syndrome and brain collateral obstruction syndrome into community 6 is also in accordance with TCM theory, which indirectly reflects that the diseases are relatively complex, and the compound syndromes with multiple disease locations and characters are commonly found in heart system.

Unlike allopathic Western medicine, traditional Chinese medicine (TCM) emphasizes managing the life-health-disease-environment relationship and regaining the balance of one's bodily functions, based on holistic, dynamic, and dialectical thinking [23]. Thus, the holistic concepts of TCM coincide with the properties of a complex system in emergence, multidimensionality, nonlinearity, etc. [24]. Moreover, compared with the abundant achievements in the study of the chemical ingredients in Chinese materia medica (CMM), the modernization of TCM has developed slowly and been obstructed by the negligence of the theoretical system of TCM.

A complex network approach has been proposed to elucidate the wide variety of complex systems in physics, mathematics, economics, sociology, biology, and medical science. These complex systems in the real world are commonly characterized by scale-free degree distribution and small-world effect rather than random graphs [25]. Complex network approach has revealed some significant properties of real world including the global properties of natural and artificial systems, and the unifying principles on the basis of network architectures [26]. Specifically speaking, complex network approach has been applied to various types of networks [27].

In order to achieve effective TCM treatment for patient, patient classification is critical issue which has been studied for recent decades. Three subissues (sign classification, syndrome differentiation, and disease classification) are extensively researched according to different TCM source data [28]. We consider the four main diagnostic methods and their fusion medical records data. After the survey from a machine learning perspective, we find out several situations and issues of current objective researches on patient classification for TCM, which are summarized as follows: (1) For the diagnostic methods, a large amount of works focuses on the inspection and palpation by using various machine learning algorithms. Hence, it may be more apparent and easier to study objective inspection and palpation in TCM. (2) For medical records analysis, the application for syndrome differentiation is the main purpose in TCM. Moreover, exploring the associations among symptoms, syndromes, and diseases has been also studied for discovering the potential knowledge of medical records. Meanwhile, some recent works also manifest the genes and proteins in WM perspective that are related to syndromes in TCM. This would help us with deeper understandings of the TCM theory. (3) For the other applications, their works are not directly related to patient classification problem. But based on the medical records and other clinical data, they always build some association models among syndromes, herbs, formulas, medicines, genes, diseases, TCM effects, TCM ingredients, and the like. All these researches are critical for TCM diagnosis and treatment after patient classification, so we also should refer to these works for facilitating the unifying system development of patient classification and treatment. (4) From the machine learning perspective, a variety of learning algorithms are introduced to process those TCM data. Some works also proposed appropriate algorithms according to the special characteristics of TCM data. More recently, several advanced machine learning techniques are applied to solve TCM patient classification, such as multilabel learning and deep learning. (5) According to the reviewed works, most of them do not study the machine learning for model construction. (6) Based on the current researches, there are no published TCM database reported to provide a benchmark for different diagnosis system evaluations. (7) In addition, even a large amount of TCM diagnosis system is developed by computational methods. Meanwhile, most of them claimed that their methods or systems could analyze TCM data from a quantitative perspective. Actually, none of them could quantize their diagnostic data with meaningful implications corresponding to TCM theory, as the clinical indicators from a western medicine perspective. If this situation could not be improved, the establishment of diagnosis standards for TCM may be very difficult. Moreover, it may also hinder the development of objective TCM diagnosis research.

Although the TCM network analysis faces serious challenges in its infancy, its prospects are still promising, especially with the development of big data, computational capabilities, and experimental methods. In the future, pharmacodynamic material basis of CMMs, synergistic combinations among CMMs, pharmacological mechanisms of CMFs, and indications of TCM therapies may be elucidated through TCM network analysis. Thus, this approach is expected to bridge the gap between traditional medicine and modern medicine, allow for investigating the scientific basis of TCM theory, and accelerate the modernization of TCM.

Conclusions

Application of community detection algorithm in the study of disease standardization can establish TCM Unfolding algorithm that conform to TCM medical record analysis by optimizing conventional Fast Unfolding algorithm, and can achieve the extraction and identification of characteristic symptoms of common syndromes of heart system by combing with the analysis of data of medical records of heart system, so as to provide evidence for the common syndromes of heart system. TCM diagnosis belongs to system science and complex science, and its connotation is difficult to be disclosed comprehensively using conventional methods. Community detection in complex networks, as one of the methods for study of complicated affairs, can be used in TCM diagnosis with hope of exploring the rationales and rules of TCM diagnosis. This study thought can be further popularized in other systems of visceral syndrome differentiation, so as to achieve the standardization and unification of date-supported high-evidence syndromes.

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Disclosure of conflict of interest

None.

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